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# Synthesis of condensed chiral pyranopyran derivatives with antiproliferative activity using domino Knoevenagel-IMHDA sequences

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We explored a domino Knoevenagel-intramolecular hetero-Diels-Alder (IMHDA) sequence, in which chiral pentaheterocyclic frameworks containing a pyrano[4,3-*b*]pyran unit condensed with a pyrone/pyridone and a tetrahydroquinoline/chroman subunit were synthesized. Substituted 2*H*-chromenes or 3,6-dihydro-2*H*-pyrans bearing an *o*-(formylaryl)-ether or -amine moiety were used as substrates, along with 4-hydroxypyrene, -pyridone, -coumarin and 2-quinolone derivatives as active methylene reagents, to assemble chiral condensed ring systems in a domino sequence. In the IMHDA cyclization step, two competing heterodiene subunits consisting of an  $\alpha,\beta$ -unsaturated ketone or an ester/lactam carbonyl afforded regioisomeric condensed coumarin or chromone rings, respectively. Both heterodienes can undergo cyclization with an *endo* or *exo* transition state, resulting in two pairs of diastereomers. Up to four possible isomers were isolated in the cyclisation reactions and their structures elucidated using 2D NMR, chiroptical methods, and two single-crystal X-ray diffraction structures. The regio- and diastereoselectivity of the cyclisation was investigated in terms of temperature, solvent and the structures of the substrate and reagent. Simplified substrates were prepared from 5,6-dihydro-2*H*-pyran derivatives, the reactions of which took place with complete regio- and stereoselectivity, providing a single product with good yields. Some of the products exhibited antiproliferative activity against human cancer cell lines with IC<sub>50</sub> values down to 5.7  $\mu$ M.

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## Introduction

The pyranopyran motif is a common core structure in various natural secondary metabolites of pharmacological interest, and all of the six possible regioisomeric bicycles (Fig. 1a) are found in bioactive derivatives.<sup>1–4</sup> The two most frequent ones are the pyrano[4,3-*b*]pyran, found in marine and fungal metabolites such as

pyripyropene,<sup>5</sup> territrems<sup>6</sup> or cyclomorulin,<sup>7</sup> (Fig. 1b) and the pyrano[3,2-*b*]pyran, which is a recurring motif in marine toxins like okadaic acid, ciguatoxins and brevetoxins.<sup>8</sup> Pyrano[3,4-*c*]pyran and pyrano[2,3-*b*]pyran are also common building blocks, as the ring systems in the aglycone unit of many secoiridoid glycosides<sup>9,10</sup> (Fig. 1c) and saponins,<sup>11–13</sup> respectively. The pyrano[3,4-*b*]pyran and pyrano[4,3-*c*]pyran ring systems are much rarer, found mainly in rotenoids<sup>14</sup> and ellagic acid. Tripyrano ring systems of a more complex nature are much less abundant, and synthetic availability is limited. It is evident that only a limited number of natural products<sup>15,16</sup> or synthetic bioactive derivatives with antiviral,<sup>17</sup> antibacterial,<sup>18</sup> or antitumor<sup>19,20</sup> activities, containing a tripyrano skeleton, are currently known.

Hetero-Diels-Alder (HDA) reactions are a valuable tool in the synthesis of pyran heterocycles. They have been used in the total synthesis of various pyran natural products.<sup>21–27</sup> The reaction can be conveniently combined with a condensation reaction in a tandem process, resulting in the domino Knoevenagel-intramolecular hetero-Diels-Alder (DKIMHDA) reaction.<sup>28–37</sup> This is a versatile and robust tool in the preparation of fused pyran derivatives, with which complex scaffolds can be assembled in a single step, with excellent diastereoselectivities. If the diene or the dienophile already incorporates a heterocycle, an

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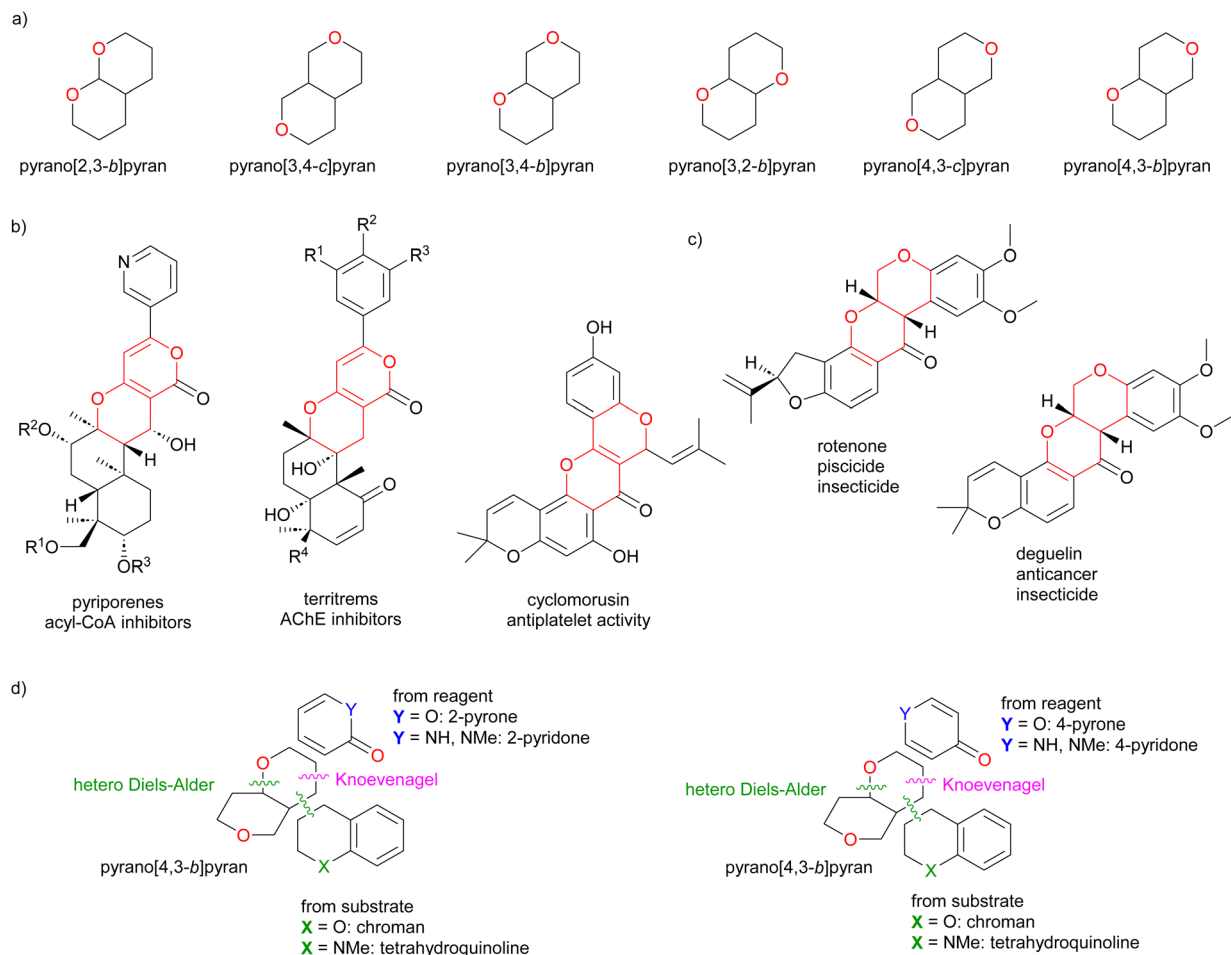


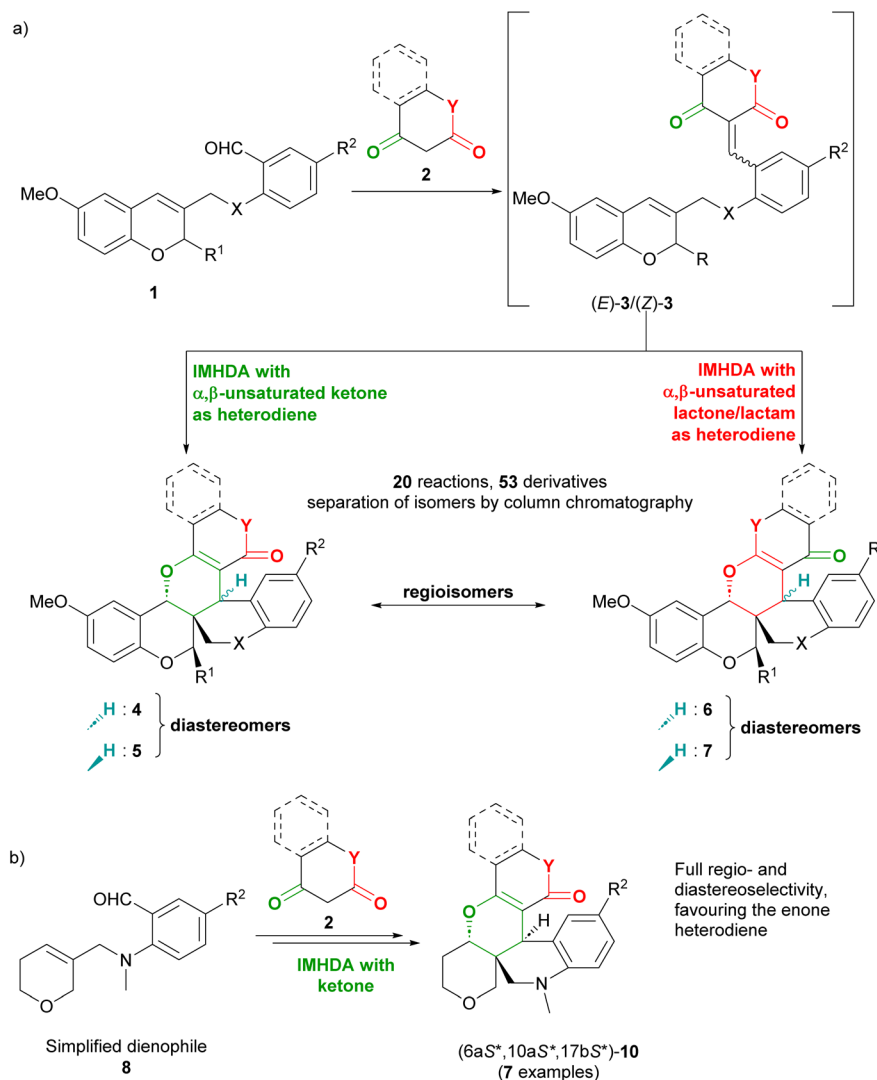
Fig. 1 (a) Structures and names of the six condensed pyranopyran bicycles and related bioactive natural products containing (b) pyrano[4,3-*b*]pyran or (c) pyrano[3,4-*b*]pyran subunits. (d) Recent work: assembling novel condensed heterocyclic ring systems possessing a pyrano[3,4-*b*]pyran subunit fused with chroman and pyrone rings ( $X, Y = O$ ) or their nitrogen analogues ( $X, Y = NMe$ ).

extended heterocyclic ring system is assembled during the cyclization reaction as also demonstrated by our recent work outlined in Fig. 1d. For the preparation of pyranopyran ring systems, 4-hydroxypyrene and -coumarin reagents were used, which are non-symmetric  $\beta$ -dicarbonyl reagents. In the Knoevenagel intermediate, there are two different heterodiene subunits, the  $\alpha, \beta$ -unsaturated ketone or acyl moiety, capable of undergoing HDA cyclization (Fig. 1d). In many cases, the cyclization step occurs with excellent regioselectivity due to the different reactivity of the two heterodienes, with the  $\alpha, \beta$ -unsaturated ketone moiety reacting exclusively.<sup>38–40</sup> The  $\alpha, \beta$ -unsaturated ester unit can also take part in the HDA reaction, especially if the cyclization is intramolecular,<sup>41–43</sup> and the selectivity can be increased by the use of microwave irradiation<sup>44–46</sup> or ionic liquids.<sup>47</sup> While the regioselectivity varies based on the structure of the substrate, mainly on the substitution pattern of the dienophile, all reported reactions share the same *cis* diastereoselectivity. Other analogue reagents, such as 4-hydroxy-2*H*-pyran-2-one<sup>48,49</sup> and 4-hydroxyquinolin-2(1*H*)-one<sup>41,50</sup> derivatives were rarely utilized in these reactions.

Our goal was to expand the scope of this reaction by using heterocyclic dienophiles (2*H*-chromene and 3,6-dihydro-2*H*-pyran) in the DKIMHDA reaction. In the reactions of 2*H*-

chromenes **1** and active methylene reagents **2**, the initial Knoevenagel intermediate **3** can undergo an IMHDA reaction through four different transition states (TSs), as demonstrated by Tietze and co-workers and our previous DFT calculations.<sup>51</sup> In the case of these non-symmetric reagents, the four TSs lead to four isomers, yielding two diastereomeric pairs of the two regioisomers (Scheme 1a). The regioselectivity and diastereoselectivity of the IMHDA reaction were both found to be influenced by the substrate (**1**) and the reagent (**2**). In most cases, the regio- and diastereomers were separated by column chromatography. The regioisomers were identified by <sup>13</sup>C-NMR and IR spectroscopy, the diastereomers by NOESY measurements, and in two cases, the planar structure and relative configuration were also confirmed by single-crystal X-ray diffraction analysis. The domino reactions of the simplified dihydropyran derivatives **8** demonstrated excellent regio- and diastereoselectivity, with each reaction yielding a single product, (6*aS*\*, 10*aS*\*, 17*bS*\*)-**10**, and no other isomers being detected (Scheme 1b). The antiproliferative effect of the products was tested on three human cancer cell lines, and several derivatives showed promising activity with low micromolar IC<sub>50</sub> values.





Scheme 1 Domino Knoevenagel-intramolecular hetero Diels–Alder reactions of (a) 2*H*-chromene derivatives **1** and (b) 3,6-dihydro-2*H*-pyrans **8** with cyclic non-symmetric  $\beta$ -dicarbonyl reagents **2**.

## Results and discussion

### Domino Knoevenagel-IMHDA reactions with 4-hydroxycoumarin reagents (2a–c)

Domino Knoevenagel-IMHDA reactions with hydroxycoumarins are usually carried out in the presence of a base and a wide variety of solvents can be utilized, including protic,<sup>49,50</sup> polar aprotic,<sup>40,52</sup> apolar<sup>41</sup> and even ionic liquids<sup>47</sup> or solvent-free conditions.<sup>38,39,44</sup> Thus, we started our investigations with a solvent screening for the reaction of **1a** and **2a** using piperidine as a base (Table 1). The numbering employed for the cyclized products is as follows: the numbers 4–7 represent the regio- and stereochemistry as outlined in Table 1. The first letter refers to the structure of the substrate, and the second letter to that of the active methylene reagent.

The yield, as well as the formation and ratio of the regio- (**4aa** and **5aa** versus **6aa** and **7aa**) and diastereomers (**4aa** versus **5aa** and **6aa** versus **7aa**), were found to be significantly dependent on

the solvent utilized in the reaction. It was observed that, of the apolar solvents, toluene was the only suitable option for the reaction, as no reaction occurred in hexane (entry 1), due to the insolubility of substrate **1a**. Toluene facilitated the formation of all four possible isomers, exhibiting low selectivity and favoring the formation of **7aa** as the main product, which could not even be observed in most solvents. Furthermore, toluene was found to provide the best overall yield of 78% (entry 2). Among the protic solvents, ethanol exhibited surprisingly analogous results to toluene, producing all four isomers in comparable ratios (entry 8). Acetic acid was found to be incompatible with the reaction, resulting solely in decomposition of the substrate (entry 10). When using polar aprotic solvents, a clear correlation between the reaction's selectivity and the polarity of the solvent is absent. The formation of **7aa** was not detected in these solvents, and **4aa** was the major product, but the ratios did not follow an obvious pattern (entry 3–7, 9, 11–12). The ratio of isomers **4aa/6aa/5aa** increased in the order ethanol < toluene <



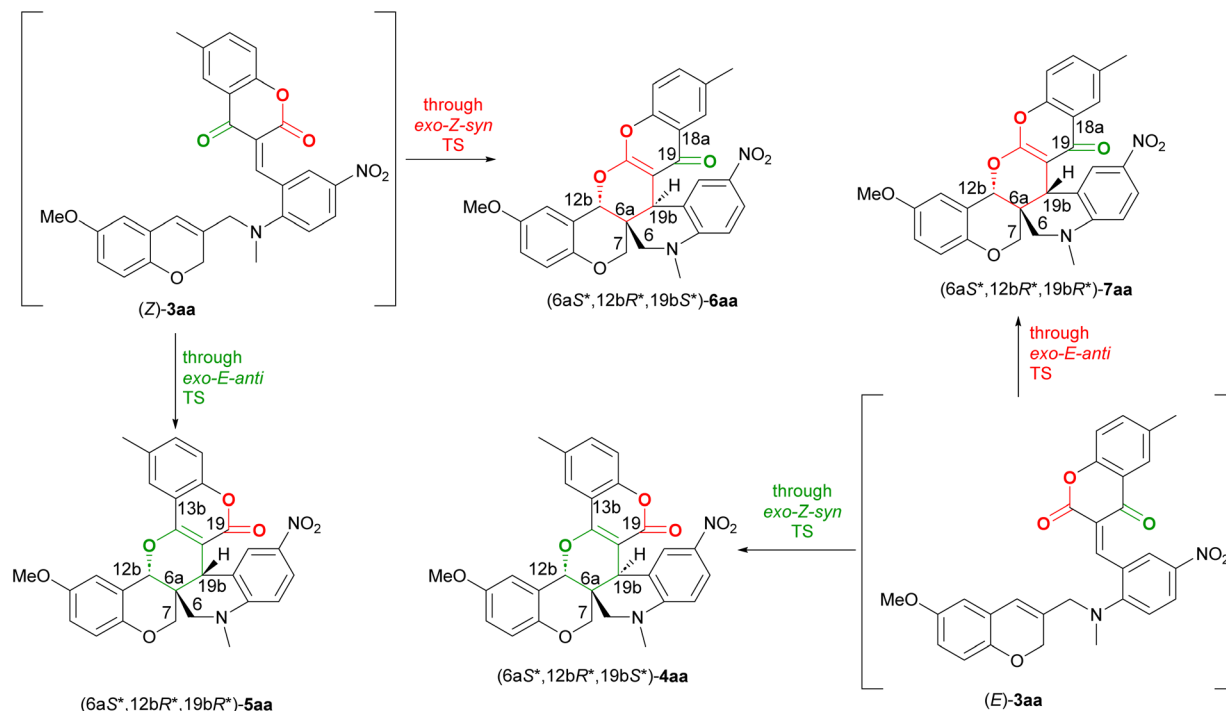


Fig. 2 Formation of the four isomeric products from intermediates (*E*)-3 and (*Z*)-3.

ethyl acetate < acetonitrile < 1,2-dichloroethane  $\approx$  chloroform  $\approx$  1,4-dioxane < tetrahydrofuran < dimethylsulfoxide  $\approx$  *N,N*-dimethylformamide from 4 : 3 : 3 to 4 : 1 : 0. Since toluene showed the best overall yield, it was selected the solvent for the domino sequence. Although it showed the lowest selectivity, the preparation and isolation of multiple isomers allow a more comprehensive stereochemical study, and could assist in establishing a structure–activity relationship.

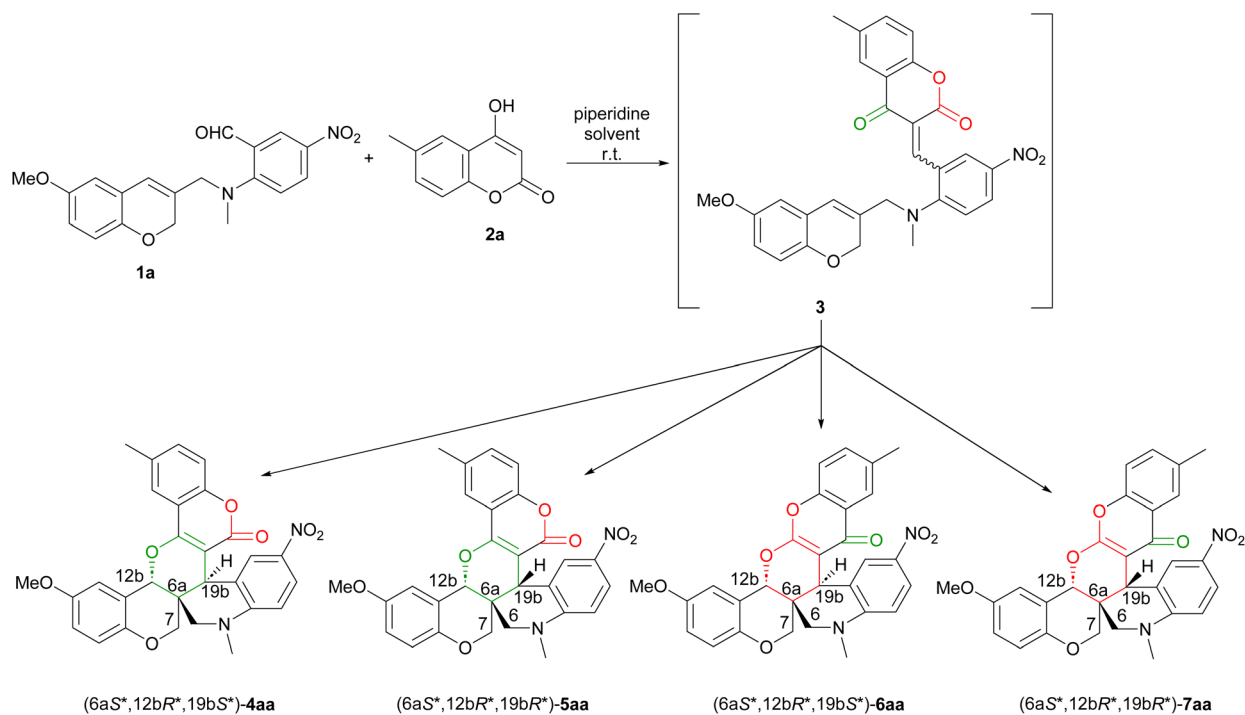
The formation of up to four isomeric products is most likely due to a lack of (*E*)/(*Z*) selectivity in the Knoevenagel condensation, since from the four possible TSs, only three are viable, according to Tietze *et al.*<sup>54</sup> This is in accordance with our previous findings; in cyclization reactions of 2*H*-chromene derivatives **1a–c**, *exo-Z-syn* and *exo-E-anti* TSs lead to epimeric products, according to our DFT calculations.<sup>34</sup> Using a non-symmetric reagent for the domino reaction, the Knoevenagel condensation likely leads to a diastereomeric mixture of (*E*)/(*Z*)-**3**. *Exo-Z-syn* TSs from (*Z*)-**3aa** and (*E*)-**3aa** lead to products **6aa** and **4aa**, respectively, with *trans* orientation of methine protons 12b-H and 19b-H corresponding to (6a*S*\*, 12b*R*\*, 19b*S*\*) relative configuration (RC) (Fig. 2). In the case of (*Z*)-**3aa**, the lactone carbonyl contributed to the heterodiene affording **6aa**, while (*E*)-**3aa** leads to **4aa** with the  $\alpha,\beta$ -unsaturated ketone moiety acting as the heterodiene. Similarly, *exo-E-anti* TSs from (*Z*)- and (*E*)-**3aa** lead to products **5aa** and **7aa**, respectively, with *cis* orientation of the protons 12b-H and 19b-H implying (6a*S*\*, 12b*R*\*, 19b*R*\*) RC. Through the *exo-E-anti* TS, (*Z*)-**3aa** produces **5aa** with the ketone carbonyl contributing to the heterodiene, while (*E*)-**3aa** leads to **7aa** with the participation of the lactone carbonyl (Fig. 2). Thus the selectivity of the domino reaction depends on two separate factors: (*E*)/(*Z*)-selectivity of the

Knoevenagel condensation and the relative energies of the TSs leading to the given isomer in the subsequent cyclization.

The reactions of **1a–e** with substituted 4-hydroxycoumarin reagents (**2a–c**) were carried out in refluxing toluene, using piperidine as the base. In the reactions of substrate **1c**, possessing an ether linker, aza-Michael addition of piperidine to intermediate **3** was observed, impeding the cyclization. In these instances, triethylamine was utilized as a base (entries 5, 10, 16 and 17). For the simplified substrates **8a** and **8b**, containing a 3,6-dihydro-2*H*-pyran moiety, all reactions took place with complete regio- and diastereoselectivity affording solely the product (6a*S*\*, 10a*S*\*, 17b*S*\*)-**10** with up to 77% yield, irrespective of the substitution pattern of the reagent (Table 2, entries 6, 11, 20 and 21).

In order to ascertain the effect of the temperature on the reaction, the reaction of **1a** and **2a** was carried out at three different conditions; at reflux temperature (entry 1), at room temperature (entry 2), and at 150 °C with microwave activation (entry 3). An increased diastereoselectivity was observed at room temperature, favouring derivatives **4aa** and **7aa** (entry 2). This is most likely caused by the different selectivity of the initial Knoevenagel condensation, as the formation of these two isomers is possible from the same (*E*)-**3aa** intermediate through *exo-Z-syn* and *exo-E-anti* transition states for **4aa** and **7aa**, respectively (Fig. 2). Microwave irradiation (150 °C) was found to provide **4aa** exclusively, but in a low yield (22%), no other isomers were detected in the reaction. The low yield is attributed to decomposition; as multiple side-products were observed in the reaction mixture (entry 3). Substrate-controlled stereo-selective domino reaction was tested with the optically active substrate (*R*)-**1b** (entries 4), which promoted the formation of





isomer **5ba** as the major product (31%) but diastereomeric **4ba** was also isolated with 28% yield. The inherent chirality of the substrate affected mostly the regioselectivity, favouring the enone subunit as the heterodiene, while the diastereoselectivity remained quite low as also demonstrated by entries 14 and 15. The dimethyl derivative **2b** showed superior selectivity in the domino reactions. The formation of isomer **7** was not detected with either substrate (entry 7–11) and full diastereoselectivity was observed with **8a** and **1a** (entries 7, 8 and 11). The effect of temperature was also assessed in the reaction of **1a** and **2b** (entries 7 and 8). The reaction afforded regioisomers **4ab** and **6ab** with full diastereoselectivity at both temperatures, and the regioselectivity was again higher at room temperature, favouring **4ab** with 54% yield. The trimethoxy-substituted reagent **2c** afforded three isomers with high regioselectivity and moderate to low diastereoselectivity in the domino reaction with all three substrates (entry 12–17). Carrying out the reaction at room temperature induced no significant change in either the regio- or diastereoselectivity (entries 13, 15 and 17). Since these products showed the best antiproliferative activities, two additional derivatives were prepared to study the effect of the substitution of the benzaldehyde moiety ( $R^2$  and  $R^3$ ). In these reactions, only the major products were isolated, but the formation of the other two minor isomers was detected (entry 18–19).

The planar structures of the regioisomers were determined on the basis of the  $^{13}\text{C}$ -chemical shift of the C-19 carbonyl carbon: the lactone moiety of the coumarin derivatives **4** and **5** exhibited a characteristic peak in the 165–166 ppm range, while the ketone of the chromone derivatives **6** and **7** in the range of

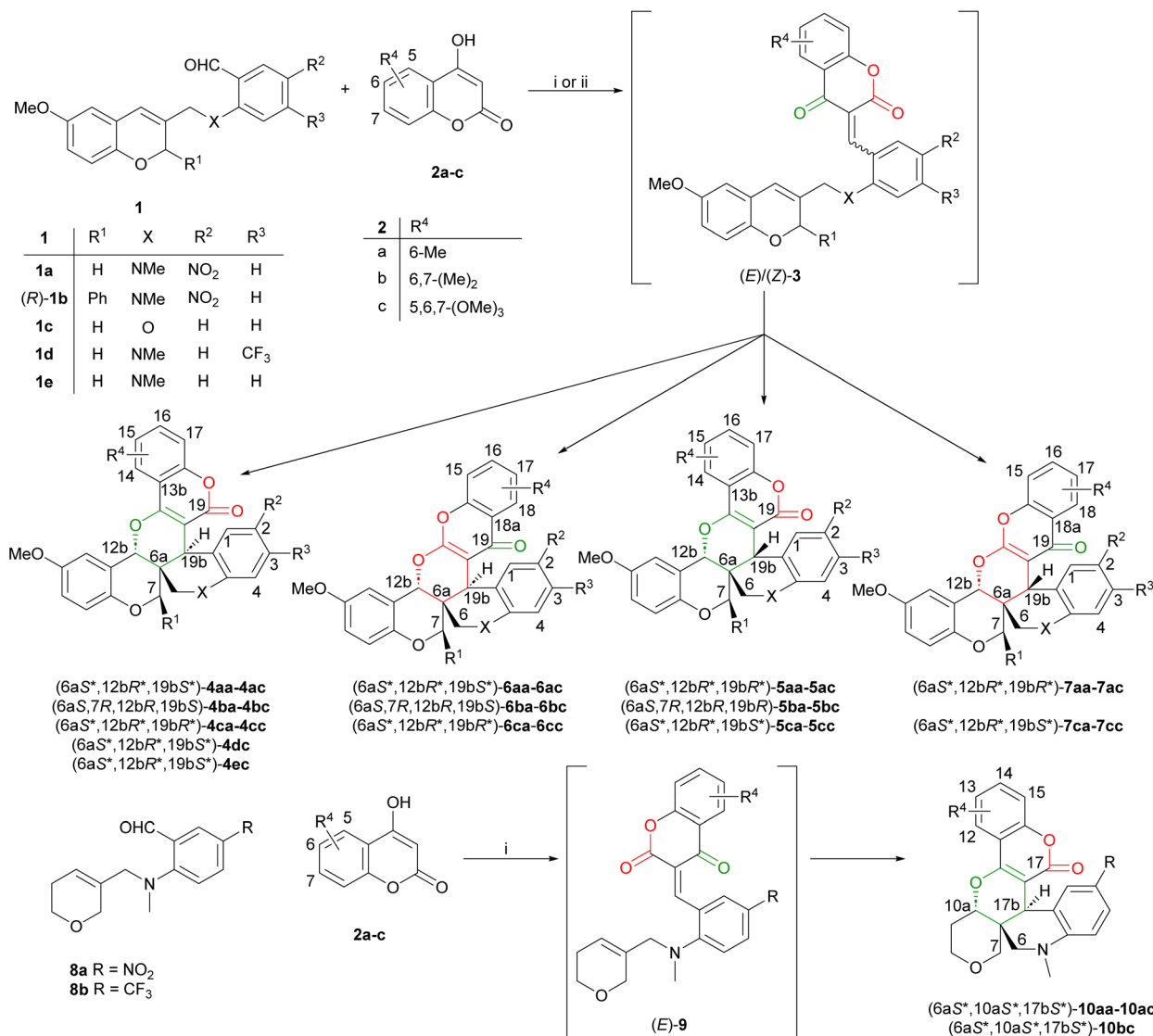
180–181 ppm. The planar structure is supported by the  $\nu_{\text{C=O}}$  stretching vibrations in the IR spectra of the products: the isomers **4/5** and **6/7** showed the characteristic IR absorption bands for  $\alpha,\beta$ -unsaturated esters (1697–1711  $\text{cm}^{-1}$ ) and ketones (1667–1669  $\text{cm}^{-1}$ ), respectively. The relative configuration of each diastereomeric product was assigned using characteristic NOE correlations. 12b-H and C-6 are *cis* in all isomers, owing to the diastereospecificity of the Diels–Alder reaction (*Z* configuration of the dienophile double bond in substrates **1a–e**). The

Table 1 Monitoring solvent effect in the domino Knoevenagel-hetero Diels–Alder reaction of **1a** and **2a**

| Entry | Solvent                       | Ratio of isomers <sup>b</sup> (%) |     |     |     | Yield <sup>a</sup> (%) |
|-------|-------------------------------|-----------------------------------|-----|-----|-----|------------------------|
|       |                               | 4aa                               | 5aa | 6aa | 7aa |                        |
| 1     | Hexane                        | —                                 | —   | —   | —   | 0% <sup>c</sup>        |
| 2     | Toluene                       | 18                                | 24  | 24  | 34  | 78%                    |
| 3     | 1,2-Dichloroethane            | 52                                | 22  | 26  | —   | 51%                    |
| 4     | Tetrahydrofuran               | 60                                | 24  | 16  | —   | 55%                    |
| 5     | Chloroform                    | 50                                | 27  | 23  | —   | 50%                    |
| 6     | Ethyl acetate                 | 39                                | 30  | 31  | —   | 50%                    |
| 7     | Dioxane                       | 52                                | 30  | 18  | —   | 58%                    |
| 8     | Ethanol                       | 16                                | 19  | 32  | 33  | 46%                    |
| 9     | Acetonitrile                  | 42                                | 27  | 31  | —   | 67%                    |
| 10    | Acetic acid                   | —                                 | —   | —   | —   | 0% <sup>d</sup>        |
| 11    | <i>N,N</i> -dimethylformamide | 81                                | —   | 19  | —   | 35%                    |
| 12    | Dimethylsulfoxide             | 77                                | 3   | 20  | —   | 33%                    |

<sup>a</sup> The products were isolated as a mixture of isomers by crystallization, yield given is isolated yield. <sup>b</sup> Ratio of isomers was determined by HPLC separation from the crystallized mixture. <sup>c</sup> No reaction. <sup>d</sup> Full conversion, but no product observed.





*trans* configuration of the methine protons 12b-H and 19b-H in products 4 and 5 was determined using key correlations 12b-H<sub>eq</sub>/6-H<sub>eq</sub>, 19b-H<sub>ax</sub>/6-H<sub>ax</sub> and 19b-H<sub>ax</sub>/7-H<sub>eq</sub> (Fig. S3 and S9). In 6 and 7, 12b-H and 19b-H are *cis*, which was determined from the characteristic 12b-H<sub>ax</sub>/6-H<sub>ax</sub>, 19b-H<sub>ax</sub>/12b-H<sub>ax</sub> and 19b-H<sub>ax</sub>/6-H<sub>ax</sub> correlations (Figure S6).

In the case of optically active products 4ba–4bc, 6ba–6bc and 5ba–5bc, since the absolute configuration (AC) of the C-2 chirality center in (R)-1b (C-7 in the products) is known,<sup>53</sup> the ACs (6aS, 7R, 12bR, 19bS)-4ba–bc, (6aS, 7R, 12bR, 19bS)-6ba–bc and (6aS, 7R, 12bR, 19bR)-5ba–bc were assigned. The enantiomers of racemates 4aa–4ac, 5aa–5ac and 6aa–6ac were separated by chiral HPLC, and the on-line HPLC-ECD spectra of the enantiomers were recorded (Fig. S181–S205). By comparing these spectra to the ECD spectra of the corresponding C-7 phenyl derivatives with known absolute configuration, the ACs

of the separated enantiomers were assigned (Fig. S182, S184 and S186). Surprisingly, the HPLC-ECD spectra of 4aa and 6aa did not show sufficient similarity with the ECD spectra of 4ba and 6ba, and hence the absolute configurations were not assigned in these cases.

The structures of racemic 4cc and 6cc were determined independently by single crystal X-ray diffraction analysis (CCDC no. 2408634 and 2408635, respectively, Fig. 3), which supported both the connectivity and the stereochemistry of the assigned structures (Tables S1–S6).

#### Domino Knoevenagel-IMHDA reactions with 4-hydroxy-2-quinolone (2d)

In order to test the effect of the substitution in the carbonyl moiety on the regioselectivity, the reaction was also carried out with the lactam derivative 4-hydroxy-2-quinolone (2d) as



**Table 2** Domino Knoevenagel-IMHDA reactions of 2*H*-chromene derivatives **1** with 4-hydroxy-coumarin derivatives **2a–c**. (i): toluene, piperidine (1 eq.), for entry 1–4, 6–9, 11–15 and 18–21; (ii): toluene, Et<sub>3</sub>N (1 eq.), for entry 5, 10, 16–17

| Entry           | 1             | 2         | Product (yield)                                                                                                                  | Regioselectivity<br>(4 + 5) : (6 + 7) | Diastereoselectivity<br>(4 + 6) : (5 + 7) |
|-----------------|---------------|-----------|----------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|-------------------------------------------|
| 1               | <b>1a</b>     | <b>2a</b> | <b>4aa</b> (14%) <sup>a</sup><br><b>6aa</b> (19%) <sup>b</sup><br><b>5aa</b> (19%) <sup>b</sup><br><b>7aa</b> (27%) <sup>a</sup> | 42 : 58                               | 42 : 58                                   |
| 2 <sup>c</sup>  | <b>1a</b>     | <b>2a</b> | <b>4aa</b> (27%) <sup>a</sup><br><b>6aa</b> (12%) <sup>b</sup><br><b>5aa</b> (6%) <sup>b</sup><br><b>7aa</b> (19%) <sup>a</sup>  | 52 : 48                               | 61 : 39                                   |
| 3 <sup>d</sup>  | <b>1a</b>     | <b>2a</b> | <b>4aa</b> (22%) <sup>a</sup>                                                                                                    | 100 : 0                               | 100 : 0                                   |
| 4               | <b>(R)-1b</b> | <b>2a</b> | <b>4ba</b> (28%) <sup>b</sup><br><b>6ba</b> (14%) <sup>b</sup><br><b>5ba</b> (34%) <sup>a</sup>                                  | 82 : 18                               | 55 : 45                                   |
| 5               | <b>1c</b>     | <b>2a</b> | <b>4ca</b> (34%) <sup>a</sup><br><b>6ca</b> (19%) <sup>a</sup><br><b>5ca</b> (17%) <sup>a</sup><br><b>7ca</b> (6%) <sup>a</sup>  | 67 : 33                               | 70 : 30                                   |
| 6               | <b>8a</b>     | <b>2a</b> | <b>10aa</b> (44%)                                                                                                                | 100 : 0                               | 100 : 0                                   |
| 7               | <b>1a</b>     | <b>2b</b> | <b>4ab</b> (40%) <sup>a</sup><br><b>6ab</b> (45%) <sup>a</sup>                                                                   | 47 : 53                               | 100 : 0                                   |
| 8 <sup>c</sup>  | <b>1a</b>     | <b>2b</b> | <b>4ab</b> (54%) <sup>a</sup><br><b>6ab</b> (19%) <sup>a</sup>                                                                   | 74 : 26                               | 100 : 0                                   |
| 9               | <b>(R)-1b</b> | <b>2b</b> | <b>4bb</b> (31%) <sup>a</sup><br><b>6bb</b> (16%) <sup>a</sup><br><b>5bb</b> (14%) <sup>a</sup>                                  | 74 : 26                               | 77 : 23                                   |
| 10              | <b>1c</b>     | <b>2b</b> | <b>4cb</b> (35%) <sup>a</sup><br><b>6cb</b> (19%) <sup>a</sup><br><b>5cb</b> (21%) <sup>a</sup>                                  | 75 : 25                               | 72 : 28                                   |
| 11              | <b>8a</b>     | <b>2b</b> | <b>10ab</b> (57%)                                                                                                                | 100 : 0                               | 100 : 0                                   |
| 12              | <b>1a</b>     | <b>2c</b> | <b>4ac</b> (49%) <sup>a</sup><br><b>6ac</b> (16%) <sup>a</sup><br><b>5ac</b> (25%) <sup>a</sup>                                  | 82 : 18                               | 72 : 28                                   |
| 13 <sup>c</sup> | <b>1a</b>     | <b>2c</b> | <b>4ac</b> (21%) <sup>a</sup><br><b>6ac</b> (10%) <sup>a</sup><br><b>5ac</b> (14%) <sup>a</sup>                                  | 78 : 22                               | 69 : 21                                   |
| 14              | <b>(R)-1b</b> | <b>2c</b> | <b>4bc</b> (42%) <sup>a</sup><br><b>6bc</b> (10%) <sup>a</sup><br><b>5bc</b> (44%) <sup>a</sup>                                  | 90 : 10                               | 54 : 46                                   |
| 15 <sup>c</sup> | <b>(R)-1b</b> | <b>2c</b> | <b>4bc</b> (32%) <sup>a</sup><br><b>6bc</b> (8%) <sup>a</sup><br><b>5bc</b> (53%) <sup>a</sup>                                   | 91 : 9                                | 43 : 57                                   |
| 16              | <b>1c</b>     | <b>2c</b> | <b>4cc</b> (34%) <sup>a</sup><br><b>6cc</b> (12%) <sup>a</sup><br><b>5cc</b> (14%) <sup>a</sup>                                  | 80 : 20                               | 77 : 23                                   |
| 17 <sup>e</sup> | <b>1c</b>     | <b>2c</b> | <b>4cc</b> (29%) <sup>a</sup><br><b>6cc</b> (8%) <sup>a</sup><br><b>5cc</b> (13%) <sup>a</sup>                                   | 84 : 16                               | 74 : 26                                   |
| 18              | <b>1d</b>     | <b>2c</b> | <b>4dc</b> (42%) <sup>a</sup>                                                                                                    | n.d. <sup>f</sup>                     | n.d. <sup>f</sup>                         |
| 19              | <b>1e</b>     | <b>2c</b> | <b>4ec</b> (32%) <sup>a</sup>                                                                                                    | n.d. <sup>f</sup>                     | n.d. <sup>f</sup>                         |
| 20              | <b>8a</b>     | <b>2c</b> | <b>10ac</b> (77%)                                                                                                                | 100 : 0                               | 100 : 0                                   |
| 21              | <b>8b</b>     | <b>2c</b> | <b>10bc</b> (52%)                                                                                                                | 100 : 0                               | 100 : 0                                   |

<sup>a</sup> Isolated yield. <sup>b</sup> Isolated as a mixture, yield calculated from NMR integrals. <sup>c</sup> Reaction carried out at room temperature. <sup>d</sup> Reaction carried out with microwave irradiation. <sup>e</sup> No reaction at r.t., reaction carried out at 55 °C. <sup>f</sup> Only one isomer isolated, ratios not determined.

a reagent (Scheme 2). Due to its poor solubility in toluene, the reactions had to be conducted in ethanol. The selectivity was governed primarily by the substitution pattern of the 4*H*-chromene substrate, and this reagent produced the largest differences among substrates. The 2*H*-chromene substrate **1a** afforded three isomers, with **4ad** being the major product

(48%), and the lactam carbonyl also reacted as part of the heterodiene to form **6ad** with 12% yield. The 2-phenyl derivative *rac*-**1b** gave a mixture of two diastereomers with full regioselectivity, favouring the formation of **4bd** (60%). In the reaction of the aryether substrate **1c**, only one isomer was isolated with 24% yield (Scheme 2). The regioselectivity was higher than



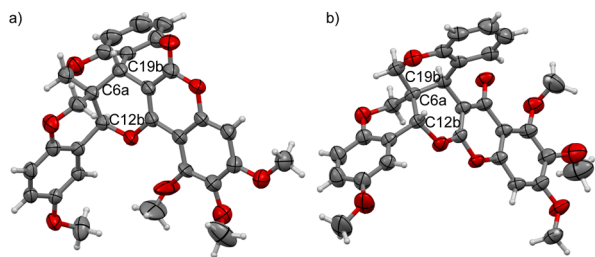
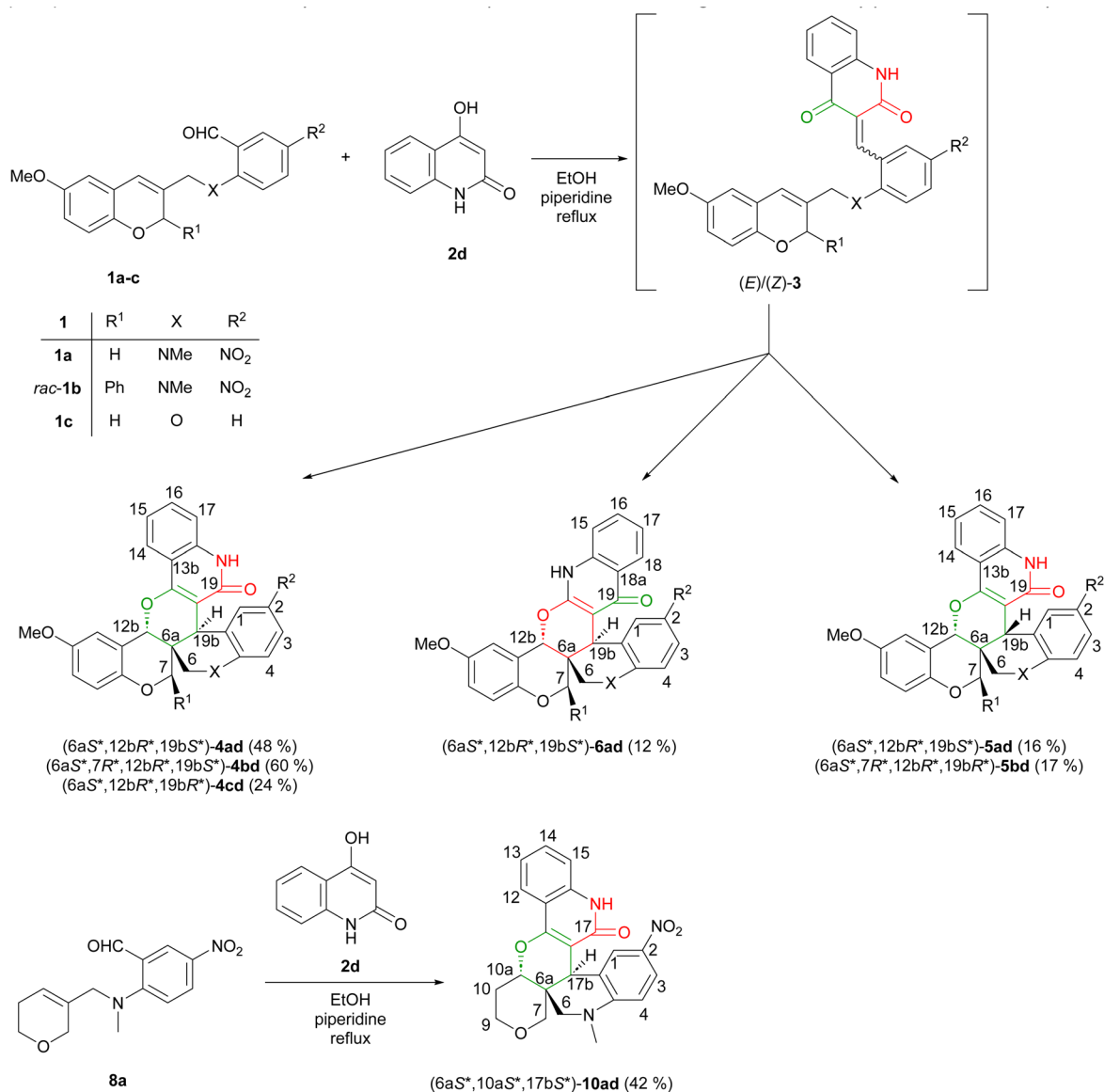


Fig. 3 ORTEP view at 50% probability level of (a) *rac*-(6a*S*\*, 12b*R*\*, 19b*R*\*)-4cc (CCDC no. 2408634) and (b) *rac*-(6a*S*\*, 12b*R*\*, 19b*R*\*)-6cc (CCDC no. 2408635).

those with the 4-hydroxycoumarins **2a-c**, as the lactam carbonyl moiety of **2d** is even less reactive than the ester group of **2a-c**. The domino sequence with the simplified analogue **8a** was completely regio- and diastereoselective, affording **10ad** as the only product with 42% yield.

### Domino Knoevenagel-IMHDA reaction with 4-hydroxypyrrone (**2e**) and -pyridone reagents (**2f**)

Since the presence or absence of the condensed benzene ring in the substrates (**1a-e** or **8a**, **8b**) had a decisive effect on both the regio- and diastereoselectivity of the domino sequence, reagents lacking the condensed benzene ring, 4-hydroxy-6-methyl-2*H*-pyran-2-one (**2e**) and its lactam derivative 4-hydroxy-1,6-dimethylpyridin-2(1*H*)-one (**2f**), were also tested. In the domino reaction, substrates containing an amine linker (**1a** and **1b**) gave three or four isomers, while the substrate **1c** containing an arylether linker afforded the two regioisomers with complete diastereoselectivity. To test the effect of the reaction temperature on the selectivity of the IMHDA reaction, the domino reaction sequences were carried out both at reflux and at room temperature as well (entries 1–6). In the reaction of (*R*)-**1b**, the temperature had a significant effect on the diastereoselectivity: the main product was **4be** at reflux, and **5be** at room



Scheme 2 Domino Knoevenagel-IMHDA reactions with 4-hydroxy-2-quinolone (**2d**).

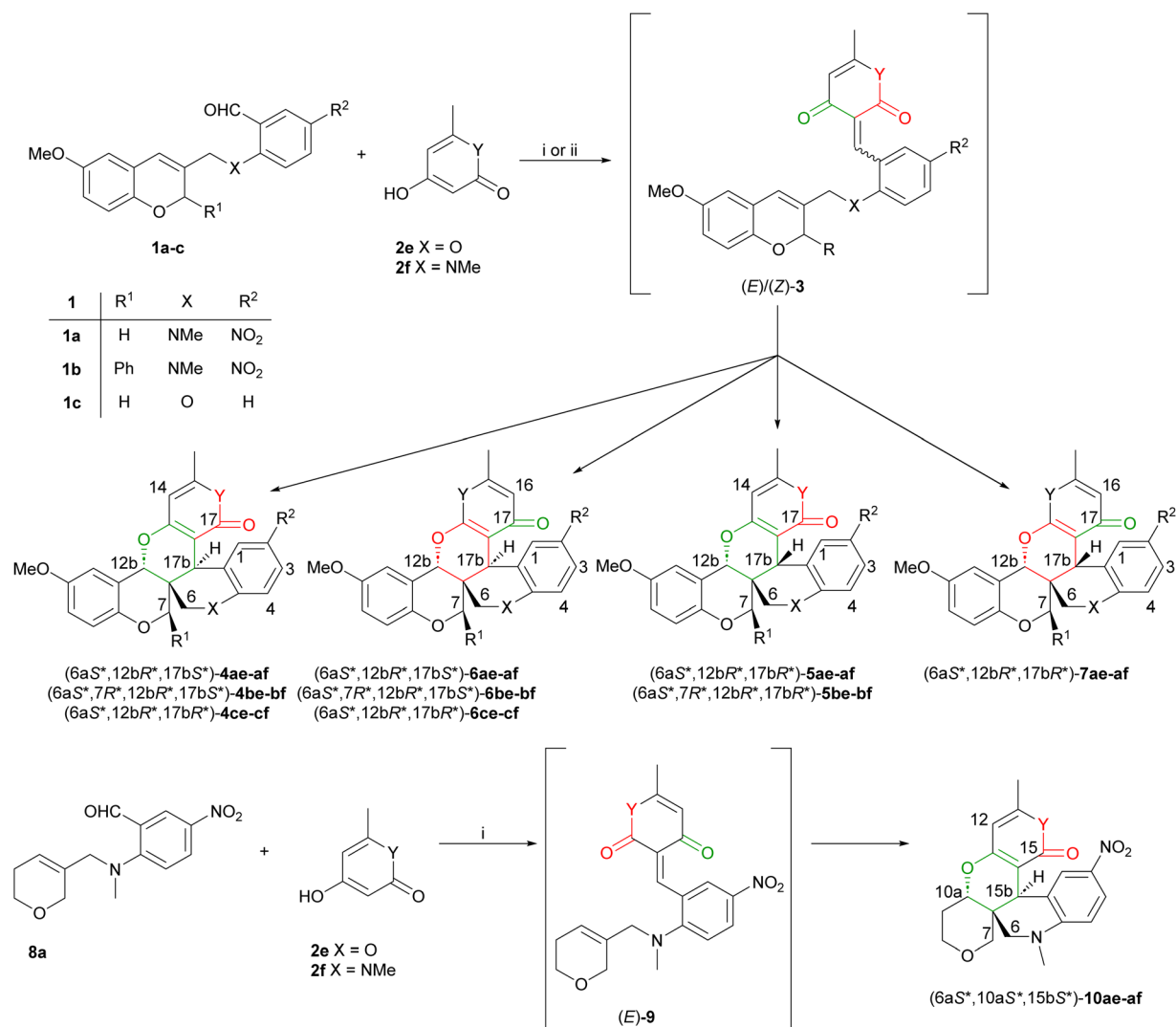


temperature. The regioselectivity however, was only slightly affected by the temperature, the ratio of **6be** increases at lower temperature (entry 3–4). In the reaction of **1a**, isomer **5ae** was the major product at both temperatures. Lowering the temperature had the same effects as for **1b**: formation of **5ae** is preferred at lower temperature, but the **4ae/6ae** ratio changes only slightly (entry 3–4). Substrate **1c** did not react at room temperature, so the reaction was carried out at 55 °C (entry 6). The temperature had no effect on the diastereoselectivity, only **4ce** and **6ce** were formed at both temperatures, the regioselectivity however, was governed by the temperature: the major product was **6ce** at reflux, and **4ce** at lower temperature (entry 5–6). In the reactions of amide derivative **2f**, the two competing heterodiene moieties are an  $\alpha,\beta$ -unsaturated lactam and a -ketone subunit. Surprisingly, there was just a minor change in the regioselectivity compared to reactions of the pyran derivative **2e**. This suggests that the decisive factor in the selectivity is the favorable or unfavorable intramolecular interactions in the

transition states (steric effects), and not the HOMO–LUMO orbital energies (electronic effects). In the reaction of **1c** with **2f** only one isomer was isolated, which was due to the observed decomposition of the other isomers, and not the selectivity of the cyclization (entry 11) (Table 3).

### Antiproliferative activity

The antiproliferative activity of the condensed heterocyclic products were tested on three human cancer cell lines, and results are shown in Table 4. Derivatives with no significant inhibition at 50  $\mu$ M concentration were considered inactive,  $IC_{50}$  values were determined where significant (>50%) anti-proliferative effect was observed. All the active derivatives have ( $S^*$ ,  $R^*$ ,  $S^*$ ) relative configuration and all except for one belong to the series of products **4**, in which the  $\alpha,\beta$ -unsaturated ketone moiety acts as a heterodiene in the IMHDA cyclization step. The trimethoxy derivative **4ac** showed the best activity with an  $IC_{50}$



**Table 3** Domino Knoevenagel-IMHDA reactions of 2*H*-chromene derivatives **1** with 4-hydroxy-6-methyl-2-pyrone **2a** and 1,6-dimethyl-4-hydroxy-1,6-dimethylpyridine-2(1*H*)-one **2b**. (i): toluene, piperidine (1 eq.), for entry 1–4, 7–8 and 9–10; (ii): toluene, Et<sub>3</sub>N (1 eq.), for entry 5–6 and 11

| Entry          | 1                       | 2         | Product (yield) <sup>a</sup>                                                | Regioselectivity<br>(4 + 5)/(6 + 7) | Diastereoselectivity<br>(4 + 6):(5 + 7) |
|----------------|-------------------------|-----------|-----------------------------------------------------------------------------|-------------------------------------|-----------------------------------------|
| 1              | <b>1a</b>               | <b>2e</b> | <b>4ac</b> (16%)<br><b>6ac</b> (35%)<br><b>5ac</b> (14%)<br><b>7ac</b> (6%) | 42 : 58                             | 72 : 28                                 |
| 2 <sup>b</sup> | <b>1a</b>               | <b>2e</b> | <b>4ac</b> (14%)<br><b>6ac</b> (37%)<br><b>5ac</b> (27%)                    | 53 : 47                             | 65 : 35                                 |
| 3              | ( <i>R</i> )- <b>1b</b> | <b>2e</b> | <b>4be</b> (32%)<br><b>6be</b> (8%)<br><b>5be</b> (14%)                     | 85 : 15                             | 74 : 26                                 |
| 4 <sup>b</sup> | ( <i>R</i> )- <b>1b</b> | <b>2e</b> | <b>4be</b> (13%)<br><b>6be</b> (14%)<br><b>5be</b> (31%)                    | 76 : 24                             | 47 : 53                                 |
| 5              | <b>1c</b>               | <b>2e</b> | <b>4ce</b> (10%)<br><b>6ce</b> (26%)                                        | 28 : 72                             | 100 : 0                                 |
| 6 <sup>c</sup> | <b>1c</b>               | <b>2e</b> | <b>4ce</b> (16%)<br><b>6ce</b> (6%)                                         | 72 : 28                             | 100 : 0                                 |
| 7              | <b>8a</b>               | <b>2e</b> | <b>10ac</b> (42%)                                                           | 100 : 0                             | 100 : 0                                 |
| 8              | <b>8b</b>               | <b>2e</b> | <b>10be</b> (32%)                                                           | 100 : 0                             | 100 : 0                                 |
| 9              | <b>1a</b>               | <b>2f</b> | <b>4af</b> (31%)<br><b>6af</b> (31%)<br><b>5af</b> (13%)<br><b>7af</b> (7%) | 54 : 46                             | 76 : 24                                 |
| 10             | <i>rac</i> - <b>1b</b>  | <b>2f</b> | <b>4bf</b> (15%)<br><b>6bf</b> (29%)<br><b>5bf</b> (13%)                    | 49 : 51                             | 77 : 23                                 |
| 11             | <b>1c</b>               | <b>2f</b> | <b>4cf</b> (11%)                                                            | n.d.                                | n.d.                                    |

<sup>a</sup> Isolated yield. <sup>b</sup> Reaction carried out at room temperature. <sup>c</sup> No reaction at r.t., reaction carried out at 55 °C.

value of 5.7 μM on the CaCo-2 cell line (entry 1), while it was inactive (>50 μM) against A2780 and WM35 cells. Doxorubicin has a reported IC<sub>50</sub> value of 12.5 μM on the Caco-2 cell line.<sup>54,55</sup> The structural analogues **4ec** and **4aa**, lacking the C-2 nitro substituent of the condensed benzene ring or two methoxy groups of the coumarin subunit, respectively, had lower activity against the CaCo-2 cell line (entry 2 and 3). In **4dc**, the replacement of the C-2 nitro group of **4ac** with a trifluoromethyl

one resulted in the complete elimination of activity (IC<sub>50</sub> > 50 μM, entry 4). The additional C-7 phenyl group and the resultant chirality center of *rac*-**4ba** and (6*aS*, 7*R*, 12*bR*, 19*bS*)-**4ba** decreased the activity compared to that of **4ac** (entry 5 and 6). Against the A2780 cell line, moderate activities with IC<sub>50</sub> values of 25.1 and 17.7 μM were identified for **4ce** and **4cd**, containing an oxygen linker instead of the NMe in position 5 and condensed 2-quinolone or 2-pyrone subunits, respectively. From the other diastereomeric (5) and regioisomeric products (**6** and **7**), only the regioisomeric **6ae** exhibited activity against the CaCo-2 cell line with an IC<sub>50</sub> value of 11.5 μM.

**Table 4** *In vitro* antiproliferative activity of the products of the domino reactions against Caco-2, A2780 and WM35 human cancer cell lines reported as IC<sub>50</sub> values<sup>a</sup>

| Entry | Compound                                                              | Cell lines/IC <sub>50</sub> (μM) |       |      |
|-------|-----------------------------------------------------------------------|----------------------------------|-------|------|
|       |                                                                       | CaCo-2                           | A2780 | WM35 |
| 1     | <b>4ac</b>                                                            | 5.7                              | >50   | >50  |
| 2     | <b>4ec</b>                                                            | 24.1                             | >50   | >50  |
| 3     | <b>4aa</b>                                                            | 13.4                             | >50   | >50  |
| 4     | <b>4dc</b>                                                            | >50                              | >50   | >50  |
| 5     | <i>rac</i> - <b>4ba</b>                                               | 13.3                             | >50   | >50  |
| 6     | (6 <i>aS</i> , 7 <i>R</i> , 12 <i>bR</i> , 19 <i>bS</i> )- <b>4ba</b> | 26.3                             | >50   | >50  |
| 7     | <b>4ce</b>                                                            | nd                               | 25.1  | >50  |
| 8     | <b>4cd</b>                                                            | nd                               | 17.7  | >50  |
| 9     | <b>6ae</b>                                                            | 11.5                             | >50   | >50  |

<sup>a</sup> nd: not determined.

## Experimental

### Materials and methods

Chemicals were purchased puriss p.a. from commercial suppliers, and solvents were purified by distillation before use. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light. Column chromatography was performed using silica gel Merck 60 (particle size 0.063–0.200 mm) (Merck, Darmstadt, Germany). Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. The NMR spectra were recorded on Bruker Avance II 400 (<sup>1</sup>H: 400 MHz, <sup>13</sup>C: 100 MHz) and Bruker Avance II 500 MHz (<sup>1</sup>H: 500 MHz, <sup>13</sup>C: 125 MHz) spectrometers using TMS



as internal standard (Bruker, Billerica, MA, USA). Chemical shifts were reported as  $\delta$  in ppm and  $^3J_{\text{H,H}}$  coupling constants in Hz. IR spectra were recorded on a JASCO (Tokyo, Japan) FT/IR-4100 spectrometer and absorption bands are presented as wave-number in  $\text{cm}^{-1}$ . The optical rotations of the compounds were measured by a PerkinElmer (Norwalk, CT) 341 polarimeter. ECD spectra were recorded on a JASCO (Tokyo, Japan) J-810 spectropolarimeter. Electrospray Quadrupole Time-of-Flight HRMS measurements were performed with a MicroTOF-Q type QqTOF MS instrument equipped with an ESI source from Bruker (Bruker Daltonik, Bremen, Germany).

### Chiral HPLC separation and ECD measurement

Separation of **4aa-af**, **5aa-af** and **6aa-af** were performed on a JASCO (Tokyo, Japan) HPLC system with Chiralpak-IC column (5  $\mu\text{m}$ , 250  $\times$  4.6 mm, hexane/dichloromethane/methanol eluent, 1  $\text{mL min}^{-1}$  flow rate) and HPLC-ECD spectra were recorded in stopped-flow mode on a JASCO (Tokyo, Japan) J-810 spectropolarimeter equipped with a 10 mm HPLC flow cell. ECD ellipticity ( $\epsilon$ ) values were not corrected for concentration. For an HPLC-ECD spectrum, three consecutive scans were recorded and averaged with 2 nm bandwidth, 1 s response, and standard sensitivity. The HPLC-ECD spectrum of the eluent recorded in the same way was used as background. The concentration of the injected sample was set so that the HT value did not exceed 500 V in the HT channel down to 230 nm.

### Microwave irradiation experiments

Reactions were performed using single-mode CEM Discover Systems (CEM Corporation, Charlotte, NC, USA) in dynamic mode. Reaction times refer to the hold time at the desired set temperature and not to the total irradiation time. Stirring speed was set to "High" (ca. 700 rpm). Standard 10 ml volume cylindrical Pyrex® reaction vessels (inner diameter 12 mm, obtained from CEM Corporation, USA) were used, equipped with small cylindrical magnetic stirring bars. The vessels were sealed with PEEK snap caps and standard PTFE-coated silicone septa. The external IR thermometer of the equipment was used to monitor the reaction temperatures. Pressure sensing is achieved by a hydraulic sensor. Reaction cooling is performed by compressed air automatically after the heating period has elapsed.

### X-ray crystallographic study

X-ray quality crystals could be grown from appropriate solvents by slow evaporation. A chosen crystal was then fixed under a microscope onto a Mitegen loop using high-density oil. Diffraction Intensity data was collected at ambient temperature on a Bruker-D8 Venture diffractometer (Bruker AXS GmbH, Karlsruhe, Germany) equipped with INCOATEC I $\mu$ S 3.0 (Incoatec GmbH, Geesthacht, Germany) dual (Cu and Mo) sealed tube micro sources and a Photon II Charge-Integrating Pixel Array detector (Bruker AXS GmbH, Karlsruhe, Germany) using Mo K $\alpha$  ( $\lambda = 0.71073 \text{ \AA}$ ) radiation. High-multiplicity data collection and integration were performed using APEX5 (version 2017.3-0, Bruker AXS Inc., 2017, Madison, WI, USA) software. Data reduction and multiscan absorption correction were performed using SAINT (version 8.38A,

Bruker AXS Inc., 2017, Madison, WI, USA). The structure was solved using direct methods and refined on  $F^2$  using the SHELXL program<sup>56</sup> incorporated into the APEX5 suite. Refinement was performed anisotropically for all non-hydrogen atoms. Hydrogen atoms were placed in idealized positions on parent atoms. The CIF file was manually edited using publCIF software,<sup>57</sup> while graphics were designed using the Mercury program.<sup>58</sup> The results for the X-ray diffraction structure determinations followed the Checkcif functionality of PLATON software (Utrecht University, Utrecht, the Netherlands).<sup>59</sup>

### Molecular structure analysis

The single crystal X-ray diffraction study had proved the relative configuration of the stereogenic carbon centers. In structure **4cc** there are two molecules in the asymmetric unit with slightly different conformation (Fig. S218). Solving the structure in centrosymmetric space group No. 14 (P21/n) gives disordered structure so the space group of Pn was accepted as correct space group. The lattice symmetry generates the enantiomeric pair of the compound. In case of **6cc** the crystals were very thin needles resulting in high  $R_{\text{int}}$  value. Nevertheless, in both cases we consider the structures as reliable and correct.

### MTT assay<sup>60,61</sup>

A2780 and WM35 cells were purchased from Sigma (St. Louis, MO, USA) and ATCC (Manassas, VA, USA), respectively. Human White colon adenocarcinoma (Caco-2) cells (European Collection of Cell Cultures (ECACC, UK) were isolated from a primary colonic tumor in a 72-year-old White male using the explant culture technique. Caco-2 human epithelial colorectal adenocarcinoma cells were grown in plastic cell culture flasks in Dulbecco's Modified Eagle's Medium, supplemented with 3.7  $\text{g L}^{-1}$   $\text{NaHCO}_3$ , 10% (v/v) heat-inactivated fetal bovine serum (FBS), 1% (v/v) non-essential amino acids solution, 1% (v/v) L-glutamine, 100  $\text{IU ml}^{-1}$  penicillin, and 100  $\mu\text{g ml}^{-1}$  streptomycin at 37  $^\circ\text{C}$  in an atmosphere of 5%  $\text{CO}_2$ . The cells were routinely maintained by regular passaging. The number of viable cells was indirectly determined by measuring the conversion of the tetrazolium salt MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, Sigma-Aldrich] to formazan by mitochondrial dehydrogenases. Cells were plated in 96-well multi-titer plates (10 000 cells per well density) in quadruplicates and were cultured for 3 days and treated by the compounds daily. Negative control group was treated with equal amount of vehicle solvent (DMSO) and the positive control group was treated with 1  $\mu\text{g ml}^{-1}$  doxorubicin (for A2780 and WM35). Cells were then incubated with 5  $\text{mg ml}^{-1}$  MTT for 3 hours, precipitated formazan crystals were desolved in acidic isopropanol (10% 1 M HCl in isopropanol supplemented with 10% Triton X 100) and concentration of formazan was assessed colorimetrically by measuring absorbance at 565 nm. Procedure is based on the one outlined in the cell proliferation kit (Sigma, St. Louis, MO, USA).

### Determination of IC<sub>50</sub>

Logistic dose-response curves were fitted using the equation  $y = A_2 + (A_1 - A_2)/(1 + (x/x_0)^p)$  where the parameters are the



following:  $A_1$ : initial value ( $y_{\min}$ ),  $A_2$ : final value ( $y_{\max}$ ),  $x_0$ : center (EC/IC<sub>50</sub>) and  $p$  is the calculated power. Fittings were carried out and parameters were calculated using Origin 8.6 (OriginLab Corporation, Northampton, MA, USA).

### General methods for the domino Knoevenagel-hetero Diels-Alder reactions

**Method A.** In a round-bottom flask, 2*H*-chromene derivative **1a–b** or **1d–e** or 5,6-dihydro-2*H*-pyran derivative **8a–b** (100 mg) and 4-hydroxycoumarin derivative **2a–c**, 4-hydroxypyron **2e** or 4-hydroxypyridone **2f** (1.2 equivalent) were dissolved in toluene (5 ml). To the solution piperidine (1 equivalent) was added, and the solution was refluxed overnight. The following day, additional reagent (0.6 equiv.) was added, and the reaction was kept at reflux temperature until the starting material was consumed. The solution was concentrated *in vacuo*, and purified by column chromatography (hexane/chloroform/ethyl acetate).

**Method B.** In a round-bottom flask, 2*H*-chromene derivative **1c** (100 mg) and 4-hydroxycoumarin derivative **2a–c**, 4-hydroxypyron **2e** or 4-hydroxypyridone **2f** (1.2 equivalent) were dissolved in toluene (5 ml). To the solution triethylamine (1 equivalent) was added, and the solution was refluxed overnight. Additional reagent (0.6 equiv.) was added every 12 hours until all the starting material was consumed. The solution was concentrated *in vacuo*, and purified by column chromatography (hexane/ethyl acetate).

**Method C.** In a round-bottom flask, 2*H*-chromene derivative **1a–c** or 5,6-dihydro-2*H*-pyran derivative **8a** (100 mg) and 2,4-dihydroxyquinoline **2d** (1.2 equivalent) were dissolved in ethanol (3 ml). To the solution piperidine (1 equivalent) was added, and then refluxed overnight. The solution was concentrated *in vacuo*, and purified by column chromatography (hexane/ethyl acetate).

### Domino Knoevenagel-IMHDA reactions of 2*H*-chromene derivatives **1a–e** with 4-hydroxy-coumarin derivatives **2a–c**

*rac*-(6*aS*\*, 12*bR*\*, 19*bS*\*)- and (6*aS*\*, 12*bR*\*, 19*bR*\*)-11-methoxy-5,15-dimethyl-2-nitro-5,19*b*-dihydro-6*H*,12*bH*,19*H*-dichromeno[3',4':5,6; 4'',3''':2,3]pyrano[3,4-*c*]quinolin-19-one [*rac*-(6*aS*\*,12*bR*\*,19*bS*\*)-4*aa* and *rac*-(6*aS*\*, 12*bR*\*, 19*bR*\*)-5*aa*] and *rac*-(6*aS*\*, 12*bR*\*, 19*bS*\*)- and (6*aS*\*, 12*bR*\*, 19*bR*\*)-11-methoxy-5,17-dimethyl-2-nitro-5,19*b*-dihydro-6*H*,12*bH*,19*H*-dichromeno[3',2':5,6; 4'',3''':2,3]pyrano[3,4-*c*]quinolin-19-one [*rac*-(6*aS*\*,12*bR*\*,19*bS*\*)-6*aa* and *rac*-(6*aS*\*, 12*bR*\*, 19*bR*\*)-7*aa*]

The reaction of **1a** and **2a** was carried out according to method A. Cooling the reaction to room temperature, a precipitate formed which was filtered and washed with cold ether, affording the mixture of *rac*-(6*aS*\*, 12*bR*\*, 19*bS*\*)-4*aa*, *rac*-(6*aS*\*, 12*bR*\*, 19*bS*\*)-6*aa*, *rac*-(6*aS*\*, 12*bR*\*, 19*bR*\*)-5*aa* and *rac*-(6*aS*\*, 12*bR*\*, 19*bR*\*)-7*aa* as yellow powder. The mixture was separated by column chromatography (hexane/chloroform/acetone 10 : 10 : 1), affording *rac*-(6*aS*\*, 12*bR*\*, 19*bS*\*)-4*aa* as yellow powder (14%), the 1 : 1 mixture of *rac*-(6*aS*\*, 12*bR*\*, 19*bS*\*)-6*aa* and *rac*-(6*aS*\*, 12*bR*\*, 19*bR*\*)-5*aa* as yellow powder (37%) and *rac*-(6*aS*\*, 12*bR*\*, 19*bR*\*)-7*aa* as yellow powder (27%).

Alternatively, the reaction was carried out at room temperature, and after workup, afforded *rac*-(6*aS*\*, 12*bR*\*, 19*bS*\*)-4*aa* as yellow powder (27%), the 2 : 1 mixture of *rac*-(6*aS*\*, 12*bR*\*, 19*bS*\*)-6*aa* and *rac*-(6*aS*\*, 12*bR*\*, 19*bR*\*)-5*aa* as yellow powder (17%) and *rac*-(6*aS*\*, 12*bR*\*, 19*bR*\*)-7*aa* as yellow powder (19%).

The reaction was also repeated using microwave irradiation. The sealed vessel was heated to 150 °C for 30 minutes, it was then cooled down, and the solvent was removed *in vacuo*. After workup, the reaction afforded *rac*-(6*aS*\*, 12*bR*\*, 19*bS*\*)-4*aa* as yellow powder (22%) and *rac*-(6*aS*\*, 12*bR*\*, 19*bR*\*)-7*aa* as yellow powder (19%).

***rac*-(6*aS*\*,12*bR*\*,19*bS*\*)-4*aa*: yellow powder, mp 311–314 °C,  $R_f = 0.44$  (hexane/ethyl acetate 1 : 1). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  2.35 (s, 3H, 3'-H), 2.97 (s, 3H, 2'-H), 3.29 (d,  $J = 13.2$  Hz, 1H, 6-H<sub>a</sub>), 3.68 (d,  $J = 13.2$  Hz, 1H, 6-H<sub>b</sub>), 3.86 (s, 3H, 1'-H), 3.91 (d,  $J = 11.4$  Hz, 1H, 7-H<sub>a</sub>), 3.98 (dd,  $J = 11.4$  and 1.8 Hz, 1H, 7-H<sub>b</sub>), 4.24 (s, 1H, 19*b*-H), 5.05 (d,  $J = 1.8$  Hz, 1H, 12*b*-H), 6.57 (d,  $J = 9.2$  Hz, 1H, 4-H), 6.90 (d,  $J = 10.0$  Hz, 1H, 9-H), 6.95–7.03 (m, 2H, 10-H and 12-H), 7.27 (d,  $J = 8.6$  Hz, 1H, 17-H), 7.36 (dd,  $J = 8.6$  and 2.2 Hz, 1H, 16-H), 7.43 (bs, 1H, 14-H), 7.99 (dd,  $J = 9.2$  and 2.7 Hz, 1H, 3-H), 8.09 (d,  $J = 2.7$  Hz, 1H, 1-H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  20.9 (C-3'), 30.7 (C-6*a*), 33.1 (C-19*b*), 39.7 (C-2'), 54.6 (C-6), 55.9 (C-1'), 67.5 (C-7), 72.2 (C-12*b*), 100.6 (C-19*a*), 110.3 (C-4), 114.4 (C-13*b*), 115.8 (C-9), 116.7 (C-14), 117.9 (C-10), 118.1 (C-12), 118.2 (C-12*a*), 121.3 (C-19*c*), 122.7 (C-17), 124.8 (C-3), 126.1 (C-1), 133.6, (C-16) 133.9 (C-15), 138.5 (C-2), 146.7 (C-8*a*), 148.9 (C-4*a*), 151.1 (C-17*a*), 154.1 (C-11), 157.2 (C-13*a*), 163.9 (C-19). IR (KBr)  $\nu$ : 1047, 1217, 1276, 1298, 1318, 1499, 1702, 2853, 2925 cm<sup>-1</sup>; HRMS: calcd for C<sub>29</sub>H<sub>24</sub>N<sub>2</sub>O<sub>7</sub>Na [M + Na]<sup>+</sup> 535.1476, found 535.1478.**

The enantiomers were separated on a Chiralpak IC column (hexane/dichloromethane/methanol 50 : 45 : 5), and the *on line* HPLC-ECD spectra were recorded.

(6*aR*,12*bS*,19*bR*)-4*aa*:  $t_R = 9.08$  min (Chiralpak IC, hexane/dichloromethane/methanol 50 : 45 : 5). ECD [nm ( $\Delta\epsilon$ ), hexane/dichloromethane/methanol 50 : 45 : 5]: 387.5 (2.30), 331.5sh (−4.01), 316 (−10.38), 304.5sh (−4.80), 289 (3.42), 277 (2.91), 254.5 (−5.33), 229 (−51.26).

(6*aS*,12*bR*,19*bS*)-4*aa*:  $t_R = 11.94$  min (Chiralpak IC, hexane/dichloromethane/methanol 50 : 45 : 5). ECD [nm ( $\Delta\epsilon$ ), hexane/dichloromethane/methanol 50 : 45 : 5]: 383.5 (−1.83), 331.5sh (2.57), 317 (6.54), 304.5sh (3.01), 289.5 (−2.62), 277.5 (−2.74), 255 (3.38), 228.5 (33.91).

***rac*-(6*aS*\*,12*bR*\*,19*bS*\*)-6*aa* and *rac*-(6*aS*\*, 12*bR*\*, 19*bR*\*)-5*aa*: yellow powder,  $R_f = 0.36$  (hexane/ethyl acetate 1 : 1). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  2.38 and 2.48 (s, 3H, 3'-H), 2.96 and 3.05 (s, 3H, 2'-H), 3.19–3.32 (m, 3H, 6-H and 6-H<sub>a</sub>), 3.35 (dd,  $J = 11.7$  and 2.1 Hz, 1H, 7-H<sub>a</sub>), 3.68 (d,  $J = 13.2$  Hz, 1H, 6-H<sub>b</sub>), 3.80 (s, 3H, 1'-H), 3.82–3.89 (m, 4H, 1'-H and 7-H<sub>b</sub>), 3.96 (s, 2H, 7-H), 4.18 and 4.47 (s, 1H, 19*b*-H), 4.89 (d,  $J = 1.1$  Hz, 1H, 12*b*-H), 5.20 (s, 1H, 12*b*-H), 6.57 (d,  $J = 9.2$  Hz, 1H, 4-H), 6.66 (d,  $J = 9.1$  Hz, 1H, 4-H), 6.83–6.91 (m, 3H, 2 × 9-H and 12-H), 6.94 (d,  $J = 3.0$  Hz, 1H, 12-H), 6.95–7.02 (m, 2H, 2 × 10-H), 7.24 (d,  $J = 8.5$  Hz, 1H, 15-H), 7.29 (d,  $J = 8.6$  Hz, 1H, 17-H), 7.39 (dd,  $J = 8.5$  and 2.3 Hz, 1H, 16-H), 7.44 (dd,  $J = 8.6$  and 2.3 Hz, 1H, 16-H), 7.52 (s, 1H, 14-H), 7.78 (d,  $J = 2.3$  Hz, 1H, 1-H), 7.98 (dd,  $J = 9.2$  and 2.3 Hz, 1H, 3-H), 8.04 (bs, 1H, 1-H), 8.09 (bs, 1H, 18-H), 8.11 (dd,  $J = 9.1$  and 2.4 Hz, 1H,**



3-H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  21.0 and 21.1 (C-3'), 31.2 (C-6a), 32.6 (C-19b), 35.5 (C-6a), 37.2 (C-19b), 38.3 and 39.8 (C-2'), 54.5 and 54.6 (C-6), 55.9 and 56.0 (C-1'), 63.2 and 67.7 (C-7), 75.0 and 76.3 (C-12b), 97.3 and 99.0 (C-19a), 109.9 and 110.4 (C-4), 114.7 (C-13b), 115.2 and 115.5 (C-10), 116.7 (C-17), 117.1 (C-15), 117.4 (C-12a), 117.8 and 118.4 (C-12), 118.5 and 119.0 (C-9), 119.6 and 121.8 (C-19c), 122.3 (C-18a), 122.3 (C-1), 122.7 (C-14), 124.8 and 125.1 (C-3), 125.9 (C-18), 126.6 (C-1), 133.8 (C-16), 134.1 (C-15), 134.7 (C-16), 135.7 (C-17), 138.1 and 138.8 (C-2), 146.9 and 148.6 (C-8a), 149.0 (C-4a), 151.2 (C-17a), 151.6 (C-14a), 151.8 (C-4a), 153.9 and 154.4 (C-11), 160.3 (C-19), 160.5 and 161.5 (C-13a), 178.3 (C-19). IR (KBr)  $\nu$ : 1215, 1289, 1318, 1498, 1606, 1630, 1732, 2926  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{29}\text{H}_{24}\text{N}_2\text{O}_7\text{Na}$  [ $\text{M} + \text{Na}$ ] $^+$  535.1476, found 535.1478.

The enantiomers of *rac*-(6a*S*\*, 12b*R*\*, 19b*R*\*)-5aa were separated on a Chiralpak IC column (hexane/dichloromethane/methanol 30 : 63 : 7), and the *on-line* HPLC-ECD spectra were recorded.

1st eluting enantiomer:  $t_{\text{R}} = 4.57$  min (Chiralpak IC, hexane/dichloromethane/methanol 30 : 63 : 7). ECD [nm ( $\Delta\epsilon$ ), hexane/dichloromethane/methanol 30 : 63 : 7]: 360.5 (−0.81), 313.5 (0.71), 293.5 (−2.03), 269 (−2.88), 248 (−2.85).

2nd eluting enantiomer:  $t_{\text{R}} = 7.41$  min (Chiralpak IC, hexane/dichloromethane/methanol 30 : 63 : 7). ECD [nm ( $\Delta\epsilon$ ), hexane/dichloromethane/methanol 30 : 63 : 7]: 352 (0.74), 313 (−0.34), 293.5 (1.66), 269 (2.84), 247.5 (3.06).

The enantiomers of *rac*-(6 a*S*\*, 12b*R*\*, 19b*S*\*)-6aa were separated on a Chiralpak IC column (hexane/dichloromethane/methanol 30 : 63 : 7), and the *on-line* HPLC-ECD spectra were recorded.

1st eluting enantiomer:  $t_{\text{R}} = 6.51$  min (Chiralpak IC, hexane/dichloromethane/methanol 30 : 63 : 7). ECD [nm ( $\Delta\epsilon$ ), hexane/dichloromethane/methanol 30 : 63 : 7]: 387 (−14.58), 314 (−18.50), 294.5sh (−7.83), 283sh (5.83), 275.5 (8.52), 241.5sh (−12.47).

2nd eluting enantiomer:  $t_{\text{R}} = 12.30$  min (Chiralpak IC, hexane/dichloromethane/methanol 30 : 63 : 7). ECD [nm ( $\Delta\epsilon$ ), hexane/dichloromethane/methanol 30 : 63 : 7]: 389 (9.21), 313.5 (11.62), 294.5sh (4.76), 284sh (−3.39), 275 (−5.29), 241.5sh (7.54).

***rac*-(6a*S*\*, 12b*R*\*, 19b*R*\*)-7aa: yellow powder, mp 235–238 °C,  $R_{\text{f}} = 0.22$  (hexane/ethyl acetate 1 : 1).**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.48 (s, 3H, 3'-H), 3.06 (s, 3H, 2'-H), 3.26 (s, 2H, 6-H), 3.36 (dd,  $J = 11.7$  and 2.2 Hz, 1H, 7-H<sub>a</sub>), 3.80 (s, 3H, 1'-H), 3.87 (d,  $J = 11.7$  Hz, 1H, 7-H<sub>b</sub>), 4.15 (s, 1H, 19b-H), 4.90 (d,  $J = 2.2$  Hz, 1H, 12b-H), 6.69 (d,  $J = 9.2$  Hz, 1H, 4-H), 6.81 (d,  $J = 8.9$  Hz, 1H, 9-H), 6.92 (d,  $J = 2.9$  Hz, 1H, 12-H), 6.95 (dd,  $J = 8.9$ , 2.9 Hz, 1H, 10-H), 7.27 (d,  $J = 8.9$  Hz, 1H, 15-H), 7.52 (dd,  $J = 8.7$  and 2.4 Hz, 1H, 16-H), 7.74 (dd,  $J = 2.7$  and 1.2 Hz, 1H, 1-H), 7.96 (bs, 1H, 18-H), 8.15 (dd,  $J = 9.2$  and 2.7 Hz, 1H, 3-H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  20.9 (C-3'), 34.9 (C-6a), 36.8 (C-19b), 38.2 (C-2'), 54.3 (C-6), 55.9 (C-1'), 62.8 (C-7), 77.0 (C-12b), 98.6 (C-19a), 109.9 (C-4), 112.1 (C-18a), 115.3 (C-12), 116.5 (C-12a), 116.8 (C-15), 117.7 (C-9), 118.7 (C-19c), 118.9 (C-10), 121.8 (C-1), 123.8 (C-18), 125.1 (C-3), 135.2 (C-17), 136.3 (C-16), 137.9 (C-2), 148.4 (C-8a), 151.6 (C-4a), 153.9 (C-14a), 154.7 (C-11), 158.9 (C-19), 162.3 (C-13a). IR (KBr)  $\nu$ : 1216, 1287, 1315, 1498, 1607, 1631, 1736, 2852,

2925  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{29}\text{H}_{24}\text{N}_2\text{O}_7\text{Na}$  [ $\text{M} + \text{Na}$ ] $^+$  535.1476, found 535.1478.

The enantiomers were separated on a Chiralpak IC column (hexane/dichloromethane/methanol 30 : 63 : 7), and the *on-line* HPLC-ECD spectra were recorded.

(6 a*S*, 12b*R*, 19b*R*)-7aa:  $t_{\text{R}} = 6.11$  min (Chiralpak IC, hexane/dichloromethane/methanol 30 : 63 : 7). ECD [nm ( $\Delta\epsilon$ ), hexane/dichloromethane/methanol 30 : 63 : 7]: 386 (−21.92), 312.5 (−16.39), 275.5 (−1.22), 258 (−20.20), 241 (−13.70).

(6 a*R*, 12b*S*, 19b*S*)-7aa:  $t_{\text{R}} = 13.64$  min (Chiralpak IC, hexane/dichloromethane/methanol 30 : 63 : 7). ECD [nm ( $\Delta\epsilon$ ), hexane/dichloromethane/methanol 30 : 63 : 7]: 387 (13.61), 312 (10.40), 254.5 (12.97), 242sh (7.80).

(6a*S*, 7*R*, 12b*R*, 19b*S*)- and (6a*S*, 7*R*, 12b*R*, 19b*R*)-11-methoxy-5,15-dimethyl-2-nitro-7-phenyl-5,19b-dihydro-6*H*,12b*H*,19*H*-dichromeno[3',4':5,6; 4'',3''':2,3]pyrano[3,4-*c*]quinolin-19-one [(6a*S*, 7*R*, 12b*R*, 19b*S*)-4ba and (6a*S*, 7*R*, 12b*R*, 19b*R*)-5ba] and (6a*S*, 7*R*, 12b*R*, 19b*S*)-11-methoxy-5,17-dimethyl-2-nitro-7-phenyl-5,19b-dihydro-6*H*,12b*H*,19*H*-dichromeno[3',2':5,6; 4'',3''':2,3]pyrano[3,4-*c*]quinolin-19-one [(6a*S*, 7*R*, 12b*R*, 19b*S*)-6ba]

The reaction of (*R*)-1b and 2a was carried out according to method A. Cooling the reaction to room temperature, a precipitate formed which was filtered and washed with cold ether, affording (6a*S*, 7*R*, 12b*R*, 19b*S*)-4ba as yellow powder (10%). The filtrate was concentrated *in vacuo*, and it was purified by column chromatography (hexane/ethyl acetate 2 : 1), affording the mixture of (6a*S*, 7*R*, 12b*R*, 19b*S*)-4ba and (6a*S*, 7*R*, 12b*R*, 19b*S*)-6ba as yellow powder (32%) and (6a*S*, 7*R*, 12b*R*, 19b*R*)-5ba as yellow powder (34%).

**(6a*S*, 7*R*, 12b*R*, 19b*S*)-4ba: yellow powder, mp 335–336 °C,  $R_{\text{f}} = 0.21$  (hexane/ethyl acetate 2 : 1).** [ $\alpha$ ]<sub>D</sub> = +35 ( $c = 0.80$  g/100 ml in  $\text{CHCl}_3$ ). ECD [nm ( $\Delta\epsilon$ ), MeCN] (231  $\mu\text{g}/4$  ml): 354sh (7.71), 323 (7.85), 296sh (−0.93), 267 (−7.81), 245.5 (9.22), 210.5 (−31.69), 197.5 (66.34).  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  2.50 (s, 3H, 3'-H), 2.93 (s, 3H, 2''-H), 3.30 (d,  $J = 13.1$  Hz, 1H, 6-H<sub>a</sub>), 3.55 (d,  $J = 13.1$  Hz, 1H, 6-H<sub>b</sub>), 3.84 (s, 3H, 1''-H), 3.97 (s, 1H, 19b-H), 5.07 (s, 1H, 7-H), 5.23 (s, 1H, 12b-H), 6.59 (d,  $J = 9.3$  Hz, 1H, 4-H), 7.03 (m, 2H, 9-H and 10-H), 7.07 (s, 1H, 12-H), 7.25 (d,  $J = 8.5$  Hz, 1H, 17-H), 7.29–7.38 (m, 2H, 2'-H and 6'-H), 7.44 (m, 3H, 3'-H, 4'-H and 5'-H), 7.54 (dd,  $J = 8.5$  and 2.3 Hz, 1H, 16-H), 7.97 (dd,  $J = 9.3$  and 2.7 Hz, 1H, 3-H), 7.99–8.06 (m, 2H, 1-H and 14-H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  21.0 (C-3''), 32.7 (C-19b), 33.1 (C-6a), 40.0 (C-2''), 50.4 (C-6), 56.0 (C-1''), 73.3 (C-12b), 77.1 (C-7), 101.2 (C-19a), 110.4 (C-4), 114.4 (C-13b), 115.8 (C-17), 116.9 (C-9), 118.0 (C-10), 118.3 (C-12), 118.4 (C-12a), 122.4 (C-19c), 122.9 (C-3), 124.6 (C-1), 126.2 (C-14), 127.5 (C-2' and C-6'), 128.6 (C-3' and C-5'), 129.3 (C-4'), 133.9 (C-16), 134.0 (C-1'), 134.1 (C-17), 138.5 (C-2), 147.9 (C-14a), 148.5 (C-8a), 151.5 (C-4a), 154.4 (C-11), 158.1 (C-13a), 163.6 (C-19). IR (KBr)  $\nu$ : 1117, 1228, 1262, 1315, 1497, 1556, 1726, 2915  $\text{cm}^{-1}$ . HRMS: calcd for  $\text{C}_{35}\text{H}_{28}\text{N}_2\text{O}_7\text{Na}$  [ $\text{M} + \text{Na}$ ] $^+$  611.1789, found 611.1790.

**(6a*S*, 7*R*, 12b*R*, 19b*S*)-4ba and (6a*S*, 7*R*, 12b*R*, 19b*S*)-6ba: yellow powder,  $R_{\text{f}} = 0.21$  (hexane/ethyl acetate 2 : 1).**  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ ): 2.37 and 2.53 (s, 3H, 3''-H), 2.88 and 2.92 (s, 3H, 2''-H), 3.26 (d,  $J = 13.2$  Hz, 1H, 6-H<sub>b</sub>), 3.54 (d,  $J = 12.8$  Hz, 1H, 6-H<sub>a</sub>), 3.85 and 3.88 (s, 3H, 1''-H), 4.05 and 4.32 (s, 1H, 19b-



H), 5.05 and 5.13 (s, 1H, 7-H), 5.15 and 5.28 (s, 1H, 12b-H), 6.52 (d,  $J = 8.8$  Hz, 1H, 4-H), 7.03 (m, 3H, 9-H, 10-H and 12-H), 7.38 (m, 8H, 16-H, 17-H, 15-H and Ph), 7.89 (d,  $J = 7.4$  Hz, 1H, 3-H), 8.06 and 8.21 (bs, 1H, 1-H), 8.14 (s, 1H, 18-H).  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ ): 20.9 and 21.0 (C-3''), 31.9 and 32.6 (C-19b), 32.9 and 33.2 (C-6a), 39.8 and 39.9 (C-2''), 50.1 and 50.3 (C-6), 55.8 and 55.9 (C-1''), 73.2 and 75.7 (C-12b), 77.0 (C-7), 97.5 and 101.1 (C-19a), 110.2 and 110.3 (C-4), 114.3 (C-13b), 114.8 and 115.6 (C-9), 116.6 and 117.0 (C-10), 117.3 and 118.3 (C-12a), 118.0 (C-15), 118.1 and 118.4 (C-12), 118.9 (C-17), 122.2 and 122.3 (C-19c), 122.6 (C-18a), 122.8 (C-18), 124.4 and 124.5 (C-3), 126.0 and 126.1 (C-1), 126.5 (C-15), 127.5 (C-3' and C-5'), 128.5 (C-2' and C-6'), 129.1 and 129.2 (C-4'), 133.7 (C-16), 133.9 and 134.0 (C-1'), 134.1 (C-17), 134.7 (C-14), 135.5 (C-16), 138.3 and 138.4 (C-2), 147.8 (C-14a), 148.3 and 148.4 (C-18a), 151.3 and 151.5 (C-4a), 154.3 and 154.4 (C-11), 158.0 (C-13a), 160.9 (C-19), 163.5 (C-13a), 177.6 (C-19). IR (KBr)  $\nu$ : 1231, 1313, 1498, 1582, 1614, 1628, 1707  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{35}\text{H}_{28}\text{N}_2\text{O}_7\text{Na}$  [ $\text{M} + \text{Na}$ ] $^+$  611.1789, found 611.1790.

**(6aS, 7R, 12bR, 19bR)-5ba: yellow powder, mp 200–202 °C,  $R_f = 0.10$  (hexane/ethyl acetate 2 : 1).** [ $\alpha$ ] $_D = -566$  ( $c = 0.83$  g/100 ml in  $\text{CHCl}_3$ ). ECD [nm ( $\Delta\epsilon$ ), MeCN] (232  $\mu\text{g}/4$  ml): 395 (−4.96), 345 (−0.41), 312.5 (−7.45), 280.5 (5.64), 251 (−7.04), 235 (3.59), 208.5 (−113.53), 197.5 (109.55).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.43 (s, 3H, 3''-H), 2.91 (s, 3H, 2''-H), 3.26 (d,  $J = 12.4$  Hz, 1H, 6-H<sub>a</sub>), 3.76 (d,  $J = 12.8$  Hz, 1H, 6-H<sub>b</sub>), 3.89 (s, 3H, 1'-H), 4.31 (s, 1H, 19b-H), 4.93 (s, 1H, 12b-H), 5.35 (s, 1H, 7-H), 5.99 (d,  $J = 9.2$  Hz, 1H, 4-H), 6.89 (m, 4H, 2'-H, 3'-H, 5'-H and 6'-H), 6.94–7.03 (m, 3H, 9-H, 12-H and 4'-H), 7.06 (dd,  $J = 8.9$  and 3.0 Hz, 1H, 10-H), 7.34 (d,  $J = 8.5$  Hz, 1H, 17-H), 7.43 (d,  $J = 1.8$  Hz, 1H, 16-H), 7.47 (dd,  $J = 8.6$  and 1.6 Hz, 1H, 1-H), 7.57 (dd,  $J = 9.2$  and 2.4 Hz, 1H, 3-H), 7.61 (s, 1H, 14-H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  20.9 C-3'', 29.7 (C-2''), 38.2 (C-6a), 38.6 (C-19b), 53.4 (C-6), 55.9 (C-1''), 77.3 (C-7), 79.3 (C-12b), 99.5 (C-19a), 109.5 (C-4), 114.6 (C-13b), 115.0 (C-12), 116.5 (C-17), 117.1 (C-12a), 117.6 (C-11), 118.2 (C-19c), 118.6 (C-10), 122.6 (C-14), 124.2 and 124.3 (C-1 and C-3), 128.3 (Ph), 133.8 (C-16), 134.0 (C-15), 136.8 (C-1'), 137.3 (C-2), 148.8 (C-8a), 151.1 (C-17a), 152.2 (C-4a), 153.9 (C-11), 160.7 (C-13a), 161.1 (C-19). IR (KBr)  $\nu$ : 1040, 1230, 1304, 1497, 1579, 1609, 1715  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{35}\text{H}_{28}\text{N}_2\text{O}_7\text{Na}$  [ $\text{M} + \text{Na}$ ] $^+$  611.1789, found 611.1790.

*rac*-(6aS\*, 12bR\*, 19bR\*)- and *rac*-(6 aS\*,12bR\*,19bS\*)-11-methoxy-15-methyl-12bH,19H,19bH-pyrano[3,2-c:3,4-c':5,6-c''] trichromen-19-one [*rac*-(6aS\*, 12bR\*, 19bR\*)-4ca and *rac*-(6aS\*, 12bR\*, 19bR\*)-5ca] and *rac*-(6aS\*, 12bR\*, 19bR\*)- and *rac*-(6 aS\*,12bR\*,19bS\*)-11-methoxy-17-methyl-12bH,19H,19bH-pyrano[2,3-b:5,4-c':5,6-c'']trichromen-19-one [*rac*-(6aS\*, 12bR\*, 19bR\*)-6ca and *rac*-(6aS\*, 12bR\*, 19bR\*)-7ca]

The reaction of **1c** and **2a** was carried out according to method B, and the crude product was purified by column chromatography (hexane/ethyl acetate 8 : 1), affording *rac*-(6aS\*, 12bR\*, 19bR\*)-4ca as white crystals (34%), *rac*-(6 aS\*,12bR\*,19bS\*)-5ca as pale yellow amorphous solid (17%), *rac*-(6aS\*, 12bR\*, 19bR\*)-6ca as pale yellow crystals (19%) and *rac*-(6 aS\*,12bR\*,19bS\*)-7ca as white crystals (6%).

***rac*-(6aS\*, 12bR\*, 19bR\*)-4ca: white crystals, mp 240–242 °C,  $R_f = 0.53$  (hexane/ethyl acetate 2 : 1).**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

$\delta$  2.36 (s, 3H, 2'-H), 3.88 (s, 3H, 1'-H), 3.95 (d,  $J = 11.7$  Hz, 1H, 7-H<sub>a</sub>), 3.99 (d,  $J = 11.6$  Hz, 1H, 7-H<sub>b</sub>), 4.14 (d,  $J = 11.8$  Hz, 1H, 6-H<sub>a</sub>), 4.28 (s, 1H, 19b-H), 4.34 (d,  $J = 11.8$  Hz, 1H, 6-H<sub>b</sub>), 5.31 (m, 1H, 12b-H), 6.86 (d,  $J = 8.2$  Hz, 1H, 4-H), 6.89–6.97 (m, 2H, 2-H and 9-H), 7.01 (dd,  $J = 8.9$  and 3.0 Hz, 1H, 10-H), 7.06 (d,  $J = 2.9$  Hz, 1H, 12-H), 7.17 (t,  $J = 7.7$  Hz, 1H, 3-H), 7.25 (d,  $J = 8.5$  Hz, 1H, 17-H), 7.35 (dd,  $J = 8.5$  and 1.6 Hz, 1H, 16-H), 7.47 (s, 1H, 14-H), 7.53 (d,  $J = 7.9$  Hz, 1H, 1-H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  20.8 (C-2'), 30.5 (C-6a), 32.0 (C-19b), 55.9 (C-1'), 66.1 (C-7), 68.4 (C-6), 71.1 (C-12b), 101.1 (C-19a), 114.5 (C-13b), 116.0 (C-12), 116.4 (C-17), 117.0, (C-4), 118.0 (C-9 and C-10), 118.2 (C-12a), 122.1 (C-2), 122.3 (C-19c), 122.8 (C-14), 128.4 (C-3), 129.9 (C-1), 133.4 (C-16), 133.9 (C-15), 146.7 (C-8a), 150.9 (C-17a), 152.3 (C-4a), 154.1 (C-11), 157.1 (C-13a), 164.3 (C-19). IR (KBr)  $\nu$ : 1048, 1219, 1498, 1583, 1631, 1698, 2928  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{28}\text{H}_{22}\text{O}_6\text{Na}$  [ $\text{M} + \text{Na}$ ] $^+$  477.1309, found 477.1308.

***rac*-(6aS\*, 12bR\*, 19bS\*)-5ca: pale yellow amorphous solid,  $R_f = 0.39$  (hexane/ethyl acetate 2 : 1).**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.37 (s, 3H, 2'-H), 3.43 (dd,  $J = 11.6$  and 2.0 Hz, 1H, 7-H<sub>a</sub>), 3.81–3.89 (m, 4H, 7-H<sub>b</sub> and 1'-H), 3.96 (dd,  $J = 10.4$  and 1.8 Hz, 1H, 6-H<sub>a</sub>), 4.24 (dd,  $J = 10.4$  and 1.0 Hz, 1H, 6-H<sub>b</sub>), 4.39 (s, 1H, 19b-H), 4.89 (d,  $J = 2.0$  Hz, 1H, 12b-H), 6.85 (d,  $J = 9.0$  Hz, 1H, 9-H), 6.88–6.98 (m, 3H, 12-H, 2-H and 4-H), 6.98 (dd,  $J = 9.0$  and 3.1 Hz, 1H, 10-H), 7.06 (d,  $J = 7.5$  Hz, 1H, 1-H), 7.16–7.25 (m, 1H, 3-H), 7.27 (d,  $J = 8.6$  Hz, 1H, 17-H), 7.37 (dd,  $J = 8.5$  and 1.8 Hz, 1H, 16-H), 7.53 (bs, 1H, 14-H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  21.0 (C-2'), 35.6 (C-19b), 36.4 (C-6a), 56.0 (C-1'), 63.4 (C-7), 69.5 (C-6), 75.6 (C-12b), 99.3 (C-19a), 114.8 (C-13b), 115.4 (C-12), 116.5 (C-17), 116.8 (C-4), 117.4 (C-12a), 117.8 (C-9), 118.5 (C-10), 121.3 (C-2), 122.8 (C-14), 122.9 (C-19c), 126.3 (C-1), 128.4 (C-3), 133.5 (C-16), 134.0 (C-15), 148.9 (C-8a), 151.2 (C-17a), 153.7 (C-11), 154.8 (C-4a), 159.7 (C-13a), 161.7 (C-19). IR (KBr)  $\nu$ : 1043, 1221, 1498, 1578, 1625, 1714, 2834, 2931  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{28}\text{H}_{22}\text{O}_6\text{Na}$  [ $\text{M} + \text{Na}$ ] $^+$  477.1309, found 477.1308.

***rac*-(6aS\*, 12bR\*, 19bR\*)-6ca: pale yellow crystals, mp 271–274 °C,  $R_f = 0.29$  (hexane/ethyl acetate 2 : 1).**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.45 (s, 3H, 2'-H), 3.82 (s, 3H, 1'-H), 3.94 (s, 2H, 7-H), 4.10 (d,  $J = 11.9$  Hz, 1H, 6-H<sub>a</sub>), 4.20 (s, 1H, 19b-H), 4.33 (d,  $J = 11.8$  Hz, 1H, 6-H<sub>b</sub>), 5.40 (s, 1H, 12b-H), 6.84 (m, 2H, 4-H and 9-H), 6.92 (m, 2H, 2-H and 10-H), 7.10 (d,  $J = 2.9$  Hz, 1H, 12-H), 7.15 (d,  $J = 8.0$  Hz, 1H, 3-H), 7.21 (d,  $J = 8.5$  Hz, 1H, 15-H), 7.36 (d,  $J = 7.8$  Hz, 1H, 1-H), 7.46 (dd,  $J = 8.5$  and 1.6 Hz, 1H, 16-H), 7.91 (s, 1H, 18-H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  20.9 (C-2'), 30.8 (C-6a), 31.7 (C-19b), 55.9 (C-1'), 66.3 (C-7), 68.2 (C-6), 71.8 (C-12b), 100.9 (C-19a), 112.3 (C-17a), 115.2 (C-12), 116.8 (C-15), 117.2 (C-9), 117.6 (C-19c), 117.9 (C-4), 119.1 (C-10), 121.5 (C-12a), 122.1 (C-2), 123.5 (C-18), 128.7 (C-3), 129.4 (C-1), 135.0 (C-17), 136.0 (C-16), 146.5 (C-8a), 151.7 (C-14a), 152.5 (C-4a), 154.4 (C-11), 159.7 (C-19), 161.8 (C-13a). IR (KBr)  $\nu$ : 1042, 1218, 1267, 1453, 1498, 1574, 1624  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{28}\text{H}_{22}\text{O}_6\text{Na}$  [ $\text{M} + \text{Na}$ ] $^+$  477.1309, found 477.1310.

***rac*-(6aS\*, 12bR\*, 19bS\*)-7ca: white crystals, mp 199–201 °C,  $R_f = 0.18$  (hexane/ethyl acetate 2 : 1).**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.47 (s, 3H, 2'-H), 3.46 (dd,  $J = 11.5$  and 2.1 Hz, 1H, 7-H<sub>a</sub>), 3.81 (s, 3H, 1'-H), 3.86 (d,  $J = 11.5$  Hz, 1H, 7-H<sub>b</sub>), 3.95 (d,  $J = 10.4$  Hz, 1H, 6-H<sub>a</sub>), 4.26 (d,  $J = 10.4$  Hz, 1H, 6-H<sub>b</sub>), 4.37 (s, 1H, 19b-H), 4.93 (d,  $J = 1.3$  Hz, 1H, 12b-H), 6.81 (d,  $J = 8.7$  Hz, 1H, 9-H),



6.90–6.98 (m, 4H, 2-H, 4-H, 10-H and 12-H), 7.01 (d,  $J = 7.3$  Hz, 1H, 3-H), 7.22 (m, 1H, 1-H), 7.26 (d,  $J = 8.6$  Hz, 1H, 15-H), 7.50 (dd,  $J = 8.6$  and 2.3 Hz, 1H, 16-H), 7.93 (bs, 1H, 18-H).  $^{13}\text{C}$  NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$  21.0 (C-2'), 35.3 (C-19b), 36.1 (C-6a), 55.9 (C-1'), 63.0 (C-7), 69.4 (C-6), 76.5 (C-12b), 99.1 (C-19a), 112.3 (C-14a), 115.1 (C-4), 116.7 (C-12a), 116.8 (C-15), 117.0 (C-12), 117.8 (C-9), 119.0 (C-10), 121.2 (C-2), 122.0 (C-19c), 123.6 (C-18), 126.0 (C-3), 128.6 (C-1), 135.1 (C-17), 136.1 (C-16), 148.7 (C-8a), 151.8 (C-17a), 153.9 (C-4a), 154.7 (C-11), 159.0 (C-19), 162.2 (C-13a). IR (KBr)  $\nu$ : 1041, 1113, 1218, 1276, 1498, 1552, 1629, 1733, 2929  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{28}\text{H}_{22}\text{O}_6\text{Na}$  [ $M + \text{Na}$ ] $^+$  477.1309, found 477.1310.

***rac*-(6a*S*<sup>\*</sup>, 12b*R*<sup>\*</sup>, 19b*S*<sup>\*</sup>)-11-methoxy-5,15,16-trimethyl-2-nitro-5,19b-dihydro-6*H*,12*bH*,19*H*-dichromeno[3',4':5,6; 4'',3'':2,3]pyrano[3,4-*c*]quinolin-19-one [*rac*-(6a*S*<sup>\*</sup>, 12b*R*<sup>\*</sup>, 19b*S*<sup>\*</sup>)-4*ab*] and *rac*-(6a*S*<sup>\*</sup>, 12b*R*<sup>\*</sup>, 19b*S*<sup>\*</sup>)-11-methoxy-5,16,17-trimethyl-2-nitro-5,19b-dihydro-6*H*,12*bH*,19*H*-dichromeno[3',2':5,6; 4'',3'':2,3]pyrano[3,4-*c*]quinolin-19-one [*rac*-(6a*S*<sup>\*</sup>, 12b*R*<sup>\*</sup>, 19b*S*<sup>\*</sup>)-6*ab*].** The reaction of **1a** and **2b** was carried out according to method A, and the crude product was purified by column chromatography (hexane/chloroform/acetone 5 : 5 : 1), affording *rac*-(6a*S*<sup>\*</sup>, 12b*R*<sup>\*</sup>, 19b*S*<sup>\*</sup>)-4*ab* as yellow crystals (40%) and *rac*-(6a*S*<sup>\*</sup>, 12b*R*<sup>\*</sup>, 19b*S*<sup>\*</sup>)-6*ab* as yellow powder (45%).

Alternatively, the reaction was carried out at room temperature, affording *rac*-(6a*S*<sup>\*</sup>, 12b*R*<sup>\*</sup>, 19b*S*<sup>\*</sup>)-4*ab* as yellow crystals (54%) and *rac*-(6a*S*<sup>\*</sup>, 12b*R*<sup>\*</sup>, 19b*S*<sup>\*</sup>)-6*ab* as yellow powder (19%).

***rac*-(6a*S*<sup>\*</sup>, 12b*R*<sup>\*</sup>, 19b*S*<sup>\*</sup>)-4*ab*: yellow crystals, mp 307–309 °C,  $R_f = 0.25$  (hexane/chloroform/acetone 5 : 5 : 1).**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.23 (s, 3H, 3'-H), 2.33 (s, 3H, 4'-H), 2.95 (s, 3H, 2'-H), 3.27 (d,  $J = 13.2$  Hz, 1H, 6-H<sub>a</sub>), 3.68 (d,  $J = 13.2$  Hz, 1H, 6-H<sub>b</sub>), 3.85 (s, 3H, 1'-H), 3.90 (d,  $J = 11.5$  Hz, 1H, 7-H<sub>a</sub>), 3.99 (d,  $J = 11.5$  Hz, 1H, 7-H<sub>b</sub>), 4.24 (s, 1H, 19b-H), 5.02 (s, 1H, 12b-H), 6.53 (d,  $J = 9.2$  Hz, 1H, 4-H), 6.89 (d,  $J = 9.8$  Hz, 1H, 9-H), 6.95–7.01 (m, 2H, 10-H and 12-H), 7.14 (s, 1H, 17-H), 7.36 (s, 1H, 14-H), 7.95 (dd,  $J = 9.2$  and 2.5 Hz, 1H, 3-H), 8.07 (bs, 1H, 1-H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  19.3 (C-3'), 20.4 (C-4'), 30.7 (C-6a), 33.2 (C-19b), 39.8 (C-2), 54.7 (C-6), 56.0 (C-1'), 67.6 (C-7), 72.2 (C-12b), 100.0 (C-19a), 110.3 (C-4), 112.4 (C-13b), 116.0 (C-12), 117.5 (C-17), 117.9 (C-10), 118.1 (C-9), 118.5 (C-12a), 121.6 (C-19c), 123.1 (C-14), 124.8 (C-3), 126.2 (C-1), 133.1 (C-15), 138.5 (C-2), 142.8 (C-16), 146.9 (C-8a), 149.1 (C-4a), 151.6 (C-17a), 154.2 (C-11), 157.5 (C-13a), 164.2 (C-19). IR (KBr)  $\nu$ : 1037, 1208, 1281, 1322, 1498, 1630, 1705, 2926,  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{30}\text{H}_{26}\text{N}_2\text{O}_7\text{Na}$  [ $M + \text{Na}$ ] $^+$  549.1632, found 549.1631.

The enantiomers of *rac*-(6a*S*<sup>\*</sup>, 12b*R*<sup>\*</sup>, 19b*S*<sup>\*</sup>)-4*ab* were separated on a Chiralpak IC column (hexane/dichloromethane/methanol 50 : 45 : 5), and the *on-line* HPLC-ECD spectra were recorded.

(6*aR*, 12*bS*, 19*bR*)-4*ab*:  $t_R = 10.14$  min (Chiralpak IC, hexane/dichloromethane/methanol 50 : 45 : 5). ECD [nm ( $\Delta\epsilon$ ), hexane/dichloromethane/methanol 50 : 45 : 5]: 390 (3.30), 330.5sh (−6.59), 316 (−16.13), 302.5sh (−7.42), 288sh (3.94), 277.5 (4.82), 255.5 (−4.44), 230 (−58.44).

(6*aS*, 12*bR*, 19*bS*)-4*ab*:  $t_R = 13.11$  min (Chiralpak IC, hexane/dichloromethane/methanol 50 : 45 : 5). ECD [nm ( $\Delta\epsilon$ ), hexane/dichloromethane/methanol 50 : 45 : 5]: 390 (−2.51), 330.5sh

(5.53), 316 (13.82), 302.5sh (5.89), 288sh (−3.85), 277.5 (−4.16), 255.5 (3.87), 230 (48.37).

***rac*-(6a*S*<sup>\*</sup>, 12b*R*<sup>\*</sup>, 19b*S*<sup>\*</sup>)-6*ab*: yellow powder, mp 185–188 °C,  $R_f = 0.19$  (hexane/chloroform/acetone 5 : 5 : 1).**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  2.37 (s, 3H, 3'-H), 2.38 (s, 3H, 4'-H), 2.96 (s, 3H, 2'-H), 3.26 (d,  $J = 13.2$  Hz, 1H, 6-H<sub>a</sub>), 3.66 (d,  $J = 13.2$  Hz, 1H, 6-H<sub>b</sub>), 3.81 (s, 3H, 1'-H), 3.95 (q,  $J = 11.8$  Hz, 2H, 7-H), 4.45 (s, 1H, 19b-H), 5.18 (s, 1H, 12b-H), 6.58 (d,  $J = 9.2$  Hz, 1H, 4-H), 6.86–6.92 (m, 2H, 9-H and 12-H), 6.97 (dd,  $J = 9.0$  and 2.9 Hz, 1H, 10-H), 7.11 (s, 1H, 15-H), 8.01 (dd,  $J = 9.0$  and 2.0 Hz, 1H, 3-H), 8.04 (s, 1H, 18-H), 8.05 (bs, 1H, 1-H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  19.4 (C-4'), 20.5 (C-3'), 31.1 (C-6a), 32.5 (C-19b), 39.8 (C-2'), 54.6 (C-6), 55.9 (C-1'), 67.7 (C-7), 74.8 (C-12b), 97.1 (C-19a), 110.3 (C-4), 115.2 (C-12), 117.5 (C-15), 118.4 (C-9), 118.9 (C-10), 120.4 (C-18a), 122.0 (C-19c), 124.8 (C-3), 126.2 (C-18), 126.6 (C-1), 134.8 (C-17), 138.7 (C-2), 143.9 (C-16), 146.9 (C-8a), 149.0 (C-4a), 151.8 (C-14a), 154.3 (C-11), 160.2 (C-13a), 178.2 (C-19). IR (KBr)  $\nu$ : 1042, 1213, 1267, 1291, 1320, 1499, 1619, 1706, 2924  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{30}\text{H}_{26}\text{N}_2\text{O}_7\text{Na}$  [ $M + \text{Na}$ ] $^+$  549.1632, found 549.1631.

The enantiomers of *rac*-(6a*S*<sup>\*</sup>, 12b*R*<sup>\*</sup>, 19b*S*<sup>\*</sup>)-6*ab* were separated on a Chiralpak IC column (hexane/dichloromethane/methanol 50 : 45 : 5), and the *on-line* HPLC-ECD spectra were recorded.

(6*aR*, 12*bS*, 19*bR*)-6*ab*:  $t_R = 8.12$  min (Chiralpak IC, hexane/dichloromethane/methanol 50 : 45 : 5). ECD [nm ( $\Delta\epsilon$ ), hexane/dichloromethane/methanol 50 : 45 : 5]: 355 (−4.02), 301.5sh (−9.02), 294 (−11.85), 264.5sh (−16.06), 246.5 (−31.16).

(6*aS*, 12*bR*, 19*bS*)-6*ab*:  $t_R = 15.72$  min (Chiralpak IC, hexane/dichloromethane/methanol 50 : 45 : 5). ECD [nm ( $\Delta\epsilon$ ), hexane/dichloromethane/methanol 50 : 45 : 5]: 355 (1.33), 301.5sh (3.11), 294 (3.90), 264.5sh (5.68), 246.5 (10.64).

(6*aS*, 7*R*, 12*bR*, 19*bS*) and (6*aS*, 7*R*, 12*bR*, 19*bR*)-11-methoxy-5,15,16-trimethyl-2-nitro-7-phenyl-5,19b-dihydro-6*H*,12*bH*,19*H*-dichromeno[3',4':5,6; 4'',3'':2,3]pyrano[3,4-*c*]quinolin-19-one [(6*aS*, 7*R*, 12*bR*, 19*bS*)-4*bb* and (6*aS*, 7*R*, 12*bR*, 19*bR*)-5*bb*] and (6*aS*, 7*R*, 12*bR*, 19*bS*)-11-methoxy-5,16,17-trimethyl-2-nitro-7-phenyl-5,19b-dihydro-6*H*,12*bH*,19*H*-dichromeno[3',2':5,6; 4'',3'':2,3]pyrano[3,4-*c*]quinolin-19-one [(6*aS*, 7*R*, 12*bR*, 19*bS*)-6*bb*]

The reaction of (*R*)-**1b** and **2b** was carried out according to method A, and the crude product was purified by column chromatography (hexane/chloroform/ethyl acetate 5 : 5 : 1), affording (6*aS*, 7*R*, 12*bR*, 19*bS*)-4*bb* as yellow powder (26%), (6*aS*, 7*R*, 12*bR*, 19*bS*)-6*bb* as yellow powder (16%) and (6*aS*, 7*R*, 12*bR*, 19*bR*)-5*bb* as yellow powder (44%).

**(6a*S*, 7*R*, 12b*R*, 19b*S*)-4*bb*: yellow powder, mp 221–223 °C,  $R_f = 0.44$  (hexane/chloroform/ethyl acetate 5 : 5 : 1).**  $[\alpha]_D = -7$  ( $c = 1.00$  g/100 ml in  $\text{CHCl}_3$ ). ECD [nm ( $\Delta\epsilon$ ), MeCN] (288  $\mu\text{g}/4$  ml): 331sh (1.67), 317 (5.73), 307sh (2.84), 288.5 (−4.26), 277 (−3.93), 252.5 (0.28), 230 (24.87), 212 (−67.01), 198.5 (113.93).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.27 (s, 3H, 3'-H), 2.36 (s, 3H, 4'-H), 2.92 (s, 3H, 2'-H), 3.24 (d,  $J = 12.9$  Hz, 1H, 6-H<sub>a</sub>), 3.53 (d,  $J = 12.9$  Hz, 1H, 6-H<sub>b</sub>), 3.88 (s, 3H, 1'-H), 4.03 (s, 1H, 19b-H), 5.05 (s, 1H, 7-H), 5.12 (s, 1H, 12b-H), 6.52 (d,  $J = 9.2$  Hz, 1H, 4-H), 7.03 (m, 3H, 9-H, 10-H and 12-H), 7.20 (s, 1H, 17-H), 7.29 (d,  $J = 6.8$  Hz, 2H, 2'-H and 6'-H), 7.38 (m, 3H, 3'-H, 4'-H and 5'-H), 7.44 (s, 1H, 14-



H), 7.93 (dd,  $J = 9.2$  and  $2.5$  Hz, 1H, 3-H), 8.12 (bs, 1H, 1-H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  19.3(C-3''), 20.5 (C-4''), 32.7 (C-19b), 33.1 (C-6a), 39.9 (C-2''), 50.5 (C-6), 56.0 (C-1''), 73.2 (C-12b), 77.1 (C-7), 100.3 (C-19a), 110.3 (C-4), 112.3 (C-13b), 115.8 (C-12), 117.6 (C-17), 118.0 (C-10), 118.2 (C-9), 118.5 (C-12a), 122.6 (C-19c), 123.1 (C-14), 124.6 (C-3), 126.2 (C-1), 127.5 (C-2' and C-6'), 128.6 (C-3' and C-5'), 129.3 (C-4'), 133.2 (C-16), 134.1 (C-1'), 138.5 (C-2), 143.0 (C-15), 148.0 (C-8a), 148.6 (C-4a), 151.8 (C-17a), 154.4 (C-11), 158.3 (C-13a), 163.8 (C-19). IR (KBr)  $\nu$ : 1036, 1233, 1314, 1498, 1630, 1705, 2921  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{36}\text{H}_{30}\text{N}_2\text{O}_7\text{Na}$   $[\text{M} + \text{Na}]^+$  625.1945, found 625.1948.

**(6aS, 7R, 12bR, 19bS)-6bb**: yellow powder, mp 210–213 °C,  $R_f = 0.33$  (hexane/chloroform/ethyl acetate 5 : 5 : 1).  $[\alpha]_D^{25} = 115$  ( $c = 1.01$  g/100 ml in  $\text{CHCl}_3$ ). ECD [nm ( $\Delta\epsilon$ ), MeCN] (299  $\mu\text{g}/4$  ml): 390 (2.15), 310.5 (−1.85), 300.5sh (1.50), 293.5 (2.27), 266sh (4.66), 246.5 (7.15), 211.5 (−33.58), 199 (35.49), 191.5 (−94.02).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.42 (s, 3H, 3''-H), 2.44 (s, 3H, 4''-H), 2.93 (s, 3H, 2''-H), 3.22 (d,  $J = 12.9$  Hz, 1H, 6-H<sub>a</sub>), 3.55 (d,  $J = 12.9$  Hz, 1H, 6-H<sub>b</sub>), 3.85 (s, 3H, 1''-H), 4.34 (s, 1H, 19b-H), 5.15 (s, 1H, 7-H), 5.27 (s, 1H, 12b-H), 6.53 (d,  $J = 9.2$  Hz, 1H, 4-H), 6.97 (s, 1H, 12-H), 7.03 (m, 2H, 9-H and 10-H), 7.19 (s, 1H, 15-H), 7.26–7.33 (m, 2H, 2'-H and 6'-H), 7.40 (m, 3H, 3'-H, 4'-H and 5'-H), 7.96 (dd,  $J = 9.1$  and  $2.6$  Hz, 1H, 3-H), 8.07 (bs, 1H, 1-H), 8.16 (s, 1H, 18-H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  19.4 (C-4''), 20.5 (C-3''), 32.0 (C-19b), 33.4 (C-6a), 39.9 (C-2''), 50.3 (C-6), 56.0 (C-1''), 75.7 (C-12b), 77.0 (C-7), 97.4 (C-19a), 110.3 (C-4), 115.0 (C-12), 117.5 (C-12a), 117.6 (C-15), 118.5 (C-10), 119.0 (C-9), 120.5 (C-18a), 122.9 (C-19c), 124.5 (C-3), 126.5 (C-18), 126.7 (C-1), 127.6 (C-2' and C-6'), 128.6 (C-3' and C-5'), 129.2 (C-4'), 134.0 (C-1'), 134.8 (C-17), 138.7 (C-2), 144.0 (C-16), 148.0 (C-8a), 148.4 (C-4a), 151.9 (C-14a), 154.5 (C-11), 160.8 (C-13a), 177.7 (C-19). IR (KBr)  $\nu$ : 1261, 1314, 1432, 1463, 1498, 1621, 2922  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{36}\text{H}_{30}\text{N}_2\text{O}_7\text{Na}$   $[\text{M} + \text{Na}]^+$  625.1945, found 625.1948.

**(6aS, 7R, 12bR, 19bR)-5bb**: yellow powder, mp 201–204 °C,  $R_f = 0.10$  (hexane/chloroform/ethyl acetate 5 : 5 : 1).  $[\alpha]_D^{25} = 453$  ( $c = 1.10$  g/100 ml in  $\text{CHCl}_3$ ). ECD [nm ( $\Delta\epsilon$ ), MeCN] (199  $\mu\text{g}/4$  ml): 399.5 (−6.64), 313 (−8.66), 282.5 (7.96), 251.5 (−9.34), 237 (2.85), 208.5 (−143.57), 198.5 (129.65).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.31 (s, 3H, 4''-H), 2.41 (s, 3H, 3''-H), 2.91 (s, 3H, 2''-H), 3.23 (d,  $J = 12.4$  Hz, 1H, 6-H<sub>a</sub>), 3.75 (d,  $J = 12.4$  Hz, 1H, 6-H<sub>b</sub>), 3.87 (s, 3H, 1''-H), 4.30 (s, 1H, 19b-H), 4.90 (s, 1H, 12b-H), 5.34 (s, 1H, 7-H), 6.00 (d,  $J = 9.1$  Hz, 1H, 4-H), 6.90 (brs, 4H, 2'-H, 3'-H, 5'-H and 6'-H), 6.93–7.00 (m, 3H, 9-H, 12-H and 4'-H), 7.05 (dd,  $J = 8.9$  and  $3.0$  Hz, 1H, 10-H), 7.23 (s, 1H, 17-H), 7.47 (d,  $J = 2.4$  Hz, 1H, 1-H), 7.55 (s, 1H, 14-H), 7.58 (dd,  $J = 9.1$  and  $2.4$  Hz, 1H, 3-H).  $^{13}\text{C}$  NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$  19.4 (C-4''), 20.6 (C-3''), 37.9 (C-2''), 38.5 (C-6a), 38.9 (C-19b), 53.7 (C-7), 56.1 (C-1''), 77.4 (C-7), 79.5 (C-12b), 98.8 (C-19c), 109.6 (C-4), 112.6 (C-13b), 115.2 (C-9), 117.4 (C-17), 117.8 (C-12), 118.6 (C-19a and C-12a), 118.7 (C-10), 123.0 (C-14), 124.4 (C-1 and C-3), 127.7–128.5 (Ph), 133.2 (C-15), 137.0 (C-16), 137.7 (C-1'), 143.1 (C-2), 149.1 (C-8a), 151.6 (C-17a), 152.3 (C-4a), 154.1 (C-11), 160.9 (C-13a), 161.4 (C-19). IR (KBr)  $\nu$ : 1037, 1228, 1302, 1319, 1498, 1613, 1717, 2920  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{36}\text{H}_{30}\text{N}_2\text{O}_7\text{Na}$   $[\text{M} + \text{Na}]^+$  625.1945, found 625.1948.

**rac-(6aS\*, 12bR\*, 19bR\*)- and rac-(6aS\*, 12bR\*, 19bS\*)-11-methoxy-15,16-dimethyl-12bH, 19H, 19bH-pyrano[3,2-c:3,4-**

**c':5,6-c'']trichromen-19-one [rac-(6aS\*, 12bR\*, 19bR\*)-4cb and rac-(6aS\*, 12bR\*, 19bR\*)-5cb] and rac-(6aS\*, 12bR\*, 19bR\*)-11-methoxy-16,17-dimethyl-12bH, 19H, 19bH-pyrano[2,3-b:5,4-c':5,6-c'']trichromen-19-one [rac-(6aS\*, 12bR\*, 19bR\*)-6cb].** The reaction of **1c** and **2b** was carried out according to method B, and the crude product was purified by column chromatography (hexane/ethyl acetate 2 : 1), affording *rac*-(6aS\*, 12bR\*, 19bR\*)-**4cb** as white crystals (35%), *rac*-(6aS\*, 12bR\*, 19bR\*)-**6cb** as pale yellow amorphous solid (19%) and *rac*-(6aS\*, 12bR\*, 19bS\*)-**5cb** as yellow amorphous solid (21%).

**rac-(6aS\*, 12bR\*, 19bR\*)-4cb**: white crystals, mp 323–324 °C,  $R_f = 0.55$  (hexane/ethyl acetate 2 : 1).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.26 (s, 3H, 3'-H), 2.35 (s, 3H, 2'-H), 3.88 (s, 3H, 1'-H), 3.95 (dd,  $J = 11.7$ , 1.4 Hz, 1H, 7-H<sub>a</sub>), 3.99 (d,  $J = 11.6$  Hz, 1H, 7-H<sub>b</sub>), 4.14 (d,  $J = 11.8$  Hz, 1H, 6-H<sub>a</sub>), 4.26 (s, 1H, 19b-H), 4.33 (d,  $J = 11.8$  Hz, 1H, 6-H<sub>b</sub>), 5.31 (s, 1H, 12b-H), 6.85 (d,  $J = 8.2$  Hz, 1H, 4-H), 6.89–6.96 (m, 2H, 2-H and 9-H), 7.00 (dd,  $J = 9.0$  and  $3.0$  Hz, 1H, 10-H), 7.05 (d,  $J = 2.9$  Hz, 1H, 12-H), 7.12–7.19 (m, 2H, 3-H and 17-H), 7.40 (s, 1H, 14-H), 7.53 (d,  $J = 7.9$  Hz, 1H, 1-H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  19.2 (C-3'), 20.3 (C-2'), 30.5 (C-6a), 32.0 (C-19b), 55.9 (C-1'), 66.1 (C-7), 68.4 (C-6), 71.0 (C-12b), 100.2 (C-19a), 112.4 (C-13b), 116.0 (C-12), 116.9 (C-4), 117.1 (C-17), 117.9 (C-2), 118.0 (C-10), 118.3 (C-12a), 122.1 (C-9), 122.5 (C-19c), 123.0 (C-14), 128.3 (C-3), 129.9 (C-1), 132.9 (C-15), 142.4 (C-16), 146.7 (C-8a), 151.2 (C-17a), 152.3 (C-4a), 154.1 (C-11), 157.3 (C-13a), 164.6 (C-19). IR (KBr)  $\nu$ : 1039, 1217, 1231, 1499, 1573, 1630, 1699, 2930  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{29}\text{H}_{24}\text{O}_6\text{Na}$   $[\text{M} + \text{Na}]^+$  491.1465, found 491.1465.

**rac-(6aS\*, 12bR\*, 19bR\*)-6cb**: pale yellow amorphous solid,  $R_f = 0.45$  (hexane/ethyl acetate 2 : 1).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.35 (s, 3H, 3'-H), 2.37 (s, 3H, 2'-H), 3.81 (s, 3H, 1'-H), 3.93 (dd,  $J = 11.8$  and  $1.5$  Hz, 1H, 7-H<sub>a</sub>), 4.01 (d,  $J = 11.8$  Hz, 1H, 7-H<sub>b</sub>), 4.13 (d,  $J = 11.8$  Hz, 1H, 6-H<sub>a</sub>), 4.28 (d,  $J = 11.7$  Hz, 1H, 6-H<sub>b</sub>), 4.48 (s, 1H, 19b-H), 5.43 (s, 1H, 12b-H), 6.81 (dd,  $J = 8.1$  and  $1.0$  Hz, 1H, 4-H), 6.85–6.91 (m, 2H, 2-H and 9-H), 6.91–7.01 (m, 2H, 10-H and 12-H), 7.07–7.17 (m, 2H, 3-H and 15-H), 7.41 (d,  $J = 7.9$  Hz, 1H, 1-H), 8.00 (s, 1H, 18-H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  19.4 (C-3'), 20.5 (C-2'), 31.0 (C-19b), 31.4 (C-6a), 55.9 (C-1'), 66.2 (C-7), 68.3 (C-6), 73.7 (C-12b), 97.4 (C-19a), 115.3 (C-10), 116.8 (C-4), 117.3 (C-18a), 117.5 (C-15), 118.3 (C-9), 119.1 (C-12), 120.5 (C-19c), 122.2 (C-2), 123.0 (C-12a), 125.8 (C-18), 128.4 (C-3), 130.5 (C-1), 134.6 (C-17), 143.8 (C-16), 146.9 (C-8a), 151.7 (C-14a), 152.3 (C-4a), 154.3 (C-11), 160.4 (C-13a), 178.7 (C-19). IR (KBr)  $\nu$ : 1217, 1267, 1464, 1498, 1563, 1620, 2925  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{29}\text{H}_{24}\text{O}_6\text{Na}$   $[\text{M} + \text{Na}]^+$  491.1465, found 491.1466.

**rac-(6aS\*, 12bR\*, 19bS\*)-5cb**: yellow amorphous solid,  $R_f = 0.36$  (hexane/ethyl acetate 2 : 1).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.26 (s, 3H, 2'-H), 2.36 (s, 3H, 3'-H), 3.43 (dd,  $J = 11.6$  and  $1.9$  Hz, 1H, 7-H<sub>a</sub>), 3.84 (s, 3H, 1'-H), 3.84 (dd,  $J = 11.6$  and  $1.5$  Hz, 1H, 7-H<sub>b</sub>), 3.96 (dd,  $J = 10.4$  and  $1.8$  Hz, 1H, 6-H<sub>a</sub>), 4.23 (d,  $J = 10.4$  Hz, 1H, 6-H<sub>b</sub>), 4.38 (s, 1H, 19b-H), 4.87 (d,  $J = 1.8$  Hz, 1H, 12b-H), 6.85 (d,  $J = 8.9$  Hz, 1H, 9-H), 6.89–6.96 (m, 3H, 2-H, 4-H and 12-H), 6.98 (dd,  $J = 8.9$  and  $3.0$  Hz, 1H, 10-H), 7.06 (d,  $J = 7.6$  Hz, 1H, 1-H), 7.15 (s, 1H, 17-H), 7.20 (t,  $J = 7.7$  Hz, 1H, 3-H), 7.46 (s, 1H, 14-H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  19.3 (C-2'), 20.5 (C-3'), 35.5 (C-6a), 36.4 (C-19b), 56.0 (C-1'), 63.4 (C-7), 69.5 (C-6),



75.5 (C-12b), 98.4 (C-19a), 112.7 (C-13b), 115.4 (C-12), 116.7 (C-4), 117.2 (C-17), 117.5 (C-12a), 117.8 (C-9), 118.5 (C-10), 121.2 (C-2), 123.0 (C-14), 123.0 (C-19c), 126.4 (C-1), 128.4 (C-3), 133.0 (C-15), 142.6 (C-16), 148.9 (C-8a), 151.4 (C-17a), 153.7 (C-11), 154.8 (C-4a), 159.9 (C-13a), 162.0 (C-19). IR (KBr)  $\nu$ : 1044, 1220, 1268, 1294, 1391, 1455, 1499, 1625, 1712, 2942  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{29}\text{H}_{24}\text{O}_6\text{Na}$   $[\text{M} + \text{Na}]^+$  491.1465, found 491.1465.

***rac*-(6aS\*, 12bR\*, 19bS\*)- and (6aS\*, 12bR\*, 19bR\*)-11,14,15,16-tetramethoxy-5-methyl-2-nitro-5,19b-dihydro-6H,12bH,19H-dichromeno[3',4':5,6; 4'',3'':2,3]pyrano[3,4-c]quinolin-19-one** [*rac*-(6 aS\*,12bR\*,19bS\*)-4ac and *rac*-(6aS\*, 12bR\*, 19bR\*)-5ac] and ***rac*-(6 aS\*,12bR\*,19bS\*)-11,16,17,18-tetramethoxy-5-methyl-2-nitro-5,19b-dihydro-6H,12bH,19H-dichromeno[3',2':5,6; 4'',3'':2,3]pyrano[3,4-c]quinolin-19-one** [*rac*-(6 aS\*,12bR\*,19bS\*)-6ac]. The reaction of **1a** and **2c** was carried out according to method A, and the crude product was purified by column chromatography (hexane/ethyl acetate 2 : 1), affording *rac*-(6aS\*, 12bR\*, 19bS\*)-4ac as yellow powder (49%), *rac*-(6aS\*, 12bR\*, 19bS\*)-6ac as yellow amorphous solid (16%) and *rac*-(6aS\*, 12bR\*, 19bR\*)-5ac as yellow powder (25%).

Alternatively, the reaction was carried out at room temperature, affording *rac*-(6aS\*, 12bR\*, 19bS\*)-4ac as yellow powder (21%), *rac*-(6aS\*, 12bR\*, 19bS\*)-6ac as yellow amorphous solid (10%) and *rac*-(6aS\*, 12bR\*, 19bR\*)-5ac as yellow powder (14%).

***rac*-(6aS\*, 12bR\*, 19bS\*)-4ac: yellow powder, mp 297–299 °C,  $R_f = 0.30$  (hexane/ethyl acetate 1 : 1).**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.96 (s, 3H, 5'-H), 3.29 (d,  $J = 13.6$  Hz, 1H, 6-H<sub>a</sub>), 3.50 (s, 3H, 2'-H), 3.69 (d,  $J = 13.2$  Hz, 1H, 6-H<sub>b</sub>), 3.78 (s, 3H, 3'-H), 3.80 (s, 3H, 1'-H), 3.92 (m, 4H, 4'-H and 7-H<sub>a</sub>), 4.01 (d,  $J = 11.2$  Hz, 1H, 7-H<sub>b</sub>), 4.23 (s, 1H, 19b-H), 5.05 (s, 1H, 12b-H), 6.53 (d,  $J = 8.8$  Hz, 1H, 4-H), 6.70 (s, 1H, 17-H), 6.86 (d,  $J = 8.8$  Hz, 1H, 9-H), 6.94 (d,  $J = 9.2$  Hz, 1H, 10-H), 6.99 (s, 1H, 12-H), 7.97–7.93 (m, 2H, 1-H and 3-H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  30.1 (C-6a), 32.8 (C-19b), 39.6 (C-5'), 54.4 (C-6), 54.4 (C-4'), 56.3 (C-1'), 61.2 (C-3'), 62.1 (C-2'), 67.6 (C-7), 72.0 (C-12b), 96.6 (C-17), 98.1 (C-19a), 103.2 (C-13b), 110.0 (C-4), 115.2 (C-12), 118.1 (C-10), 118.2 (C-12a), 118.3 (C-9), 121.2 (C-19c), 138.1 (C-2), 140.3 (C-15), 146.6 (C-8a), 148.8 (C-4a), 150.6 (C-14), 150.8 (C-17a), 154.0 (C-11), 157.0 (C-16), 158.8 (C-13a), 163.6 (C-19). IR (KBr)  $\nu$ : 1042, 1100, 1285, 1299, 1317, 1391, 1498, 1607, 1703  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{31}\text{H}_{28}\text{N}_2\text{O}_{10}\text{Na}$   $[\text{M} + \text{Na}]^+$  611.1636, found 611.1637.

The enantiomers were separated on a Chiralpak IC column (hexane/dichloromethane/methanol 50 : 45 : 5), and the *on-line* HPLC-ECD spectra were recorded.

(6aR, 12bS, 19bR)-4ac:  $t_R = 8.00$  min (Chiralpak IC, hexane/dichloromethane/methanol 50 : 45 : 5). ECD [nm ( $\Delta\epsilon$ ), hexane/dichloromethane/methanol 50 : 45 : 5]: 389 (2.05), 335sh (−6.63), 318 (−14.22), 298sh (3.92), 289.5 (4.10), 236 (−26.08).

(6aS, 12bR, 19bS)-4ac:  $t_R = 11.35$  min (Chiralpak IC, hexane/dichloromethane/methanol 50 : 45 : 5). ECD [nm ( $\Delta\epsilon$ ), hexane/dichloromethane/methanol 50 : 45 : 5]: 388.5 (−1.82), 335sh (4.38), 318 (9.87), 297sh (−3.65), 285.5 (−3.73), 236 (18.61).

***rac*-(6aS\*, 12bR\*, 19bS\*)-6ac: yellow amorphous solid,  $R_f = 0.18$  (hexane/ethyl acetate 1 : 1).**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.95 (s, 3H, 5'-H), 3.24 (d,  $J = 13.2$  Hz, 1H, 6-H<sub>a</sub>), 3.71 (d,  $J = 13.2$  Hz, 1H, 6-H<sub>b</sub>), 3.80 (s, 3H, 1'-H), 3.89 (s, 3H, 2'-H), 3.90–3.98

(m, 4H, 3'-H and 7-H<sub>a</sub>), 4.01 (dd,  $J = 11.7$  and 2.0 Hz, 1H, 7-H<sub>b</sub>), 4.08 (s, 3H, 4'-H), 4.49 (s, 1H, 19b-H), 5.14 (d,  $J = 2.0$  Hz, 1H, 12b-H), 6.55 (d,  $J = 9.3$  Hz, 1H, 4-H), 6.61 (s, 1H, 15-H), 6.85–6.93 (m, 2H, 9-H and 12-H), 6.97 (dd,  $J = 9.1$  and 3.0 Hz, 1H, 10-H), 7.98 (dd,  $J = 9.3$  and 2.7 Hz, 1H, 3-H), 8.08 (d,  $J = 2.7$  Hz, 1H, 1-H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  31.0 (C-6a), 32.0 (C-19b), 39.7 (C-5'), 54.5 (C-6), 55.8 (C-1'), 56.3 (C-2'), 61.6 (C-3'), 62.5 (C-4'), 67.5 (C-7), 74.6 (C-12b), 95.9 (C-15), 97.1 (C-19a), 110.1 (C-4), 111.1 (C-18a), 115.0 (C-12), 117.4 (C-12a), 118.3 (C-9), 118.8 (C-10), 121.9 (C-19c), 124.6 (C-1), 126.5 (C-3), 138.5 (C-2), 140.8 (C-17), 146.8 (C-8a), 148.8 (C-4a), 151.3 (C-14a), 153.0 (C-18), 154.2 (C-11), 157.5 (C-16), 158.8 (C-13a), 177.0 (C-19). IR (KBr)  $\nu$ : 1217, 1265, 1421, 1498, 1604, 2852, 2925  $\text{cm}^{-1}$ . HRMS: calcd for  $\text{C}_{31}\text{H}_{28}\text{N}_2\text{O}_{10}\text{Na}$   $[\text{M} + \text{Na}]^+$  611.1636, found 611.1639.

The enantiomers were separated on a Chiralpak IC column (hexane/dichloromethane/methanol 50 : 45 : 5), and the *on-line* HPLC-ECD spectra were recorded.

(6aR, 12bS, 19bR)-6ac:  $t_R = 8.44$  min (Chiralpak IC, hexane/dichloromethane/methanol 50 : 45 : 5). ECD [nm ( $\Delta\epsilon$ ), hexane/dichloromethane/methanol 50 : 45 : 5]: 365.5 (−1.80), 322.5 (0.93), 299.5 (−10.31), 281 (2.24), 251.5 (−20.78), 232.5 (−2.41).

(6aS, 12bR, 19bS)-6ac:  $t_R = 15.56$  min (Chiralpak IC, hexane/dichloromethane/methanol 50 : 45 : 5). ECD [nm ( $\Delta\epsilon$ ), hexane/dichloromethane/methanol 50 : 45 : 5]: 365.5 (1.03), 321.5 (−0.36), 300 (4.28), 281.5 (−1.79), 249.5 (9.07).

***rac*-(6aS\*, 12bR\*, 19bR\*)-5ac: yellow powder, mp 205–208 °C,  $R_f = 0.13$  (hexane/ethyl acetate 1 : 1).**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.05 (s, 3H, 5'-H), 3.26 (m, 2H, 6-H), 3.35 (dd,  $J = 11.8$  and 2.1 Hz, 1H, 7-H<sub>a</sub>), 3.63 (s, 3H, 2'-H), 3.81 (s, 3H, 1'-H), 3.83 (s, 3H, 3'-H), 3.89 (d,  $J = 11.8$  Hz, 1H, 7-H<sub>b</sub>), 3.94 (s, 3H, 4'-H), 4.13 (s, 1H, 19b-H), 4.86 (d,  $J = 2.1$  Hz, 1H, 12b-H), 6.66 (d,  $J = 9.2$  Hz, 1H, 4-H), 6.73 (s, 1H, 17-H), 6.84 (d,  $J = 8.9$  Hz, 1H, 9-H), 6.91 (d,  $J = 3.0$  Hz, 1H, 12-H), 6.97 (dd,  $J = 8.9$  and 3.0 Hz, 1H, 10-H), 7.73 (d,  $J = 2.6$  Hz, 1H, 1-H), 8.12 (dd,  $J = 9.1$  and 2.6 Hz, 1H, 3-H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  34.9 (C-6a), 36.9 (C-19b), 38.2 (C-5'), 54.4 (C-6), 55.9 (C-1'), 56.4 (C-4'), 61.4 (C-3'), 62.2 (C-2'), 63.1 (C-7), 76.0 (C-12b), 96.4 (C-19a), 96.5 (C-17), 103.4 (C-13b), 109.7 (C-4), 115.0 (C-12), 117.4 (C-12a), 117.7 (C-9), 118.3 (C-10), 119.6 (C-19c), 122.1 (C-1), 124.9 (C-3), 138.0 (C-2), 140.4 (C-15), 148.4 (C-8a), 150.6 (C-14), 150.8 (C-17a), 151.7 (C-4a), 153.7 (C-11), 157.1 (C-16), 161.2 (C-19), 161.7 (C-13a). IR (KBr)  $\nu$ : 1290, 1313, 1498, 1607, 1707, 2853, 2926  $\text{cm}^{-1}$ . HRMS: calcd for  $\text{C}_{31}\text{H}_{28}\text{N}_2\text{O}_{10}\text{Na}$   $[\text{M} + \text{Na}]^+$  611.1636, found 611.1639.

The enantiomers were separated on a Chiralpak IC column (hexane/dichloromethane/methanol 30 : 63 : 7), and the *on-line* HPLC-ECD spectra were recorded.

(6aS, 12bR, 19bR)-5ac:  $t_R = 5.99$  min (Chiralpak IC, hexane/dichloromethane/methanol 30 : 63 : 7). ECD [nm ( $\Delta\epsilon$ ), hexane/dichloromethane/methanol 30 : 63 : 7]: 387 (−13.22), 314 (−18.67), 288.5 (6.43), 264.5sh (3.90).

(6aR, 12bS, 19bS)-5ac:  $t_R = 14.05$  min (Chiralpak IC, hexane/dichloromethane/methanol 30 : 63 : 7). ECD [nm ( $\Delta\epsilon$ ), hexane/dichloromethane/methanol 30 : 63 : 7]: 387.5 (6.79), 315 (9.23), 287.5 (−3.37), 265sh (−2.31).

(6aS, 7R, 12bR, 19bS)- and (6aS, 7R, 12bR, 19bR)-11,14,15,16-tetramethoxy-5-methyl-2-nitro-7-phenyl-5,19b-dihydro-6H,12bH,19H-dichromeno[3',4':5,6; 4'',3'':2,3]pyrano[3,4-c]



quinolin-19-one [(6aS, 7R, 12bR, 19bS)-4bc and (6aS, 7R, 12bR, 19bR)-5bc] and (6aS, 7R, 12bR, 19bS)-11,16,17,18-tetramethoxy-5-methyl-2-nitro-7-phenyl-5,19b-dihydro-6H,12bH,19H-dichromeno[3',2':5,6; 4'',3'':2,3]pyrano[3,4-c]quinolin-19-one [(6aS, 7R, 12bR, 19bS)-6bc]

The reaction of (R)-**1b** and **2c** was carried out according to method A, and the crude product was purified by column chromatography (hexane/chloroform/ethyl acetate 4 : 4 : 1), affording (6aS, 7R, 12bR, 19bS)-**4bc** as yellow powder (42%), (6aS, 7R, 12bR, 19bS)-**6bc** as yellow amorphous solid (10%) and (6aS, 7R, 12bR, 19bR)-**5bc** as yellow crystals (44%).

Alternatively, the reaction was carried out at room temperature, affording (6aS, 7R, 12bR, 19bS)-**4bc** as yellow powder (32%), (6aS, 7R, 12bR, 19bS)-**6bc** as yellow amorphous solid (8%) and (6aS, 7R, 12bR, 19bR)-**5bc** as yellow crystals (53%).

**(6aS, 7R, 12bR, 19bS)-4bc: yellow powder, mp 184–186 °C,  $R_f = 0.20$  (hexane/chloroform/ethyl acetate 4 : 4 : 1).**  $[\alpha]_D = 0.2$  ( $c = 0.88$  g/100 ml in  $\text{CHCl}_3$ ). ECD [nm ( $\Delta\epsilon$ ), MeCN] (218  $\mu\text{g}/4$  ml): 319 (9.42), 296.5 (−5.63), 235 (19.47), 219 (−40.95), 199.5 (92.52).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.93 (s, 3H, 5''-H), 3.25 (d,  $J = 13.0$  Hz, 1H, 6-H<sub>a</sub>), 3.54 (m, 4H, 3''-H and 6-H<sub>b</sub>), 3.81 (s, 3H, 2''-H), 3.84 (s, 3H, 1''-H), 3.95 (s, 3H, 4''-H), 4.04 (s, 1H, 19b-H), 5.07 (s, 1H, 7-H), 5.15 (s, 1H, 12b-H), 6.52 (d,  $J = 9.2$  Hz, 1H, 4-H), 6.77 (s, 1H, 17-H), 6.99 (s, 2H, 9-H and 10-H), 7.05 (s, 1H, 12-H), 7.31 (d,  $J = 6.9$  Hz, 2H, 2'-H and 6'-H), 7.35–7.46 (m, 3H, 3'-H, 4'-H and 5'-H), 7.96 (dd,  $J = 9.2$  and 2.7 Hz, 1H, 3-H), 8.05 (s, 1H, 1-H).  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ ): 32.4 (C-19b), 32.7 (C-6a), 39.8 (C-5''), 50.2 (C-6), 55.9 (C-1''), 56.4 (C-3''), 61.3 (C-2''), 62.2 (C-3''), 73.0 (C-12b), 77.2 (C-7), 96.8 (C-17), 98.5 (C-13b), 103.2 (C-19a), 110.0 (C-19c), 110.1 (C-4), 115.1 (C-12), 118.2 (C-9), 118.3 (C-10), 118.4 (C-12a), 122.4 (C-1'), 124.5 (C-3), 126.1 (C-1), 127.5 (C-3' and C-5'), 128.5 (C-2' and C-6'), 129.2 (C-4'), 133.9 (C-15), 138.4 (C-2), 147.7 (C-14), 148.4 (C-17a), 150.8 (C-8a), 151.2 (C-4a), 154.3 (C-11), 157.2 (C-16), 159.5 (C-13a), 163.1 (C-19). IR (KBr)  $\nu$ : 1036, 1098, 1233, 1300, 1314, 1393, 1460, 1498, 1607, 1705  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{37}\text{H}_{32}\text{N}_2\text{O}_{10}\text{Na}$   $[\text{M} + \text{Na}]^+$  687.1949, found 687.1952.

**(6aS, 7R, 12bR, 19bS)-6bc: yellow amorphous solid,  $R_f = 0.15$  (hexane/chloroform/ethyl acetate 4 : 4 : 1).**  $[\alpha]_D = 45$  ( $c = 1.00$  g/100 ml in  $\text{CHCl}_3$ ). ECD [nm ( $\Delta\epsilon$ ), MeCN] (197  $\mu\text{g}/4$  ml): 389.5 (3.53), 319.5 (−0.94), 298.5 (8.06), 281 (−0.32), 248 (15.29), 235sh (8.35), 212 (−20.71), 201.5 (18.73), 191.5 (−123.48).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.90 (s, 3H, 5''-H), 3.20 (d,  $J = 12.9$  Hz, 1H, 6-H<sub>a</sub>), 3.50 (d,  $J = 12.9$  Hz, 1H, 6-H<sub>b</sub>), 3.83 (s, 3H, 1''-H), 3.92 (s, 3H, 2''-H), 3.98 (s, 3H, 3''-H), 4.12 (s, 3H, 4''-H), 4.37 (s, 1H, 19b-H), 5.14 (s, 1H, 7-H), 5.21 (s, 1H, 12b-H), 6.51 (d,  $J = 9.2$  Hz, 1H, 4-H), 6.66 (s, 1H, 15-H), 6.93 (m, 1H, 12-H), 7.02 (m, 2H, 9-H and 10-H), 7.30 (m, 2H, 2'-H and 6'-H), 7.37 (m, 1H, 4'-H), 7.42 (m, 2H, 3'-H and 5'-H), 7.94 (dd,  $J = 9.2$  and 2.6 Hz, 1H, 3-H), 8.16 (dd,  $J = 2.6$  and 1.3 Hz, 1H, 1-H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  31.5 (C-19b), 33.1 (C-6a), 39.8 (C-5''), 50.2 (C-6), 55.8 (C-1''), 56.3 (C-2''), 61.8 (C-3''), 62.7 (C-4''), 75.4 (C-12b), 76.8 (C-7), 96.0 (C-15), 97.6 (C-19c), 110.2 (C-4), 111.3 (C-18a), 114.9 (C-12), 117.4 (C-12a), 118.3 (C-9), 118.8 (C-10), 122.9 (C-19c), 124.2 (C-1), 126.7 (C-3), 127.5 (C-2' and C-6'), 128.5 (C-3' and C-5'), 129.1 (C-4'), 133.8 (C-1'), 138.5 (C-2), 140.9 (C-17), 147.8 (C-8a),

148.2 (C-4a), 151.4 (C-14a), 153.1 (C-18), 154.3 (C-11), 157.5 (C-16), 159.3 (C-13a), 176.5 (C-19). IR (KBr)  $\nu$ : 1234, 1264, 1313, 1421, 1498, 1604, 1628, 2926  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{37}\text{H}_{32}\text{N}_2\text{O}_{10}\text{Na}$   $[\text{M} + \text{Na}]^+$  687.1949, found 687.1951.

**(6aS, 7R, 12bR, 19bR)-5bc: yellow crystals, mp 181–184 °C,  $R_f = 0.03$  (hexane/chloroform/ethyl acetate 4 : 4 : 1).**  $[\alpha]_D = -424$  ( $c = 0.82$  g/100 ml in  $\text{CHCl}_3$ ). ECD [nm ( $\Delta\epsilon$ ), MeCN] (212  $\mu\text{g}/4$  ml): 397.5 (−8.02), 315.5 (−10.95), 283.5 (10.44), 248.5 (−14.47), 210.5 (−121.64), 199.5 (70.97).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.91 (s, 3H, 5''-H), 3.28 (d,  $J = 12.4$  Hz, 1H, 6-H<sub>a</sub>), 3.70 (s, 3H, 2''-H), 3.78 (d,  $J = 12.5$  Hz, 1H, 6-H<sub>b</sub>), 3.84 (s, 3H, 4''-H), 3.88 (s, 3H, 3''-H), 3.98 (s, 3H, 1''-H), 4.29 (s, 1H, 19b-H), 4.91 (s, 1H, 12b-H), 5.41 (s, 1H, 7-H), 5.96 (d,  $J = 9.2$  Hz, 1H, 4-H), 6.77 (s, 1H, 17-H), 6.81–6.99 (m, 7H, Ph, 9-H and 12-H), 7.03 (dd,  $J = 8.9$  and 2.9 Hz, 1H, 10-H), 7.46 (d,  $J = 2.3$  Hz, 1H, 1-H), 7.58 (dd,  $J = 9.1$  and 2.3 Hz, 1H, 3-H).  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ ): 37.7 (C-6a), 37.8 (C-5''), 38.7 (C-19b), 53.5 (C-6), 55.9 (C-4''), 56.4 (C-1''), 61.3 (C-3''), 62.2 (C-2''), 77.3 (C-7), 79.3 (C-12b), 96.5 (C-17), 97.2 (C-19a), 103.4 (C-13b), 109.4 (C-4), 114.6 (C-12), 117.3 (C-12a), 117.7 (C-9), 118.3 (C-10), 118.5 (C-19c), 124.0 (C-1), 124.3 (C-3), 128.3 (C-2', C-3', C-4', C-5' and C-6'), 136.9 (C-2), 137.3 (C-15), 140.4 (C-1'), 148.8 (C-8a), 150.5 (C-4a), 150.7 (C-14), 152.2 (C-17a), 153.8 (C-11), 157.2 (C-16), 160.8 (C-13a), 162.2 (C-19). IR (KBr)  $\nu$ : 1231, 1302, 1389, 1497, 1608, 1712  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{37}\text{H}_{32}\text{N}_2\text{O}_{10}\text{Na}$   $[\text{M} + \text{Na}]^+$  687.1949, found 687.1949.

**rac-(6aS\*, 12bR\*, 19bR\*)- and (6aS\*, 12bR\*, 19bS\*)-11,14,15,16-tetramethoxy-12bH,19H,19bH-pyrano[3,2-c:3,4-c':5,6-c'']trichromen-19-one [rac-(6aS\*, 12bR\*, 19bR\*)-4cc and rac-(6aS\*, 12bR\*, 19bS\*)-5cc] and rac-(6aS\*, 12bR\*, 19bR\*)-11,16,17,18-tetramethoxy-12bH,19H,19bH-pyrano[2,3-b:5,4-c':5,6-c'']trichromen-19-one [rac-(6aS\*, 12bR\*, 19bR\*)-6cc].** The reaction of **1c** and **2c** was carried out according to method B, and the crude product was purified by column chromatography (hexane/ethyl acetate 2 : 1), affording *rac*-(6aS\*, 12bR\*, 19bR\*)-**4cc** as pale yellow powder (34%), *rac*-(6aS\*, 12bR\*, 19bR\*)-**6cc** as pale yellow powder (12%) and *rac*-(6aS\*, 12bR\*, 19bS\*)-**5cc** as pale yellow powder (14%).

Alternatively, the reaction was carried out at 55 °C (there is no reaction at room temperature), affording *rac*-(6aS\*, 12bR\*, 19bR\*)-**4cc** as pale yellow powder (29%), *rac*-(6aS\*, 12bR\*, 19bR\*)-**6cc** as pale yellow powder (8%) and *rac*-(6aS\*, 12bR\*, 19bS\*)-**5cc** as pale yellow powder (13%).

**rac-(6aS\*, 12bR\*, 19bR\*)-4cc: pale yellow powder, mp 231–234 °C,  $R_f = 0.32$  (hexane/ethyl acetate 2 : 1).**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.53 (s, 3H, 2'-H), 3.77 (s, 3H, 3'-H), 3.80 (s, 3H, 1'-H), 3.89 (s, 3H, 4'-H), 3.95 (m, 2H, 7-H), 4.11 (d,  $J = 11.8$  Hz, 1H, 6-H<sub>a</sub>), 4.22 (s, 1H, 19b-H), 4.31 (d,  $J = 11.8$  Hz, 1H, 6-H<sub>b</sub>), 5.30 (s, 1H, 12b-H), 6.67 (s, 1H, 17-H), 6.82 (m, 1H, 4-H), 6.88 (m, 2H, 2-H and 9-H), 6.93 (dd,  $J = 8.9$  and 3.0 Hz, 1H, 10-H), 7.03 (d,  $J = 2.9$  Hz, 1H, 12-H), 7.12 (t,  $J = 7.8$  Hz, 1H, 3-H), 7.39 (d,  $J = 8.0$  Hz, 1H, 1-H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  30.0 (C-6a), 31.8 (C-19b), 55.8 (C-1'), 56.3 (C-4'), 61.2 (C-3'), 62.3 (C-2'), 66.2 (C-7), 68.3 (C-6), 70.9 (C-12b), 96.4 (C-17), 98.6 (C-13b), 103.3 (C-19a), 115.3 (C-12), 116.9 (C-4), 118.1 (C-9), 118.1 (C-12a), 118.5 (C-10), 122.0 (C-2), 122.4 (C-19c), 128.3 (C-3), 129.8 (C-1), 140.3 (C-15), 146.6 (C-8a), 150.7 (C-17a), 150.7 (C-14), 152.3 (C-4a), 154.0 (C-11), 156.9 (C-16), 158.7 (C-13a), 164.1 (C-19). IR (KBr)  $\nu$ : 1040, 1102, 1215,



1282, 1398, 1463, 1498, 1605, 1697  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{30}\text{H}_{26}\text{O}_9\text{Na}$   $[\text{M} + \text{Na}]^+$  533.1469, found 533.1468.

***rac*-(6aS\*, 12bR\*, 19bR\*)-6cc: pale yellow powder, mp 221–224 °C,  $R_f = 0.21$  (hexane/ethyl acetate 2 : 1).**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.82 (s, 3H, 1'-H), 3.91 (s, 3H, 2'-H), 3.92–3.96 (m, 4H, 3'-H and 7-H<sub>a</sub>), 4.01 (d,  $J = 11.7$  Hz, 1H, 7-H<sub>b</sub>), 4.07 (s, 3H, 4'-H), 4.15 (d,  $J = 11.8$  Hz, 1H, 6-H<sub>a</sub>), 4.29 (d,  $J = 11.8$  Hz, 1H, 6-H<sub>b</sub>), 4.48 (s, 1H, 19b-H), 5.42 (d,  $J = 1.2$  Hz, 1H, 12-H), 6.62 (s, 1H, 15-H), 6.83 (dd,  $J = 8.2$  and 1.1 Hz, 1H, 4-H), 6.87–6.93 (m, 2H, 2-H and 9-H), 6.94 (d,  $J = 2.9$  Hz, 1H, 12-H), 6.98 (dd,  $J = 8.9$  and 3.0 Hz, 1H, 10-H), 7.15 (td,  $J = 7.4$  and 1.2 Hz, 1H, 3-H), 7.46 (d,  $J = 7.8$  Hz, 1H, 1-H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  31.0 (C-6a), 31.0 (C-19b), 55.8 (C-1'), 56.2 (C-2'), 61.5 (C-3'), 62.3 (C-4'), 66.1 (C-7), 68.1 (C-6), 73.5 (C-12b), 95.9 (C-15), 97.3 (C-19a), 111.2 (C-12), 115.1 (C-4), 116.7 (C-12a), 117.3 (C-9), 118.2 (C-10), 122.1 (C-2), 122.8 (C-19c), 128.2 (C-3), 130.5 (C-1), 140.6 (C-17), 146.7 (C-8a), 151.2 (C-13a), 152.2 (C-4a), 152.8 (C-18), 154.2 (C-11), 157.3 (C-16), 159.1 (C-12a), 177.4 (C-19). IR (KBr)  $\nu$ : 1218, 1274, 1420, 1499, 1616, 2938  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{30}\text{H}_{26}\text{O}_9\text{Na}$   $[\text{M} + \text{Na}]^+$  533.1469, found 533.1469.

***rac*-(6aS\*, 12bR\*, 19bS\*)-5cc: pale yellow powder, mp 207–210 °C,  $R_f = 0.16$  (hexane/ethyl acetate 2 : 1).**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.45 (d,  $J = 11.6$  Hz, 1H, 7-H<sub>a</sub>), 3.61 (s, 3H, 4'-H), 3.80 (s, 3H, 1'-H), 3.82 (s, 3H, 3'-H), 3.89 (d,  $J = 12.1$  Hz, 1H, 7-H<sub>b</sub>), 3.93 (s, 3H, 2'-H), 3.97 (d,  $J = 10.5$  Hz, 1H, 6-H<sub>a</sub>), 4.27 (d,  $J = 10.3$  Hz, 1H, 6-H<sub>b</sub>), 4.36 (s, 1H, 19b-H), 4.88 (s, 1H, 12b-H), 6.70 (s, 1H, 17-H), 6.83 (d,  $J = 8.9$  Hz, 1H, 9-H), 6.93 (m, 4H, 2-H, 4-H, 10-H and 12-H), 7.01 (d,  $J = 7.4$  Hz, 1H, 1-H), 7.20 (t,  $J = 7.6$  Hz, 1H, 3-H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  35.3 (C-19b), 35.9 (C-6a), 55.9 (C-1'), 56.3 (C-2'), 61.3 (C-3'), 62.2 (C-4'), 63.3 (C-7), 69.5 (C-6), 75.4 (C-12b), 96.3 (C-17), 96.7 (C-19a), 103.5 (C-13b), 114.9 (C-9), 116.6 (C-4), 117.4 (C-12a), 117.7 (C-10), 118.4 (C-2), 121.0 (C-12), 122.8 (C-19c), 126.1 (C-1), 128.2 (C-3), 140.3 (C-15), 148.7 (C-8a), 150.7 (C-14), 152.2 (C-17a), 153.6 (C-11), 154.7 (C-4a), 156.9 (C-16), 161.1 (C-13a), 161.3 (C-19). IR (KBr)  $\nu$ : 1226, 1390, 1497, 1609, 1704  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{30}\text{H}_{26}\text{O}_9\text{Na}$   $[\text{M} + \text{Na}]^+$  533.1469, found 533.1469.

***rac*-(6aS\*, 12bR\*, 19bS\*)-11,14,15,16-tetramethoxy-5-methyl-3-(trifluoromethyl)-5,19b-dihydro-6H,12bH,19H-dichromeno[3',4':5,6; 4'',3'':2,3]pyrano[3,4-c]quinolin-19-one [*rac*-(6aS\*, 12bR\*, 19bS\*)-4dc].** The reaction of **1d** and **2c** was carried out according to method A, and the crude product was purified by column chromatography (hexane/ethyl acetate 2 : 1), affording *rac*-(6 aS\*,12bR\*,19bS\*)-4dc as pale yellow powder (32%). Two other isomers were detected, but were not isolated.

***rac*-(6aS\*, 12bR\*, 19bS\*)-4dc: pale yellow powder, mp 186–189 °C,  $R_f = 0.25$  (hexane/ethyl acetate 2 : 1).**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.87 (s, 1H, 5'-H), 3.16 (d,  $J = 12.4$  Hz, 1H, 6-H<sub>a</sub>), 3.46 (d,  $J = 12.8$  Hz, 1H, 6-H<sub>b</sub>), 3.52 (s, 3H, 2'-H), 3.79 (s, 3H, 3'-H), 3.81 (s, 3H, 1'-H), 3.91 (s, 3H, 4'-H), 3.93 (s, 2H, 7-H), 4.16 (s, 1H, 17b-H), 5.16 (s, 1H, 12b-H), 6.68 (s, 1H, 17-H), 6.83 (s, 1H, 4-H), 6.86 (d,  $J = 9.0$  Hz, 1H, 9-H), 6.88–6.96 (m, 2H, 2-H and 10-H), 7.00 (d,  $J = 2.8$  Hz, 1H, 12-H), 7.31 (d,  $J = 8.0$  Hz, 1H, 1-H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  30.9 (C-6a), 33.4 (C-19b), 39.4 (C-5'), 54.9 (C-6), 55.8 (C-3'), 56.2 (C-4'), 61.8 (C-1'), 62.2 (C-2'), 67.5 (C-7), 72.4 (C-12b), 96.4 (C-17), 98.5 (C-19a), 103.3 (C-13b), 108.0 (C-4), 114.4 (C-2), 115.3 (C-12), 118.0 (C-9), 118.2 (C-10), 118.5 (C-

12a), 126.1 (C-19c), 129.8 (C-1), 130.1 (d,  $J = 31.9$  Hz, C-3), 140.3 (C-15), 144.9 (C-4a), 146.7 (C-8a), 150.8 (C-4a and C-17a), 153.9 (C-11), 156.9 (C-16), 158.7 (C-13a), 163.8 (C-19). IR (KBr)  $\nu$ : 1038, 1100, 1120, 1151, 1172, 1214, 1339, 1399, 1498, 1608, 1703  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{32}\text{H}_{28}\text{F}_3\text{NO}_8\text{Na}$   $[\text{M} + \text{Na}]^+$  634.1659, found 634.1662.

The enantiomers were separated on a Chiralpak IC column (hexane/dichloromethane/methanol 70 : 27 : 3), and the *on-line* HPLC-ECD spectra were recorded.

(6aR, 12bS, 19bR)-4dc:  $t_R = 6.43$  min (Chiralpak IC, hexane/dichloromethane/methanol 70 : 27 : 3). ECD [nm ( $\Delta\epsilon$ ), hexane/dichloromethane/methanol 70 : 27 : 3]: 324.5 (–34.27), 299 (7.18), 273.5 (–7.78), 262.5 (4.18), 255 (–3.16), 250 (5.51), 236.5 (–37.73).

(6aS, 12bR, 19bS)-4dc:  $t_R = 6.80$  min (Chiralpak IC, hexane/dichloromethane/methanol 70 : 27 : 3). ECD [nm ( $\Delta\epsilon$ ), hexane/dichloromethane/methanol 70 : 27 : 3]: 326.5 (47.92), 298.5 (–10.57), 275 (11.34), 263 (–5.37), 255.5 (4.57), 250 (–7.34), 237 (53.12).

***rac*-(6aS\*, 12bR\*, 19bS\*)-11,14,15,16-tetramethoxy-5-methyl-5,19b-dihydro-6H,12bH,19H-dichromeno[3',4':5,6; 4'',3'':2,3]pyrano[3,4-c]quinolin-19-one [*rac*-(6aS\*,12bR\*,19bS\*)-4ec].** The reaction of **1e** and **2c** was carried out according to method A, and the crude product was purified by column chromatography (hexane/ethyl acetate 2 : 1), affording *rac*-(6 aS\*,12bR\*,19bS\*)-4ec as pale yellow amorphous solid (32%). Two other isomers were detected, but were not isolated.

***rac*-(6aS\*, 12bR\*, 19bS\*)-4ec: pale yellow amorphous solid,  $R_f = 0.38$  (hexane/ethyl acetate 2 : 1).**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.82 (s, 1H, 5'-H), 3.09 (d,  $J = 12.4$  Hz, 1H, 6a-H), 3.41 (d,  $J = 12.4$  Hz, 1H, 6b-H), 3.52 (s, 3H, 2'-H), 3.79 (s, 3H, 3'-H), 3.81 (s, 3H, 1'-H), 3.93 (s, 3H, 4'-H), 3.93 (s, 2H, 7-H), 4.15 (s, 1H, 17b-H), 5.22 (s, 1H, 12b-H), 6.64–6.71 (m, 3H, 2-H, 4-H and 17-H), 6.85 (d,  $J = 9.2$  Hz, 1H, 9-H), 6.93 (dd,  $J = 9.2$  and 2.8 Hz, 1H, 10-H), 7.00 (d,  $J = 2.8$  Hz, 1H, 12-H), 7.13 (t,  $J = 7.6$  Hz, 1H, 3-H), 7.20 (d,  $J = 8.0$  Hz, 1H, 1-H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  33.3 (C-5'), 36.6 (C-6a), 39.5 (C-19b), 55.1 (C-6), 55.8 (C-1'), 56.2 (C-4'), 61.2 (C-3'), 62.2 (C-2'), 67.7 (C-7), 72.5 (C-12b), 96.4 (C-17), 99.2 (–19a), 103.5 (13b), 111.7 (C-4), 115.4 (C-2), 117.9 (C-10), 118.0 (C-12), 118.2 (C-9), 120.6 (C-12a), 122.7 (C-19c), 127.8 (C-3), 129.3 (C-1), 141.2 (C-15), 144.8 (C-4a), 146.9 (C-14), 150.7 (C-17a), 153.8 (C-11), 156.6 (C-16), 158.5 (C-13a), 163.9 (C-19). IR (KBr)  $\nu$ : 1217, 1228, 1365, 1497, 1608, 1713, 1738  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{31}\text{H}_{29}\text{NO}_8\text{Na}$   $[\text{M} + \text{Na}]^+$  566.1785, found 566.1781.

The enantiomers were separated on a Chiralpak IC column (hexane/dichloromethane/methanol 80 : 18 : 2), and the *on-line* HPLC-ECD spectra were recorded.

(6aR, 12bS, 19bR)-4ec:  $t_R = 20.57$  min (Chiralpak IC, hexane/dichloromethane/methanol 80 : 18 : 2). ECD [nm ( $\Delta\epsilon$ ), hexane/dichloromethane/methanol 80 : 18 : 2]: 318 (–3.13), 275 (–1.04), 260 (0.89), 248.5 (1.65), 230.5 (–7.35).

(6aS, 12bR, 19bS)-4ec:  $t_R = 21.95$  min (Chiralpak IC, hexane/dichloromethane/methanol 80 : 18 : 2). ECD [nm ( $\Delta\epsilon$ ), hexane/dichloromethane/methanol 80 : 18 : 2]: 319 (3.41), 282 (1.51), 261.5 (–0.44), 246 (–1.19), 231 (8.39).



### Domino Knoevenagel-IMHDA reactions of 2*H*-chromene derivatives 1a-c with 2,4-dihydroxyquinoline 2d

*rac*-(6a*S*\*, 12b*R*\*, 19b*S*\*) and (6a*S*\*, 12b*R*\*, 19b*R*\*)-11-methoxy-5-methyl-2-nitro-5,6,18,19b-tetrahydro-12*bH*,19*H*-chromeno[3',4':5,6]quinolino[4',3':4,5]pyrano[3,2-*c*]quinolin-19-one [*rac*-(6 a*S*\*,12b*R*\*,19b*S*\*)-4ad and *rac*-(6a*S*\*, 12b*R*\*, 19b*R*\*)-5ad] and *rac*-(6a*S*\*, 12b*R*\*, 19b*S*\*)-11-methoxy-5-methyl-2-nitro-5,6,14,19b-tetrahydro-12*bH*,19*H*-chromeno[3',4':5,6]quinolino[4',3':4,5]pyrano[2,3-*b*]quinolin-19-one [*rac*-(6 a*S*\*,12b*R*\*,19b*S*\*)-6ad]. The reaction of 1a and 2d was carried out according to method C. The product precipitated from the hot solution, it was cooled to room temperature, filtered and washed with cold ether, affording the mixture of *rac*-(6a*S*\*, 12b*R*\*, 19b*S*\*)-4ad, *rac*-(6a*S*\*, 12b*R*\*, 19b*R*\*)-5ad and *rac*-(6 a*S*\*,12b*R*\*,19b*S*\*)-6ad as yellow powder (46%).  $R_f = 0.24$  (hexane/ethyl acetate 1 : 1).

$^1\text{H NMR}$  (400 MHz, DMSO- $d_6$ )  $\delta$  2.94 and 2.95 (s, 3H, 2''-H), 3.04 (d,  $J = 8.3$  Hz, 4H, 2'-H and 6-H<sub>a</sub>), 3.12–3.24 (m, 2H, 6-H<sub>a</sub>), 3.49 (d,  $J = 11.7$  Hz, 1H, 6-H<sub>b</sub>), 3.71 (d,  $J = 11.2$  Hz, 4H, 1'-H and 7-H<sub>a</sub>), 3.76 and 3.77 (s, 3H, 1'-H), 3.84 (d,  $J = 13.4$  Hz, 2H, 6-H<sub>b</sub> and 7-H<sub>b</sub>), 4.09 (d,  $J = 11.3$  Hz, 1H, 7-H<sub>b</sub>), 4.23, 4.32 and 4.43 (s, 1H, 19-H<sub>b</sub>), 5.07 and 5.18 (s, 1H, 12b-H), 6.74 (d,  $J = 9.4$  Hz, 1H, 4-H), 6.81 (d,  $J = 9.3$  Hz, 1H, 4-H), 6.84 (d,  $J = 9.0$  Hz, 1H, 9-H), 6.87 (d,  $J = 8.9$  Hz, 1H, 9-H), 6.95–7.03 (m, 1H, 10-H), 7.07 (d,  $J = 3.0$  Hz, 1H, 12-H), 7.11 (d,  $J = 8.0$  Hz, 1H, 15-H), 7.16 (d,  $J = 7.9$  Hz, 1H, 15-H), 7.19 and 7.23 (d,  $J = 3.0$  Hz, 1H, 12-H), 7.34 (d,  $J = 8.3$  Hz, 1H, 17-H), 7.37–7.42 (m, 1H, 17-H), 7.50 (t,  $J = 8.3$  Hz, 1H, 16-H), 7.55 (d,  $J = 8.5$  Hz, 1H, 16-H), 7.59 (d,  $J = 8.0$  Hz, 1H, 14-H), 7.67 (d,  $J = 8.7$  Hz, 1H, 14-H), 7.93 (dd,  $J = 9.3, 2.5$  Hz, 1H, 3-H), 7.96 and 8.03 (m, 1H, 1-H), 8.06 and 8.18 (m, 1H, 3-H), 11.85 (s, 1H, N-H).  $^{13}\text{C NMR}$  (100 MHz, DMSO- $d_6$ )  $\delta$  30.3 and 30.6 (C-6a), 32.1 and 32.3 (C-19b), 34.6 (C-6a), 37.2 (C-19b), 38.5 and 39.8 (C-2'), 54.2 and 55.3 (C-6), 56.1 and 56.2 (C-1'), 63.3 (C-6), 67.5 and 67.6 (C-7), 71.0, 72.4 and 74.4 (C-12b), 99.2, 105.0 and 107.4 (C-19a), 110.0, 110.9 and 111.1 (C-4), 114.12 and 114.6 (C-13b), 115.6 and 115.8 (C-17), 116.2, 116.5 and 116.6 (C-12), 117.4 and 117.9 (C-9), 118.0 (C-10), 118.0 (C-9), 118.4 and 118.5 (C-10), 118.9, 119.1, and 119.8 (C-12a), 120.2 (C-19c), 122.0 and 122.1 (C-15), 122.2 (C-19c), 122.7 (C-14), 122.9 (C-19c), 123.1 (C-14), 123.5 (C-18a), 124.6 and 125.6 (C-3), 126.2 and 126.5 (C-1), 131.3 and 131.9 (C-16), 136.6 and 137.2 (C-2), 137.3 (C-17a), 138.5 (C-17a and C-14a), 146.8, 147.0 and 148.5 (C-8a), 149.8, 150.0 and 152.6 (C-4a), 153.4, 153.7 and 153.9 (C-13a), 154.0 and 154.1 (C-11), 157.3, 162.4 and 163.7 (C-19). IR (KBr)  $\nu$ : 1215, 1297, 1319, 1498, 1606, 1649  $\text{cm}^{-1}$ ; HRMS: calcd for C<sub>28</sub>H<sub>23</sub>N<sub>3</sub>O<sub>6</sub>Na [M + Na]<sup>+</sup> 520.1479, found 520.1479.

*rac*-(6a*S*\*,7*R*\*,12b*R*\*,19b*S*\*) and (6a*S*\*,7*R*\*,12b*R*\*,19b*R*\*)-11-methoxy-5-methyl-2-nitro-7-phenyl-5,6,18,19b-tetrahydro-12*bH*,19*H*-chromeno[3',4':5,6]quinolino[4',3':4,5]pyrano[3,2-*c*]quinolin-19-one [*rac*-(6 a*S*\*,7*R*\*,12b*R*\*,19b*S*\*)-4bd and *rac*-(6 a*S*\*,7*R*\*,12b*R*\*,19b*R*\*)-5bd]. The reaction of *rac*-1b and 2d was carried out according to method C, and the crude product was purified by column chromatography (toluene/ethyl acetate 7 : 1), affording *rac*-(6a*S*\*, 7*R*\*, 12b*R*\*, 19b*S*\*)-4bd as yellow powder (60%) and *rac*-(6a*S*\*, 7*R*\*, 12b*R*\*, 19b*R*\*)-5bd as yellow powder (17%).

*rac*-(6a*S*\*, 7*R*\*, 12b*R*\*, 19b*S*\*)-4bd: yellow powder, mp > 340 °C,  $R_f = 0.14$  (hexane/ethyl acetate 2 : 1).  $^1\text{H NMR}$  (400 MHz, DMSO- $d_6$ )  $\delta$  2.92 (s, 3H, 2''-H), 3.28 (d,  $J = 13.5$  Hz, 1H, 6-H<sub>a</sub>), 3.53 (d,  $J = 13.5$  Hz, 1H, 6-H<sub>b</sub>), 3.79 (s, 3H, 1''-H), 3.87 (s, 1H, 19b-H), 5.01 (s, 1H, 7-H), 5.17 (s, 1H, 12b-H), 6.72 (d,  $J = 9.4$  Hz, 1H, 4-H), 7.00 (d,  $J = 9.0$  Hz, 1H, 9-H), 7.04 (dd,  $J = 9.0$  and 2.8 Hz, 1H, 10-H), 7.15 (t,  $J = 7.5$  Hz, 1H, 15-H), 7.24–7.30 (m, 2H, 2'-H and 6'-H), 7.31 (d,  $J = 2.8$  Hz, 1H, 12-H), 7.34–7.45 (m, 4H, 3'-H, 4'-H, 5'-H and 17-H), 7.54 (td,  $J = 7.7$  and 1.1 Hz, 1H, 16-H), 7.67 (d,  $J = 7.9$  Hz, 1H, 14-H), 7.89 (dd,  $J = 9.2$  and 2.6 Hz, 1H, 3-H), 8.01 (m, 1H, 1-H), 11.92 (s, 1H, N-H).  $^{13}\text{C NMR}$  (100 MHz, DMSO- $d_6$ )  $\delta$  31.6 (C-19b), 32.1 (C-6a), 49.8 (C-6), 55.5 (C-1''), 71.3 (C-12b), 76.7 (C-7), 106.8 (C-19a), 110.9 (C-4), 113.6 (C-13b), 115.4 (C-17), 115.9 (C-12), 117.5 (C-9 and C-10), 119.3 (C-12a), 121.8 (C-15), 122.3 (C-14), 122.4 (C-19c), 124.0 (C-3), 125.6 (C-1), 127.8 (C-2' and C-6'), 128.0 (C-3' and C-5'), 128.7 (C-4'), 131.1 (C-16), 134.4 (C-1'), 136.6 (C-2), 138.2 (C-17a), 147.3 (C-8a), 148.9 (C-4a), 153.8 (C-11), 154.2 (C-13a), 163.0 (C-19). IR (KBr)  $\nu$ : 1261, 1299, 1312, 1499, 1605, 1646, 2854, 2925  $\text{cm}^{-1}$ ; HRMS: calcd for C<sub>34</sub>H<sub>27</sub>N<sub>3</sub>O<sub>6</sub>Na [M + Na]<sup>+</sup> 596.1792, found 596.1792.

*rac*-(6a*S*\*, 7*R*\*, 12b*R*\*, 19b*R*\*)-5bd: yellow powder, mp 138–140 °C,  $R_f = 0.05$  (hexane/ethyl acetate 2 : 1).  $^1\text{H NMR}$  (400 MHz, DMSO- $d_6$ )  $\delta$  2.90 (s, 3H, 2''-H), 3.44 (d,  $J = 12.8$  Hz, 1H, 6-H<sub>a</sub>), 3.61 (d,  $J = 12.7$  Hz, 1H, 6-H<sub>b</sub>), 3.79 (s, 3H, 1''-H), 4.36 (s, 1H, 19b-H), 5.27 (s, 1H, 12b-H), 5.34 (s, 1H, 7-H), 6.02 (d,  $J = 9.2$  Hz, 1H, 4-H), 6.82 (m, 2H, 2'-H and 6'-H), 6.91 (d,  $J = 8.9$  Hz, 1H, 9-H), 7.05 (dd,  $J = 8.9$  and 3.0 Hz, 1H, 10-H), 7.10 (d,  $J = 3.0$  Hz, 1H, 12-H), 7.19 (t,  $J = 7.6$  Hz, 1H, 15-H), 7.39 (d,  $J = 8.2$  Hz, 1H, 17-H), 7.41 (m, 1H, 1-H), 7.45 (dd,  $J = 9.1$  and 2.6 Hz, 1H, 3-H), 7.58 (td,  $J = 7.7$  and 1.2 Hz, 1H, 16-H), 7.74 (d,  $J = 7.9$  Hz, 1H, 14-H), 11.82 (s, 1H, N-H).  $^{13}\text{C NMR}$  (100 MHz, DMSO- $d_6$ )  $\delta$  36.7 (C-6a), 37.4 (C-2''), 38.2 (C-19b), 52.6 (C-6), 55.6 (C-1''), 76.8 (C-12b), 76.9 (C-7), 105.1 (C-19a), 108.9 (C-4), 114.2 (C-13b), 115.0 (C-12 and C-17), 116.8 (C-9), 118.0 (C-10), 118.3 (C-19c), 118.3 (C-12a), 121.5 (C-15), 122.3 (C-14), 123.4 (C-3), 124.6 (C-1), 127.5 (C-2' and C-6'), 130.9 (C-16), 135.3 (C-2), 137.6 (C-1'), 137.9 (C-17a), 148.3 (C-8a), 152.6 (C-4a), 153.2 (C-11), 157.4 (C-13a), 161.9 (C-19). IR (KBr)  $\nu$ : 1230, 1289, 1497, 1607, 1644, 2853, 2924  $\text{cm}^{-1}$ ; HRMS: calcd for C<sub>34</sub>H<sub>27</sub>N<sub>3</sub>O<sub>6</sub>Na [M + Na]<sup>+</sup> 596.1792, found 596.1792.

*rac*-(6a*S*\*, 12b*R*\*, 19b*R*\*)-11-methoxy-18,19b-dihydro-12*bH*,19*H*-dichromeno [3',4':5,6; 4'',3'':4,5]pyrano[3,2-*c*]quinolin-19-one [*rac*-(6a*S*\*, 12b*R*\*, 19b*R*\*)-4cd]. The reaction of 1c and 2d was carried out according to method C, and the crude product was purified by column chromatography (hexane/acetone/chloroform 4 : 1 : 1), affording *rac*-(6a*S*\*, 12b*R*\*, 19b*R*\*)-4cd as white powder (24%), mp > 330 °C.  $R_f = 0.14$  (hexane/ethyl acetate 2 : 1).

$^1\text{H NMR}$  (400 MHz, CDCl<sub>3</sub>)  $\delta$  3.85 (s, 3H, 1'-H), 3.94 (dd,  $J = 11.7$  and 1.5 Hz, 1H, 7-H<sub>a</sub>), 4.00 (d,  $J = 11.6$  Hz, 1H, 7-H<sub>b</sub>), 4.20 (d,  $J = 11.8$  Hz, 1H, 6-H<sub>a</sub>), 4.36 (d,  $J = 11.8$  Hz, 1H, 6-H<sub>b</sub>), 4.48 (s, 1H, 19b-H), 5.31 (s, 1H, 12b-H), 6.82–6.91 (m, 3H, 9-H, 2-H and 4-H), 6.96 (dd,  $J = 9.0$  and 3.0 Hz, 1H, 10-H), 7.06 (d,  $J = 2.9$  Hz, 1H, 12-H), 7.14 (t,  $J = 7.6$  Hz, 2H, 3-H and 15-H), 7.38 (d,  $J = 8.1$  Hz, 1H, 17-H), 7.47 (td,  $J = 7.7$  and 1.1 Hz, 2H, 16-H), 7.63 (d,  $J = 7.8$  Hz, 1H, 1-H), 7.78 (d,  $J = 8.1$  Hz, 1H, 14-H), 11.89 (s, 1H, N-H).  $^{13}\text{C NMR}$  (100



MHz, CDCl<sub>3</sub>)  $\delta$  30.5 (C-6a), 31.8 (C-19b), 56.0 (C-1'), 66.5 (C-7), 68.7 (C-6), 70.4 (C-12b), 106.6 (C-19a), 114.8 (C-12a), 115.9 (C-12), 115.9 (C-17), 117.0 (C-9), 118.0 (C-10), 118.0 (C-4), 119.1 (C-13b), 122.0 (C-2), 122.4 (C-15), 123.1 (C-19c), 123.2 (C-14), 128.3 (C-3), 130.6 (C-1), 131.2 (C-16), 137.7 (C-17a), 146.8 (C-8a), 152.6 (C-4a), 154.2 (C-11), 155.4 (C-13a), 165.8 (C-19). IR (KBr)  $\nu$ : 1043, 1215, 1259, 1401, 1498, 1605, 1646, 2862, 2947, 2993 cm<sup>-1</sup>; HRMS: calcd for C<sub>27</sub>H<sub>21</sub>NO<sub>5</sub>Na [M + Na]<sup>+</sup> 462.1312, found 462.1311.

### Domino Knoevenagel-IMHDA reactions of 2H-chromene derivatives 1a-c with 4-hydroxy-6-methyl-2H-pyran-2-one 2e and 4-hydroxy-1,6-dimethyl-pyridine-2(1H)-one 2f

*rac*-(6aS\*,12bR\*,17bS\*)- (6aS\*,12bR\*,17bS\*)-11-methoxy-5,15-dimethyl-2-nitro-5,17b-dihydro-6H,12bH,17H-chromeno [4',3':2,3]pyrano[3',4':5,6]pyrano[3,4-c]quinolin-17-one [*rac*-(6aS\*,12bR\*,17bS\*)-4ae and *rac*-(6aS\*,12bR\*,17bS\*)-5ae] and *rac*-(6aS\*,12bR\*,17bS\*)- and *rac*-(6aS\*,12bR\*,17bR\*)-11-methoxy-5,15-dimethyl-2-nitro-5,17b-dihydro-6H,12bH,17H-chromeno [4',3':2,3]pyrano[3',2':5,6]pyrano[3,4-c]quinolin-17-one [*rac*-(6aS\*,12bR\*,17bS\*)-6ae and *rac*-(6aS\*,12bR\*,17bR\*)-7ae]

The reaction of 1a and 2e was carried out according to method A, and the crude product was purified by column chromatography (hexane/ethyl acetate 2 : 1), affording *rac*-(6aS\*,12bR\*,17bS\*)-4ae as yellow powder (16%), *rac*-(6aS\*,12bR\*,17bS\*)-6ae as yellow oil (35%), *rac*-(6aS\*,12bR\*,17bS\*)-5ae as orange powder (14%) and *rac*-(6aS\*,12bR\*,17bR\*)-7ae as yellow powder (6%).

Alternatively, the reaction was carried out at room temperature, affording *rac*-(6aS\*,12bR\*,17bS\*)-4ae as yellow powder (14%), *rac*-(6aS\*,12bR\*,17bS\*)-6ae as yellow oil (37%) and *rac*-(6aS\*,12bR\*,17bS\*)-5ae as orange powder (27%).

***rac*-(6aS\*,12bR\*,17bS\*)-4ae: yellow powder, mp 275–276 °C, R<sub>f</sub> = 0.36 (hexane/ethyl acetate 1 : 1).** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  2.26 (s, 3H, 3'-H), 2.94 (s, 3H, 2'-H), 3.24 (d, *J* = 13.2 Hz, 1H, 6-H<sub>a</sub>), 3.64 (d, *J* = 13.2 Hz, 1H, 6-H<sub>b</sub>), 3.81 (s, 3H, 1'-H), 3.87 (d, *J* = 11.5 Hz, 1H, 7-H<sub>a</sub>), 3.96 (dd, *J* = 11.4 and 1.1 Hz, 1H, 7-H<sub>b</sub>), 4.09 (s, 1H, 17b-H), 4.89 (s, 1H, 12b-H), 5.76 (s, 1H, 14-H), 6.55 (d, *J* = 9.2 Hz, 1H, 4-H), 6.85 (d, *J* = 2.9 Hz, 1H, 12-H), 6.89 (d, *J* = 9.0 Hz, 1H, 9-H), 6.97 (dd, *J* = 9.0 and 2.9 Hz, 1H, 10-H), 7.99 (dd, *J* = 9.2 and 2.5 Hz, 1H, 3-H), 8.11 (m, 1H, 1-H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  20.1 (C-3'), 30.7 (C-6a), 32.6 (C-17b), 39.8 (C-2'), 54.7 (C-6), 55.9 (C-7), 67.5 (C-12b), 72.0 (C-17a), 98.5 (C-14), 100.1 (C-14), 110.3 (C-4), 115.4 (C-12), 118.2 (C-10), 118.3 (C-9 and C-12a), 121.6 (C-17c), 124.9 (C-3), 126.2 (C-1), 138.5 (C-2), 146.7 (C-8a), 149.0 (C-4a), 154.2 (C-11), 162.1 (C-13a), 162.5 (C-15), 165.6 (C-17). IR (KBr)  $\nu$ : 1211, 1266, 1326, 1498, 1579, 1697 cm<sup>-1</sup>; HRMS: calcd for C<sub>25</sub>H<sub>22</sub>N<sub>2</sub>O<sub>7</sub>Na [M + Na]<sup>+</sup> 485.1319, found 485.1319.

The enantiomers were separated on a Chiralpak IC column (hexane/dichloromethane/methanol 50 : 45 : 5), and the *on-line* HPLC-ECD spectra were recorded.

(6aR,12bS,17bR)-4ae: *t*<sub>R</sub> = 9.31 min (Chiralpak IC, hexane/dichloromethane/methanol 50 : 45 : 5). ECD [nm ( $\Delta\epsilon$ ), hexane/dichloromethane/methanol 50 : 45 : 5]: 387 (1.25), 335 (−0.83), 316.5 (−1.13), 310 (0.66), 291 (−7.98), 248.5 (−3.10), 226.5 (−25.04).

(6aS,12bR,17bS)-4ae: *t*<sub>R</sub> = 12.02 min (Chiralpak IC, hexane/dichloromethane/methanol 50 : 45 : 5). ECD [nm ( $\Delta\epsilon$ ), hexane/dichloromethane/methanol 50 : 45 : 5]: 392.5 (−0.87), 334.5 (1.06), 316.5 (1.49), 309 (−0.24), 291 (7.85), 250 (3.05), 226 (23.20).

***rac*-(6aS\*,12bR\*,17bS\*)-5ae: orange powder, mp 251–253 °C, R<sub>f</sub> = 0.32 (hexane/ethyl acetate 1 : 1).** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  2.30 (s, 3H, 3'-H), 3.02 (s, 3H, 2'-H), 3.18 (s, 2H, 6-H), 3.32 (d, *J* = 11.7 Hz, 1H, 7-H<sub>a</sub>), 3.79 (m, 4H, 1'-H and 7-H<sub>b</sub>), 4.02 (s, 1H, 17b-H), 4.73 (s, 1H, 12b-H), 5.86 (s, 1H, 14-H), 6.65 (d, *J* = 9.1 Hz, 1H, 4-H), 6.82 (m, 2H, 9-H and 12-H), 6.95 (dd, *J* = 9.0 and 3.0 Hz, 1H, 10-H), 7.79 (d, *J* = 2.7 Hz, 1H, 1-H), 8.12 (dd, *J* = 9.1 and 2.7 Hz, 1H, 3-H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  20.1 (C-3'), 35.2 (C-6a), 36.4 (C-17b), 38.3 (C-2'), 54.4 (C-6), 56.0 (C-1'), 63.1 (C-7), 75.9 (C-12b), 96.4 (C-17a), 100.1 (C-14), 109.9 (C-4), 115.0 (C-12), 117.2 (C-12a), 117.8 (C-9), 118.7 (C-10), 119.4 (C-17c), 122.5 (C-1), 125.1 (C-3), 138.2 (C-2), 148.4 (C-8a), 151.8 (C-4a), 153.9 (C-11), 162.7 (C-15), 163.1 (C-17), 164.9 (C-13a). IR (KBr)  $\nu$ : 1040, 1217, 1289, 1313, 1498, 1575, 1604, 1710, 2925 cm<sup>-1</sup>; HRMS: calcd for C<sub>25</sub>H<sub>22</sub>N<sub>2</sub>O<sub>7</sub>Na [M + Na]<sup>+</sup> 485.1319, found 485.1319.

The enantiomers were separated on a Chiralpak IC column (hexane/dichloromethane/methanol 30 : 63 : 7), and the *on-line* HPLC-ECD spectra were recorded.

(6aS,12bR,17bR)-5ae: *t*<sub>R</sub> = 6.03 min (Chiralpak IC, hexane/dichloromethane/methanol 30 : 63 : 7). ECD [nm ( $\Delta\epsilon$ ), hexane/dichloromethane/methanol 30 : 63 : 7]: 387 (−19.42), 312 (−24.98), 264.5 (5.93), 236.5 (−13.46).

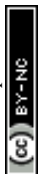
(6aR,12bS,17bS)-5ae: *t*<sub>R</sub> = 13.46 min (Chiralpak IC, hexane/dichloromethane/methanol 30 : 63 : 7). ECD [nm ( $\Delta\epsilon$ ), hexane/dichloromethane/methanol 30 : 63 : 7]: 388.5 (10.03), 312 (12.61), 263 (−3.35), 238 (6.60).

***rac*-(6aS\*,12bR\*,17bS\*)-6ae: yellow powder, mp 188–190 °C, R<sub>f</sub> = 0.27 (hexane/ethyl acetate 1 : 1).** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  2.19 (s, 3H, 3'-H), 2.89 (s, 3H, 2'-H), 3.18 (d, *J* = 13.3 Hz, 1H, 6-H<sub>a</sub>), 3.67 (d, *J* = 13.2 Hz, 1H, 6-H<sub>b</sub>), 3.76 (s, 3H, 1'-H), 3.87 (d, *J* = 11.6 Hz, 1H, 7-H<sub>a</sub>), 4.01 (dd, *J* = 11.6, 1.2 Hz, 1H, 7-H<sub>b</sub>), 4.33 (s, 1H, 17b-H), 5.07 (s, 1H, 12b-H), 6.13 (s, 1H, 16-H), 6.47 (d, *J* = 9.3 Hz, 1H, 4-H), 6.83 (d, *J* = 2.9 Hz, 1H, 12-H), 6.86 (d, *J* = 9.0 Hz, 1H, 9-H), 6.93 (dd, *J* = 9.0 and 3.0 Hz, 1H, 10-H), 7.88 (dd, *J* = 9.2 and 2.5 Hz, 1H, 3-H), 7.96 (d, *J* = 2.5, 1H, 1-H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  19.2 (C-3'), 30.7 (C-6a), 31.8 (C-17b), 39.6 (C-2'), 54.2 (C-6), 55.8 (C-1'), 67.2 (C-7), 74.6 (C-12b), 99.8 (C-17a), 110.1 (C-4), 112.6 (C-16), 115.0 (C-9), 117.3 (C-17c), 118.2 (C-10), 118.7 (C-12), 121.5 (C-12a), 124.6 (C-3), 126.4 (C-1), 138.2 (C-2), 146.7 (C-8a), 148.8 (C-4a), 154.1 (C-11), 160.4 (C-15), 161.4 (C-13a), 180.1 (C-17). IR (KBr)  $\nu$ : 1265, 1300, 1323, 1498, 1585, 1603, 1668 cm<sup>-1</sup>; HRMS: calcd for C<sub>25</sub>H<sub>22</sub>N<sub>2</sub>O<sub>7</sub>Na [M + Na]<sup>+</sup> 485.1319, found 485.1319.

The enantiomers were separated on a Chiralpak IC column (hexane/dichloromethane/methanol 30 : 63 : 7), and the *on-line* HPLC-ECD spectra were recorded.

(6aR,12bS,17bR)-6ae: *t*<sub>R</sub> = 5.81 min (Chiralpak IC, hexane/dichloromethane/methanol 30 : 63 : 7). ECD [nm ( $\Delta\epsilon$ ), hexane/dichloromethane/methanol 30 : 63 : 7]: 402.5 (0.73), 319 (−3.48), 296 (5.98), 243.5 (−58.93).

(6aS,12bR,17bS)-6ae: *t*<sub>R</sub> = 11.71 min (Chiralpak IC, hexane/dichloromethane/methanol 30 : 63 : 7). ECD [nm ( $\Delta\epsilon$ ), hexane/



dichloromethane/methanol 30 : 63 : 7]: 406.5 (−0.51), 318.5 (3.23), 297.5 (−5.76), 242 (54.73).

***rac*-(6aS\*, 12bR\*, 17bS\*)-7ae: yellow powder, mp 211–214 °C,  $R_f = 0.14$  (hexane/ethyl acetate 1 : 1).**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.29 (s, 3H, 3'-H), 3.03 (s, 3H, 2'-H), 3.20 (s, 2H, 6-H), 3.34 (dd,  $J = 11.7$  and 1.6 Hz, 1H, 7-H<sub>a</sub>), 3.80 (s, 3H, 1'-H), 3.88 (d,  $J = 11.7$  Hz, 1H, 7-H<sub>b</sub>), 4.14 (s, 1H, 17b-H), 4.94 (d,  $J = 1.4$  Hz, 1H, 12b-H), 6.19 (s, 1H, 16-H), 6.64 (d,  $J = 9.1$  Hz, 1H, 4-H), 6.83 (m, 2H, 9-H and 12-H), 6.96 (dd,  $J = 8.9$  and 3.1 Hz, 1H, 10-H), 7.66 (d,  $J = 2.5$  Hz, 1H, 1-H), 8.11 (dd,  $J = 9.1$  and 2.5 Hz, 1H, 3-H).  $^{13}\text{C}$  NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$  19.2 (C-3'), 35.6 (C-6a), 36.9 (C-17b), 38.3 (C-2'), 54.2 (C-69, 56.0 (C-1'), 63.1 (C-7), 78.1 (C-12b), 97.4 (C-17a), 109.7 (C-4), 113.5 (C-16), 114.9 (C-12), 116.2 (C-12a), 118.0 (C-9), 119.3 (C-10), 119.3 (C-17c), 123.0 (C-1), 125.1 (C-3), 138.2 (C-2), 148.6 (C-8a), 151.6 (C-4a), 153.9 (C-11), 161.1 (C-15), 162.4 (C-13a), 179.4 (C-17). IR (KBr)  $\nu$ : 1216, 1364, 1498, 1604, 1715, 2925, 2969, 3005  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{25}\text{H}_{22}\text{N}_2\text{O}_7\text{Na}$  [ $\text{M} + \text{Na}$ ] $^+$  485.1319, found 485.1321.

The enantiomers were separated on a Chiralpak IC column (hexane/dichloromethane/methanol 30 : 63 : 7), and the *on-line* HPLC-ECD spectra were recorded.

1st eluting enantiomer:  $t_R = 7.29$  min (Chiralpak IC, hexane/dichloromethane/methanol 30 : 63 : 7). ECD [nm ( $\Delta\epsilon$ ), hexane/dichloromethane/methanol 30 : 63 : 7]: 389.5 (−18.95), 325.5 (0.30), 313.5 (−10.49), 275 (4.80), 230 (−64.54).

2nd eluting enantiomer:  $t_R = 21.45$  min (Chiralpak IC, hexane/dichloromethane/methanol 30 : 63 : 7). ECD [nm ( $\Delta\epsilon$ ), hexane/dichloromethane/methanol 30 : 63 : 7]: 387.5 (5.05), 326 (−0.56), 313.5 (2.47), 276 (−2.02), 227.5 (17.86).

**(6aS, 7R, 12bR, 17bS)- and (6aS, 7R, 12bR, 17bR)-11-methoxy-5,15-dimethyl-2-nitro-7-phenyl-5,17b-dihydro-6H,12bH,17H-chromeno[4',3':2,3]pyrano[3',4':5,6]pyrano[3,4-c]quinolin-17-one [(6aS, 7R, 12bR, 17bS)-4be and (6aS, 7R, 12bR, 17bR)-5be] and (6aS, 7R, 12bR, 17bS)-11-methoxy-5,15-dimethyl-2-nitro-7-phenyl-5,17b-dihydro-6H,12bH,17H-chromeno[4',3':2,3]pyrano[3',2':5,6]pyrano[3,4-c]quinolin-17-one [(6aS, 7R, 12bR, 17bS)-6be]**

The reaction of (*R*)-1b and 2e was carried out according to method A, and the crude product was purified by column chromatography (hexane/chloroform/ethyl acetate 8 : 8 : 1), affording (6aS, 7R, 12bR, 17bS)-4be as yellow powder (32%), (6aS, 7R, 12bR, 17bS)-6be as orange powder (8%) and (6aS, 7R, 12bR, 17bR)-5be as orange powder (14%).

Alternatively, the reaction was carried out at room temperature, affording (6aS, 7R, 12bR, 17bS)-4be as yellow powder (13%), (6aS, 7R, 12bR, 17bS)-6be as orange powder (14%) and (6aS, 7R, 12bR, 17bR)-5be as orange powder (31%).

**(6aS, 7R, 12bR, 17bS)-4be: yellow powder, mp 324–325 °C,  $R_f = 0.43$  (hexane/chloroform/ethyl acetate 4 : 4 : 1).** [ $\alpha$ ]<sub>D</sub> = +41 ( $c = 0.81$  g/100 ml in  $\text{CHCl}_3$ ). ECD [nm ( $\Delta\epsilon$ ), MeCN] (211  $\mu\text{g}/4$  ml): 372 (1.41), 323.5 (−0.56), 309.5 (−1.66), 293 (3.46), 269.5 (−2.09), 223 (17.38), 202.5 (−69.51), 195.5 (−32.93), 191.5 (−45.85).  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ ): 2.23 (s, 3H, 3''-H), 2.81 (s, 3H, 2''-H), 3.11 (d,  $J = 12.8$  Hz, 1H, 6-H<sub>a</sub>), 3.39 (d,  $J = 12.8$  Hz, 1H, 6-H<sub>b</sub>), 3.74 (s, 3H, 1''-H), 3.81 (s, 1H, 17b-H), 4.89 (s, 1H, 12b-

H), 4.93 (s, 1H, 7-H), 5.76 (s, 1H, 14-H), 6.42 (d,  $J = 9.2$  Hz, 1H, 4-H), 6.81 (s, 1H, 12-H), 6.92 (s, 2H, 9-H and 10-H), 7.31 (d,  $J = 6.9$  Hz, 1H, 2'-H and 6'-H), 7.31 (m, 3H, 3'-H, 4'-H and 5'-H), 7.86 (d,  $J = 9.2$  Hz, 1H, 3-H), 8.05 (s, 1H, 1-H).  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ ): 20.0 (C-3''), 32.0 (C-17b), 32.9 (C-6a), 39.8 (C-2''), 50.3 (C-6), 55.8 (C-1''), 72.8 (C-12b), 76.9 (C-7), 98.6 (C-17a), 100.0 (C-14), 110.2 (C-4), 115.1 (C-12), 118.1 (C-9 and C-10), 118.3 (C-12a), 122.4 (C-17c), 124.5 (C-3), 126.1 (C-1), 127.4 (C-2' and C-6'), 128.5 (C-3' and C-5'), 129.2 (C-4'), 134.0 (C-1'), 138.4 (C-2), 147.7 (C-8a), 148.4 (C-4a), 154.2 (C-11), 162.8 (C-13a and C-15), 165.1 (C-17). IR (KBr)  $\nu$ : 1038, 1232, 1261, 1313, 1497, 1574, 1698  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{31}\text{H}_{26}\text{N}_2\text{O}_7\text{Na}$  [ $\text{M} + \text{Na}$ ] $^+$  561.1632, found 561.1636.

**(6aS, 7R, 12bR, 17bS)-6be: orange powder, mp 167–170 °C,  $R_f = 0.13$  (hexane/chloroform/ethyl acetate 4 : 4 : 1).** [ $\alpha$ ]<sub>D</sub> = +13 ( $c = 0.80$  g/100 ml in  $\text{CHCl}_3$ ). ECD [nm ( $\Delta\epsilon$ ), MeCN] (204  $\mu\text{g}/4$  ml): 386.5 (1.71), 299 (−4.03), 237.5 (20.15), 208 (−36.62), 193.5 (−107.66).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.30 (s, 3H, 3''-H), 2.90 (s, 3H, 2''-H), 3.18 (d,  $J = 12.9$  Hz, 1H, 6-H<sub>a</sub>), 3.49 (d,  $J = 12.9$  Hz, 1H, 6-H<sub>b</sub>), 3.82 (s, 3H, 1''-H), 4.13 (s, 1H, 17b-H), 5.07 (s, 1H, 7-H), 5.18 (s, 1H, 12b-H), 6.30 (d,  $J = 1.4$  Hz, 1H, 16-H), 6.51 (d,  $J = 9.2$  Hz, 1H, 4-H), 6.88 (m, 1H, 12-H), 7.01 (m, 2H, 9-H and 10-H), 7.20–7.31 (m, 2H, 2'-H and 6'-H), 7.31–7.46 (m, 3H, 3'-H, 4'-H and 5'-H), 7.95 (dd,  $J = 9.2$  and 2.6 Hz, 1H, 3-H), 8.03 (dd,  $J = 2.6$  and 1.4 Hz, 1H, 1-H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  19.5 (C-3''), 31.6 (C-17b), 33.3 (C-6a), 39.9 (C-2''), 50.1 (C-6), 55.9 (C-1''), 75.7 (C-12b), 76.9 (C-7), 100.1 (C-17a), 110.3 (C-4), 113.1 (C-16), 114.9 (C-12), 117.4 (C-12a), 118.5 (C-10), 118.9 (C-9), 122.5 (C-17c), 124.6 (C-3), 126.6 (C-1), 127.5 (C-2' and C-6'), 128.6 (C-3' and C-5'), 129.3 (C-4'), 133.8 (C-1'), 138.7 (C-2), 147.9 (C-8a), 148.3 (C-4a), 154.5 (C-11), 161.1 (C-13a), 161.8 (C-15), 179.7 (C-17). IR (KBr)  $\nu$ : 1242, 1312, 1428, 1498, 1583, 1604, 1668, 2925  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{31}\text{H}_{26}\text{N}_2\text{O}_7\text{Na}$  [ $\text{M} + \text{Na}$ ] $^+$  561.1632, found 561.1636.

**(6aS, 7R, 12bR, 17bR)-5be: orange powder, mp 198–201 °C,  $R_f = 0.08$  (hexane/chloroform/ethyl acetate 4 : 4 : 1).** [ $\alpha$ ]<sub>D</sub> = −556 ( $c = 0.84$  g/100 ml in  $\text{CHCl}_3$ ). ECD [nm ( $\Delta\epsilon$ ), MeCN] (211  $\mu\text{g}/4$  ml): 401.5 (−5.77), 336.5 (−0.30), 309 (−9.31), 280 (5.38), 251 (−5.26), 232.5 (8.35), 207.5 (−105.70).  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ ): 2.34 (s, 3H, 3''-H), 2.87 (s, 3H, 2''-H), 3.16 (d,  $J = 12.4$  Hz, 1H, 6-H<sub>a</sub>), 3.70 (d,  $J = 12.5$  Hz, 1H, 6-H<sub>b</sub>), 3.83 (s, 3H, 1''-H), 4.14 (s, 1H, 17b-H), 4.76 (s, 1H, 12b-H), 5.27 (s, 1H, 7-H), 5.94 (m, 1H, 14-H), 5.97 (d,  $J = 9.2$  Hz, 1H, 4-H), 6.85–6.95 (m, 6H, 12-H and Ph), 6.98 (d,  $J = 3.0$  Hz, 1H, 9-H), 7.01 (m, 1H, 10-H), 7.47 (dd,  $J = 2.5$  and 1.2 Hz, 1H, 1-H), 7.57 (dd,  $J = 9.1$  Hz and 2.5 Hz, 1H, 3-H).  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ ): 19.9 (C-3''), 37.8 (C-2''), 37.9 (C-17b), 38.0 (C-6a), 53.4 (C-6), 55.9 (C-1''), 77.2 (C-7), 79.0 (C-12b), 96.9 (C-17a), 99.8 (C-14), 109.4 (C-4), 114.6 (C-12), 117.1 (C-17c), 117.7 (C-10), 118.7 (C-9), 122.4 (C-12a), 124.3 (C-3), 124.3 (C-1), 127.4 (C-2' and C-6'), 129.2 (C-3', C-4' and C-5'), 136.8 (C-1'), 137.3 (C-2), 148.7 (C-8a), 152.2 (C-11), 153.8 (C-4a), 162.6 (C-15), 162.7 (C-13a), 165.3 (C-17). IR (KBr)  $\nu$ : 1002, 1034, 1166, 1231, 1288, 1301, 1317, 1496, 1576, 1606, 1711, 2838, 2915  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{31}\text{H}_{26}\text{N}_2\text{O}_7\text{Na}$  [ $\text{M} + \text{Na}$ ] $^+$  561.1632, found 561.1635.

***rac*-(6aS\*, 12bR\*, 17bR\*)-11-methoxy-15-methyl-12bH,17H,17bH-chromeno[3',4':3,4]pyrano [3',4':5,6]pyrano**



[3,2-*c*]chromen-17-one [*rac*-(6*aS*<sup>\*</sup>, 12*bR*<sup>\*</sup>, 17*bR*<sup>\*</sup>)-4*ce*] and *rac*-(6*aS*<sup>\*</sup>, 12*bR*<sup>\*</sup>, 17*bR*<sup>\*</sup>)-11-methoxy-15-methyl-12*bH*,17*H*,17*bH*-chromeno[3',4':3,4]pyrano [3',2':5,6]pyrano[3,2-*c*]chromen-17-one [*rac*-(6*aS*<sup>\*</sup>, 12*bR*<sup>\*</sup>, 17*bR*<sup>\*</sup>)-5*ce*]. The reaction of **1c** and **2e** was carried out according to method B, and the crude product was purified by column chromatography (hexane/ethyl acetate 2 : 1), affording *rac*-(6*aS*<sup>\*</sup>, 12*bR*<sup>\*</sup>, 17*bR*<sup>\*</sup>)-4*ce* as pale yellow amorphous solid (10%) and *rac*-(6*aS*<sup>\*</sup>, 12*bR*<sup>\*</sup>, 17*bR*<sup>\*</sup>)-6*ce* as yellow powder (26%).

Alternatively, the reaction was carried out at 55 °C (there is no reaction at room temperature), affording *rac*-(6*aS*<sup>\*</sup>, 12*bR*<sup>\*</sup>, 17*bR*<sup>\*</sup>)-4*ce* as pale yellow amorphous solid (16%) and *rac*-(6*aS*<sup>\*</sup>, 12*bR*<sup>\*</sup>, 17*bR*<sup>\*</sup>)-6*ce* as yellow powder (6%).

***rac*-(6*aS*<sup>\*</sup>, 12*bR*<sup>\*</sup>, 17*bR*<sup>\*</sup>)-4*ce*: pale yellow amorphous solid,  $R_f = 0.45$  (hexane/ethyl acetate 1 : 1).** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  2.21 (s, 3H, 2'-H), 3.79 (s, 3H, 1'-H), 3.87 (d,  $J = 11.7$  Hz, 1H, 7-H<sub>a</sub>), 3.91 (d,  $J = 11.6$  Hz, 1H, 7-H<sub>b</sub>), 4.05 (d,  $J = 11.8$  Hz, 1H, 6-H<sub>a</sub>), 4.08 (s, 1H, 17b-H), 4.25 (d,  $J = 11.7$  Hz, 1H, 6-H<sub>b</sub>), 5.12 (s, 1H, 12b-H), 5.73 (s, 1H, 14-H), 6.81 (d,  $J = 8.1$  Hz, 1H, 4-H), 6.86 (m, 2H, 9-H and 12-H), 6.88–7.00 (m, 2H, 10-H and 2-H), 7.15 (t,  $J = 7.6$  Hz, 1H, 3-H), 7.52 (d,  $J = 7.8$  Hz, 1H, 1-H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  20.0 (C-2'), 30.6 (C-6a), 31.6 (C-17b), 55.9 (C-1'), 66.2 (C-7), 68.5 (C-6), 70.9 (C-12b), 98.9 (C-17a), 100.2 (C-14), 115.5 (C-12), 117.0 (C-4), 118.1 (C-9), 118.2 (C-12a), 118.5 (C-10), 122.2 (C-2), 122.7 (C-17c), 128.5 (C-3), 130.1 (C-1), 146.7 (C-8a), 152.4 (C-4a), 154.2 (C-11), 161.9 (C-15), 162.0 (C-13a), 166.1 (C-17). IR (KBr)  $\nu$ : 1046, 1215, 1269, 1489, 1501, 1583, 1697, 2833, 2875, 2925, 2953 cm<sup>-1</sup>; HRMS: calcd for C<sub>24</sub>H<sub>20</sub>O<sub>6</sub>Na [M + Na]<sup>+</sup> 427.1152, found 427.1152.

***rac*-(6*aS*<sup>\*</sup>, 12*bR*<sup>\*</sup>, 17*bR*<sup>\*</sup>)-6*ce*: yellow powder, mp 204–207 °C,  $R_f = 0.18$  (hexane/ethyl acetate 1 : 1).** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  2.20 (s, 3H, 2'-H), 3.79 (s, 3H, 1'-H), 3.92 (m, 2H, 7-H), 4.07 (d,  $J = 11.8$  Hz, 1H, 6-H<sub>a</sub>), 4.24 (d,  $J = 11.8$  Hz, 1H, 6-H<sub>b</sub>), 4.29 (s, 1H, 17b-H), 5.34 (s, 1H, 12b-H), 6.13 (s, 1H, 16-H), 6.80 (d,  $J = 8.1$  Hz, 1H, 4-H), 6.86 (m, 2H, 9-H and 12-H), 6.91 (d,  $J = 7.5$  Hz, 1H, 2-H), 6.95 (dd,  $J = 8.9$  and 3.0 Hz, 1H, 10-H), 7.14 (t,  $J = 7.6$  Hz, 1H, 3-H), 7.41 (d,  $J = 7.8$  Hz, 1H, 1-H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  19.3 (C-2'), 31.0 (C-17b), 31.0 (C-6a), 55.9 (C-1'), 66.1 (C-7), 68.2 (C-6), 73.7 (C-12b), 100.1 (C-17a), 112.7 (C-16), 115.2 (C-12), 116.9 (C-4), 117.3 (C-12a), 118.3 (C-9), 119.1 (C-10), 122.3 (C-2), 122.7 (C-17c), 128.4 (C-3), 130.4 (C-1), 146.8 (C-8a), 152.3 (C-4a), 154.3 (C-11), 160.7 (C-13a), 161.2 (C-15), 180.8 (C-17). IR (KBr)  $\nu$ : 1019, 1047, 1217, 1245, 1262, 1422, 1498, 1587, 1667 cm<sup>-1</sup>; HRMS: calcd for C<sub>24</sub>H<sub>20</sub>O<sub>6</sub>Na [M + Na]<sup>+</sup> 427.1152, found 427.1154.

***rac*-(6*aS*<sup>\*</sup>, 12*bR*<sup>\*</sup>, 17*bR*<sup>\*</sup>)- and *rac*-(6*aS*<sup>\*</sup>, 12*bR*<sup>\*</sup>, 17*bS*<sup>\*</sup>)-11-methoxy-5,15,16-trimethyl-2-nitro-5,6,16,17b-tetrahydro-12*bH*,17*H*-chromeno[4',3':2,3]pyrido[3',4':5,6]pyrano[3,4-*c*]quinolin-17-one [*rac*-(6*aS*<sup>\*</sup>, 12*bR*<sup>\*</sup>, 17*bR*<sup>\*</sup>)-4*af* and *rac*-(6*aS*<sup>\*</sup>, 12*bR*<sup>\*</sup>, 17*bS*<sup>\*</sup>)-5*af*] and *rac*-(6*aS*<sup>\*</sup>, 12*bR*<sup>\*</sup>, 17*bR*<sup>\*</sup>)- and *rac*-(6*aS*<sup>\*</sup>, 12*bR*<sup>\*</sup>, 17*bS*<sup>\*</sup>)-11-methoxy-5,14,15-trimethyl-2-nitro-5,6,14,17b-tetrahydro-12*bH*,17*H*-chromeno[4',3':2,3]pyrido[3',2':5,6]pyrano[3,4-*c*]quinolin-17-one [*rac*-(6*aS*<sup>\*</sup>, 12*bR*<sup>\*</sup>, 17*bR*<sup>\*</sup>)-6*af* and *rac*-(6*aS*<sup>\*</sup>, 12*bR*<sup>\*</sup>, 17*bS*<sup>\*</sup>)-7*af*]. The reaction of **1a** and **2f** was carried out according to method A, and the crude product was purified by column chromatography (hexane/dichloromethane/**

methanol 15 : 9 : 1), affording *rac*-(6*aS*<sup>\*</sup>, 12*bR*<sup>\*</sup>, 17*bS*<sup>\*</sup>)-4*af* as yellow powder (31%), *rac*-(6*aS*<sup>\*</sup>, 12*bR*<sup>\*</sup>, 17*bS*<sup>\*</sup>)-6*af* as yellow powder (31%), *rac*-(6*aS*<sup>\*</sup>, 12*bR*<sup>\*</sup>, 17*bS*<sup>\*</sup>)-5*af* as yellow powder (13%) and *rac*-(6*aS*<sup>\*</sup>, 12*bR*<sup>\*</sup>, 17*bS*<sup>\*</sup>)-7*af* as yellow powder (7%).

***rac*-(6*aS*<sup>\*</sup>, 12*bR*<sup>\*</sup>, 17*bS*<sup>\*</sup>)-4*af*: yellow powder, mp 289–292 °C,  $R_f = 0.41$  (toluene/methanol 4 : 1).** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  2.33 (s, 3H, 4'-H), 2.95 (s, 3H, 2'-H), 3.23 (d,  $J = 13.1$  Hz, 1H, 6-H<sub>a</sub>), 3.62 (s, 3H, 3'-H), 3.65 (d,  $J = 13.1$  Hz, 1H, 6-H<sub>b</sub>), 3.80 (s, 3H, 1'-H), 3.87 (s, 2H, 7-H), 4.25 (s, 1H, 17b-H), 4.82 (s, 1H, 12b-H), 5.74 (s, 1H, 14-H), 6.55 (d,  $J = 9.2$  Hz, 1H, 4-H), 6.81–6.90 (m, 2H, 9-H and 12-H), 6.94 (dd,  $J = 9.0$  and 3.0 Hz, 1H, 10-H), 8.00 (dd,  $J = 9.1$  and 2.7 Hz, 1H, 3-H), 8.07 (s, 1H, 1-H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  21.1 (C-4'), 30.6 (C-6a), 31.4 (C-3'), 33.3 (C-17b), 39.7 (C-2'), 55.0 (C-6), 55.8 (C-1'), 68.0 (C-7), 70.6 (C-12b), 100.1 (C-14), 104.5 (C-17a), 110.0 (C-4), 115.5 (C-12), 117.9 (C-10), 117.9 (C-9), 119.4 (C-12a), 122.4 (C-17c), 124.6 (C-3), 126.7 (C-1), 138.5 (C-2), 146.3 (C-15), 146.7 (C-8a), 149.2 (C-4a), 154.0 (C-11), 158.0 (C-13a), 164.8 (C-17). IR (KBr)  $\nu$ : 1215, 1229, 1495, 1545, 1644, 1717, 1738, 2923, 2969 cm<sup>-1</sup>; HRMS: calcd for C<sub>32</sub>H<sub>29</sub>N<sub>3</sub>O<sub>6</sub>Na [M + Na]<sup>+</sup> 498.1636, found 498.1636.

***rac*-(6*aS*<sup>\*</sup>, 12*bR*<sup>\*</sup>, 17*bR*<sup>\*</sup>)-5*af*: yellow powder, turns amorphous above 200 °C,  $R_f = 0.38$  (toluene/methanol 4 : 1).** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  2.36 (s, 3H, 4'-H), 3.03 (s, 3H, 2'-H), 3.15 (d,  $J = 11.7$  Hz, 1H, 6-H<sub>a</sub>), 3.19 (d,  $J = 11.7$  Hz, 1H, 6-H<sub>b</sub>), 3.29 (dd,  $J = 11.6$  and 1.5 Hz, 1H, 7-H<sub>a</sub>), 3.56 (s, 3H, 3'-H), 3.80 (s, 3H, 1'-H), 3.86 (d,  $J = 11.5$  Hz, 1H, 7-H<sub>b</sub>), 4.07 (s, 1H, 17b-H), 4.60 (d,  $J = 1.2$  Hz, 1H, 12b-H), 5.85 (s, 1H, 14-H), 6.63 (d,  $J = 9.1$  Hz, 1H, 4-H), 6.76–6.84 (m, 2H, 9-H and 12-H), 6.92 (dd,  $J = 8.9$  and 3.0 Hz, 1H, 10-H), 7.69 (d,  $J = 2.5$  Hz, 1H, 1-H), 8.09 (dd,  $J = 9.1$  and 2.5 Hz, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  21.0 (C-4'), 31.3 (C-3'), 35.3 (C-6a), 37.6 (C-17b), 38.2 (C-2'), 54.8 (C-6), 56.0 (C-1'), 63.5 (C-7), 75.0 (C-12b), 100.2 (C-14), 102.1 (C-17a), 109.6 (C-4), 115.0 (C-9), 117.6 (C-12), 118.1 (C-12a), 118.4 (C-10), 120.1 (C-17c), 123.1 (C-1), 124.7 (C-3), 137.9 (C-2), 146.3 (C-15), 148.5 (C-8a), 152.1 (C-4a), 153.7 (C-11), 160.8 (C-13a), 163.4 (C-17). IR (KBr)  $\nu$ : 1216, 1227, 1365, 1498, 1571, 1636, 1717, 1738, 2926, 2970, 3003 cm<sup>-1</sup>; HRMS: calcd for C<sub>32</sub>H<sub>29</sub>N<sub>3</sub>O<sub>6</sub>Na [M + Na]<sup>+</sup> 498.1636, found 498.1636.

***rac*-(6*aS*<sup>\*</sup>, 12*bR*<sup>\*</sup>, 17*bS*<sup>\*</sup>)-6*af*: yellow powder, mp 267–270 °C,  $R_f = 0.31$  (toluene/methanol 4 : 1).** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  2.31 (s, 3H, 4'-H), 2.97 (s, 3H, 2'-H), 3.24 (d,  $J = 13.2$  Hz, 1H, 6-H<sub>a</sub>), 3.35 (s, 3H, 3'-H), 3.66 (d,  $J = 13.2$  Hz, 1H, 6-H<sub>b</sub>), 3.83 (m, 4H, 1'-H and 7-H<sub>a</sub>), 3.91 (dd,  $J = 11.5$  and 1.0 Hz, 1H, 7-H<sub>b</sub>), 4.42 (s, 1H, 17b-H), 5.05 (s, 1H, 12b-H), 6.30 (s, 1H, 16-H), 6.56 (d,  $J = 9.1$  Hz, 1H, 4-H), 6.85–6.93 (m, 2H, 9-H and 12-H), 6.97 (dd,  $J = 8.9$  and 3.0 Hz, 1H, 10-H), 8.00 (dd,  $J = 9.1$  and 2.4 Hz, 1H, 3-H), 8.03 (bs, 1H, 1-H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  20.4 (C-4'), 30.8 (C-6a), 31.9 (C-3'), 32.4 (C-17b), 39.7 (C-2'), 54.7 (C-6), 55.9 (C-1'), 68.0 (C-7), 73.3 (C-12b), 105.0 (C-17a), 110.0 (C-4), 115.0 (C-16), 115.5 (C-12), 117.9 (C-10), 118.3 (C-9), 118.6 (C-12a), 121.9 (C-17c), 124.7 (C-3), 126.8 (C-1), 138.6 (C-2), 145.7 (C-15), 146.9 (C-8a), 149.1 (C-4a), 151.4 (C-13a), 154.2 (C-11), 178.1 (C-17). IR (KBr)  $\nu$ : 1234, 1297, 1316, 1494, 1638 cm<sup>-1</sup>; HRMS: calcd for C<sub>32</sub>H<sub>29</sub>N<sub>3</sub>O<sub>6</sub>Na [M + Na]<sup>+</sup> 498.1636, found 498.1638.

***rac*-(6*aS*<sup>\*</sup>, 12*bR*<sup>\*</sup>, 17*bR*<sup>\*</sup>)-7*af*: yellow powder, turns amorphous above 150 °C,  $R_f = 0.29$  (toluene/methanol 4 : 1).** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  2.34 (s, 3H, 4'-H), 3.02 (s, 3H, 2'-H), 3.16 (d,  $J =$



= 11.2 Hz, 1H, 6-H<sub>a</sub>), 3.22 (d, *J* = 11.2 Hz, 1H, 6-H<sub>b</sub>), 3.32 (d, *J* = 11.9 Hz, 1H, 7-H<sub>a</sub>), 3.45 (s, 3H, 3'-H), 3.81 (s, 3H, 1'-H), 3.85 (d, *J* = 11.9 Hz, 1H, 7-H<sub>b</sub>), 4.20 (s, 1H, 17b-H), 4.79 (s, 1H, 12b-H), 6.27 (s, 1H, 16-H), 6.61 (d, *J* = 9.1 Hz, 1H, 4-H), 6.79–6.87 (m, 2H, 9-H and 12-H), 6.97 (dd, *J* = 9.0 and 3.0 Hz, 1H, 10-H), 7.68 (d, *J* = 2.5 Hz, 1H, 1-H), 8.08 (dd, *J* = 9.1 and 2.5 Hz, 1H, 3-H). <sup>13</sup>C NMR (90 MHz, CDCl<sub>3</sub>) δ 20.2 (C-4'), 32.0 (C-3'), 35.2 (C-6a), 37.7 (C-17b), 38.3 (C-2'), 54.5 (C-6), 56.0 (C-1'), 63.5 (C-7), 76.9 (C-12b) 102.2 (C-17a), 109.6 (C-4), 115.3 (C-12), 115.8 (C-16), 117.2 (C-12a), 117.8 (C-9), 118.4 (C-10), 119.9 (C-17c), 123.2 (C-1), 124.8 (C-3), 138.2 (C-2), 145.3 (C-15), 148.8 (C-8a), 151.9 (C-4a), 153.7 (C-11), 177.9 (C-17). IR (KBr) *ν*: 1217, 1364, 1603, 1639, 1716, 1738, 2925, 2970 cm<sup>-1</sup>; HRMS: calcd for C<sub>32</sub>H<sub>29</sub>N<sub>3</sub>O<sub>6</sub>Na [M + Na]<sup>+</sup> 498.1636, found 498.1639.

***rac*-(6aS\*, 7R\*, 12bR\*, 17bS\*)- and (6aS\*, 7R\*, 12bR\*, 17bR\*)-11-methoxy-5,15,16-trimethyl-2-nitro-7-phenyl-5,6,16,17b-tetrahydro-12bH,17H-chromeno[4',3':2,3]pyrido [3',4':5,6]pyrano[3,4-c]quinolin-17-one [rac-(6aS\*, 7R\*, 12bR\*, 17bS\*)-4bf and rac-(6aS\*, 7R\*, 12bR\*, 17bR\*)-5bf] and rac-(6aS\*, 7R\*, 12bR\*, 17bS\*)-11-methoxy-5,14,15-trimethyl-2-nitro-7-phenyl-5,6,14,17b-tetrahydro-12bH,17H-chromeno [4',3':2,3]pyrido[3',2':5,6]pyrano[3,4-c]quinolin-17-one [rac-(6aS\*, 7R\*, 12bR\*, 17bS\*)-6bf].** The reaction of *rac*-1b and 2f was carried out according to method A, and the crude product was purified by column chromatography (toluene/ethyl acetate 4 : 1), affording *rac*-(6aS\*, 7R\*, 12bR\*, 17bS\*)-4bf as yellow powder (29%), *rac*-(6aS\*, 7R\*, 12bR\*, 17bR\*)-5bf as yellow powder (29%) and *rac*-(6aS\*, 7R\*, 12bR\*, 17bS\*)-6bf as yellow powder (13%).

***rac*-(6aS\*, 7R\*, 12bR\*, 17bS\*)-4bf: yellow powder, mp 259–262 °C, R<sub>f</sub> = 0.25 (toluene/ethyl acetate 2 : 1).** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.37 (s, 3H, 4''-H), 2.87 (s, 3H, 2''-H), 3.14 (d, *J* = 12.8 Hz, 1H, 6-H<sub>a</sub>), 3.45 (d, *J* = 12.8 Hz, 1H, 6-H<sub>b</sub>), 3.69 (s, 3H, 3''-H), 3.81 (s, 3H, 1''-H), 4.10 (s, 1H, 17b-H), 4.87 (s, 1H, 12b-H), 5.05 (s, 1H, 7-H), 5.77 (s, 1H, 14-H), 6.47 (d, *J* = 9.1 Hz, 1H, 4-H), 6.89 (s, 1H, 12-H), 6.98 (s, 2H, 9-H and 10-H), 7.26 (m, 2H, 2'-H and 6'-H), 7.30–7.46 (m, 3H, 3'-H, 4'-H and 5'-H), 7.93 (d, *J* = 9.1 Hz, 1H, 3-H), 8.09 (s, 1H, 1-H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 21.2 (C-4''), 31.6 (C-3''), 32.7 (C-17b), 32.9 (C-6a), 39.8 (C-2''), 50.6 (C-6), 55.9 (C-1''), 71.5 (C-12b), 77.0 (C-7), 99.8 (C-14), 104.8 (C-17a), 110.0 (C-4), 115.2 (C-12), 118.0 (C-10), 118.0 (C-9), 119.4 (C-12a), 123.4 (C-17c), 124.3 (C-3), 126.9 (C-1), 127.5 (C-2' and C-6'), 128.5 (C-3' and C-5'), 128.9 (C-4'), 134.6 (C-1'), 138.5 (C-2), 146.6 (C-15), 147.8 (C-8a), 148.7 (C-4a), 154.2 (C-11), 158.5 (C-13a), 164.2 (C-17). IR (KBr) *ν*: 1226, 1364, 1499, 1573, 1643, 1715, 2970, 3005 cm<sup>-1</sup>; HRMS: calcd for C<sub>32</sub>H<sub>29</sub>N<sub>3</sub>O<sub>6</sub>Na [M + Na]<sup>+</sup> 574.1949, found 574.1954.

***rac*-(6aS\*, 7R\*, 12bR\*, 17bR\*)-5bf: yellow powder, mp 242–244 °C, R<sub>f</sub> = 0.12 (toluene/ethyl acetate 2 : 1).** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.40 (s, 3H, 4''-H), 2.87 (s, 3H, 2''-H), 3.17 (d, *J* = 12.3 Hz, 1H, 6-H<sub>a</sub>), 3.56 (s, 3H, 3''-H), 3.67 (dd, *J* = 12.3 and 1.2 Hz, 1H, 6-H<sub>b</sub>), 3.82 (s, 3H, 1''-H), 4.20 (s, 1H, 17b-H), 4.62 (s, 1H, 12b-H), 5.37 (s, 1H, 7-H), 5.91 (m, 2H, 4-H and 14-H), 6.47–7.00 (m, 8H, 9-H, 10-H, 12-H and Ph), 7.42 (dd, *J* = 2.6 and 1.2 Hz, 1H, 1-H), 7.54 (dd, *J* = 9.1 and 2.6 Hz, 1H, 3-H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 21.0 (C-4''), 31.3 (C-3''), 37.8 (C-2''), 38.0 (C-6a), 39.3 (C-17b), 53.9 (C-6), 56.0 (C-1''), 77.6 (C-7), 78.2 (C-12b),

100.0 (C-14), 102.7 (C-17a), 109.3 (C-4), 114.6 (C-12), 117.6 (C-9), 118.0 (C-12a), 118.5 (C-10), 118.7 (C-17c), 124.2 (C-3), 125.2 (C-1), 128.2 (C-3' and C-5'), 137.3 (C-2), 137.5 (C-1'), 146.4 (C-15), 148.8 (C-8a), 152.6 (C-4a), 153.8 (C-11), 161.4 (C-13a), 163.3 (C-17). IR (KBr) *ν*: 1224, 1284, 1365, 1494, 1644, 1715, 2927, 2969, 3003 cm<sup>-1</sup>; HRMS: calcd for C<sub>32</sub>H<sub>29</sub>N<sub>3</sub>O<sub>6</sub>Na [M + Na]<sup>+</sup> 574.1949, found 574.1956.

***rac*-(6aS\*, 7R\*, 12bR\*, 17bS\*)-6bf: yellow powder, mp 230–232 °C, R<sub>f</sub> = 0.07 (toluene/ethyl acetate 2 : 1).** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.34 (s, 3H, 4''-H), 2.88 (s, 3H, 2''-H), 3.13 (d, *J* = 12.9 Hz, 1H, 6-H<sub>a</sub>), 3.39 (s, 3H, 3''-H), 3.48 (d, *J* = 12.9 Hz, 1H, 6-H<sub>b</sub>), 3.83 (s, 3H, 1''-H), 4.27 (s, 1H, 17b-H), 5.03 (s, 1H, 7-H), 5.08 (s, 1H, 12b-H), 6.38 (s, 1H, 16-H), 6.47 (d, *J* = 9.2 Hz, 1H, 4-H), 6.92 (s, 1H, 12-H), 7.00 (m, 2H, 9-H and 10-H), 7.29 (d, *J* = 7.2 Hz, 2H, 2'-H and 6'-H), 7.35 (d, *J* = 7.2 Hz, 1H, 4'-H), 7.40 (m, 2H, 3'-H and 5'-H), 7.93 (dd, *J* = 9.2 and 2.5 Hz, 1H, 3-H), 8.05 (dd, *J* = 2.5 and 1.2 Hz, 1H, 1-H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 20.5 (C-4''), 31.9 (C-17b and C-3''), 33.0 (C-6a), 39.8 (C-2''), 50.3 (C-6), 56.0 (C-1''), 74.2 (C-12b), 77.0 (C-7), 105.2 (C-17a), 109.9 (C-4), 115.4 (C-12), 115.5 (C-16), 118.0 (C-10), 118.3 (C-9), 118.6 (C-12a), 123.0 (C-17c), 124.4 (C-3), 127.0 (C-1), 127.6 (C-2' and C-6'), 128.6 (C-3' and C-5'), 129.1 (C-4'), 134.0 (C-1'), 138.7 (C-2), 145.7 (C-15), 148.0 (C-8a), 148.5 (C-4a), 151.9 (C-13a), 154.3 (C-11), 177.6 (C-17). IR (KBr) *ν*: 1224, 1364, 1494, 1644, 1714, 2924, 2969, 3005 cm<sup>-1</sup>; HRMS: calcd for C<sub>32</sub>H<sub>29</sub>N<sub>3</sub>O<sub>6</sub>Na [M + Na]<sup>+</sup> 574.1949, found 574.1954.

***rac*-(6aS\*, 12bR\*, 17bR\*)-11-methoxy-15,16-dimethyl-16,17b-dihydro-12bH,17H-dichromeno[3',4':5,6; 4'',3'':4,5]pyrano[3,2-c]pyridin-17-one [rac-(6aS\*, 12bR\*, 17bR\*)-4cf].** The reaction of 1c and 2f was carried out according to method B, and the crude product was purified by column chromatography (hexane/ethyl acetate 2 : 1), affording *rac*-(6aS\*, 12bR\*, 17bR\*)-4cf as white powder (11%).

***rac*-(6aS\*, 12bR\*, 17bR\*)-4cf: white powder, mp 293–296 °C, R<sub>f</sub> = 0.06 (hexane/ethyl acetate 2 : 1).** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.28 (s, 3H, 3'-H), 3.58 (s, 3H, 2'-H), 3.79 (s, 3H, 1'-H), 3.83 (dd, *J* = 11.6 and 1.5 Hz, 1H, 7-H<sub>a</sub>), 3.90 (d, *J* = 11.6 Hz, 1H, 7-H<sub>b</sub>), 4.09 (d, *J* = 11.7 Hz, 1H, 6-H<sub>a</sub>), 4.20–4.31 (m, 2H, 6-H<sub>b</sub> and 17b-H), 5.06 (d, *J* = 1.5 Hz, 1H, 12b-H), 5.71 (s, 1H, 14-H), 6.79 (dd, *J* = 7.7 and 1.0 Hz, 1H, 4-H), 6.83 (d, *J* = 8.8 Hz, 1H, 9-H), 6.85–6.96 (m, 3H, 2-H, 10-H and 12-H), 7.11 (t, *J* = 7.7 Hz, 1H, 3-H), 7.48 (d, *J* = 7.8 Hz, 1H, 1-H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 21.0 (C-3'), 30.4 (C-6a), 31.3 (C-2'), 32.2 (C-17b), 55.8 (C-1'), 66.4 (C-7), 68.7 (C-6), 69.6 (C-12b), 100.3 (C-14), 105.1 (C-17a), 115.5 (C-2), 116.7 (C-4), 117.9 (C-9), 118.1 (C-10), 119.2 (C-12a), 121.9 (C-12), 123.5 (C-17c), 128.0 (C-3), 130.5 (C-1), 145.5 (C-15), 146.6 (C-8a), 152.4 (C-4a), 154.0 (C-11), 158.0 (C-13a), 165.2 (C-17). IR (KBr) *ν*: 1216, 1227, 1276, 1365, 1497, 1577, 1643, 1715, 2938, 2970 cm<sup>-1</sup>; HRMS: calcd for C<sub>25</sub>H<sub>23</sub>NO<sub>5</sub>Na [M + Na]<sup>+</sup> 440.1468, found 440.1468.

### Domino Knoevenagel-IMHDA reactions of 5,6-dihydro-2H-pyran derivatives 8a–b

***rac*-(6aS\*, 10aS\*, 17bS\*)-5,13-dimethyl-2-nitro-5,10,10a,17b-tetrahydro-6H,9H,17H-chromeno[3',4':5,6]pyrano[4',3':2,3]pyrano[3,4-c]quinolin-17-one [rac-(6aS\*, 10aS\*, 17bS\*)-10aa].** The



reaction of **8a** and **2a** was carried out according to method A, and the crude product was purified by column chromatography (hexane/ethyl acetate 1 : 2), affording *rac*-(**6aS\***, **10aS\***, **17bS\***)-**10aa** as yellow amorphous solid (44%).  $R_f = 0.17$  (hexane/ethyl acetate 1 : 1).

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.09 (d,  $J = 14.6$  Hz, 1H, 10- $\text{H}_a$ ), 2.27 (m, 1H, 10- $\text{H}_b$ ), 2.41 (s, 3H, 2'-H), 3.13 (s, 3H, 1'-H), 3.42 (d,  $J = 12.0$  Hz, 1H, 7- $\text{H}_a$ ), 3.50 (d,  $J = 11.7$  Hz, 1H, 7- $\text{H}_b$ ), 3.55 (d,  $J = 13.1$  Hz, 1H, 6- $\text{H}_a$ ), 3.68 (t,  $J = 11.4$  Hz, 1H, 9- $\text{H}_a$ ), 3.86 (d,  $J = 13.2$  Hz, 1H, 6- $\text{H}_b$ ), 3.88–3.98 (m, 2H, 17b-H and 9- $\text{H}_b$ ), 4.52 (s, 1H, 10a-H), 6.55 (d,  $J = 9.2$  Hz, 1H, 4-H), 7.28 (d,  $J = 8.4$  Hz, 1H, 15-H), 7.38 (d,  $J = 8.4$  Hz, 1H, 14-H), 7.57 (s, 1H, 12-H), 7.93 (dd,  $J = 9.1$  and 2.4 Hz, 1H, 3-H), 8.10 (s, 1H, 1-H).  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  20.9 (C-2'), 27.7 (C-10), 31.6 (C-6a), 34.1 (C-17b), 39.8 (C-1'), 55.9 (C-6), 62.8 (C-9), 69.4 (C-7), 72.1 (C-10a), 101.3 (C-17a), 110.3 (C-4), 114.4 (C-11b), 116.7 (C-15), 121.8 (C-17c), 122.3 (C-12), 124.5 (C-3), 126.2 (C-1), 133.5 (C-14), 134.0 (C-13), 138.3 (C-2), 149.1 (C-15a), 151.0 (C-4a), 159.0 (C-17), 164.0 (C-11a). IR (KBr)  $\nu$ : 1305, 1319, 1497, 1581, 1630, 1702, 2859, 2925  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{24}\text{H}_{22}\text{N}_2\text{O}_6\text{Na}$   $[\text{M} + \text{Na}]^+$  457.1370, found 457.1370.

*rac*-(**6aS\***, **10aS\***, **17bS\***)-**5,13,14-trimethyl-2-nitro-5,10,10a,17b-tetrahydro-6H,9H,17H-chromeno[3',4':5,6]pyrano[4',3':2,3]pyrano[3,4-c]quinolin-17-one [rac-(6aS\*, 10aS\*, 17bS\*)-10ab]**. The reaction of **8a** and **2b** was carried out according to method A. The product crystallized upon cooling to room temperature, the precipitate was filtered and washed with cold ether, affording *rac*-(**6aS\***, **10aS\***, **17bS\***)-**10ab** as yellow powder (57%), mp 234–236 °C.  $R_f = 0.38$  (hexane/ethyl acetate 1 : 2).

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.09 (d,  $J = 14.7$  Hz, 1H, 10- $\text{H}_a$ ), 2.21–2.30 (m, 1H, 10- $\text{H}_b$ ), 2.32 (s, 3H, 3'), 2.37 (s, 3H, 2'-H), 3.13 (s, 3H, 1'-H), 3.42 (d,  $J = 12.1$  Hz, 1H, 7- $\text{H}_a$ ), 3.48 (d,  $J = 12.1$  Hz, 1H, 7- $\text{H}_b$ ), 3.54 (d,  $J = 13.1$  Hz, 1H, 6- $\text{H}_a$ ), 3.69 (t,  $J = 11.4$  Hz, 1H, 9- $\text{H}_a$ ), 3.85 (d,  $J = 13.2$  Hz, 1H, 6- $\text{H}_b$ ), 3.90–4.00 (m, 2H, 17b-H and 9- $\text{H}_b$ ), 4.52 (s, 1H, 10a-H), 6.56 (d,  $J = 9.2$  Hz, 1H, 4-H), 7.17 (s, 1H, 15-H), 7.51 (s, 1H, 12-H), 7.95 (dd,  $J = 9.2$  and 2.5 Hz, 1H, 3-H), 8.12 (s, 1H, 1-H).  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  19.3 (C-3'), 20.3 (C-2'), 27.7 (C-10), 31.7 (C-6a), 34.1 (C-17b), 39.8 (C-1'), 56.0 (C-6), 62.8 (C-9), 69.4 (C-7), 71.9 (C-10a), 100.4 (C-17a), 110.3 (C-4), 112.3 (C-11b), 117.4 (C-15), 122.0 (C-17c), 122.6 (C-12), 124.5 (C-3), 126.5 (C-1), 133.1 (C-13), 138.4 (C-2), 142.6 (C-14), 149.1 (C-15a), 151.3 (C-4a), 159.2 (C-17), 164.2 (C-11a). IR (KBr)  $\nu$ : 1289, 1305, 1629, 1697, 2869, 2927  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{25}\text{H}_{24}\text{N}_2\text{O}_6\text{Na}$   $[\text{M} + \text{Na}]^+$  471.1527, found 471.1526.

*rac*-(**6aS\***, **10aS\***, **17bS\***)-**12,13,14-trimethoxy-5-methyl-2-nitro-5,10,10a,17b-tetrahydro-6H,9H,17H-chromeno[3',4':5,6]pyrano[4',3':2,3]pyrano[3,4-c]quinolin-17-one [rac-(6aS\*, 10aS\*, 17bS\*)-10ac]**. The reaction of **8a** and **2c** was carried out according to method A, and the crude product was purified by column chromatography (hexane/ethyl acetate 1 : 2), affording *rac*-(**6aS\***, **10aS\***, **17bS\***)-**10ac** as yellow amorphous solid (77%).  $R_f = 0.23$  (hexane/ethyl acetate 1 : 2).

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.00 (d,  $J = 14.1$  Hz, 1H, 10- $\text{H}_a$ ), 2.23 (s, 1H, 10- $\text{H}_b$ ), 3.09 (s, 3H, 4'-H), 3.38–3.59 (m, 3H, 7-H and 6- $\text{H}_a$ ), 3.59–3.74 (m, 1H, 9- $\text{H}_a$ ), 3.74–3.86 (m, 7H, 1'-H, 2'-H and 6- $\text{H}_b$ ), 3.91 (s, 5H, 3'-H, 17b-H and 9- $\text{H}_b$ ), 4.49 (s, 1H, 10a-H),

6.52 (d,  $J = 8.9$  Hz, 1H, 4-H), 6.71 (s, 1H, 15-H), 7.90 (d,  $J = 8.9$  Hz, 1H, 3-H), 8.00 (s, 1H, 1-H).  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  27.8 (C-10), 31.1 (C-6a), 34.0 (C-17b), 39.8 (C-4'), 55.9 (C-6), 56.4 (C-1'), 61.3 (C-2'), 62.1 (C-3'), 62.9 (C-9), 69.4 (C-7), 71.9 (C-10a), 96.7 (C-15), 98.9 (C-17a), 103.0 (C-11b), 110.3 (C-4), 122.1 (C-17c), 124.6 (C-3), 126.5 (C-1), 138.3 (C-2), 140.4 (C-13), 149.1 (C-4a), 150.8 (C-12), 157.0 (C-14), 160.8 (C-11a), 163.8 (C-17). IR (KBr)  $\nu$ : 1094, 1291, 1607, 1700, 2856, 2925  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{26}\text{H}_{26}\text{N}_2\text{O}_9\text{Na}$   $[\text{M} + \text{Na}]^+$  533.1531 found 533.1530.

*rac*-(**6aS\***, **10aS\***, **17bS\***)-**12,13,14-trimethoxy-5-methyl-2-(trifluoromethyl)-5,10,10a,17b-tetrahydro-6H,9H,17H-chromeno[3',4':5,6]pyrano[4',3':2,3]pyrano[3,4-c]quinolin-17-one [rac-(6aS\*, 10aS\*, 17bS\*)-10bc]**. The reaction of **8b** and **2c** was carried out according to method A, and the crude product was purified by column chromatography (hexane/ethyl acetate 1 : 1), affording *rac*-(**6aS\***, **10aS\***, **17bS\***)-**10bc** as white powder (52%), mp 232–235 °C.  $R_f = 0.28$  (hexane/ethyl acetate 1 : 2).

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.01 (d,  $J = 14.7$  Hz, 1H, 10- $\text{H}_a$ ), 2.23 (m, 1H, 10- $\text{H}_b$ ), 3.02 (s, 3H, 4'-H), 3.39 (d,  $J = 12.5$  Hz, 1H, 6- $\text{H}_a$ ), 3.46 (s, 2H, 7-H), 3.68 (d,  $J = 12.5$  Hz, 1H, 6- $\text{H}_b$ ), 3.73 (m, 1H, 9- $\text{H}_a$ ), 3.85 (s, 3H, 2'-H), 3.87 (s, 4H, 1'-H, 17b-H), 3.91 (d,  $J = 5.2$  Hz, 1H, 9- $\text{H}_b$ ), 3.94 (s, 3H, 3'-H), 4.58 (s, 1H, 10a-H), 6.67 (d,  $J = 8.6$  Hz, 1H, 4-H), 6.73 (s, 1H, 15-H), 7.33 (d,  $J = 8.5$  Hz, 1H, 3-H), 7.44 (s, 1H, 1-H).  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  27.7 (C-10), 31.7 (C-6a), 34.3 (C-17b), 39.6 (C-4'), 56.3 (C-3'), 56.3 (C-6), 61.2 (C-2'), 62.0 (C-1'), 62.8 (C-9), 69.4 (C-7), 72.1 (C-10a), 96.6 (C-15), 99.1 (C-17a), 103.1 (C-11b), 110.0 (CF<sub>3</sub>), 111.2 (C-4), 119.7 (q,  $J = 32.3$  Hz, C-2), 123.0 (C-17c), 123.4 (CF<sub>3</sub>), 124.93 (d,  $J = 3.5$  Hz, C-3), 126.1 (CF<sub>3</sub>), 126.83 (d,  $J = 3.2$  Hz, C-1), 140.3 (C-13), 147.2 (C-4a), 150.7 (C-15a), 150.8 (C-12), 156.8 (C-14), 160.8 (C-11a), 163.9 (C-17). IR (KBr)  $\nu$ : 1099, 1330, 1399, 1606, 1700, 2940  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{27}\text{H}_{26}\text{F}_3\text{NO}_7\text{Na}$   $[\text{M} + \text{Na}]^+$  556.1554 found 556.1554.

*rac*-(**6aS\***, **10aS\***, **17bS\***)-**5-methyl-2-nitro-5,10,10a,17b-tetrahydro-6H,9H,17H-chromeno [3',4':5,6]pyrano[4',3':2,3]pyrano[3,4-c]quinolin-17-one [rac-(6aS\*, 10aS\*, 17bS\*)-10ad]**. The reaction of **8a** and **2d** was carried out according to method C, and the crude product was purified by column chromatography (hexane/ethyl acetate 1 : 2), affording *rac*-(**6aS\***, **10aS\***, **17bS\***)-**10ad** as yellow powder (42%), mp 244–246 °C.  $R_f = 0.29$  (hexane/ethyl acetate 1 : 2).

$^1\text{H NMR}$  (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  1.84 (s, 2H, 10-H), 2.39 (s, 3H, 1'-H), 3.18 (s, 2H, 6-H), 3.40 (m, 2H, 7-H), 3.46 (s, 2H, 9-H), 5.40 (s, 1H, 10a-H), 6.49 (s, 1H, 17b-H), 7.23 (d,  $J = 9.0$  Hz, 1H, 4-H), 7.27 (t,  $J = 7.6$  Hz, 1H, 13-H), 7.43 (d,  $J = 8.2$  Hz, 1H, 15-H), 7.57 (t,  $J = 7.7$  Hz, 1H, 14-H), 7.94 (d,  $J = 7.5$  Hz, 1H, 12-H), 8.00 (d,  $J = 2.0$  Hz, 1H, 1-H), 8.06 (dd,  $J = 8.9$  and 2.6 Hz, 1H, 3-H), 12.22 (s, 1H, N-H).  $^{13}\text{C NMR}$  (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$  25.0 (C-10), 34.7 (C-17b), 58.1 (C-6), 63.5 (C-7), 66.2 (C-9), 116.3 (C-15), 116.8 (C-17a), 121.5 (C-4), 123.0 (C-13), 123.0 (C-3), 123.3 (C-10a), 123.6 (C-12), 125.4 (C-1), 130.6 (C-13b), 131.6 (C-14), 134.0 (C-17c), 137.2 (C-2), 141.8 (C-15a), 158.3 (C-4a), 161.6 (C-13a), 166.1 (C-17). IR (KBr)  $\nu$ : 1333, 1393, 1492, 1604, 1637  $\text{cm}^{-1}$ ; HRMS: calcd for  $\text{C}_{23}\text{H}_{21}\text{N}_3\text{O}_5\text{Na}$   $[\text{M} + \text{Na}]^+$  442.1373 found 442.1373.

*rac*-(**6aS\***, **10aS\***, **15bS\***)-**5,13-dimethyl-2-nitro-5,10,10a,15b-tetrahydro-6H,9H,15H-dipyran[3',4':5,6; 4'',3'':2,3]pyrano[3,4-c]quinolin-15-one [rac-(6aS\*, 10aS\*, 15bS\*)-10ae]**. The reaction



of **8a** and **2e** was carried out according to method A, and the crude product was purified by column chromatography (hexane/ethyl acetate 1 : 2), affording *rac*-(6 *aS*<sup>\*</sup>, 10*aS*<sup>\*</sup>, 15*bS*<sup>\*</sup>)-**10ae** as yellow powder (42%), mp 279–282 °C. *R*<sub>f</sub> = 0.29 (hexane/ethyl acetate 1 : 2).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.87 (d, *J* = 14.6 Hz, 1H, 10-H<sub>a</sub>), 2.16 (t, *J* = 11.7 Hz, 1H, 10-H<sub>b</sub>), 2.27 (s, 3H, 2'-H), 3.08 (s, 3H, 1'-H), 3.32–3.55 (m, 3H, 7-H and 6-H<sub>a</sub>), 3.62 (t, *J* = 11.6 Hz, 1H, 9-H<sub>a</sub>), 3.78 (m, 2H, 15b-H and 6-H<sub>b</sub>), 3.87 (d, *J* = 7.0 Hz, 1H, 9-H<sub>b</sub>), 4.33 (s, 1H, 10a-H), 5.83 (s, 1H, 12-H), 6.52 (d, *J* = 9.2 Hz, 1H, 4-H), 7.93 (d, *J* = 9.0 Hz, 1H, 3-H), 8.10 (s, 1H, 1-H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 19.9 (C-2'), 27.5 (C-10), 31.7 (C-6a), 33.5 (C-15b), 39.7 (C-1'), 55.9 (C-6), 62.6 (C-9), 69.2 (C-7), 71.6 (C-10a), 98.9 (C-15a), 99.8 (C-12), 110.2 (C-4), 122.0 (C-15c), 124.5 (C-3), 126.4 (C-1), 138.3 (C-2), 149.1 (C-4a), 162.1 (C-13), 163.9 (C-11a), 165.6 (C-15). IR (KBr) *ν*: 1243, 1301, 1587, 1704, 2861, 2925 cm<sup>-1</sup>; HRMS: calcd for C<sub>20</sub>H<sub>20</sub>N<sub>2</sub>O<sub>6</sub>Na [M + Na]<sup>+</sup> 407.1214, found 407.1213.

*rac*-(6*aS*<sup>\*</sup>, 10*aS*<sup>\*</sup>, 15*bS*<sup>\*</sup>)-5,13-dimethyl-2-(trifluoromethyl)-5,10,10a,15b-tetrahydro-6*H*,9*H*,15*H*-dipyran[3',4':5,6;4'',3'':2,3]pyrano[3,4-*c*]quinolin-15-one [*rac*-(6*aS*<sup>\*</sup>, 10*aS*<sup>\*</sup>, 15*bS*<sup>\*</sup>)-**10be**]. The reaction of **8b** and **2e** was carried out according to method A, and the crude product was purified by column chromatography (hexane/ethyl acetate 2 : 1), affording *rac*-(6*aS*<sup>\*</sup>, 10*aS*<sup>\*</sup>, 15*bS*<sup>\*</sup>)-**10be** as white amorphous solid (32%). *R*<sub>f</sub> = 0.18 (hexane/ethyl acetate 2 : 1).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.84 (d, *J* = 14.6 Hz, 1H, 10-H<sub>a</sub>), 2.13 (m, 1H, 10-H<sub>b</sub>), 2.26 (s, 3H, 2'-H), 2.98 (s, 3H, 1'-H), 3.31 (d, *J* = 12.5 Hz, 1H, 6-H<sub>a</sub>), 3.37 (s, 2H, 7-H), 3.63 (m, 2H, 6-H<sub>b</sub> and 9-H<sub>a</sub>), 3.70 (s, 1H, 15b-H), 3.86 (dd, *J* = 11.8 and 5.4 Hz, 1H, 9-H<sub>b</sub>), 4.40 (s, 1H, 10a-H), 5.82 (s, 1H, 12-H), 6.64 (d, *J* = 8.6 Hz, 1H, 4-H), 7.32 (d, *J* = 8.6 Hz, 1H, 3-H), 7.52 (s, 1H, 1-H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 19.9 (C-2'), 27.5 (C-10), 32.4 (C-6a), 33.8 (C-15b), 39.6 (C-1'), 56.3 (C-6), 62.6 (C-9), 69.2 (C-7), 99.1 (C-15a), 99.8 (C-12), 111.2 (C-4), 119.6 and 119.9 (C-2), 123.0 (C-15c), 124.9 (C-3), 126.1 (C-1), 147.2 (C-4a), 161.7 (C-13), 163.9 (C-11a), 165.8 (C-15). IR (KBr) *ν*: 1106, 1328, 1524, 1583, 1617, 1655, 1702, 2861, 2937 cm<sup>-1</sup>; HRMS: calcd for C<sub>21</sub>H<sub>20</sub>F<sub>3</sub>NO<sub>4</sub>Na [M + Na]<sup>+</sup> 430.1237, found 430.1235.

## Conclusion

Pentaheterocyclic chiral frameworks of novel skeletons containing a pyrano[4,3-*b*]pyran unit condensed with a pyrone or pyridone and a tetrahydroquinoline or chroman subunit were prepared in a domino Knoevenagel-intramolecular hetero-Diels-Alder reaction, utilizing heterocyclic dienophiles and heterodienes. Solvent-dependence was explored and toluene was selected as the solvent of the reaction, affording the best overall yields and access to four isomers, which could be readily separated by column chromatography. The reaction of 2*H*-chromene derivatives **1a–e** with 4-hydroxycoumarin reagents **2a–c** produced isomer **4** as the main product in most cases with the  $\alpha,\beta$ -unsaturated ketone subunit acting as the heterodiene in the IMHDA step. Simplified 3,6-dihydro-2*H*-pyran substrates **8a–b**, containing a dihydropyran moiety as the dienophile showed a remarkable improvement in both regio- and diastereoselectivity, affording a single isomer irrespective of the

substitution pattern of the reagent or the substrate. 4-Hydroxy-2-pyrone and -2-pyridone reagents **2e** and **2f**, lacking the condensed benzene ring, were also tested in the domino reaction, in which substrates **1a–c** afforded a mixture of 2–4 regio- and diastereomers, while substrate **8a** gave a single isomer in each case. The planar structure and relative configuration of the products **4–7** were determined on the basis of <sup>13</sup>C chemical shifts, NOE correlations and IR carbonyl stretching vibrations supported by two single crystal X-ray diffraction analysis. The antiproliferative activities of the condensed heterocycles were tested on three human cancer cell lines, which revealed that all the active derivatives have the same (*S*<sup>\*</sup>, *R*<sup>\*</sup>, *S*<sup>\*</sup>) relative configuration and all except for one belong to the series of products **4**, in which the  $\alpha,\beta$ -unsaturated ketone moiety acts as a heterodiene in the IMHDA cyclization step. Compound **4ac**, containing a condensed trimethoxycoumarin residue, exhibited promising antiproliferative activity with an IC<sub>50</sub> value of 5.7  $\mu$ M.

## Author contributions

Conceptualization, S. B. K. and T. K.; methodology, S. B. K., B. I. T. and G. V.; software, A. B., B. I. T. and G. V.; validation, B. I. T., G. V., E. L., D. N. and A. B.; formal analysis, A. B.; investigation, S. B. K., B. B., O. M. O., D. O., K. B., A. B., E. L., G. V., B. I. T. and D. N.; resources, T. K., F. F., M. V. and T. B.; data curation, S. B. K., B. I. T. and T. K.; writing – original draft preparation, S. B. K.; writing – review and editing, S. B. K., T. K., F. F., T. B. and M. V.; visualization, S. B. K., A. B., B. I. T. and D. N.; supervision, S. B. K., T. K., T. B., F. F. and M. V.; project administration, T. K.; funding acquisition, T. K., T. B., E. L., F. F. and M. V. All authors have read and agreed to the published version of the manuscript.

## Conflicts of interest

There are no conflicts to declare.

## Data availability

CCDC 2408634 (**4cc**) and 2408635 (**6cc**) contain the supplementary crystallographic data for this paper.<sup>62a,b</sup>

All experimental (recipes for the preparation of substrates **1a–e** and **8a–b**), spectral (<sup>1</sup>H, <sup>13</sup>C and 2D-NMR, ECD and on-line HPLC-ECD spectra of products) and bioactivity (inhibitory effect at 50  $\mu$ M concentration and concentration-dependent effect) data is available in the supporting information (SI). Supplementary information is available. See DOI: <https://doi.org/10.1039/d6ra02756c>.

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## References

- 1 A. Evidente, L. Maddau, E. Spanu, A. Franceschini, S. Lazzaroni and A. Motta, *J. Nat. Prod.*, 2003, **66**, 313–315.
- 2 L. C. Meade-Tollin, E. M. K. Wijeratne, D. Cooper, M. Guild, E. Jon, A. Fritz, G.-X. Zhou, L. Whitesell, J.-y. Liang and A. A. L. Gunatilaka, *J. Nat. Prod.*, 2004, **67**, 2–4.
- 3 M. C. Edler, R. M. Buey, R. Gussio, A. I. Marcus, C. D. Vanderwal, E. J. Sorensen, J. F. Diaz, P. Giannakakou and E. Hamel, *Biochemistry*, 2005, **44**, 11525–11538.
- 4 M. J. Towle, K. A. Salvato, J. Budrow, B. F. Wels, G. Kuznetsov, K. K. Aalfs, S. Welsh, W. Zheng, B. M. Seletsky, M. H. Palme, G. J. Habgood, L. A. Singer, L. V. DiPietro, Y. Wang, J. J. Chen, D. A. Quincy, A. Davis, K. Yoshimatsu, Y. Kishi, M. J. Yu and B. A. Littlefield, *Cancer Res.*, 2001, **61**, 1013–1021.
- 5 S. Omura, H. Tomoda, Y. K. Kim and H. Nishida, *J. Antibiot.*, 1993, **46**, 1168–1169.
- 6 K. H. Ling, C. K. Yang and F. T. Peng, *Appl. Environ. Microbiol.*, 1979, **37**, 355–357.
- 7 J. Du, Z.-D. He, R.-W. Jiang, W.-C. Ye, H.-X. Xu and P. P.-H. But, *Phytochemistry*, 2003, **62**, 1235–1238.
- 8 T. Yasumoto and M. Murata, *Chem. Rev.*, 1993, **93**, 1897–1909.
- 9 S. Ray, H. K. Majumder, A. K. Chakravarty, S. Mukhopadhyay, R. R. Gil and G. A. Cordell, *J. Nat. Prod.*, 1996, **59**, 27–29.
- 10 I. Souzu and H. Mitsuhashi, *Tetrahedron Lett.*, 1969, **10**, 2725–2728.
- 11 H. Otsuka, T. Akiyama, K.-I. Kawai, S. Shibata, O. Inoue and Y. Ogihara, *Phytochemistry*, 1978, **17**, 1349–1352.
- 12 A. K. Chakravarty, T. Sarkar, K. Masuda, K. Shiojima, T. Nakane and N. Kawahara, *Phytochemistry*, 2001, **58**, 553–556.
- 13 E. Fujita, M. Taoka, M. Shibuya, T. Fujita and T. Shingu, *J. Chem. Soc., Perkin Trans. 1*, 1973, 2277–2281.
- 14 L. Li, H.-K. Wang, J.-J. Chang, A. T. McPhail, D. R. McPhail, H. Terada, T. Konoshima, M. Kokumai, M. Kozuka, J. R. Estes and K.-H. Lee, *J. Nat. Prod.*, 1993, **56**, 690–698.
- 15 T. Tanaka, T. Ito, M. Iinuma, Y. Takahashi and H. Naganawa, *Phytochemistry*, 1998, **48**, 1423–1427.
- 16 J. Li, Y.-F. Tan, S. Liu, X.-Q. Wu, J. Wang, K.-P. Xu, G.-S. Tan, Z.-X. Zou and W.-X. Wang, *Phytochemistry*, 2022, **200**, 113205.
- 17 N. Damuka, K. Kammari, A. M. Potshangbam, A. K. Kondapi and V. Vindal, *ChemistrySelect*, 2021, **6**, 5941–5948.
- 18 N. C. Dige, P. G. Mahajan and D. M. Pore, *Med. Chem. Res.*, 2018, **27**, 224–233.
- 19 R. Sagar, J. Park, M. Koh and S. B. Park, *J. Org. Chem.*, 2009, **74**, 2171–2174.
- 20 P. Kumari, S. Gupta, C. Narayana, S. Ahmad, N. Vishnoi, S. Singh and R. Sagar, *New J. Chem.*, 2018, **42**, 13985–13997.
- 21 L. Zeng, S. Liu, Y. Lan and L. Gao, *Nat. Commun.*, 2023, **14**, 3511.
- 22 M. Jin, C. Tang, Y. Li, S. Yang, Y.-T. Yang, L. Peng, X.-N. Li, W. Zhang, Z. Zuo, F. Gagosz and L.-L. Wang, *Nat. Commun.*, 2021, **12**, 7188.
- 23 Y. Zheng, S. Qian, P. Xu, T. Ma and S. Huang, *Adv. Synth. Catal.*, 2022, **364**, 3800–3804.
- 24 V. Arredondo, D. E. Roa, S. Yan, F. Liu-Smith and D. L. Van Vranken, *Org. Lett.*, 2019, **21**, 1755–1759.
- 25 X. R. Nan Zhao, J. Ren, H. Lu, S. Ma, R. Gao, Y. Li, S. Xu, Li Li and S. Yu, *Org. Lett.*, 2015, **17**, 3118–3121.
- 26 L. N. Aldrich, E. S. Dawson and C. W. Lindsley, *Org. Lett.*, 2010, **12**, 1048–1051.
- 27 B. B. Snider and Q. Lu, *J. Org. Chem.*, 1996, **61**, 2839–2844.
- 28 S. Bhuyan, D. Das, A. Chakraborty, S. Mandal, K. Dhanabal and B. G. Roy, *Chem.-Asian J.*, 2021, **16**, 4108–4121.
- 29 K. A. Krasnov, P. V. Dorovatovskii, Y. V. Zubavichus, T. V. Timofeeva and V. N. Khrustalev, *Tetrahedron*, 2017, **73**, 542–549.
- 30 P. Padmaja, B. V. Subba Reddy, N. Jain, S. R. Mutheneni, P. Bolleppelli, S. Polepalli, G. Rambabu and P. N. Reddy, *New J. Chem.*, 2016, **40**, 8305–8315.
- 31 A. Mishra, N. Rastogi and S. Batra, *Tetrahedron*, 2012, **68**, 2146–2154.
- 32 S. Majumder and P. J. Bhuyan, *Tetrahedron Lett.*, 2012, **53**, 137–140.
- 33 S. B. Király, A. Bényei, E. Lisztes, T. Bíró, B. I. Tóth and T. Kurtán, *Eur. J. Org. Chem.*, 2021, **2021**, 6161–6170.
- 34 S. Balázs Király, L. Tóth, T. Kovács, A. Bényei, E. Lisztes, B. István Tóth, T. Bíró, A. Kiss-Szikszai, K. E. Kövér, A. Mándi and T. Kurtán, *Adv. Synth. Catal.*, 2023, **365**, 3301–3319.
- 35 L.-F. Tietze, S. Brand and T. Pfeiffer, *Angew. Chem., Int. Ed.*, 1985, **24**, 784–786.
- 36 B. Baruah and P. J. Bhuyan, *Tetrahedron*, 2009, **65**, 7099–7104.
- 37 L. F. Tietze and P. Saling, *Synlett*, 1992, **1992**, 281–282.
- 38 M. Bakthadoss and D. Kannan, *RSC Adv.*, 2014, **4**, 11723–11731.
- 39 M. Bakthadoss and G. Sivakumar, *Tetrahedron Lett.*, 2014, **55**, 1765–1770.
- 40 S. Kathiravan and R. Raghunathan, *Synlett*, 2010, **2010**, 1927–1930.
- 41 Y. R. Lee and T. V. Hung, *Tetrahedron*, 2008, **64**, 7338–7346.
- 42 N. J. Parmar, S. B. Teraiya, H. A. Barad, D. Sharma and V. K. Gupta, *Synth. Commun.*, 2013, **43**, 1577–1586.
- 43 S. Maiti, S. K. Panja and C. Bandyopadhyay, *Tetrahedron*, 2010, **66**, 7625–7632.
- 44 E. Ramesh and R. Raghunathan, *Tetrahedron Lett.*, 2008, **49**, 1812–1817.
- 45 M. Shanmugasundaram, S. Manikandan and R. Raghunathan, *Tetrahedron*, 2002, **58**, 997–1003.
- 46 R. D. R. S. Manian, J. Jayashankaran and R. Raghunathan, *Tetrahedron Lett.*, 2007, **48**, 1385–1389.
- 47 J. S. Yadav, B. V. S. Reddy, V. Naveenkumar, R. S. Rao and K. Nagaiah, *Synthesis*, 2004, 1783–1788.
- 48 M. Ghandi, S. Feizi, M. T. Nazeri and B. Notash, *J. Iran. Chem. Soc.*, 2017, **14**, 177–187.



- 49 Y. Dommaraju, S. Borthakur and D. Prajapati, *ChemistrySelect*, 2016, **1**, 6768–6771.
- 50 S. Manikandan, M. Shanmugasundaram and R. Raghunathan, *Tetrahedron*, 2002, **58**, 8957–8962.
- 51 L. F. Tietze, H. Geissler, J. Fennen, T. Brumby, S. Brand and G. Schulz, *J. Org. Chem.*, 1994, **59**, 182–191.
- 52 G. Cravotto, G. M. Nano, S. Tagliapietra, G. Palmisano and T. Pilati, *J. Heterocycl. Chem.*, 2001, **38**, 965–971.
- 53 H. Sunden, I. Ibrahim, G. L. Zhao, L. Eriksson and A. Cordova, *Chem. Eur. J.*, 2007, **13**, 574–581.
- 54 R. R. Raslan, Y. A. Ammar, S. A. Fouad, S. A. Hessein, N. A. M. Shmiess and A. Ragab, *RSC Adv.*, 2023, **13**, 10440–10458.
- 55 A. Ragab, R. R. Raslan, M. S. Abusaif, H. K. Thabet, Y. A. Ammar and N. A. Gohar, *Eur. J. Med. Chem.*, 2025, **294**, 117751.
- 56 G. Sheldrick, *Acta Crystallogr., Sect. A*, 2008, **64**, 112–122.
- 57 S. Westrip, *J. Appl. Crystallogr.*, 2010, **43**, 920–925.
- 58 C. F. Macrae, I. Sovago, S. J. Cottrell, P. T. A. Galek, P. McCabe, E. Pidcock, M. Platings, G. P. Shields, J. S. Stevens, M. Towler and P. A. Wood, *J. Appl. Crystallogr.*, 2020, **53**, 226–235.
- 59 A. Spek, *J. Appl. Crystallogr.*, 2003, **36**, 7–13.
- 60 A. Szappanos, A. Mandi, K. Gulacsi, E. Lisztes, B. I. Toth, T. Biro, S. Antus and T. Kurtan, *Org. Biomol. Chem.*, 2020, **18**, 2148–2162.
- 61 Á. Szappanos, A. Mándi, K. Gulácsi, E. Lisztes, B. I. Tóth, T. BÍró, A. Kónya-Ábrahám, A. Kiss-Szikszai, A. Bényei, S. Antus and T. Kurtán, *Biomolecules*, 2020, **10**, 1462.
- 62 (a) CCDC 2408634: Experimental Crystal Structure Determination, 2026, DOI: [10.5517/ccdc.csd.cc2lvcwq](https://doi.org/10.5517/ccdc.csd.cc2lvcwq); (b) CCDC 2408635: Experimental Crystal Structure Determination, 2026, DOI: [10.5517/ccdc.csd.cc2lvexr](https://doi.org/10.5517/ccdc.csd.cc2lvexr).

