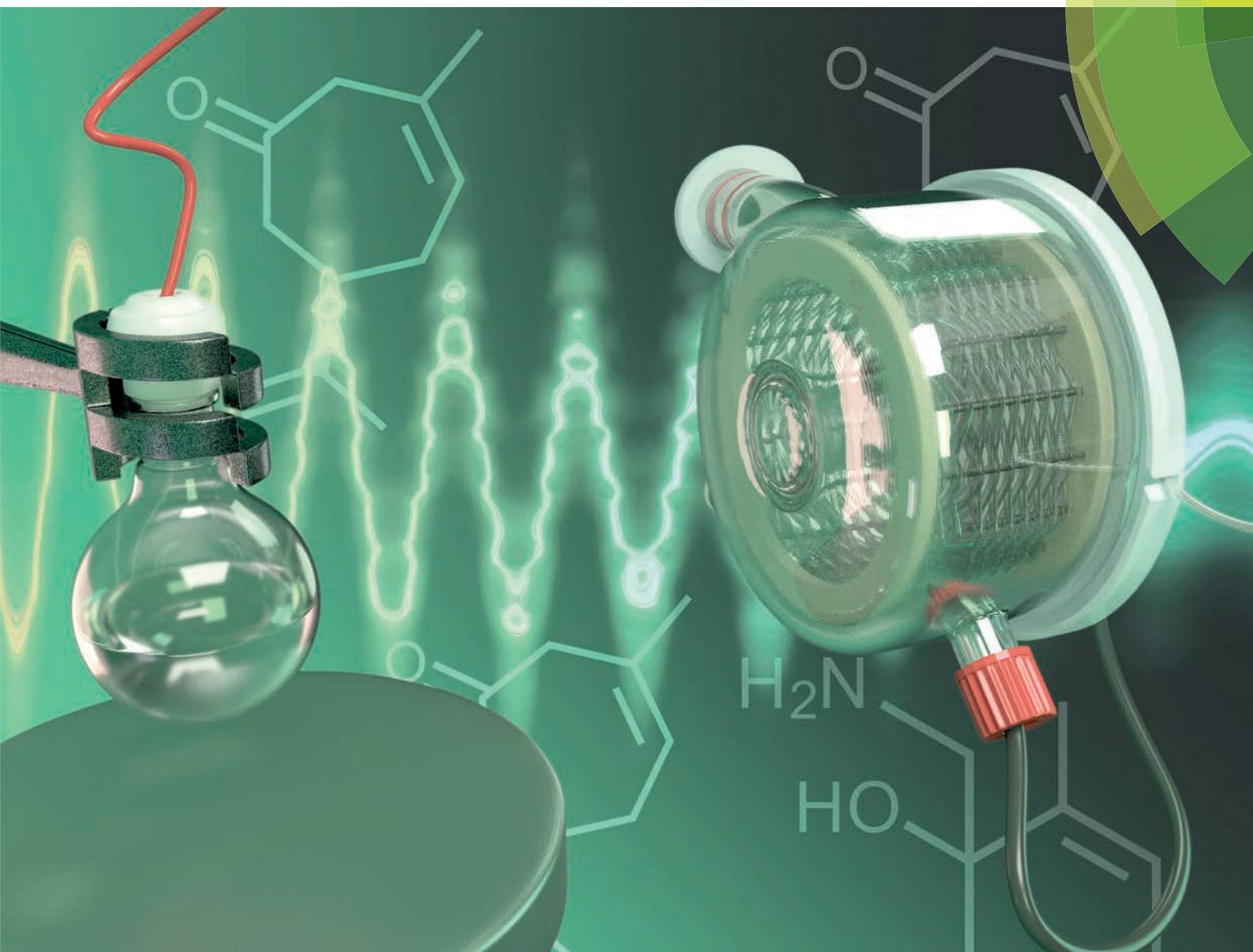


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## PAPER

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## A practical deca-gram scale ring expansion of (*R*)-(–)-carvone to (*R*)-(+)-3-methyl-6-isopropenyl-cyclohept-3-enone-1†

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A route to enantiopure (*R*)-(+)-3-methyl-6-isopropenyl-cyclohept-3-enone-1, an intermediate for terpenoids, has been developed and includes a highly chemo- and regioselective Tiffeneau–Demjanov reaction. Starting from readily available (*R*)-(–)-carvone, this robust sequence is available on a deca-gram scale and uses flow chemistry for the initial epoxidation reaction. The stereochemistry of the addition of two nucleophiles to the carbonyl group of (*R*)-(–)-carvone has been determined by X-ray diffraction studies and chemical correlation.

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## Introduction

The synthesis of bioactive terpenoids and alkaloids containing an all carbon seven-membered ring is of current interest.<sup>1,2</sup> Examples of such natural product syntheses include longifolene,<sup>3</sup> and the guaiane sesquiterpenes thapsigargins,<sup>4</sup> the englerins,<sup>5</sup> echinopines<sup>6</sup> and nanolobatolide (a sesqui- plus 3 C).<sup>7</sup> The higher terpenoid examples include phorbol (prostratin),<sup>8</sup> ingenol,<sup>9</sup> guanacastepenes,<sup>10</sup> icetexanes,<sup>11</sup> and the mero-terpenoids perovskone,<sup>12</sup> frondosin<sup>13</sup> and the cortistatins.<sup>14</sup> Among the alkaloids, colchicine,<sup>15</sup> diterpenoid alkaloids,<sup>16</sup> nominine<sup>16a,17</sup> and the daphniphyllums<sup>18</sup> can be cited as being part of this class of compounds (Fig. 1).

The synthesis of all carbon seven-membered rings can be effected by cyclization reactions<sup>19</sup> and ring-closing metathesis,<sup>20</sup> (4 + 3)<sup>21</sup> or (5 + 2)<sup>22</sup> or (3 + 2 + 2)<sup>23</sup> cycloadditions, and 6 + 1 or 5 + 2 ring expansions.<sup>24</sup> The terpenoid natural products<sup>11a,25</sup> frequently present the seven membered-ring in fusion with a five-membered ring (sesquiterpenoids), the diterpenoids having a further six-membered ring (Scheme 1).

The perhydroazulene sesquiterpenes<sup>26,27</sup> and diterpenes<sup>28,29</sup> generally possess methyl and isopropyl group sub-

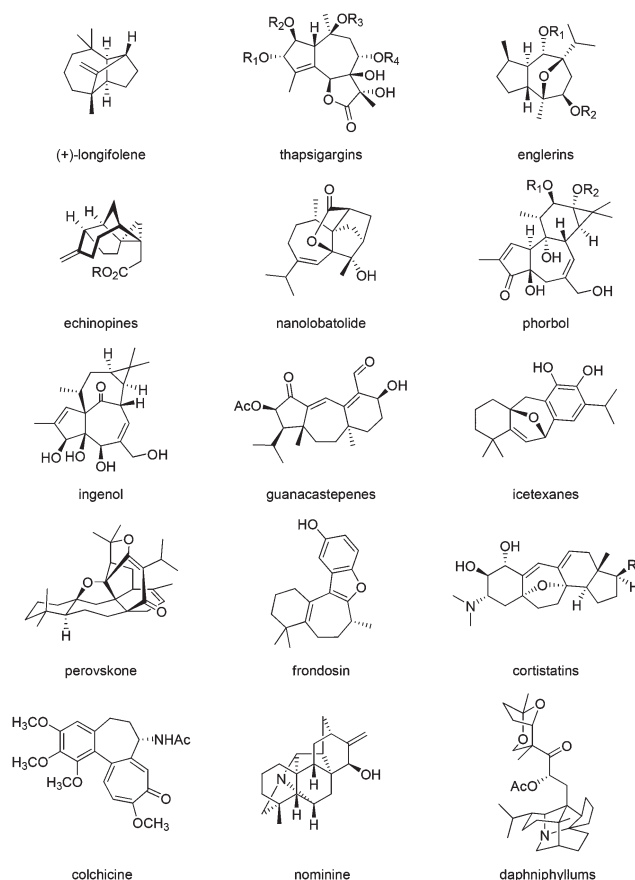


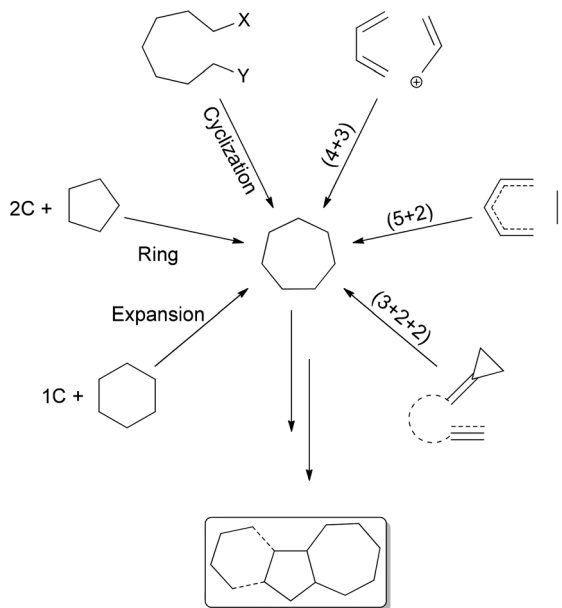
Fig. 1 Examples of natural product synthetic targets containing an all carbon cycloheptane moiety.

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†Electronic supplementary information (ESI) available: Analytical characterization of compounds, NMR spectra, experimental details and X-ray details. CCDC 1051801 CIF format for structure 4a has been deposited at the Cambridge Crystallographic Data Centre. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ob00525f



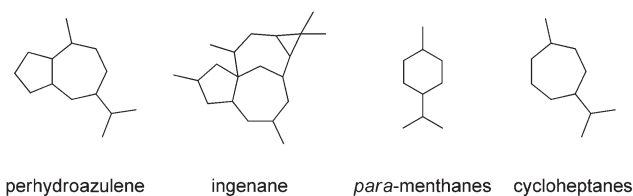


**Scheme 1** Synthetic methods to obtain cycloheptane rings, with target terpenoid carbon skeletons.

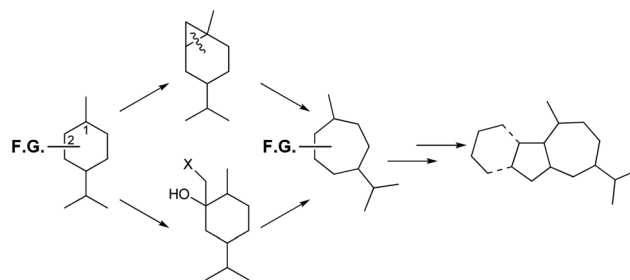
stitutions in a 1,4-relationship, thus displaying a carbon skeleton similarity to naturally occurring *para*-menthane monoterpenes, and embedding a 1,4-methyl, isopropyl-cycloheptane residue (Fig. 2).

Synthetic approaches to the perhydroazulene structures from *para*-menthanes have involved the contraction of the six-membered ring to cyclopentanoids followed by heptanyl-annulation,<sup>30,31</sup> or much less frequently expansion to cycloheptanoids and pentanyl-annulation.<sup>32</sup> This last strategy has been studied in our laboratory for the synthesis of cycloheptanoids,<sup>33</sup> and thus access to perhydroazulene terpenoids and alkaloids.<sup>34</sup> The ring expansions occur by two different methods: cyclopropanation of a suitable *para*-menthene-1 to an overbred bicyclic system followed by cleavage of the common C–C bond.<sup>35</sup> The second sequence requires an appropriate nucleophile addition to a *para*-menthanone-2 followed by a regioselective rearrangement, as presented in Scheme 2.

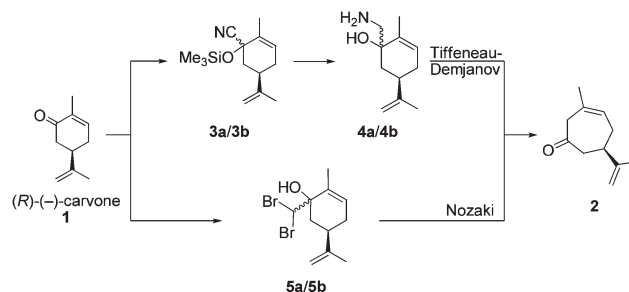
Recently, we developed a synthetic route to transform (*R*)-(-)-carvone (**1**) into (*R*)-(+)-3-methyl-6-isopropenyl-cyclohept-3-enone-1 (**2**), based upon a completely chemo- and regio-selective Tiffeneau–Demjanov ring expansion reaction



**Fig. 2** Structural relationships amongst perhydroazulene sesquiterpenes and diterpenes, *para*-menthane monoterpenes and cycloheptanes.



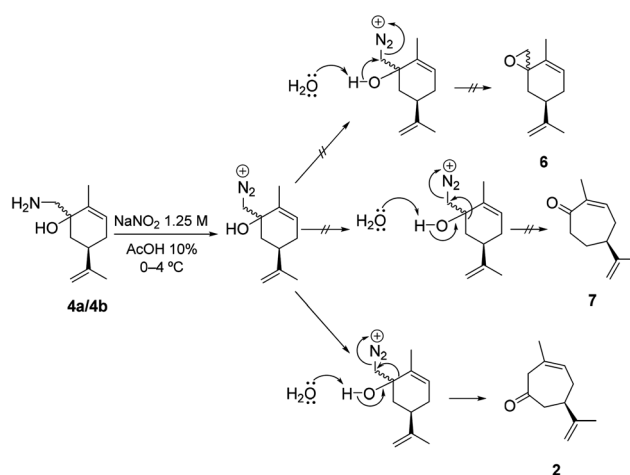
**Scheme 2** Ring expansion strategies to obtain 1,4-methyl, isopropyl-cycloheptanes, and thus terpenoids.



**Scheme 3** Ring expansions of carvone by the Tiffeneau–Demjanov rearrangement and Nozaki reaction.

(Scheme 3).<sup>36</sup> The addition of TMS-cyanide to (*R*)-(-)-carvone (**1**) furnishes the TMS-cyanohydrins **3a/3b**, as a 90:10 diastereoisomeric mixture. Reduction of **3a/3b** with  $\text{LiAlH}_4$  provides the required amino-alcohols **4a/4b** for the Tiffeneau–Demjanov rearrangement, which leads to the non-conjugated cycloheptenone (*R*)-(+)-**2**.

We were pleasantly surprised to discover the complete chemo- and regioselectivity in this rearrangement, as can be seen in Scheme 4, where the epoxide **6** and the regio-isomeric



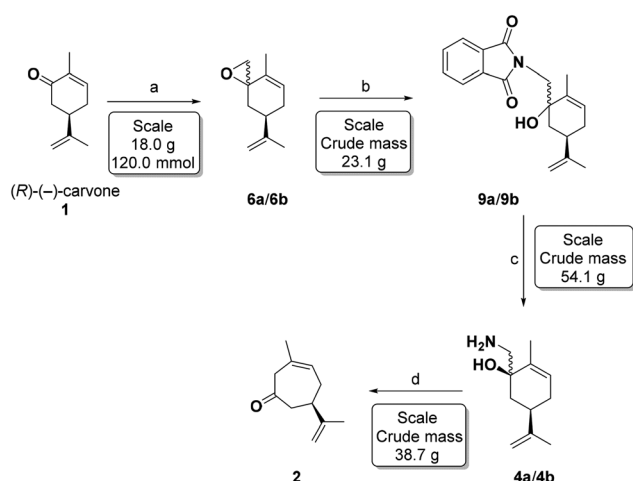
**Scheme 4** Chemo- and regioselectivity in the Tiffeneau–Demjanov rearrangement.

cycloheptenone **7** were not observed. Similarly, the Nozaki ring expansion with addition of the dibromomethyl carbanion to carvone, and subsequent rearrangement of **5** are also highly effective (Scheme 3).<sup>36</sup>

Encouraged by the total chemo- and regioselectivity observed in the Tiffeneau–Demjanov rearrangement, we have now examined an attractive alternative by Corey–Chaykovsky epoxidation of (*R*)-(–)-carvone (**1**) and *N*-nucleophile ring opening to the same intermediate amino-alcohols **4a/4b** obtained in Scheme 3. We now demonstrate significant improvements over the previous synthetic routes, which allow a deca-gram scale-up, in less bench time, with very simple purifications, thus reducing substantially problems of synthesis logistics. This route also avoids the practical problems of using KCN and LiAlH<sub>4</sub>, or the preparation and use of the CHBr<sub>2</sub> carbanion, on a large scale. We also present a structural assignment of **4a** by X-ray diffraction and a chemical correlation, and thus the stereochemistry of 1,2 nucleophilic additions to the carbonyl group of (*R*)-(–)-carvone (**1**).

## Results and discussion

Our initial experiments with the Corey–Chaykovsky epoxidation of (*R*)-(–)-carvone (**1**),<sup>37</sup> using the original NaH procedure for generating the sulfur ylide, were not reproducible on a large scale, besides presenting some practical difficulties with the manipulation of large quantities of NaH. This led us to try the modification using methyl lithium or *n*-butyl lithium hexane solutions with DMSO,<sup>38</sup> and in these conditions, the epoxidation of (*R*)-(–)-carvone (**1**) led to a 90 : 10 ratio (by GC and <sup>1</sup>H-NMR) of **6a** and **6b** in 90–95% yields (Scheme 5), and this mixture was used as such in the following reaction.



**Scheme 5** Reagents and conditions: (a) Me<sub>3</sub>S<sup>+</sup>I<sup>−</sup>, *n*-BuLi, DMSO-THF, 90–95%; (b) K phthalimide, phthalimide, DMF, 155–160 °C, 3 h, (c) NH<sub>2</sub>NH<sub>2</sub>·H<sub>2</sub>O, EtOH, 80–85 °C, 2 h, 64% for 2 steps (d) NaNO<sub>2</sub> 1.25 M, AcOH 10% (v/v), 0–4 °C, 4 h, 35–71%.

To test the quality of our commercial Me<sub>3</sub>S<sup>+</sup>I<sup>−</sup>, we prepared this reagent freshly by reaction of Me<sub>2</sub>S with MeI,<sup>39</sup> and after recrystallisation the Me<sub>3</sub>S<sup>+</sup>I<sup>−</sup> turned out to be slightly more efficient in our reaction. We conclude, however, that the commercial product is perfectly adequate for our purposes, not justifying the time spent on its preparation and purification.

The base used to form the ylide and reaction conditions were also studied, and the results are shown in Table 1. A solution of the alkyl-lithium was added to DMSO at room temperature, a biphasic mixture was formed, the dimsly-Li (heavier phase) was transferred, *via* cannula, to a previously prepared solution of Me<sub>3</sub>S<sup>+</sup>I<sup>−</sup> in THF/DMSO at −10 °C. The (*R*)-(–)-carvone solution in THF was added, and after 3 h a crude oil containing the mixture of epoxides **6a/6b** was obtained, to be used as such in the following reaction.

The epoxides **6a/6b** were formed on a 23 gram scale from 18 g (120 mmol) of carvone under the conditions shown in Table 1 (entry 9), and used as such in the subsequent reaction.

However, a significant improvement was found while conducting this reaction under continuous flow conditions.<sup>40</sup> We used a Vapourtec E-series<sup>41,42</sup> flow equipment, with 3 peristaltic pumps (A, B and C), a 10 mL coil reactor and 1.0 mm i.d. PTFE tubing. The equipment schematics with the best results are shown in Scheme 6.

*n*-BuLi in hexanes was pumped through C (we used a red end crimped fluoropolymer in this pump, compatible with organometallic solutions) and then mixed with a solution of Me<sub>3</sub>S<sup>+</sup>I<sup>−</sup> in DMSO pumped by B. The ylide then meets the (*R*)-(–)-carvone stream from A, and the reaction takes place in the 10 mL reactor coil kept at room temperature. After the continuous off-line aqueous work-up the desired epoxides **6a/6b** were obtained. DMSO (99%+, Alfa-Aesar) was used directly from the bottle, without any further treatment in the flow experiments.

In the initial experiments, our attempts to optimise the procedure were accompanied by blockages within 15 min of processing. The blockages came from the precipitation of the Me<sub>3</sub>S<sup>+</sup>I<sup>−</sup> and/or LiOH from *n*-BuLi hydrolysis. This problem was solved using a wider bore T-piece and tubing (2.0 mm i.d.) as shown in Scheme 6.

After the standard parameters had been optimised, the preparation was continuously run for over 2 hours, to generate the epoxides **6a/6b** (9.4 g, 57 mmol) in 95% isolated yield, from 9.0 g (60 mmol) of (*R*)-(–)-carvone, 18.4 g (90 mmol) of Me<sub>3</sub>S<sup>+</sup>I<sup>−</sup> and 40 mL (90 mmol) of *n*-BuLi 2.25 M in hexanes. The crude colourless oil was used in the next step without any need of further purification.

In the batch process using NaH as the base, we obtained the epoxides **6a/6b** in 87% yield, whereas the batch process using *n*-BuLi as the base and a continuous flow process led to 95% yield without the need for purification, and ready for the next synthetic step. The continuous flow procedure was also better due to the ease of operation at much larger scales with minimum manual interactions, resulting in an increase in bench time and simplicity.

Initially the ring opening of the epoxides **6a/6b** (Scheme 5) was studied with the obvious nucleophiles ammonia<sup>43</sup> and

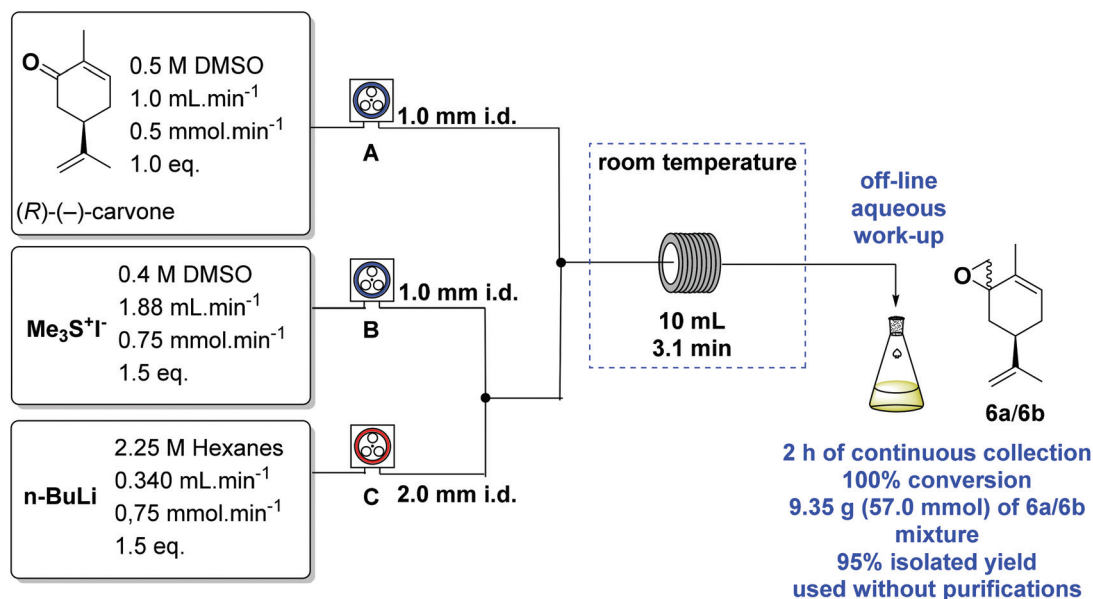




**Table 1** Corey–Chaykovsky epoxidation of (*R*)-(-)-carvone in the batch mode

Entry	Scale gram (mmol)	Base (eq.)	Me <sub>3</sub> S <sup>+</sup> I <sup>-</sup> (eq.)	Conversion <sup>a</sup> (%)	Crude mass obtained <sup>b</sup> (g)
1	0.15 (1.0)	MeLi 1.56 M in Et <sub>2</sub> O (1.2)	1.2	87	0.065
2	0.45 (3.0)	MeLi 1.56 M in Et <sub>2</sub> O (1.2)	1.2	78	0.48
3	0.15 (1.0)	<i>n</i> -BuLi 1.50 M in hexanes (1.2)	1.2	80	0.17
5	0.45 (3.0)	MeLi 1.56 M in Et <sub>2</sub> O (1.5)	1.5	100	0.52
6	1.50 (10)	<i>n</i> -BuLi 2.50 M in hexanes (1.5)	1.5	100	1.41
7	3.02 (20)	<i>n</i> -BuLi 2.50 M in hexanes (2.0)	2.0	95	3.38
8	9.00 (60)	<i>n</i> -BuLi 2.50 M in hexanes (2.0)	2.0	95	15.03
9	18.02 (120)	<i>n</i> -BuLi 2.50 M in hexanes (2.0)	2.0	95	23.13

<sup>a</sup> Conversion based on <sup>1</sup>H-NMR signal ratios between H-2 of (*R*)-(-)-carvone and H-2 of **6a/6b**. <sup>b</sup> Based on the crude product mass after aqueous work-up; 90 : 10 ratio in all entries; increased base and Me<sub>3</sub>SI with scale was used to maintain high conversions.

**Scheme 6** Corey–Chaykovsky epoxidation of (*R*)-(-)-carvone under continuous flow conditions.

sodium amide,<sup>44</sup> but with limited success. For example, we used a commercial ammonia solution in H<sub>2</sub>O (25–30%, Fisher Scientific) and prepared other ammonia solutions by bubbling ammonia gas, at room temperature, into the desired solvent for 2 h. The solutions were titrated with a 0.12 M aqueous HCl standard solution containing bromocresol green.

We obtained ammonia solutions in MeOH (8.0 N), isopropanol (4.0 M), dimethoxyethane (2.9 M). These ammonia solutions were then reacted in screw cap sealed pressure tubes with the epoxide mixture **6a/6b**, and led to the formation of the desired amino-alcohols **4a/4b**, and unidentified by-products. The corresponding diols were also formed when we used aqueous ammonia solutions, due to the presence of water (in a 26 : 10 ratio) (Table 2). The separation of the amino-alcohols on a multi-gram scale we deemed to be impracticable.

On the other hand, sodium amide led to complex mixtures as shown by TLC analysis, probably due to its reactivity as a base.

Ring opening of the epoxides **6a/6b** was easily accomplished by potassium phthalimide and phthalimide in dimethylacetamide (DMA) or DMF at 155–160 °C, according to the classic Gabriel procedure.<sup>45</sup> Table 3 summarizes our epoxide ring opening results under conventional or microwave (MW) heating, with DMA presenting better results.

Microwave heating at 150–160 °C in DMA gave the best results, but due to the volume limitation of the microwave tubes (~14 mL), the large scale reactions (2 flasks with 8.2 g, 50 mmol each and 23.1 g, 120 mmol; Table 3 entries 15 and 16) were performed with conventional heating. The crude product obtained as a brown oil was used directly in the next step.

Hydrazinolysis of the phthalimido-alcohols **9a/9b** produced the same amino-alcohols **4a/4b** obtained in the previous sequence (Scheme 3). After reacting with hydrazine monohydrate (1.5 equivalents) in refluxing ethanol for 3 hours, the starting material **9a/9b** was completely consumed. The crude



**Table 2** The opening of epoxides **6a/6b** with ammonia solutions

Entry	Scale grams (mmol)	Solvent (eq. NH <sub>3</sub> )	Conditions	<b>4a/4b</b> <sup>a</sup> (%)	<b>8</b> <sup>a</sup> (%)	By-products <sup>a</sup> (%)
1	2 (12.2)	H <sub>2</sub> O/THF (10)	90–100 °C, 6 h	26	10	64
2	0.2 (1.2)	MeOH (10)	50 °C, 1 h	2	—	8
3	0.2 (1.2)	MeOH (10)	70 °C, 1 h	11	—	32
4	0.2 (1.2)	MeOH (10)	90 °C, 2.5 h	33	—	67
5	0.16 (1.0)	MeOH (10)	130 °C, 15 min, MW	29	—	61
6	0.16 (1.0)	Isopropanol (10)	90 °C, 2 h	8	—	10
7	0.32 (2.0)	DME (10)	90 °C, 1.5 h	—	—	—
8	0.32 (2.0)	DME (10)	130 °C, 15 min, MW	—	—	—
9	0.16 (1.0)	Dioxane (10)	130 °C, 25 min, MW	—	—	—

<sup>a</sup> Conversion based on <sup>1</sup>H-NMR signal ratios of H-2 of **4a/4b**, **8** and by-products.

**Table 3** Epoxide ring opening with potassium phthalimide and phthalimide using conventional or microwave heating

Entry	Scale grams (mmol)	Conditions	<b>6a/6b</b> <sup>a</sup> (%)	<b>9a/9b</b> <sup>a</sup> (%)	<b>10</b> <sup>a</sup> (%)
1	0.49 (3.0)	<i>t</i> -BuOH, 160 °C, 2 h	100	—	—
2	0.49 (3.0)	EtOAc, 160 °C, 2 h	100	—	—
3	0.49 (3.0)	MeCN, 160 °C, 5 h	Degradation	—	—
4	0.82 (5.0)	DMF, 80 °C, 2 h	100	—	—
5	0.82 (5.0)	DMF, 110 °C, 2 h	100	—	—
6	0.82 (5.0)	DMF, 140 °C, 7 h	—	70	30
7	0.16 (1.0)	DMF, 160 °C, 1.5 h	—	80	20
8	0.16 (1.0)	DMF, 100 °C, 7.5 min (MW)	97	2	1
9	0.16 (1.0)	DMF, 125 °C, 7.5 min (MW)	88	7	5
10	0.16 (1.0)	DMF, 150 °C, 7.5 min (MW)	—	77	23
11	0.16 (1.0)	DMA, 150 °C, 7.5 min (MW)	—	86	14
12	0.16 (1.0)	DMA, 150 °C, 5.0 min (MW)	—	86	14
13	0.16 (1.0)	DMA, 150 °C, 2.5 min (MW)	—	85	15
14	1.64 (10.0)	DMA, 160 °C, 1 h (MW)	—	84	16
15	16.40 (100.0) <sup>b</sup>	DMA, 160 °C, 6 h	—	87	13
16	23.13 (120.0)	DMF, 160 °C, 3 h	—	78	22

<sup>a</sup> Conversion based on the <sup>1</sup>H-NMR signal ratios of H-11 of **6a/6b**, **9a/9b** and **10**. <sup>b</sup> Performed simultaneously in two flasks containing the same quantities (8.21 g, 50.0 mmol) of epoxides **6a/6b**.

reaction product (13.9 g, 77 mmol) was characterized as the amino-alcohols **4a/4b** with an 85 : 15 ratio as determined by <sup>1</sup>H-NMR. Recrystallization from hot hexanes afforded 12.2 g (73.7 mmol) of amino-alcohol **4a** in 64% yield for the last 2 steps.

The phthalimido-alcohol **9a/9b** reduction described by Ganem *et al.*<sup>46</sup> was also examined using NaBH<sub>4</sub> in isopropanol:H<sub>2</sub>O at room temperature for 24 h. A yellow oil was obtained containing the amino-alcohols **4a/4b** together with a complex mixture of by-products. As the product **4a/4b**



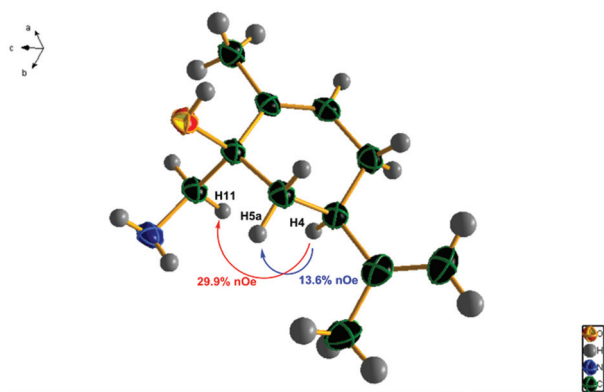


Fig. 3 Structure of the major amino-alcohol **4a**, obtained by X-ray diffraction studies, indicating observed nOe interactions. (Ellipsoids shown at 40% probability level).

crystallizes along with the by-product phthalide, and required large amounts of sodium borohydride, this procedure was not investigated further.

The Tiffeneau–Demjanov<sup>47,48</sup> rearrangement was performed by treatment of a solution of **4a/4b** (38.7 g, 214 mmol, divided in 3 flasks with 12.9 g each), in 10% (v/v) aqueous AcOH with an aqueous NaNO<sub>2</sub> solution (1.25 M, 103 mL, 8.83 g, 128 mmol, 1.8 equiv.) for each flask. The temperature was maintained at 0–4 °C (ice-water bath) for 4 hours. Aqueous work-up then produced a brown oil which underwent immediate chromatographic purification affording the non-conjugated cycloheptenone **2** (15.9 g, 96 mmol) in 35% yield ( $[\alpha]_D^{25} = +44.3$  (*c* 1.15, CHCl<sub>3</sub>); lit.<sup>36</sup>  $[\alpha]_D^{25} = +30.0$  (*c* 0.26 CHCl<sub>3</sub>). Under these conditions we did not observe the formation of the conjugated cycloheptenone.

The assignment of the stereochemistry of **3a/3b** and thus **6a/6b** was made by chemical correlation with **4a**, from the mono-crystal X-ray diffraction studies (Fig. 3) and nOe irradiation (see ESI†) of the major amino-alcohol **4a**, obtained by reduction of the TMS–cyanohydrin mixture **3a/3b**. Other nucleophilic addition reactions to the carbonyl group of carvone have been studied previously,<sup>49</sup> and the stereochemistry of major approaches has been shown to be preferentially *anti*- to the isopropenyl group.<sup>50</sup> We have now confirmed that this is the correct stereochemistry for the major isomers **3a** and **6a**. The structure of **4a** is shown in Fig. 3, and the chemical correlation of the amino-alcohols **4a/4b** obtained in both sequences, establishes the same 90:10 diastereomeric preference of addition of cyanide and the sulfonium ylide nucleophiles.

## Conclusions

In summary, we have developed a very efficient synthetic route to the appropriately functionalized (*R*)-(+)-3-methyl-6-isopropenyl-3-cycloheptenone-1 (**2**), a useful enantiopure intermediate for bioactive terpenoid synthesis. Using this methodology,

cycloheptenone **2** has been prepared on a deca-gram scale with minimal chromatographic separation needed. Starting from 18.0 g of (*R*)-(-)-carvone (**1**), we have obtained 8.1 g (41% overall yield) of the cycloheptenone **2**.

## Experimental

### General protocol for preparation of **6a/6b** in flow

The continuous flow preparation of the epoxides **6a/6b** was carried out using a three-stream reactor assembly. The Vapourtec E-Series machine was charged with a 0.5 M solution of (*R*)-(-)-carvone in DMSO (pump A) at the rate of 1.0 mL min<sup>-1</sup>, a 0.4 M solution of Me<sub>3</sub>S<sup>+</sup>I<sup>-</sup> in DMSO (pump B) at the rate of 1.88 mL min<sup>-1</sup> and a solution of *n*-BuLi (2.25 M in hexanes) pumped directly from the bottle through C at the rate of 0.340 mL min<sup>-1</sup>. The DMSO was used directly without any purification. The desired flow rates were set and all pumps were started. DMSO and hexane were pumped for 5 min. Pump C was timed to switch to pumping *n*-BuLi for 5 min before switching pumps A and B simultaneously to (*R*)-(-)-carvone and Me<sub>3</sub>S<sup>+</sup>I<sup>-</sup> at the rates as determined above. The streams of pumps B and C were mixed through a T-piece generating the sulfur ylide which was mixed with a stream of (*R*)-(-)-carvone from pump A. A PTFE tubing of 2.00 mm i.d. was used between pump C and the second T-piece. The resulting stream was driven to a 10 mL coil reactor at room temperature with a residence time of 3.1 min at these flow rates. The quenching was achieved by continuously collecting the output in a conical flask with cold water for 2 h.

**Compounds 6a/6b data.** *R<sub>f</sub>* 0.59 (*n*-hexane–EtOAc, 95 : 5); **ratio 6a/6b**: 90 : 10 (<sup>1</sup>H NMR and GC);  $[\alpha]_D^{25} = +24.3$  (*c* 1.42, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) major isomer **6a**: δ 5.82–5.70 (1H, m), 4.74 (1H, br s), 4.72 (1H, br s), 2.93 (1H, dd, *J* = 4.9, 1.4 Hz), 2.67 (1H, d, *J* = 5.0 Hz), 2.44–2.56 (1H, m), 2.16–2.26 (1H, m), 2.06–2.12 (1H, m), 1.98–2.05 (1H, m), 1.73 (3H, br s), 1.50 (3H, br s), 1.45–1.56 (1H, m); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) major isomer **6a**: δ 148.4, 133.0, 128.7, 109.5, 59.0, 53.3, 41.6, 36.8, 31.4, 20.6, 15.6; **IR** (neat, cm<sup>-1</sup>): 2971, 2919, 1645, 1450, 1436, 888; **LRMS**: *m/z* 164, 149, 135, 121, 107, 93, 91, 77, 55, 41; **HRMS** (ESI+): *m/z* calc. for C<sub>11</sub>H<sub>17</sub>O [M + H]<sup>+</sup> 165.1279, found 165.1278; **GC**: 9.975 min = **6a**, 9.817 min = **6b**.

### Representative procedure for the epoxide opening with ammonia

A screw-cap pressure tube was charged with the epoxides **6a/6b** and ammonia solution. The pressure tubes were stoppered and heated. The mixtures were cooled down to room temperature, and the pressure tubes were opened and gently heated in order to remove the residual ammonia.

**Compound 8 data.** *R<sub>f</sub>* 0.43 (*n*-hexane–EtOAc, 50 : 50);  $[\alpha]_D^{25} = -0.71$  (*c* 0.11, CHCl<sub>3</sub>); **m.p.** 103.6–104.5 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 5.66–5.74 (1H, m), 4.74–4.77 (2H, m), 3.70 (1H, d, *J* = 10.7 Hz), 3.54 (1H, d, *J* = 10.7 Hz), 2.29–2.40 (1H, m), 2.12–2.20 (1H, m), 1.90–1.96 (1H, m), 1.82–1.89 (1H, m), 1.73–1.79 (6H, m), 1.55–1.64 (1H, m), 1.49–2.45 (2H, m, after



D<sub>2</sub>O exchange this resonance disappears); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 149.1, 134.2, 128.7, 109.3, 72.8, 68.8, 39.2, 37.1, 31.4, 21.0, 18.0; IR (neat, cm<sup>-1</sup>): 3305, 2946, 2911, 2854, 1645, 1445, 1359, 1011, 889; LRMS: *m/z* 182, 164, 151, 123, 109, 93, 91, 67, 55, 41; HRMS (ESI+): *m/z* calc. for C<sub>11</sub>H<sub>18</sub>O<sub>2</sub>Na [M + Na]<sup>+</sup> 205.1205, found 205.1201; GC: 12.983 min = 8.

### Representative procedure for the epoxide opening with sodium amide

A screw cap pressure tube was charged with the epoxides **6a/6b**, THF and sodium amide. Ammonia was condensed from the cylinder with a cold-finger condenser and added to a screw cap tube maintained at -78 °C with magnetic stirring. The pressure tube was closed and allowed to warm to room temperature, and left stirring for 12 h. After this time, the tube was opened and gently heated in order to remove the residual ammonia. The amino-alcohols **4a/4b** were not observed by TLC.

### Procedure for the epoxide opening with phthalimide/phthalimide K

To a round-bottomed flask were added sequentially phthalimide, potassium phthalimide, the epoxides **6a/6b** and DMF. The suspension was heated at 160 °C for 3 h and after cooling down to room temperature the reaction mixture was diluted with EtOAc, water and brine. The crude product was used in the next step without any further purification.

**Compounds 9a/9b data.** *R<sub>f</sub>* 0.30 (*n*-hexane-EtOAc, 80 : 20); **ratio 9a/9b**: 85 : 15 (<sup>1</sup>H NMR); [α]<sub>D</sub><sup>25</sup> = -34.4 (*c* 1.40, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) major isomer **9a**: δ 7.81–7.90 (2H, m), 7.68–7.75 (2H, m), 5.58 (1H, br s), 4.76 (1H, br s), 4.70 (1H, br s), 3.98 (1H, d, *J* = 14.6 Hz), 3.84 (1H, d, *J* = 14.6 Hz), 3.18 (1H, s, after D<sub>2</sub>O exchange this resonance disappears), 2.52–2.65 (1H, m), 2.07–2.17 (1H, m), 1.92–2.02 (1H, m), 1.85 (3H, br s), 1.77–1.87 (1H, m), 1.70 (3H, br s), 1.44–1.53 (1H, m); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) major isomer **9a**: δ 169.5, 148.7, 135.7, 134.3, 131.9, 126.0, 123.6, 109.5, 75.0, 44.4, 39.0, 38.1, 31.1, 20.5, 17.2; IR (neat, cm<sup>-1</sup>): 3486, 2940, 2920, 1772, 1705, 890, 716; LRMS: *m/z* 311, 293, 268, 252, 238, 196, 178, 161, 151, 133, 123, 109, 91, 77, 67, 41; HRMS (ESI+): *m/z* calc. for C<sub>19</sub>H<sub>22</sub>NO<sub>3</sub> [M + H]<sup>+</sup> 312.1600, found 312.1594; GC: 26.925 min = **9a**, 27.025 min = **9b**.

**Compound 10 data.** *R<sub>f</sub>* 0.33 (*n*-hexane-EtOAc, 90 : 10); [α]<sub>D</sub><sup>25</sup> = +113 (*c* 1.16, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 10.13 (1H, s), 4.73 (1H, br s), 4.69 (1H, br s), 2.44–2.65 (1H, m), 2.26–2.37 (2H, m), 2.13 (3H, s), 2.01–2.10 (1H, m), 1.87–1.95 (1H, m), 1.78–1.86 (1H, m), 1.73 (3H, br s), 1.38–1.51 (1H, m); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 191.0, 155.7, 149.0, 133.3, 109.2, 40.3, 34.8, 27.6, 26.9, 20.9, 18.1; IR (neat, cm<sup>-1</sup>): 2933, 2865, 1666, 1643, 1438, 1232, 888; LRMS: *m/z* 164, 149, 123, 121, 95, 93, 68, 53, 41; HRMS: *m/z* calc. mass for C<sub>11</sub>H<sub>17</sub>O [M + H]<sup>+</sup> 165.1279, found 165.1273; GC: 11.825 min = **10**.

### Procedure for hydrazinolysis of phthalimido-alcohols

To a suspension of the crude products **9a/9b** in EtOH was added NH<sub>2</sub>NH<sub>2</sub>·H<sub>2</sub>O. The reaction system was heated at

80–85 °C for 3 h, cooled down to room temperature, and the white solid formed (phthalyl hydrazide) was filtered off in a sintered funnel and washed with EtOH. The ethanolic filtrate afforded after evaporation *in vacuo* a yellowish oil mixed with a solid characterized as **4a/4b**. The crude mixture of amino-alcohols **4a/4b** can be used directly in the next step.

**Compound 4a.** *R<sub>f</sub>* 0.29 (MeOH-EtOAc, 50 : 50); **ratio 4a/4b**: 85 : 15 (<sup>1</sup>H NMR and GC); [α]<sub>D</sub><sup>25</sup> = -118 (*c* 1.03, CHCl<sub>3</sub>) {lit.<sup>36</sup> [α]<sub>D</sub><sup>25</sup> = -92.2 (*c* 2.0 CHCl<sub>3</sub>)}; **m.p.** 100.9–101.5 °C {lit.<sup>36</sup> m.p. 99.2–99.7 °C}; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz): δ 5.51 (1H, br s), 4.72 (1H, br s), 4.71 (1H, br s), 2.78 (1H, d, *J* = 13.0 Hz), 2.72 (1H, d, *J* = 13.0), 2.21–2.29 (1H, m), 2.04–2.11 (1H, m), 1.88–1.96 (2H, m), 1.72 (3H, br s), 1.70 (3H, br s), 1.45–1.54 (1H, m), 0.5–3.5 (3H, m, after D<sub>2</sub>O exchange this resonance disappears). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz): δ 149.1, 137.2, 125.2, 109.2, 73.0, 46.6, 39.5, 38.3, 31.3, 20.6, 17.3; IR (film, cm<sup>-1</sup>): 3372, 3309, 3082, 2955, 2914, 1645, 1596, 940, 891; LRMS: *m/z* 181, 164, 151, 123, 109, 91, 81, 67, 55, 41; HRMS (ESI+): *m/z* calc. for C<sub>11</sub>H<sub>20</sub>NO [M + H]<sup>+</sup> 182.1545, found 182.1541; GC: 12.958 min = **4a**, 13.017 min = **4b**.

### Procedure for Tiffeneau–Demjanov rearrangement

A solution of the amino-alcohols **4a/4b** in 10% (v/v) aqueous AcOH at 0 °C was treated with a 1.25 M aqueous solution of NaNO<sub>2</sub>. The reaction mixture was stirred for 4 h at 0 °C. The aqueous phase was extracted with EtOAc and the combined organic extracts were washed with 10% (m/v) solution of NaHCO<sub>3</sub>, brine, water and dried over MgSO<sub>4</sub>. The solvent was removed *in vacuo* and the residue was immediately purified by flash column chromatography to afford **2**.

**Compound 2 data.** *R<sub>f</sub>* 0.53 (*n*-hexane-EtOAc, 90 : 10); [α]<sub>D</sub><sup>25</sup> = +44.3 (*c* 1.15, CHCl<sub>3</sub>) {lit.<sup>36</sup> [α]<sub>D</sub><sup>25</sup> = +30.0 (*c* 0.26 CHCl<sub>3</sub>)}; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 5.51–5.59 (1H, m), 4.75 (1H, br s), 4.72 (1H, br s), 3.30 (1H, d, *J* = 14.8 Hz), 2.99 (1H, d, *J* = 14.8 Hz), 2.70–2.80 (1H, m), 2.60 (1H, br s), 2.58 (1H, br s), 2.16–2.35 (2H, m), 1.77 (3H, br s), 1.72 (3H, br s); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 208.0, 148.3, 130.4, 124.5, 110.2, 49.0, 48.3, 43.3, 33.1, 26.1, 20.5; IR (neat, cm<sup>-1</sup>): 2969, 2913, 1704, 890; LRMS: *m/z* 164, 149, 136, 122, 107, 93, 80, 68, 53, 41; HRMS: *m/z* calc. for C<sub>11</sub>H<sub>17</sub>O [M + H]<sup>+</sup> 165.1279, found 165.1278; GC: 10.242 min = **2**.

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## Notes and references

- 1 K. T. de Oliveira, B. M. Servilha, L. de C. Alves, A. L. Desiderá and T. J. Brocksom, *Stud. Nat. Prod. Chem.*, 2014, **42**, 421–463.
- 2 T. V. Nguyen, J. M. Hartmann and D. Enders, *Synthesis*, 2013, 845–873.
- 3 (a) E. J. Corey, M. Ohno, P. A. Vatakencherry and R. B. Mitra, *J. Am. Chem. Soc.*, 1961, **83**, 1251–1253; (b) E. J. Corey, M. Ohno, R. B. Mitra and P. A. Vatakencherry, *Am. Chem. Soc.*, 1964, **86**, 478–485.
- 4 (a) S. V. Ley, A. Antonello, E. P. Balskus, D. T. Booth, S. B. Christensen, E. Cleator, H. Gold, K. Högenauer, U. Hüniger, R. M. Myers, S. F. Oliver, O. Simic, M. D. Smith, H. Søhoel and A. J. A. Woolford, *Proc. Nat. Acad. Sci. U. S. A.*, 2004, **101**, 12073–12078; (b) S. P. Andrews, M. Ball, F. Wierschem, E. Cleator, S. Oliver, K. Högenauer, O. Simic, A. Antonello, U. Hüniger, M. D. Smith and S. V. Ley, *Chem. – Eur. J.*, 2007, **13**, 5688–5712.
- 5 (a) R. H. Pouwer, J.-A. Richard, C.-C. Tseng and D. Y.-K. Chen, *Chem. – Asian J.*, 2012, **7**, 22–35; (b) K. Molawi, N. Delpont and A. M. Echavarren, *Angew. Chem., Int. Ed.*, 2010, **49**, 3517–3519.
- 6 (a) D. Y.-K. Chen, *Synlett*, 2011, 2459–2481; (b) W. Xu, S. Wu, L. Zhou and G. Liang, *Org. Lett.*, 2013, **15**, 1978–1981.
- 7 (a) H. M. Cheng, W. Tian, P. A. Peixoto, B. Dhudshia and D. Y.-K. Chen, *Angew. Chem., Int. Ed.*, 2011, **50**, 4165–4168; (b) L. Chang, H. Jiang, J. Fu, B. Liu, C.-c. Li and Z. Yang, *J. Org. Chem.*, 2012, **77**, 3609–3614.
- 8 (a) P. A. Wender, K. D. Rice and M. E. Schnute, *J. Am. Chem. Soc.*, 1997, **119**, 7897–7898; (b) P. A. Wender, H. Kogen, H. Y. Lee, J. D. Munger, R. S. Wilhelm and P. D. Williams, *J. Am. Chem. Soc.*, 1989, **111**, 8957–8958; (c) See also, P. A. Wender, *Tetrahedron*, 2013, **69**, 7529–7550.
- 9 (a) L. Jørgensen, S. J. McKerrall, C. A. Kuttruff, F. Ungeheuer, J. Felding and P. S. Baran, *Science*, 2013, **341**, 878–882; (b) G. Grue-Sørensen, X. Liang, K. Månsson, P. Vedsø, M. D. Sørensen, A. Soor, M. Stahlhut, M. Bertelsen, K. M. Engell and T. Högberg, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 54–60; (c) S. J. McKerrall, L. Jørgensen, C. A. Kuttruff, F. Ungeheuer and P. S. Baran, *J. Am. Chem. Soc.*, 2014, **136**, 5799–5810.
- 10 (a) A. K. Miller, C. C. Hughes, J. J. Kennedy-Smith, S. N. Gradl and D. Trauner, *J. Am. Chem. Soc.*, 2006, **128**, 17057–17062; (b) C. C. Hughes, J. J. Kennedy-Smith and D. Trauner, *Org. Lett.*, 2003, **5**, 4113–4115; (c) A. Srikrishna and D. H. Dethe, *Org. Lett.*, 2004, **6**, 165–168; (d) C. A. McGowan, A.-K. Schmieder, L. Roberts and M. F. Greaney, *Org. Biomol. Chem.*, 2007, **5**, 1522–1524.
- 11 (a) J. R. Hanson, *Nat. Prod. Rep.*, 2013, **30**, 1346–1356; (b) D. L. Chen, X. Y. Liu, H. Cheng and F. P. Wang, *Chin. Chem. Lett.*, 2011, **22**, 774–776; (c) F. de J. Cortez, D. Lapointe, A. M. Hamlin, E. M. Simmons and R. Sarpong, *Tetrahedron*, 2013, **69**, 5665–5676; (d) F. de J. Cortez and R. Sarpong, *Org. Lett.*, 2010, **12**, 1428–1431.
- 12 (a) G. Majetich and Y. Zhang, *J. Am. Chem. Soc.*, 1994, **116**, 4979–4980; (b) G. Majetich, Y. Zhang, X. Tian, J. E. Britton, Y. Li and R. Phillips, *Tetrahedron*, 2011, **67**, 10129–10146.
- 13 (a) M. Reiter, S. Torssell, S. Lee and D. W. C. MacMillan, *Chem. Sci.*, 2010, **1**, 37–42; (b) D. R. Laplace, B. Verbraeken, K. V. Hecke and J. M. Winne, *Chem. – Eur. J.*, 2014, **20**, 253–262.
- 14 (a) A. R. Hardin-Narayan, E. M. Simmons and R. Sarpong, *Eur. J. Org. Chem.*, 2010, 3553–3567; (b) C. F. Nising and S. Bräse, *Angew. Chem., Int. Ed.*, 2008, **47**, 9389–9391; (c) M. Dai and S. J. Danishefsky, *Tetrahedron Lett.*, 2008, **49**, 6610–6612; (d) K. C. Nicolaou, X.-S. Peng, Y.-P. Sun, D. Polet, B. Zou, C. S. Lim and D. Y.-K. Chen, *J. Am. Chem. Soc.*, 2009, **131**, 10587–10597; (e) E. M. Simmons, A. R. Hardin-Narayan, X. Guo and R. Sarpong, *Tetrahedron*, 2010, **66**, 4696–4700.
- 15 T. Graening and H.-G. Schmalz, *Angew. Chem., Int. Ed.*, 2004, **43**, 3230–3256.
- 16 (a) K. M. Peese and D. Y. Gin, *J. Am. Chem. Soc.*, 2006, **128**, 8734–8735; (b) S. S. Bhar and M. M. V. Ramana, *Stud. Nat. Prod. Chem.*, 2008, **35**, 399–422.
- 17 H. Muratake and M. Natsume, *Angew. Chem., Int. Ed.*, 2004, **43**, 4646–4649.
- 18 (a) C. H. Heathcock, M. M. Hansen, R. B. Ruggeri and J. C. Kath, *J. Org. Chem.*, 1992, **57**, 2544–2553; (b) Z. Lu, Y. Li, J. Deng and A. Li, *Nat. Chem.*, 2013, **5**, 679–684; (c) H. Wu, X. Zhang, L. Ding, S. Chen, J. Yang and X. Xu, *Planta Med.*, 2013, **79**, 1589–1598.
- 19 C. Thebtaranonth and Y. Thebtaranonth, *Cyclization Reactions*, CRC Press Inc., Boca Raton, FL, 1994.
- 20 (a) Y.-D. Zhang, Y.-F. Tang, T.-P. Luo, J. Shen, J.-H. Chen and Z. Yang, *Org. Lett.*, 2006, **8**, 107–110; (b) J. A. Enquist and B. M. Stoltz, *Nature*, 2008, **453**, 1228–1231; (c) J. A. Enquist, S. C. Virgil and B. M. Stoltz, *Chem. – Eur. J.*, 2011, **17**, 9957–9969; (d) T. Magauer, J. Mulzer and K. Tiefenbacher, *Org. Lett.*, 2009, **11**, 5306–5309; (e) M. S. Dowling and C. D. Vanderwal, *J. Am. Chem. Soc.*, 2009, **131**, 15090–15091; (f) B. Shi, N. A. Hawryluk and B. B. Snider, *J. Org. Chem.*, 2003, **68**, 1030–1042; (g) D. S. Tan, G. B. Dudley and S. J. Danishefsky, *Angew. Chem., Int. Ed.*, 2002, **41**, 2185–2188; (h) S. Lin, G. B. Dudley, D. S. Tan and S. J. Danishefsky, *Angew. Chem., Int. Ed.*, 2002, **41**, 2188–2191; (i) G. S. Weatherhead, G. A. Cortez, R. R. Schrock and A. H. Hoveyda, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5805–5809.
- 21 (a) M. Harmata, *Tetrahedron*, 1997, **53**, 6235–6280; (b) M. Harmata, *Chem. Commun.*, 2010, **46**, 8886–8903; (c) E. H. Krenske, K. N. Houk and M. Harmata, *Org. Lett.*, 2010, **12**, 444–447; (d) Y. Lian, L. C. Miller, S. Born, R. Sarpong and H. M. L. Davies, *J. Am. Chem. Soc.*, 2010, **132**, 12422–12425.
- 22 P. A. Wender, H. Takahashi and B. Witulski, *J. Am. Chem. Soc.*, 1995, **117**, 4720–4721.



- 23 (a) P. A. Evans, T. Baikstis and P. A. Inglesby, *Tetrahedron*, 2013, **69**, 7826–7830; (b) L. Saya, G. Bhargava, M. A. Navarro, M. Guliás, F. López, I. Fernández, L. Castedo and J. L. Mascareñas, *Angew. Chem., Int. Ed.*, 2010, **49**, 9886–9890; (c) N. Etkin, T. L. Dzwiniel, K. E. Schweibert and J. M. Stryker, *J. Am. Chem. Soc.*, 1998, **120**, 9702–9703.
- 24 E. J. Kantorowski and M. J. Kurth, *Tetrahedron*, 2000, **56**, 4317–4353.
- 25 B. M. Fraga, *Nat. Prod. Rep.*, 2013, **30**, 1226–1264.
- 26 D. A. Foley and A. R. Maguire, *Tetrahedron*, 2010, **66**, 1131–1175.
- 27 (a) T.-L. Ho, *Carbocycle Construction in Terpene Synthesis*, VCH, New York, NY, 1988; (b) T.-L. Ho, *Enantioselective Synthesis: Natural Products From Chiral Terpenes*, Wiley, New York, NY, 1992.
- 28 A. Mendoza, Y. Ishihara and P. S. Baran, *Nat. Chem.*, 2012, **4**, 21–25.
- 29 (a) I. Ojima, M. Tzamarioudaki, Z. Li and R. J. Donovan, *Chem. Rev.*, 1996, **96**, 635–662; (b) C. P. Dell, *Contemp. Org. Synth.*, 1997, **4**, 87–117; (c) K. I. Booker-Milburn and A. Sharpe, *Contemp. Org. Synth.*, 1996, **3**, 473–498; (d) R. C. Hartley and S. T. Caldwell, *J. Chem. Soc., Perkin Trans. 1*, 2000, 477–501.
- 30 T. Harayama, Y. Shinkai, Y. Hashimoto, H. Fukushi and Y. Inubushi, *Tetrahedron Lett.*, 1983, **24**, 5241–5244.
- 31 A. R. Angeles, D. C. Dorn, C. A. Kou, M. A. S. Moore and S. J. Danishefsky, *Angew. Chem., Int. Ed.*, 2007, **46**, 1451–1454.
- 32 G. Kieselmeier and B. Föhlisch, *Tetrahedron Lett.*, 2000, **41**, 1375–1379.
- 33 T. J. Brocksom, E. T. C. Pesquero and F. T. Lopes, *Synth. Commun.*, 1990, **20**, 1181–1191.
- 34 (a) J. Zukerman-Schpector, I. Caracelli, C. C. Carvalho, M. L. de Faria, F. C. Silva, L. G. de O Matias and T. J. Brocksom, *J. Braz. Chem. Soc.*, 2001, **12**, 154–158; (b) T. J. Brocksom, U. Brocksom and D. Frederico, *Tetrahedron Lett.*, 2004, **45**, 9289–9291; (c) T. J. Brocksom, A. G. Corrêa, R. M. Naves, F. Silva Jr., V. Catani, M. A. Ceschi, J. Zukerman-Schpector, A. P. Toloi, M. L. Ferreira and U. Brocksom, in *Organic Synthesis: Theory and Applications*, ed. T. Hüdlický, Elsevier Science Ltd, 2001, vol. 5, pp. 39–87.
- 35 (a) M. L. de Faria, R. de A. Magalhães, F. C. Silva, L. G. de O. Matias, M. A. Ceschi, U. Brocksom and T. J. Brocksom, *Tetrahedron: Asymmetry*, 2000, **11**, 4093–4103; (b) T. J. Brocksom, U. Brocksom and F. P. Barbosa, *J. Braz. Chem. Soc.*, 2006, **17**, 792–796. The term overbred was introduced in R. W. Hoffmann, *Elements of Synthesis Planning*, Springer, Berlin, p. 106, 2009, to describe synthesis by way of an intermediate with more rings than in the final product.
- 36 T. J. Brocksom, U. Brocksom, D. P. Sousa and D. Frederico, *Tetrahedron: Asymmetry*, 2005, **16**, 3628–3632. The exclusive regioselectivity of our Tiffeneau–Demjanov rearrangement is attributed to the preferential migratory aptitude of sp<sup>2</sup> carbon atoms over sp<sup>3</sup> carbon atoms.
- 37 (a) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1962, **84**, 3782–3783; (b) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, **87**, 1345–1353; (c) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, **87**, 1354–1364; (d) E. J. Corey and M. Chaykovsky, *Org. Synth. Coll.*, 1973, **5**, 755–757.
- 38 (a) B. Zhou, X. Li, H. Feng and Y. Li, *Tetrahedron*, 2010, **66**, 5396–5401; (b) M. E. Kuehne and F. Xu, *J. Org. Chem.*, 1993, **58**, 7490–7497; (c) S. J. Danishefsky, J. J. Masters, W. B. Young, J. T. Link, L. B. Snyder, T. V. Magee, D. K. Jung, R. C. A. Isaacs, W. G. Bornmann, C. A. Alaimo, C. A. Coburn and M. J. di Grandi, *J. Am. Chem. Soc.*, 1996, **118**, 2843–2859.
- 39 H. J. Emeléus and H. G. Heal, *J. Chem. Soc.*, 1946, 1126–1131.
- 40 Selected publications featuring flow chemistry: (a) J. Wegner, S. Ceylan and A. Kirschning, *Adv. Synth. Catal.*, 2012, **354**, 17–57; (b) J. P. McMullen and K. F. Jensen, *Annu. Rev. Anal. Chem.*, 2010, **3**, 19–42; (c) D. Webb and T. F. Jamison, *Chem. Sci.*, 2010, **1**, 675–680; (d) I. R. Baxendale, *J. Chem. Technol. Biotechnol.*, 2013, **88**, 519–552; (e) S. Marre and K. F. Jensen, *Chem. Soc. Rev.*, 2010, **39**, 1183–1202; (f) J.-i. Yoshida, *Chem. Rec.*, 2010, **10**, 332–341; (g) J. C. Pastre, D. L. Browne and S. V. Ley, *Chem. Soc. Rev.*, 2013, **42**, 8849–8869; (h) S. Newton, C. F. Carter, C. M. Pearson, L. de C. Alves, H. Lange, P. Thansandote and S. V. Ley, *Angew. Chem., Int. Ed.*, 2014, **53**, 4915–4920; (i) X. Y. Mak, P. Laurino and P. H. Seeberger, *Beilstein J. Org. Chem.*, 2009, **5**, 19; (j) L. M. Kreis, S. Krautwald, N. Pfeiffer, R. E. Martin and E. M. Carreira, *Org. Lett.*, 2013, **15**, 1634–1637.
- 41 <http://www.vapourtec.co.uk/products/eseriessystem> (accessed December 2014).
- 42 Recent publications featuring organometallics in flow: (a) P. R. D. Murray, D. L. Browne, J. C. Pastre, C. Butters, D. Guthrie and S. V. Ley, *Org. Process Res. Dev.*, 2013, **17**, 1192–1208; (b) J. A. Newby, L. Huck, D. W. Blaylock, P. M. Witt, S. V. Ley and D. L. Browne, *Chem. – Eur. J.*, 2014, **20**, 263–271; (c) W. Shu and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2012, **51**, 5355–5358; (d) D. Webb and T. F. Jamison, *Org. Lett.*, 2011, **14**, 568–571.
- 43 (a) W. F. Newhall, *J. Org. Chem.*, 1959, **24**, 1673–1676; (b) M. W. Bedore, N. Zaborenko, K. F. Jensen and T. F. Jamison, *Org. Process Res. Dev.*, 2010, **14**, 432–440; (c) M. Nagel, H.-J. Hansen and G. Fráter, *Synlett*, 2002, 280–284.
- 44 M. A. McKinney and P. P. Patel, *J. Org. Chem.*, 1973, **38**, 4059–4064.
- 45 (a) J. C. Sheehan and V. A. Bolhofer, *J. Am. Chem. Soc.*, 1950, **72**, 2786–2788; (b) M. S. Gibson and R. W. Bradshaw, *Angew. Chem., Int. Ed. Engl.*, 1968, **7**, 919–930.
- 46 J. O. Osby, M. G. Martin and B. Ganem, *Tetrahedron Lett.*, 1984, **25**, 2093–2096.
- 47 (a) M. Tiffeneau, M. P. Weill and B. Tehoubar, *Compt. Rend.*, 1937, 54–56; (b) P. A. S. Smith and D. R. Baer, *Org. React.*, 1960, **11**, 157–188.
- 48 D. Fattori, S. Henry and P. Vogel, *Tetrahedron*, 1993, **49**, 1649–1664.



- 49 (a) P. Klahn, A. Duschek, C. Liébert and S. F. Kirsch, *Org. Lett.*, 2012, **14**, 1250–1253; (b) H.-J. Liu and B.-Y. Zhu, *Can. J. Chem.*, 1991, **69**, 2008–2013; (c) Y. Liu, K. Lu, M. Dai, K. Wang, W. Wu, J. Chen, J. Quan and Z. Yang, *Org. Lett.*, 2007, **9**, 805–808; (d) J. Le Nôtre, A. C. Martinez, P. H. Dixneuf and C. Bruneau, *Tetrahedron*, 2003, **59**, 9425–9432.
- 50 (a) B. M. Trost, J. Florez and D. J. Jebaratnam, *J. Am. Chem. Soc.*, 1987, **109**, 613–615; (b) Y.-D. Wu, K. N. Houk and B. M. Trost, *J. Am. Chem. Soc.*, 1987, **109**, 5560–5561; (c) B. M. Trost and D. J. Jebaratnam, *Tetrahedron Lett.*, 1987, **28**, 1611–1614; (d) E. Toromanoff, *Tetrahedron*, 1980, **36**, 2809–2931.

