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Synthesis of the AB ring system of clifednamide utilizing Claisen rearrangement and Diels–Alder reaction as key steps†

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In order to construct the functionalized AB ring system of clifednamide, member of the class of macrocyclic tetramic acid lactams, a synthesis was developed which utilized an Ireland–Claisen rearrangement and an intramolecular Diels–Alder reaction. Starting from di-*O*-isopropylidene-D-mannitol the allyl carboxylate precursor for the sigmatropic rearrangement was prepared. This rearrangement proceeded diastereoselectively only in the presence of an allyl silyl ether instead of the parent enone in the side chain, as suggested by deuteration experiments. A subsequent Diels–Alder reaction yielded the target ethyl hexahydro-1*H*-indene-carboxylate with high diastereoselectivity. Quantum-chemical investigations of this intramolecular Diels–Alder reaction support the proposed configuration of the final product.

Introduction

Macrocyclic tetramic acid lactams are a subfamily among the 2,4-pyrrolidinedione (tetramic acid) natural products[1] with a wide range of biological activities. This class of structurally complex molecules is characterized by a macrocyclic lactam ring with incorporated tetramic acid moiety, fused to carbocycles based on either bicyclo[3.3.0]octane or a dodecahydro-*as*-indacene or a related system. Representative examples are ikarugamycin (**1**), maltophilin (**2**), clifednamide A (**3a**) and B (**3b**) as well as cylindramide (**4**) (Fig. 1).

Ikarugamycin (**1**) which was isolated in 1972 from a culture broth of *Streptomyces phaeochromogenes*[2] shows strong specific antiprotozoal activity, antiamoebic activity and activity against some Gram-positive bacteria.[2] The structure and absolute stereochemistry of **1** was assigned by chemical degradation and spectroscopic methods,[3] and recently, its biosynthesis has been reconstituted in *Escherichia coli*.[4] Maltophilin (**2**), bearing a cyclopenta[*a*]indene core, was obtained from strains of *Stenotrophomonas maltophilia* R3089.[5] It is an antifungal compound which is active against various human-pathogenic and phytopathogenic fungi.[5]

In 2010 Clardy and coworkers isolated clifednamide A (**3a**) and B (**3b**) from a strain *Streptomyces* sp. JV178.[6] They postulated a biosynthetic pathway and common biosynthetic origins for polycyclic tetramate macrolactams.[7] Cylindramide (**4**) originally isolated in 1993 from the marine sponge *Halichondria cylindrata* exhibits pronounced cytotoxicity against B16 melanoma cells[8] and other mammalian cell lines, as was published in 2007.[9] The cytotoxicity of **4** was found to be correlated with its complexation of Ca^{2+}.[9]

Both the challenging molecular architecture and the broad variety of biological activities of these natural products have kindled an interest in their total synthesis. Two total syntheses of ikarugamycin (**1**) have been independently developed by Boeckman[10] and by Paquette[11] employing an intramolecular Diels–Alder reaction and an anionic oxy-Cope rearrangement as key steps, respectively. Convergent, highly stereoselective total syntheses of cylindramide (**4**) were developed by the group of Phillips[12] and Laschat,[13] and furthermore, numerous synthetic routes to the carbocyclic dodecahydro-*as*-indacene fragment of **1** have been established.[14–17] However, surprisingly no synthetic strategies for the related clifednamides **3** have been reported, so far. Motivated by Boeckman's initial success on ikarugamycin (**1**) we anticipated that a related approach might be suitable for **3** as well. Herein we report on our route towards the bicyclic AB system of clifednamide **3**.

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†Electronic supplementary information (ESI) available: Attempted preparation of phosphonium salt **8a**, preparation of derivatives **16**, **17**, **19** and **20**, preparation of **15b** and its rearrangement, alternative route to **15a**, quantum-chemical investigation of the intramolecular Diels–Alder cycloaddition to **11a**, biological activity studies as well as ^{1}H and ^{13}C NMR spectra of new compounds. See DOI: 10.1039/c5ob01491c

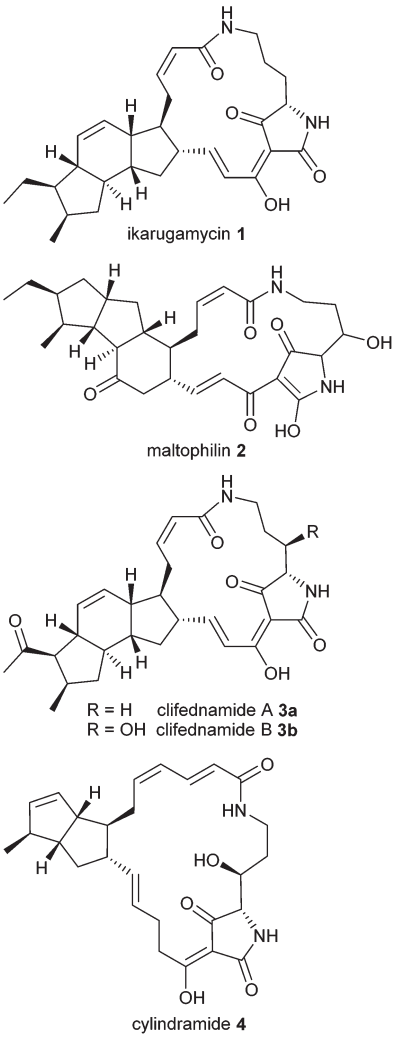
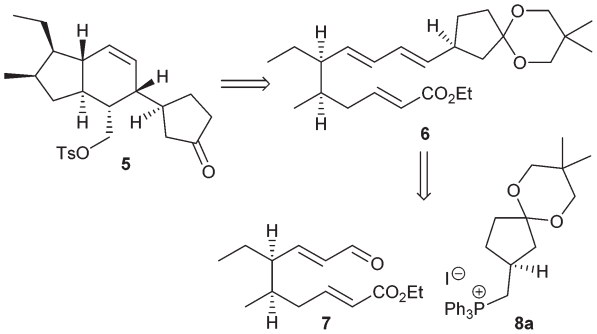
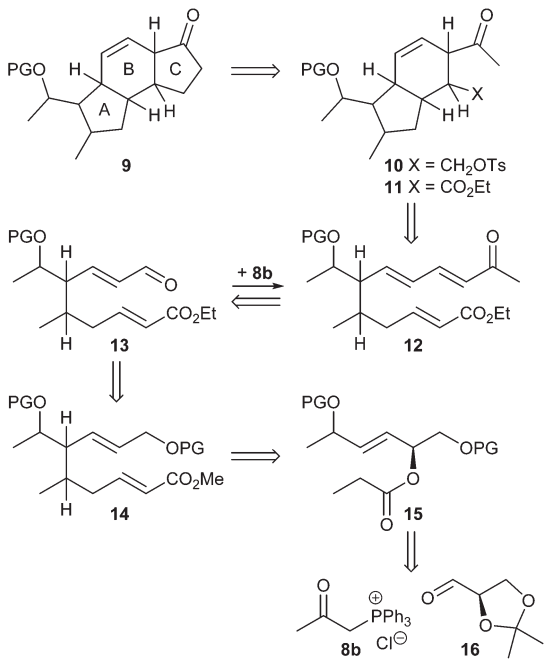


Fig. 1 Representative polycyclic tetramate macrolactams **1–4**.



Scheme 1 Subunits for Boeckman's key intramolecular Diels–Alder reaction to the AB system of ikarugamycin (**1**).[10]



Scheme 2 Retrosynthetic pathway to the AB system of clifednamide **3**.

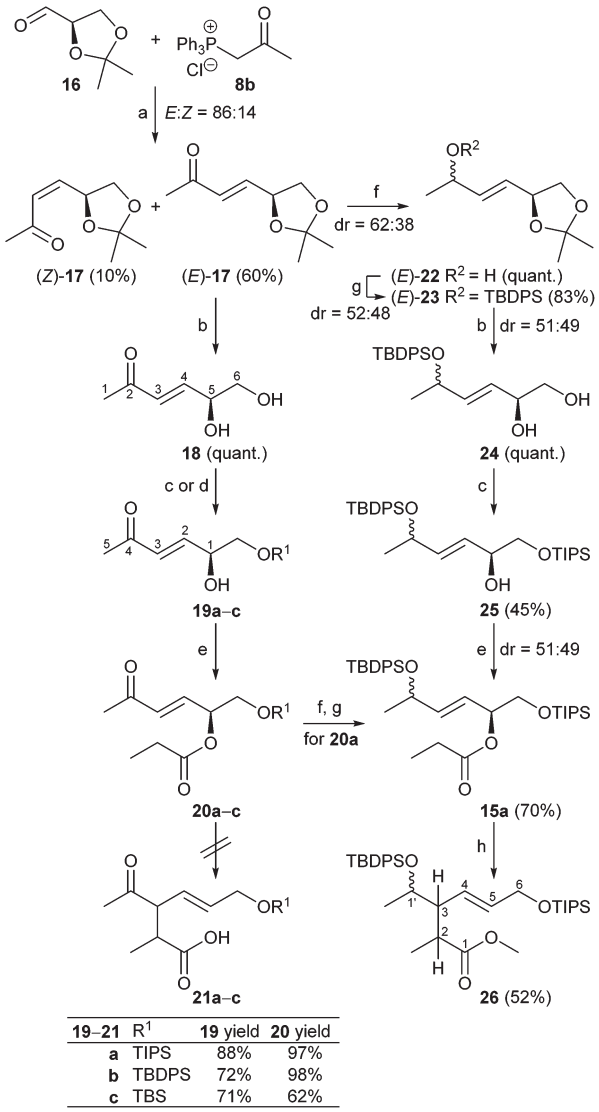
Results and discussion

The construction of the AB system **5** in ikarugamycin (**1**) according to Boeckman's synthesis was based on an intramolecular Diels–Alder reaction of triene **6** prepared from the two subunits **7** and **8a** (Scheme 1).[10]

We initially intended to adopt the ikarugamycin route for clifednamide A (**3a**). However, all attempts failed to obtain phosphonium salt **8a** from the precursor iodide (see ESI† for details). Thus, we envisaged a modified Boeckman route to **3** using **8b** instead of **8a** and encompassing a functionalization of the C-ring of tricyclic compound **9** at a later stage as well as an intramolecular enolate alkylation of **10** (Scheme 2).

As shown in Scheme 3, (*R*)-glyceraldehyde acetonide **16** prepared from di-*O*-isopropylidene-D-mannitol as described in the literature[18] was submitted to a Wittig reaction with **8b** giving a (86 : 14) mixture of *E*/*Z*-isomers **17**.[19] Chromatographic separation yielded (*E*)-**17** and (*Z*)-**17** in 60% and 10%, respectively. Acetal cleavage of (*E*)-**17** with a mixture of acetic acid/H_2O/THF (4 : 2 : 1) according to Horiguchi[20] gave the diol **18** quantitatively. Silylation to **19a** with only a small excess of TIPSCl and base to avoid double silylation and subsequent esterification of the secondary hydroxy group with propionyl chloride afforded compound **20a** in 97% yield. Silyl ethers **20b** and **c** were prepared analogously in 98% and 62% yield, respectively.

The Ireland–Claisen rearrangement was investigated in detail with silyl ethers **20b,c** (Table 1). For example, deprotonation of **20c** with LDA in THF at −78 °C and addition of TMSCl for 4 days following the Ireland protocol[21] did not provide any trace of the rearranged product **21c** according to the crude NMR spectra (entry 1). Using LiHMDS with NEt_3 in toluene according to the method by Collum[22] also failed to give **21b,c** (entries 2, 4, and 11). It should be mentioned that a substrate closely related to **20c** but without the ketone moiety was



19–21	R^1	19 yield	20 yield
a	TIPS	88%	97%
b	TBDPS	72%	98%
c	TBS	71%	62%

Scheme 3 Reagents and conditions: (a) NEt_3, CH_2Cl_2, reflux, 4 h; (b) AcOH/H_2O/THF (4 : 2 : 1), reflux, 2 h; (c) TIPSCl (1.1 equiv.), imidazole (1.1 equiv.), DMF, 0 °C → r.t., 20 h; (d) TBDPSCl or TBSCl (1.1 equiv.), NEt_3, DMF, r.t., 20 h; (e) propionyl chloride (1.2 equiv.), pyridine (1.2 equiv.), CH_2Cl_2, 0 °C → r.t., 4 h; (f) $NaBH_4$ (0.6 equiv.), EtOH, r.t., 3 h; (g) TBDPSCl (1.2 equiv.), imidazole (2 equiv.), DMF, r.t., 6 h; (h) (1) LDA (1.8 equiv.), TMSCl (1.1 equiv.), THF, –100 °C, 1 h, r.t., 20 h; (2) CH_2N_2 (2 equiv.), Et_2O, 0 °C, 1 h, for details concerning dr of **26** see Scheme 5. Numbering for NMR assignment.

converted to the rearranged product using Collum's conditions.[23] Next a method by Kishi[24] was tested, employing LiHMDS and TIPSCl in THF. Alternatively LDA was used, but neither method worked (entries 3, 5, 7, and 10).

Finally, a protocol by Burke was employed,[25] which he had been successfully applied to a Claisen substrate carrying an enone moiety in a similar fashion as compared to **20c** (entries 8 and 9). Even this method failed. Presumably, the enolizable enone (or ketone) might interfere with the Claisen rearrangement under basic conditions. However, it should be noted that Paterson realized the Claisen rearrangement with a complex polyketide substrate in high yield despite the presence of an additional enolizable ketone.[26]

In order to prove the hypothesis of competing enolate formation, a deuteration experiment was carried out. *tert*-Butyldiphenylsilyl ether **20b** was deprotonated with LDA and the reaction was quenched with D_2O. Chromatographic purification gave a pure fraction suitable for ^{1}H NMR investigation, where the signals of the olefinic protons H-2 and H-3 which remain unaffected by the deuteration were set to 1 as reference (see ESI† for details).

Integration of the H-5 protons resulted in a value of 2.01 instead of the expected 3. That means, the derivative with fully deuterated CD_3 (no signal in the ^{1}H NMR spectrum) was obtained with 33% percentage (Scheme 4). In contrast, double deuteration at C-6 proceeded with 9%, as shown by the integration value of 1.82 instead of 2 for the H-6 proton. Furthermore, the spectra were analyzed regarding a H/D isotope effect.[27] Indeed, the H/D exchange caused an upfield shift of the H-5 proton signals, allowing independent integration of the triplet for CH_2D and the quintet for CHD_2 formed by coupling between H and D. Thus, integration of signals for the deuteration at position 5 gave a percentage of 13% (**20b**), of 25% monodeuterated and of 28% double deuterated derivative. The degree of deuteration is 87%.

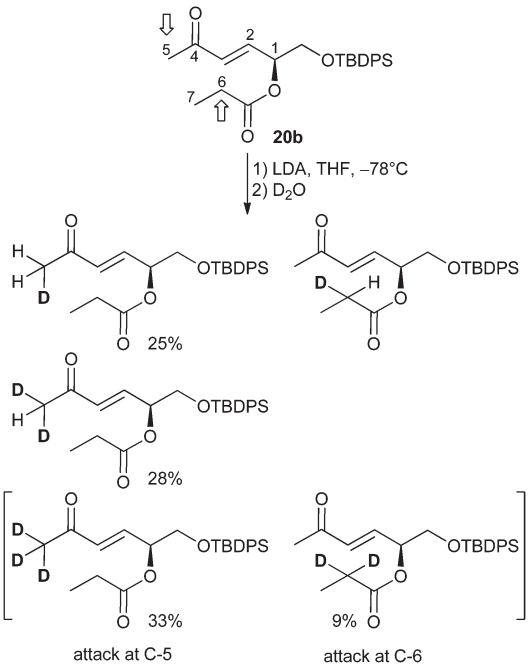
A comparison of the fully deuterated CD_3 group (C-5) with the double deuterated CD_2 group at C-6 indicates a more facile H/D exchange of H-5 protons than of H-6 ones. Thus the attack of the base at the CH_3 group is preferred.

The results revealed that indeed under kinetic deprotonation conditions competing enolate formation of both ester and methylvinylketone had taken place. In order to circumvent this problem, the enone moiety in **20a** was first reduced with $NaBH_4$ to a (52 : 48) mixture of diastereomeric allylic alcohols (88%) that was subsequently protected with TBDPSCl, imidazole to afford ester **15a** with a primary OTIPS and secondary OTBDPS group in 70% yield with dr 51 : 49 (Scheme 3). Alternatively, a (51 : 49) mixture of ester **15a** was accessible starting from (*E*)-**17** as depicted in Scheme 3 (see ESI† for details). Then ester **15a** was treated at −100 °C with LDA in THF in the presence of TMSCl as trapping agent, followed by esterification of the rearranged product with diazomethane in Et_2O at 0 °C. After workup, the ester **26** was obtained in 52% yield (Scheme 3). As outlined in Scheme 5, the Claisen rearrangement resulted in four diastereomeric esters **26a–d** (dr = 50 : 47 : 2 : 1). This ratio, however, varied throughout the follow-up reaction sequence (Scheme 6) presumably due to partial enrichment of diastereomers during chromatographic purification steps.

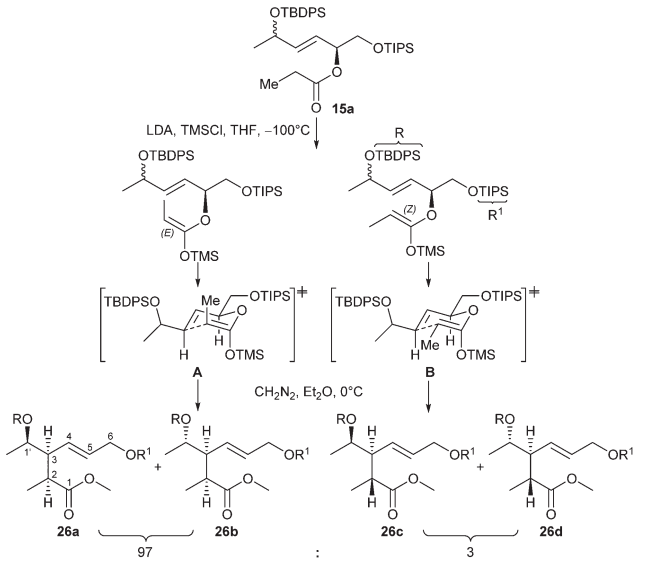
The observed diastereoselectivity concerning the newly generated stereogenic centres C-2, C-3 (**26a,b** : **26c,d** = 97 : 3) is due to the known preference of LDA to generate the (*E*)-enolate, which resulted in the formation of **26a,b** as major diastereomers *via* transition state **A**, whereas **26c,d** were generated from small amounts of (*Z*)-enolate *via* transition state **B**. In contrast, nearly equimolar mixtures were obtained regarding stereocentre C-1′.

Table 1 Rearrangement of derivatives **20b,c** under various conditions[21–25]

Entry	Compd	Base 1	Base 2	Additive	Solvent	T (°C)	t (h)
1	**20c**	LDA	—	TMSCl	THF	−78 → 60	96
2	**20c**	LiHMDS	Et_3N	—	Toluene	−78 → r.t.	20
3	**20c**	LiHMDS	—	TIPSCl	THF	−78 → 0	24
4	**20c**	LiHMDS	Et_3N	TIPSCl	Toluene	−78 → r.t.	24
5	**20b**	LDA	—	TIPSCl	THF	−78 → 0 → r.t. → 40	24
6	**20b**	LDA	—	TESCl	THF	−78 → 0 → r.t. → 40	24
7	**20b**	LiHMDS	—	TIPSCl	THF	−78 → 0	24
8	**20b**	LDA	Et_3N	TMSCl	THF	−100 → r.t. → 50	24
9	**20b**	LDA	Et_3N	TIPSCl	THF	−100 → r.t.	24
10	**20b**	LiHMDS	—	TIPSCl	THF	−100 → r.t.	4
11	**20b**	LiHMDS	Et_3N	—	Toluene	−100 → r.t.	4



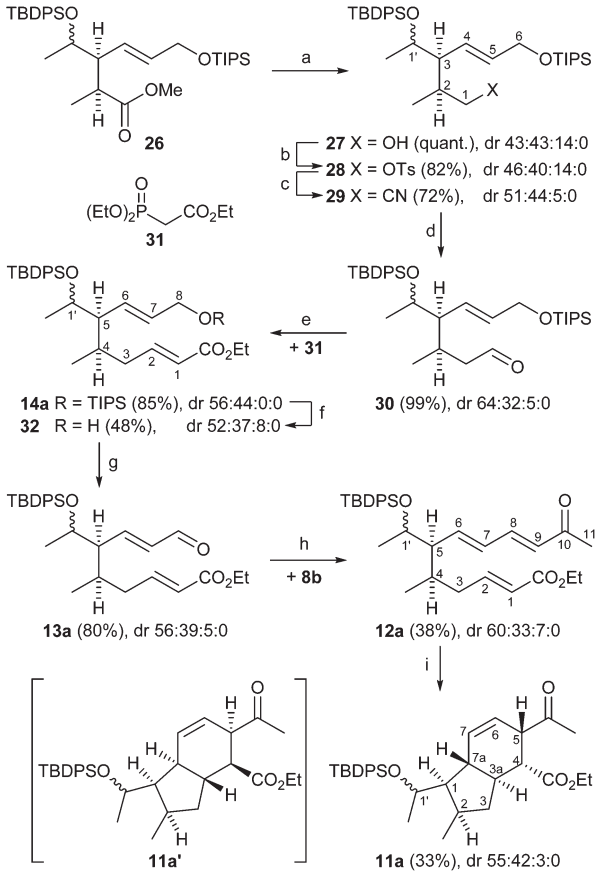
Scheme 4 Deuteration experiment of **20b** and percentage obtained for differently deuterated derivatives by integration of ^{1}H NMR signals. The percentage of the C-6 monodeuterated derivative could not be determined due to signal overlap.



Scheme 5 Ireland–Claisen rearrangement of ester **15a** with LDA in the presence of TMSCl *via* assumed preferred transition states for the (*E*)-enolate (**A**) and (*Z*)-enolate (**B**), resulting in the diastereomeric products **26a–d** in a ratio of 50 : 47 : 2 : 1 in 52% total yield.

Reduction of diastereomeric esters **26** with DIBAL afforded alcohols **27** quantitatively, which were tosylated to **28** (82%). Nucleophilic substitution with KCN in DMF at 80 °C provided nitriles **29** in 72% yield (Scheme 6). Reduction of the nitriles **29** with DIBAL in hexane gave aldehydes **30** (99%), which were submitted to a Horner–Wadsworth–Emmons olefination with phosphonate **31** in the presence of LiCl and DBU to yield (*E*)-crotonates **14a** in 85%. Conversion to enals **13a** (dr 56 : 39 : 5 : 0) was effected in 38% yield over two steps by treatment of **14a** with TBAF in THF at 0 °C followed by Dess–Martin oxidation of the resulting allylic alcohol **32**. By running the desilylation on a small scale product **32** could be obtained quantitatively. However, performing the reaction on a preparative scale led to a decreased yield presumably due to the large excess of basic TBAF resulting in partial deprotection of the TBDPS group or attack at the enoate.

Assembly of the key *E*,*E*-ketotriene ester **12a** (38%) was accomplished by Wittig olefination of **13a** with the ylide generated *in situ* from phosphonium salt **8b** and NEt_3. Triene **12a** underwent an intramolecular Diels–Alder cycloaddition by heating in the presence of 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT) in toluene[28] under reflux for 4 days providing, after aqueous workup, the desired hexahydroindene **11a** in 33% yield. It should be noted that triene **12a** is rather sensitive towards polymerization during workup and purification. This problem was also encountered in the Diels–Alder reaction of **12a** to **11a**. Even in the presence of radical inhibitor BHT polymerization could not be completely suppressed, resulting



Scheme 6 Reagents and conditions: (a) DIBAL (3.0 equiv.), THF, 0 °C, 3 h; (b) *p*TsCl (1.1 equiv.), NEt_3, DMAP, CH_2Cl_2, 0 °C → r.t., 20 h; (c) KCN (5.5 equiv.), DMF, 80 °C, 3 h; (d) DIBAL (1.06 equiv.), hexane, –78 °C, 1 h; (e) **31** (1.4 equiv.), DBU, LiCl, $MeCN/CH_2Cl_2$ (1 : 1), 0 °C → r.t., 15 h; (f) TBAF (3 equiv.), THF, 0 °C, 1 h; (g) DMP (1.3 equiv.) CH_2Cl_2, 0 °C, 3 h; (h) **8b** (1.1 equiv.), NEt_3 (2 equiv.), CH_2Cl_2, reflux, 23 h; (i) BHT (0.1 equiv.), toluene, reflux, 4 d. Numbering for NMR assignment.

in a moderate yield of 33%. The NMR spectra of **11a** showed only two sets of signals in a 1 : 1 ratio due to the undefined stereogenic centre at C-1′ in the side chain. Since no further sets of NMR signals were observed, we anticipated that the cycloaddition proceeded in stereospecific fashion as reported by Boeckman[10b] yielding only one relative configuration.

In order to understand the stereoselectivity of this Diels–Alder reaction, we carried out a set of quantum-chemical calculations using density functional theory (DFT) (see ESI† chapter 7 for details of the computations). The transition state structures leading to the two diastereomers **11a** and **11a′** shown in Scheme 6 have been determined (Fig. 2). According to the computations, the reaction barriers of the two pathways differ by more than 30 kJ mol^{-1}, furthermore the final product **11a** is energetically more favourable than **11a′** by nearly the same amount. While the computations are not fully exhaustive in terms of exploring the entire conformational space (in particular concerning the OTBDPS residue) and full thermal averaging, the energy differences appear sufficiently significant to understand the selectivity of the reaction and to claim that indeed **11a** is the preferred product.

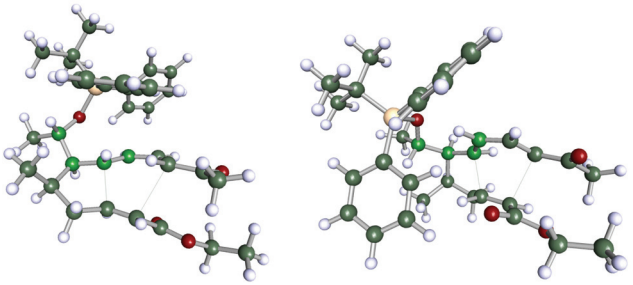


Fig. 2 Computed transition structures leading to **11a** (left) and **11a′** (right), respectively (see ESI† for details of computations). The centres C-1′, C-5, C-6, C-7 (*cf.* Scheme 6) are highlighted to emphasize the main conformational difference of the two structures.

Investigation of the structural differences of the two transition states confirms the proposal by Boeckman.[10] In the less favourable pathway, the diene group is forced into a nearly eclipsed conformation with respect to one of the residues at centre C-5 (Fig. 2). The selectivity of the reaction is maintained for less bulky substituents, as well. In a set of computations in which the OTBDPS residue was replaced by OMe we found the same energetic preference for the reaction path leading to the OMe equivalent of **11a**. However, the difference between the activation energies was somewhat smaller (around 10 kJ mol^{-1}), suggesting that large residues at the C-1′ position increase the selectivity of the reaction.

So far no informations about the biological properties of clifednamide **3** are available. As there are several examples in the literature that truncated natural products and fragments often still retain biological activity,[29] we preliminary investigated some synthetic precursors and bicyclic ester **11a** with respect to antiproliferative activities (see ESI†).

Conclusions

In summary, a stereoselective route to the AB-ring system **11a** of clifednamide **3** was developed with Ireland–Claisen rearrangement and intramolecular thermal Diels–Alder reaction as the key steps in the sequence. In comparison with Boeckman's ikarugamycin synthesis our strategy circumvents the use of optically pure cyclopentane-derived ylide **8a** and utilizes the simpler ylide **8b** instead. The study clearly showed that the Ireland–Claisen rearrangement required a silyl ether in the side chain of the allyl carboxylate **15a** rather than a ketone (**20a**). Compound **11a** was obtained in 17 steps and 1.3% overall yield from D-mannitol. Quantum-chemical calculations explain the selectivity of the final Diels–Alder reaction and confirm the proposed conformation of **11a**. Further work is already underway to convert compound **11a** to the tricyclic ABC system of clifednamide.

Experimentals

General information

NMR spectra were recorded on a Bruker Avance 300 or a Bruker Avance 500 spectrometer in $CDCl_3$ with TMS as an internal standard. IR spectra were recorded on a Bruker FT-IR-spectrometer Vektor 22 with MKII golden gate single reflection Diamant ATR-system. Mass spectra were recorded on a Varian MAT 711 (EI, 70 eV) and a Bruker Daltonics micrOTOF_Q (ESI) with nitrogen as carrier gas. Optical rotations were measured with a Perkin-Elmer 241 polarimeter at 20 °C. Flash chromatography was performed on silica gel, grain size 40–63 μm (Fluka). Moisture-sensitive reactions were performed under nitrogen atmosphere in oven-dried glassware. All reagents were used as purchased unless otherwise noted. Solvents used for chromatography were distilled. THF was distilled from potassium/benzophenone, CH_2Cl_2 and toluene from CaH_2. The reactions were monitored by TLC (Merck 60 F_{254} plates).

(1*S*,4*E*)-4-{[*tert*-Butyl(diphenyl)silyl]oxy}-1-{[(triisopropylsilyl)oxy]methyl}pent-2-enyl propionate (15a). (a) To a solution of **20a** (1.33 g, 3.88 mmol) in EtOH (13 mL) $NaBH_4$ (88.0 mg, 2.33 mmol) was added portionwise and the reaction mixture stirred at r.t. for 3 h. After addition of a 1 N HCl solution (2 mL) and H_2O (10 mL), the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed to give (1*S*,2*E*)-4-hydroxy-1-{[(triisopropylsilyl)oxy]methyl}pent-2-enyl propionate (1.20 g, 3.40 mmol, 88%, purity 98% by ^{1}H NMR) as an orange-brown liquid (dr = 52 : 48 by ^{13}C NMR), which was used without further purification. FT-IR (ATR) ($\tilde{\nu}$ cm^{-1}) 3433 (w), 2943 (s), 2866 (vs), 1740 (s), 1463 (m), 1367 (w), 1186 (vs), 1129 (vs), 1068 (s), 1014 (w), 970 (w), 920 (w), 882 (vs), 788 (m), 682 (s). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99–1.10 [m, 21H, $CH(CH_3)_2$], 1.15 (t, J = 7.5 Hz, 3H, CH_2CH_3), 1.27 (d, J = 6.5 Hz, 3H, H-5), 1.87 (br, 1H, OH), 2.35 (q, J = 7.5 Hz, 2H, CH_2CH_3), 3.66–3.85 (m, 2H, CH_2), 4.26–4.38 (m, 1H, H-4), 5.32–5.42 (m, 1H, H-1), 5.68 (dddd, J = 15.6, 6.2, 2.2, 1.1 Hz, 1H, H-2), 5.83 (dddd, J = 15.6, 5.7, 3.2, 0.9 Hz, 1H, H-3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.1 (CH_2CH_3), 11.9 [$CH(CH_3)_2$], 17.9 [$CH(CH_3)_2$], 23.12, 23.15 (C-5), 27.8 (CH_2CH_3), 65.1 (CH_2), 68.1, 68.2 (C-4), 74.19, 74.23 (C-1), 125.2, 125.3 (C-2), 137.52, 137.54 (C-3), 173.7 (COO). MS (ESI) m/z 367.2 [M + Na]$^+$, 271.2 [M + H − $C_3H_6O_2$]$^+$, 253.2 [M + H − $C_3H_6O_2$ − H_2O]$^+$, 213.2, 191.1, 175.2, 163.1, 137.1, 119.1, 97.1. HRMS (ESI) obsd 367.2259, calc. for $C_{18}H_{36}O_4SiNa^+$: 367.2275.

(b) To a solution of 4-hydroxy-1-{[(triisopropylsilyl)oxy]-methyl}pent-2-enyl propionate (4.00 g, 11.6 mmol) in DMF (60 mL) imidazole (1.58 g, 23.2 mmol) was added followed by dropwise addition of TBDPSCl (3.62 mL, 3.83 g, 13.9 mmol) and the reaction mixture stirred at r.t. for 6 h. The solvent was removed under vacuum and the residue purified by chromatography on SiO_2 with hexanes/EtOAc (100 : 1) to give **15a** (4.76 g, 8.17 mmol, 70%) as a colorless oil (dr 51 : 49 by ^{13}C NMR). R_f = 0.36 (hexanes/EtOAc, 50 : 1). FT-IR (ATR) ($\tilde{\nu}$ cm^{-1}) 2942 (m), 2864 (m), 1740 (s), 1463 (m), 1428 (m), 1367 (w), 1184 (m), 1111 (vs), 1081 (s), 997 (m), 967 (m), 882 (m), 822 (w), 789 (w), 738 (m), 701 (vs), 688 (s), 612 (m). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02–1.06 [m, 60H, $CH(CH_3)_2$, $C(CH_3)_3$], 1.11–1.16 (m, 12H, H-5, CH_2CH_3), 2.31 (q, J = 7.3 Hz, 2H, CH_2CH_3), 2.32 (q, J = 7.7 Hz, 2H, CH_2CH_3), 3.60–3.68 (m, 4H, CH_2), 4.26–4.33 (m, 2H, H-4), 5.29–5.35 (m, 2H, H-1), 5.49 (ddd, J = 15.4, 1.6, 1.6 Hz, 1H, H-2), 5.50 (ddd, J = 15.6, 1.4, 1.4 Hz, 1H, H-2), 5.75 (ddd, J = 15.4, 1.5, 1.5 Hz, 1H, H-3), 5.76 (ddd, J = 15.6, 1.3, 1.3 Hz, 1H, H-3), 7.31–7.44 (m, 12H, *o*-H, *p*-H), 7.60–7.69 (m, 8H, *m*-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.1 (CH_2CH_3), 11.9 [$CH(CH_3)_2$], 17.9 [$CH(CH_3)_2$], 19.2 [$C(CH_3)_3$], 24.0 (C-5), 27.0 [$C(CH_3)_3$], 27.8 (CH_2CH_3), 65.17, 65.20 (CH_2), 69.4, 69.5 (C-4), 74.2, 74.4 (C-1), 124.11, 124.13 (C-2), 127.4, 127.5 (*o*-C), 129.50, 129.51 (*p*-C), 134.1, 134.4 (i-C), 135.8, 135.9 (*m*-C), 137.7, 137.9 (C-3), 173.55, 173.58 (COO). MS (ESI) m/z 605.4 [M + Na]$^+$, 509.3 [M − $C_3H_5O_2$]$^+$, 431.3, 391.3, 327.2, 293.2, 253.2, 223.1, 193.1, 163.1, 145.1, 127.1, 97.1. HRMS (ESI) obsd 605.3446, calc. for $C_{34}H_{54}O_4Si_2Na^+$: 605.3453.

Methyl (3*S*,4*E*)-3-(1-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-2-methyl-6-[(triisopropylsilyl)oxy]hex-4-enoate (26). To a solution of diisopropylamine (1.87 mL, 1.35 g, 13.3 mmol) in THF (35 mL) at −100 °C a 1.6 M solution of *n*-BuLi in *n*-hexane (7.49 mL, 12.0 mmol) was added, the mixture warmed to r.t. for 5 min and then recooled to −100 °C. A solution of **15a** (3.88 g, 6.66 mmol) in THF (10 mL) was added dropwise over 20 min followed by addition of TMSCl (0.94 mL, 795 mg, 7.32 mmol). After stirring for 1 h, the reaction mixture was warmed to r.t. and stirred for a further 20 h. A 0.1 M solution of NaOH (6 mL) was added and the reaction mixture stirred for 5 min prior to addition of H_2O (5 mL). The organic solvent was removed under vacuum and the remaining aqueous layer was extracted with Et_2O (3 × 7 mL). To the combined extracts a 1 M solution of HCl (2 mL) was added, the layers were separated and the aqueous layer was extracted with Et_2O (1 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The residue was taken up in Et_2O (35 mL) and at 0 °C an ethereal solution of diazomethane (23 mL) was added dropwise. The reaction mixture was stirred for a further 1 h, warmed to r.t. and the solvent was then removed by a stream of nitrogen. The residue was purified by chromatography on SiO_2 with hexanes/EtOAc (150 : 1 → 100 : 1) to give **26** (2.11 g, 3.45 mmol, 52%) as a colorless oil (dr = 50 : 47 : 2 : 1 by ^{1}H NMR). R_f = 0.33 (hexanes/EtOAc, 50 : 1). FT-IR (ATR) ($\tilde{\nu}$ cm^{-1}) 2930 (m), 2863 (m), 1736 (s), 1698 (w), 1461 (m), 1428 (m), 1376 (w), 1257 (m), 1130 (s), 1105 (vs), 1053 (s), 975 (m), 882 (m), 821 (m), 766 (w), 739 (m), 701 (vs), 686 (s), 610 (m). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (d, J = 6.3 Hz, 3H, 1′-CH_3*), 0.976 (d, J = 5.8 Hz, 3H, 1′-CH_3), 0.981 (d, J = 7.3 Hz, 3H, 2-CH_3), 0.96–1.03 [m, 60H, $CH(CH_3)_2$, $C(CH_3)_3$], 1.00 (d, J = 7.1 Hz, 3H, 2-CH_3*), 2.17–2.24 (m, 1H, H*-3), 2.60–2.66 (m, 1H, H-3), 2.84 (qd, J = 7.3, 7.1 Hz, 1H, H-2), 2.86 (qd, J = 10.4, 7.1 Hz, 1H, H*-2), 3.51 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3*), 3.73 (qd, J = 6.9, 5.8 Hz, 1H, H-1′), 3.79 (qd, J = 6.3, 2.1 Hz, 1H, H*-1′), 4.19 (ddd, J = 4.2, 3.0, 1.4 Hz, 2H, H-6), 4.30 (ddd, J = 4.2, 3.0, 1.5 Hz, 2H, H*-6), 5.41 (ddt, J = 15.3, 9.8, 1.4 Hz, 1H, H-4), 5.59 (ddt, J = 15.4, 4.2, 0.8 Hz, 1H, H*-5), 5.60 (ddt, J = 15.3, 4.2, 0.9 Hz, 1H, H-5), 5.73 (ddt, J = 15.4, 10.0, 1.5 Hz, 1H, H*-4), 7.30–7.46 (m, 12H, *o*-H, *p*-H), 7.60–7.73 (*m*-H). ^{13}C NMR

(125 MHz, $CDCl_3$) δ 10.99, 11.04 [$CH(CH_3)_2$], 11.8 (2-CH_3), 15.8 (2-CH_3*), 16.98, 17.04 [$CH(CH_3)_2$], 18.31, 18.35 [$C(CH_3)_3$], 19.6 (1′-CH_3), 21.3 (1′-CH_3*), 26.0 [$C(CH_3)_3$], 39.2, (C-2), 39.4 (C-2*), 50.3 (OCH_3), 51.8 (C-3), 52.3 (C-3*), 62.5 (C-6), 62.7 (C-6*), 68.9 (C-1′), 69.7 (C-1′*), 124.9 (C-4), 125.2 (C-4*), 126.1, 126.3, 216.5, 126.6 (*o*-C), 128.2, 128.4, 128.55, 128.59 (*p*-C), 132.0, 132.4, 133.8, 134.1 (i-C), 132.7 (C-5), 133.1 (C-5*), 134.88, 134.91, 134.96, 134.99 (*m*-C), 175.3 (C-2), 176.3 (C-2*). MS (EI) *m*/*z* 581.4 [1%, $(M - CH_3)^+$], 565.4 [4, $(M - CH_3O)^+$], 553.3 [56, $(M - C_3H_7)^+$], 539.3 [100, $(M - C_4H_9)^+$], 495.3 (3), 466.4 (5), 448.5 (4), 399.2 (7), 355.2 (8), 335.3 (2), 297.2 (3), 283.1 (39), 253.2 (4), 248.2 (8), 213.0 (18), 182.4 (13), 139.1 (5), 135.0 (27), 111.1 (12), 97.1 (14), 71.0 (18), 57.0 [26, $(C_4H_9)^+$], 55.0 (14). HRMS (ESI) obsd 619.3616, calc. for $C_{35}H_{56}O_4Si_2Na^+$: 619.3609.

(3*S*,4*E*)-3-(1-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)-2-methyl-6-[(triisopropylsilyl)oxy]hex-4-en-1-ol (27). To a solution of **26** (5.33 g, 8.92 mmol) in THF (80 mL) at 0 °C a 1 N solution of DIBAL in hexane (26.8 mL, 18.9 mg, 26.8 mmol) was slowly added and the reaction mixture stirred at 0 °C for 3 h. Then MeOH (20 mL) was added followed by a 1 N solution of HCl (20 mL). The mixture was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give **27** (5.05 g, 8.88 mmol, quant.) as a colorless oil (dr 43 : 43 : 14 : 0 by ^{1}H NMR). FT-IR (ATR) ($\tilde{\nu}$ cm^{-1}) 3396 (m), 2931 (w), 2862 (w), 1464 (w), 1428 (w), 1111 (m), 1050 (s), 1024 (vs), 881 (m), 821 (m), 704 (s), 607 (m). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.72 (d, J = 7.1 Hz, 3H, 2-CH_3*), 0.81 (d, J = 6.8 Hz, 3H, 2-CH_3), 0.99 (d, J = 6.1 Hz, 3H, 1′-CH_3*), 1.01–1.14 [m, 63H, $CH(CH_3)_2$, $C(CH_3)_3$, 1′-CH_3], 1.73 (br, 2H, OH), 1.95–2.03 (m, 1H, H-3), 2.30–2.11 (m, 2H, H*-2, H*-3), 3.39–3.45 (m, 2H, H-1), 3.47–3.50 (m, 2H, H-1), 3.82–3.88 (m, 1H, H*-1′), 3.94 (qd, J = 6.3, 3.6 Hz, 1H, H-1′), 4.14–4.30 (m, 4H, H-6), 5.36 (dt, J = 15.4, 4.6 Hz, 1H, H-5), 5.47 (ddt, J = 17.8, 9.3, 2.0 Hz, 1H, H*-4), 5.53–5.73 (m, 2H, H*-5, H-4), 7.30–7.52 (m, 12H, *o*-H, *p*-H), 7.59–7.80 (m, 8H, *m*-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.1 (2-CH_3), 12.2 [$CH(CH_3)_2$], 15.9 (2-CH_3*), 18.2 [$CH(CH_3)_2$], 19.3, 19.5 [$C(CH_3)_3$], 20.4 (1′-CH_3*), 22.2 (1′-CH_3), 27.17, 27.20 [$C(CH_3)_3$], 35.3 (C-2), 35.6 (C-2*), 52.2 (C-3), 52.9 (C-3*), 63.77 (C-6*), 63.84 (C-6), 67.3 (C-1*), 67.4 (C-1), 70.2 (C-1′), 72.4 (C-1′*), 127.5 (*m*-C), 127.52 (C-4), 127.6, 127.7, 127.9 (*m*-C), 129.5 (C-4*), 129.73, 129.74, 129.9 (*p*-C), 132.3 (C-5*), 133.0 (C-5), 133.8, 134.4 (i-C), 136.1, 136.2 (*o*-C). MS (ESI) *m*/*z* 591.4 $[M + Na]^+$, 317.2, 273.2, 239.1, 199.1, 139.1, 121.1, 95.1. HRMS (ESI) obsd 591.3671, calc. for $C_{34}H_{56}O_3Si_2Na^+$: 591.3660.

(3*S*,4*E*)-3-(1-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)-2-methyl-6-[(triisopropylsilyl)oxy]hex-4-enyl 4-methylbenzenesulfonate (28). To a solution of **27** (80.0 mg, 0.14 mmol) in CH_2Cl_2 (1 mL) at 0 °C NEt_3 (0.03 mL, 0.21 mmol) was added and the mixture stirred for 2 min. Then TsCl (29.0 mg, 0.15 mmol) and DMAP (4.00 mg, 0.03 mmol) were added and the reaction mixture was stirred at r.t. for 20 h. After addition of additional NEt_3 (6 μL, 0.04 mmol), TsCl (8.00 mg, 0.04 mmol) and DMAP (2.00 mg, 0.01 mmol), the mixture was stirred for a further 2 h. The mixture was successively washed with H_2O and a solution of NaCl (4 mL each). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 with hexanes/EtOAc (30 : 1) to give **28** (83.0 mg, 0.11 mmol, 82%) as a colorless oil (dr 46 : 40 : 14 : 0 by ^{1}H NMR). R_f = 0.55 (hexanes/EtOAc, 10 : 1). FT-IR (ATR) ($\tilde{\nu}$ cm^{-1}) 2941 (m), 2864 (m), 1462 (m), 1428 (w), 1363 (s), 1259 (w), 1188 (m), 1177 (s), 1103 (vs), 1059 (m), 966 (vs), 882 (m), 814 (s), 738 (m), 702 (vs), 686 (s), 666 (vs), 611 (m), 554 (s). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.63 (d, J = 7.1 Hz, 3H, 2-CH_3), 0.77–0.95 (m, 9H, 1′-CH_3, 1′-CH_3*, 2-CH_3*), 1.10–0.97 [m, 60H, $C(CH_3)_3$, $CH(CH_3)_2$], 1.87 (ddd, J = 10.6, 7.5, 3.3 Hz, 1H, H*-3), 2.01–2.12 (m, 1H, H*-2), 2.19 (ddd, J = 9.6, 8.5, 3.3 Hz, 1H, H-3), 2.43 (s, 3H, CH_{3Tos}), 2.44 (s, 3H, CH_{3Tos}*), 2.45–2.52 (m, 1H, H-2), 3.66–3.77 (m, 4H, H-1′, H-1, H_a*-1), 3.77–3.82 (m, 1H, H*-1′), 3.95–4.14 (m, 3H, H_b*-1, H-6), 4.10–4.20 (m, 2H, H*-6), 5.24 (ddt, J = 15.4, 9.8, 1.4 Hz, 1H, H-4), 5.31–5.42 (m, 2H, H-5, H*-5), 5.50–5.63 (m, 1H, H*-4), 7.23–7.48 (m, 16H, *o*-H, *p*-H, *o*-H_{Tos}*), 7.57–7.82 (m, 12H, *m*-H, *m*-H_{Tos}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.3 (2-CH_3), 12.1, 12.2 [$CH(CH_3)_2$], 15.0 (2-CH_3*), 18.1, 18.2 [$CH(CH_3)_2$], 19.4, 19.5 [$C(CH_3)_3$], 21.4 (1′-CH_3*), 21.8 (CH_{3Tos}), 22.4 (1′-CH_3), 27.1, 27.2 [$C(CH_3)_3$], 32.1 (C-2), 33.2 (C-2*), 51.4 (C-3, C-3*), 63.4 (C-6*), 63.5 (C-6), 69.8 (C-1′), 70.7 (C-1′*), 74.0 (C-1*), 74.0 (C-1), 125.3 (C-4), 127.0 (C-4*), 127.5, 127.8 (*m*-C), 127.8, 128.05, 128.08 (*o*-C_{Tos}), 129.56, 129.60, 129.8, 129.9 (*p*-C), 129.87, 129.89 (*m*-C_{Tos}), 133.41, 133.43 (i-C_{Tos}), 133.8 (C-5*), 134.0 (C-5), 134.7, 134.9 (i-C), 136.0, 136.10, 136.13 (*o*-C), 144.6 (*p*-C_{Tos}).

(4*R*,5*E*)-4-(1-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)-3-methyl-7-[(triisopropylsilyl)oxy]hept-5-enenitrile (29). To a solution of **28** (100 mg, 0.14 mmol) in DMF (2 mL) KCN (50 mg, 0.77 mmol) was added and the mixture was stirred at 80 °C for 3 h. The reaction mixture was then cooled to 0 °C and H_2O and EtOAc (3 mL each) were added. The mixture was stirred at 0 °C for 1 h prior to extraction with EtOAc (3 × 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 with hexanes/EtOAc (50 : 1) to give **29** (57.8 mg, 0.10 mmol, 72%) as a colorless oil (dr 51 : 44 : 5 : 0 by ^{1}H NMR). R_f: 0.71 (hexanes/EtOAc, 10 : 1). FT-IR (ATR) ($\tilde{\nu}$ cm^{-1}) 2940 (m), 2863 (m), 1462 (m), 1427 (m), 1382 (m), 1104 (s), 1058 (m), 1012 (w), 978 (m), 918 (w), 882 (m), 821 (m), 739 (s), 701 (vs), 686 (s), 660 (m), 611 (m). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77 (d, J = 6.9 Hz, 3H, 2-CH_3), 0.96–1.18 [m, 69H, $C(CH_3)_3$, $CH(CH_3)_2$, 1′-CH_3, 2-CH_3*, 1′-CH_3*], 1.77–1.88 (m, 1H, H*-3), 1.96–2.29 (m, 6H, H-1, H*-1, H*-2, H-3), 2.48–2.61 (m, 1H, H-2), 3.69–3.81 (m, 1H, H-1′), 3.82–3.93 (m, 1H, H*-1′), 4.19 (dd, J = 4.4, 1.5 Hz, 2H, H-6), 4.23 (dd, J = 4.0, 1.1 Hz, 2H, H*-6), 5.30 (dd, J = 15.3, 10.3 Hz, 1H, H-4), 5.52 (dt, J = 15.3, 4.2 Hz, 1H, H-5), 5.58–5.73 (m, 2H, H*-4, H*-5), 7.30–7.51 (m, 12H, *o*-H, *p*-H), 7.59–7.78 (m, 8H, *m*-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.1, 12.2 [$CH(CH_3)_2$], 14.4 (2-CH_3), 18.1, 18.2 [$CH(CH_3)_2$], 19.4, 19.5 [$C(CH_3)_3$], 21.9 (1′-CH_3*), 22.6 (1′-CH_3), 22.9 (C-1*), 23.5 (C-1), 27.0, 27.2 [$C(CH_3)_3$], 30.2 (C-2*), 30.5 (C-2), 54.6 (C-3*), 54.8 (C-3), 63.51 (C-6*), 63.53 (C-6), 69.95 (C-1′*), 70.0 (C-1′), 119.1 (CN*), 119.5 (CN), 125.0 (C-4), 126.8 (C-4*), 127.5, 127.8, 128.0 (*o*-C), 129.6, 129.7, 129.9, 130.0 (*p*-C), 133.6,

133.7 (i-C), 133.9 (C-5*), 134.6 (i-C), 134.7 (C-5), 134.8 (i-C), 136.02, 136.06, 136.13, 136.15 (*m*-C). MS (ESI) *m*/*z* 578.4 $[M + H]^+$, 404.2 $[M - C_9H_{22}OSi]^+$, 360.2, 283.2 $[C_{18}H_{23}OSi]^+$, 265.1, 241.1, 163.1, 137.1, 105.1. HRMS (ESI) obsd 600.3661, calc. for $C_{35}H_{55}NO_2Si_2Na^+$: 600.3664.

(4*R*,5*E*)-4-(1-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)-3-methyl-7-[(triisopropylsilyl)oxy]-hept-5-enal (30). To a solution of **29** (100 mg, 0.17 mmol) in hexane (1.5 mL) at −78 °C a 1 N solution of DIBAL in hexane (0.18 mL, 0.18 mmol) was added and the reaction mixture stirred for 1 h. After addition of a 1 M HCl solution (7 mL), the mixture was stirred for 15 min. Then it was warmed to r.t., extracted with Et_2O (3 × 5 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give **30** (97 mg, 0.17 mmol, 99%) as a yellow oil (dr 64 : 32 : 5 : 0 by ^{1}H-NMR, CHO). FT-IR (ATR) ($\tilde{\nu}$ cm^{-1}) 2941 (m), 2864 (m), 1707 (m), 1462 (w), 1427 (w), 1382 (w), 1105 (s), 1058 (m), 977 (m), 882 (m), 832 (m), 738 (s), 701 (vs), 686 (s), 610 (m). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.72 (d, J = 6.9 Hz, 3H, 2-CH_3), 0.83 (d, J = 6.8 Hz, 3H, 2-CH_3*), 0.95–1.19 [m, 66H, C(CH_3)$_3$, CH(CH_3)$_2$, 1′-CH_3, 1′-CH_3*], 1.70–1.79 (m, 1H, H*-3), 1.93–2.46 (m, 6H, H-1, H*-1, H*-2, H-3), 2.66–2.80 (m, 1H, H-2), 3.72–3.85 (m, 1H, H-1′), 3.85–3.97 (m, 1H, H*-1′), 4.19 (dd, J = 4.7, 1.7 Hz, 2H, H-6), 4.25 (dd, J = 4.7, 1.8 Hz, 2H, H*-6), 5.34 (ddt, J = 15.4, 10.0, 1.7 Hz, 1H, H-4), 5.42–5.59 (m, 2H, H-5, H*-5), 5.60–5.73 (m, 1H, H*-4), 7.29–7.50 (m, 12H, *o*-H, *p*-H), 7.59–7.79 (m, 8H, *m*-H), 9.59 (dd, J = 2.9, 1.0 Hz, 1H, CHO*), 9.69 (t, J = 2.4 Hz, 1H, CHO). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.15, 12.20 [CH(CH_3)$_2$], 15.0 (1′-CH_3*), 18.1 (1′-CH_3), 18.2 [CH(CH_3)$_2$], 19.5, 19.6 [C(CH_3)$_3$], 22.2, 22.4 (2-CH_3, 2-CH_3*), 27.2 [C(CH_3)$_3$], 27.5 (C-2*), 28.3 (C-2), 49.4 (C-1), 50.1 (C-1*), 55.3 (C-3), 55.6 (C-3*), 63.7, 63.8 (C-6), 70.0 (C-1′*), 70.2 (C-1′), 126.2 (C-4*), 127.4, 127.5, 127.75, 127.80 (*o*-C), 127.9 (C-4), 129.6, 129.8, 129.9 (*p*-C), 133.3 (C-5), 133.8 (C-5*), 133.9, 134.0, 134.9, 135.0 (i-C), 136.11, 136.15, 136.18 (*m*-C), 203.20, 203.22 (CHO, CHO*). MS (ESI) *m*/*z* 581.4 $[MH]^+$, 407.3 $[M - OTIPS]^+$, 393.2, 360.2, 325.3 $[M - OTBDPS]^+$, 301.1, 283.2, 227.1, 211.2, 183.1, 151.1 $[M - OTIPS - OTBDPS]^+$, 133.1, 105.1. HRMS (ESI) obsd 603.3660, calc. for $C_{35}H_{56}O_3Si_2Na^+$: 603.3660.

Ethyl (2*E*,6*R*,7*E*)-6-(1-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-5-methyl-9-[(triisopropylsilyl)oxy]nona-2,7-dienoate (14a). To a solution of LiCl (12.0 mg, 0.27 mmol) in CH_3CN (0.5 mL) **31** (0.05 mL, 0.24 mmol) and DBU (0.03 mL, 30.6 mg, 0.20 mmol) were added and the mixture was stirred at r.t. for 10 min and then cooled to 0 °C. An ice-cold solution of **30** (100 mg, 0.17 mmol) in CH_2Cl_2 (0.5 mL) was added and the reaction mixture stirred at 0 °C for 1.5 h and at r.t. for a further 15 h. The reaction was quenched with brine (1 mL) and Et_2O (1 mL) and the mixture was extracted with Et_2O (3 × 3 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by chromatography on SiO_2 with hexanes/EtOAc (50 : 1) to give **14a** (77.8 mg, 0.12 mmol, 85%) as a colorless oil (dr 56 : 44 by ^{13}C NMR). R_f = 0.56 (hexanes/EtOAc, 10 : 1). FT-IR (ATR) ($\tilde{\nu}$ cm^{-1}) 2931 (w), 2864 (w), 2341 (w), 1714 (m), 1428 (w), 1261 (w), 1105 (m), 978 (w), 907 (s), 882 (w), 804 (w), 730 (vs), 702 (s), 686 (m), 648 (w). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.66 (d, J = 6.8 Hz, 3H, 4-CH_3), 0.79 (d, J = 6.7 Hz, 3H, 4-CH_3*), 0.95–1.00 (m, 6H, 1′-CH_3, 1′-CH_3*), 1.01–1.13 [m, 60H, C(CH_3)$_3$, CH(CH_3)$_2$], 1.29 (t, J = 7.0 Hz, 3H, CH_2CH_3*), 1.30 (t, J = 7.0 Hz, 3H, CH_2CH_3), 1.68–1.77 (m, 1H, H*-3), 1.94–2.28 (m, 6H, H-1, H*-1, H*-2, H-2, H-3), 3.72–3.84 (m, 1H, H-1′), 3.89–3.98 (m, 1H, H*-1′), 4.20 (q, J = 7.0 Hz, 4H, CH_2CH_3, CH_2CH_3*), 5.32 (ddt, J = 15.3, 10.1, 1.7 Hz, 1H, H-6), 5.40–5.59 (m, 2H, H-7, H*-7), 5.65 (dd, J = 15.4, 1.4 Hz, 1H, H*-6), 5.68 (dt, J = 15.4, 2.0 Hz, 1H, H*-2), 5.77 (dt, J = 15.6, 1.6 Hz, 1H, H-2), 6.77–6.98 (m, 2H, H-1, H*-1), 7.30–7.48 (m, 12H, *o*-H, *p*-H), 7.61–7.76 (m, 8H, *m*-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.17, 12.22 [CH(CH_3)$_2$], 14.4 [CH_2CH_3], 15.0 (1′-CH_3), 17.6 (1′-CH_3*), 18.15, 18.21 [C(CH_3)$_3$], 19.49, 19.54 [CH(CH_3)$_2$], 22.29–22.38 (4-CH_3, 4-CH_3*), 27.1 [C(CH_3)$_3$], 31.8 (C-4), 32.5 (C-4*), 37.9 (C-3*), 38.6 (C-3), 55.1 (C-5), 55.2 (C-5*), 60.3 (CH_2CH_3), 63.9 (C-8), 70.1 (C-1′), 70.2 (C-1′*), 122.4 (C-1), 122.6 (C-1*), 126.8 (C-6), 127.4, 127.6, 127.71, 127.74 (*o*-C), 128.3 (C-6*), 129.5, 129.7, 129.8 (*m*-C), 132.9 (C-7*), 133.4 (C-7), 134.0, 135.06, 135.10 (i-C), 136.1, 136.2 (*m*-C), 148.3 (C-2*), 148.8 (C-2), 166.8 (COO*), 166.9 (COO). MS (ESI) *m*/*z* 673.4 $[M + Na]^+$, 477.3 $[M - OTIPS]^+$, 433.3 $[M - OTIPS - OC_3H_5]^+$, 399.2. HRMS (ESI) obsd 673.4057, calc. for $C_{39}H_{62}O_4Si_2Na^+$: 673.4079.

Ethyl (2*E*,6*R*,7*E*)-6-(1-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-9-hydroxy-5-methylnona-2,7-dienoate (32). To a solution of **14a** (1.51 g, 2.33 mmol) in THF (30 mL) a 1 M solution of TBAF in THF (6.99 mL, 6.99 mmol) was added and the reaction mixture stirred at 0 °C for 1 h. Then the solvent was removed and the residue purified by chromatography on SiO_2 with hexanes/EtOAC (2 : 1 → 1 : 1) to give **32** (558 mg, 1.13 mmol, 48%) as a colorless oil (dr 52 : 37 : 8 : 0 by ^{1}H NMR). FT-IR (ATR) ($\tilde{\nu}$ cm^{-1}) 2929 (m), 2856 (m), 1720 (s), 1651 (w), 1461 (w), 1427 (m), 1367 (w), 1313 (w), 1261 (m), 1176 (m), 1109 (s), 976 (s), 937 (w), 821 (m), 739 (s), 702 (vs), 686 (s), 610 (m). MS (ESI) *m*/*z* 517.3 $[M + Na]^+$, 400.2, 284.2, 221.2, 149.1, 105.1. HRMS (ESI) obsd 517.2726, calc. for $C_{30}H_{42}O_4SiNa^+$: 517.2745. Diastereomer 1: R_f = 0.46 (hexanes/EtOAc, 3 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.76 (d, J = 6.5 Hz, 3H, 4-CH_3), 1.02 (d, J = 6.3 Hz, 3H, 1′-CH_3), 1.04 [s, 9H, C(CH_3)$_3$], 1.29 (t, J = 7.1 Hz, 3H, CH_2CH_3), 1.50 (br, 1H, OH), 1.76–1.81 (m, 1H, H-5), 1.84–1.94 (m, 2H, H_a-3, H-4), 2.16–2.24 (m, 1H, H_b-3), 3.96 (qd, J = 6.3, 4.4 Hz, 1H, H-1′), 4.09–4.11 (m, 2H, H-8), 4.18 (q, J = 7.1 Hz, 2H, CH_2CH_3), 5.50–5.58 (m, 2H, H-6, H-7), 5.68 (dt, J = 15.6, 1.6 Hz, 1H, H-1), 6.83 (dt, J = 15.6, 7.6 Hz, 1H, H-2), 7.33–7.46 (m, 6H, *o*-H, *p*-H), 7.63–7.71 (m, 4H, *m*-H). ^{1}H NMR (500 MHz, C_6D_6) δ 0.68 (d, J = 6.6 Hz, 3H, 4-CH_3), 0.99 (t, J = 7.1 Hz, 3H, CH_2CH_3), 1.00 (d, J = 6.3 Hz, 3H, 1′-CH_3), 1.15 [s, 9H, C(CH_3)$_3$], 1.32 (br, 1H, OH), 1.64–1.74 (m, 2H, H-4, H-5), 1.79–1.87 (m, 1H, H_a-3), 2.05–2.12 (m, 1H, H_b-3), 3.87 (dt, J = 5.5, 1.6 Hz, 2H, H-8), 3.98 (qd, J = 6.3, 4.3 Hz, 1H, H-1′), 4.06 (q, J = 7.1 Hz, 2H, CH_2CH_3), 5.36 (dt, J = 15.4, 5.5 Hz, 1H, H-7), 5.55 (ddt, J = 15.4, 9.9, 1.6 Hz, 1H, H-6), 5.88 (dt, J = 15.5, 1.5 Hz, 1H, H-1), 7.09 (ddd, J = 15.5, 8.2, 6.8 Hz, 1H, H-2), 7.12–7.27 (m, 6H, *o*-H, *p*-H), 7.73–7.80 (m, 4H, *m*-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3 (CH_2CH_3), 16.9 (4-CH_3), 19.4 [C(CH_3)$_3$], 22.1 (1′-CH_3), 27.0 [C(CH_3)$_3$], 32.2 (C-4), 37.9 (C-3), 55.0 (C-5), 60.2 (CH_2CH_3), 63.8 (C-8), 70.0 (C-1′), 122.6 (C-1),

127.4, 127.6 (*o*-C), 129.5, 129.7 (*p*-C), 131.1 (C-7), 132.4 (C-8), 133.9, 134.7 (i-C), 135.9, 136.0 (*m*-C), 147.9 (C-3), 166.6 (*C*OEt). Diastereomer 2: R_f = 0.45 (hexanes/EtOAc, 3 : 1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.68 (d, J = 6.9 Hz, 3H, 4-CH_3), 0.98 (d, J = 6.1 Hz, 3H, 1′-CH_3), 1.04 [s, 9H, C(CH_3)$_3$], 1.30 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.58 (br, 1H, OH), 1.93 (dddd, J = 14.5, 7.4, 7.4, 1.5 Hz, 1H, H_a-3), 2.03–2.12 (m, 2H, H_b-3, H-5), 2.16–2.26 (m, 1H, H-4), 3.79 (dq, J = 7.6, 6.1 Hz, 1H, H-1′), 4.06–4.10 (m, 2H, H-8), 4.20 (q, J = 7.2 Hz, 2H, CH_2CH_3), 5.35 (ddt, J = 15.4, 10.2, 1.4 Hz, 1H, H-6), 5.61 (dt, J = 15.4, 5.7 Hz, 1H, H-7), 5.77 (dt, J = 15.5, 1.5 Hz, 1H, H-1), 6.91 (dt, J = 15.5, 7.4 Hz, 1H, H-2), 7.34–7.46 (m, 6H, *o*-H, *p*-H), 7.65–7.72 (m, 4H, *m*-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3 (CH_2CH_3), 15.1 (4-CH_3), 19.4 [C(CH_3)$_3$], 22.1 (1′-CH_3), 27.1 [C(CH_3)$_3$], 31.6 (C-4), 38.4 (C-3), 54.9 (C-5), 60.2 (CH_2CH_3), 63.6 (C-8), 69.8 (C-1′), 122.4 (C-1), 127.4, 127.6 (*o*-C), 129.4 (*p*-C), 129.7 (C-6), 132.8 (C-7), 133.8, 134.7 (i-C), 135.95, 136.00 (*m*-C), 148.3 (C-2), 166.7 (*C*OEt).

Ethyl (2*E*,6*R*,7*E*)-6-(1-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-5-methyl-9-oxonona-2,7-dienoate (13a). To a solution of **32** (443 mg, 0.90 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C DMP (496 mg, 1.17 mmol) was added and the reaction mixture stirred for 3 h. The solution was concentrated under reduced pressure. The crude product was purified by chromatography on SiO_2 with hexanes/EtOAc (10 : 1) and a small quantity of CH_2Cl_2 to dissolve the remaining DMP to give **13a** (356 mg, 0.72 mmol, 80%) as colorless oil (dr 56 : 39 : 5 : 0 by ^{1}H NMR, CHO). R_f = 0.33 (hexanes/EtOAc, 10 : 1). $[\alpha]_D^{20}$ −190 (*c* 1.0 in $CHCl_3$). FT-IR (ATR) ($\tilde{\nu}$ cm^{-1}) 2962 (w), 2931 (w), 2857 (w), 2253 (w), 1716 (m), 1689 (m), 1653 (w), 1473 (w), 1427 (w), 1390 (w), 1367 (w), 1314 (w), 1265 (w), 1225 (w), 1178 (w), 1110 (m), 1043 (w), 979 (m), 906 (s), 821 (w), 729 (vs), 702 (vs), 648 (m), 610 (m). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.74 (d, J = 6.9 Hz, 3H, 4-CH_3), 0.79 (d, J = 6.3 Hz, 3H, 4-CH_3*), 1.00–1.06 [m, 24H, C(CH_3)$_3$, C(CH_3)$_3$*, 1′-CH_3, 1′-CH_3*], 1.30 (t, J = 7.1 Hz, 6H, CH_2CH_3, CH_2CH_3*), 1.81–1.88 (m, 1H, H_a*-3), 1.88–1.95 (m, 1H, H_a-3), 1.99–2.05 (m, 2H, H*-4, H*-5), 2.05–2.10 (m, 1H, H_b-3), 2.13–2.19 (m, 1H, H_b*-3), 2.19–2.27 (m, 1H, H-4), 2.31–2.38 (m, 1H, H-5), 3.90–3.97 (m, 1H, H*-1′), 4.03–4.09 (m, 1H, H-1′), 4.15–4.23 (m, 4H, CH_2CH_3, CH_2CH_3*), 5.67 (d, J = 15.5 Hz, 1H, H*-1), 5.77 (d, J = 15.7 Hz, 1H, H-1), 6.00–6.10 (m, 2H, H-7, H*-7), 6.57 (dd, J = 15.7, 10.4 Hz, 1H, H-6), 6.72–6.80 (m, 1H, H*-6), 6.80–6.88 (m, 2H, H-2, H*-2), 7.33–7.49 (m, 12H, *o*-H, *p*-H), 7.59–7.72 (m, 8H, *m*-H), 9.47 (d, J = 7.8 Hz, 1H, CHO), 9.54 (d, J = 8.1 Hz, 1H, CHO). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4 (CH_2CH_3), 15.8 (4-CH_3), 17.3 (4-CH_3*), 19.45, 19.48 [C(CH_3)$_3$], 21.7 (1′-CH_3), 22.7 (1′-CH_3*), 27.15, 27.17 [C(CH_3)$_3$], 32.2 (C-4), 32.4 (C-4*), 37.4 (C-3*), 38.1 (C-3), 55.4 (C-5), 55.9 (C-5*), 60.4 (CH_2CH_3), 69.26, 69.30 (C-1′, C-1′*), 123.2 (C-1*), 123.4 (C-1), 127.59, 127.63, 127.90, 127.96 (*o*-C), 129.81, 129.84, 130.04 (*m*-C), 133.3, 133.5, 134.3, 134.4 (*p*-C), 136.06, 136.08 (C-7, C-7*), 146.6 (C-6*), 145.0 (C-2, C-2*), 156.1 (C-6), 157.8 (COO*), 166.5 (COO), 193.5, 193.8 (CHO, CHO*). MS (ESI) *m*/*z* 515.26 [M + Na]$^+$, 284.15 [M − $C_{18}H_{23}$OSi + H]$^+$, 259.13, 233.11. HRMS (ESI) obsd 515.2582, calc. for $C_{30}H_{40}O_4SiNa^+$: 515.2588.

Ethyl (2*E*,6*R*,7*E*,9*E*)-6-(1-{[*tert*-butyl(diphenyl)silyl]oxy}-ethyl)-5-methyl-11-oxododeca-2,7,9-trienoate (12a). To a solution of **8b** (38.0 mg, 0.11 mmol) in CH_2Cl_2 (1 mL) NEt_3 (0.03 mL, 0.20 mmol) was added and the mixture stirred for 15 min. Then a solution **13a** (50 mg, 0.10 mmol) in CH_2Cl_2 (1 mL) was added and the reaction mixture heated at reflux for 23 h. The solvent was removed under reduced pressure and the residue was purified by chromatography on SiO_2 with hexanes/EtOAc (10 : 1) to give **12a** (20 mg, 0.04 mmol, 38%) as a colorless liquid (dr 60 : 33 : 7 : 0 by ^{1}H NMR). R_f = 0.24. FT-IR (ATR) ($\tilde{\nu}$ cm^{-1}) 3071 (w), 2960 (m), 2930 (m), 2893 (w), 2857 (w), 1717 (s), 1870 (w), 1668 (s), 1630 (w), 1593 (m), 1473 (w), 1427 (m), 1364 (m), 1312 (w), 1251 (s), 1222 (w), 1176 (w), 1107 (vs), 1043 (w), 999 (s), 980 (w), 938 (w), 909 (w), 822 (m), 770 (w), 735 (s), 702 (vs), 686 (w), 646 (w), 608 (m). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.70 (d, J = 6.8 Hz, 3H, 4-CH_3), 0.77 (d, J = 6.9 Hz, 3H, 4-CH_3*), 0.99 (d, J = 6.1 Hz, 3H, 1′-CH_3), 1.02 (d, J = 6.5 Hz, 3H, 1′-CH_3*), 1.03–1.06 (m, 18H, C(CH_3)$_3$, C(CH_3)$_3$*), 1.30 (t, J = 7.1 Hz, 3H, CH_2CH_3), 1.31 (t, J = 7.1 Hz, 3H, CH_2CH_3*), 1.80–2.00 (m, 4H, H_a-3, H_a*-3, H*-4, H-5), 2.00–2.10 (m, 1H, H_b-3), 2.11–2.24 (m, 3H, H_b*-3, H-4, H*-5), 2.26 (s, 3H, H-11), 2.28–2.32 (m, 3H, H*-11), 3.83–3.90 (m, 1H, H-1′), 3.96–4.02 (m, 1H, H*-1′), 4.19 (q, J = 7.1 Hz, CH_2CH_3), 4.20 (q, J = 7.1 Hz, CH_2CH_3*), 5.66 (dt, J = 15.8, 1.5 Hz, H*-1), 5.76 (dt, J = 15.6, 1.4 Hz, 1H, H-1), 5.89 (dd, J = 15.5, 9.9 Hz, 1H, H-6), 6.05–6.12 (m, 4H, H-6, H*-7, H-9, H*-9), 6.15 (dd, J = 15.3, 10.8 Hz, 1H, H-7), 6.79 (ddd, J = 15.1, 8.4, 6.6 Hz, 1H, H*-2), 6.87 (dt, J = 15.6, 7.4 Hz, 1H, H-2), 7.05 (dd, J = 15.6, 10.8 Hz, 1H, H-8), 7.08–7.21 (m, 1H, H*-8), 7.33–7.47 (m, 12H, *o*-H, *p*-H), 7.60–7.73 (m, 8H, *m*-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4 (CH_2CH_3, CH_2CH_3*), 15.6 (4-CH_3), 17.5 (4-CH_3*), 19.4, 19.5 [C(CH_3)$_3$], 22.0 (1′-CH_3), 22.6 (1′-CH_3*), 27.2, 27.5, 27.49, 27.52 [C(CH_3)$_3$], 32.2 (C-4), 32.6 (C-4*), 37.7 (C-3), 38.4 (C-3*), 56.0 (C-5), 56.2 (C-5*), 60.4 (CH_2CH_3, CH_2CH_3*), 69.7 (C-11, C-11*), 122.9 (C-1*), 123.0 (C-1), 127.5, 127.6, 127.80, 127.83 (*o*-C), 129.3 (C-9, C-9*), 129.5, 129.7, 129.9, 130.0 (*m*-C), 131.9, 132.2 (C-7, C-7*), 133.7, 133.8, 134.6, 134.7, 136.06, 136.1, 136.13 (*p*-C), 142.6 (C-6, C-6*), 143.2 (C-8), 143.6 (C-8*), 147.4 (C-2*), 147.8 (C-2), 166.6, 166.7 (CO_2Et), 198.8, 199.0 (C-10). MS (ESI) *m*/*z* 283.15 [M − $C_{18}H_{23}$OSi]$^+$, 265.14, 231.14, 105.08. HRMS (ESI) obsd 555.2890, calc. for $C_{33}H_{44}O_4SiNa^+$: 555.2901.

Ethyl (2*R*,3a*S*,4*R*,5*S*,7a*R*)-5-acetyl-1-(1-{[*tert*-butyl(diphenyl)-silyl]oxy}ethyl)-2-methyl-2,3,3a,4,5,7a-hexahydro-1*H*-indene-4-carboxylate (11a). To a solution of **12a** (80 mg, 0.15 mmol) in toluene (2 mL) BHT (3.31 mg, 0.02 mmol) was added and the reaction mixture heated at reflux for 93 h. The solvent was removed under reduced pressure and the residue was purified by chromatography on SiO_2 with hexanes/EtOAC (10 : 1) to give **11a** (25 mg, 0.05 mmol, 33%) as a colorless oil (dr 55 : 42 : 3 : 0 by ^{1}H NMR, H-1′). R_f = 0.39. FT-IR (ATR) ($\tilde{\nu}$ cm^{-1}) 3072 (w), 2959 (m), 2930 (m), 2856 (m), 2359 (w), 2255 (w), 1729 (s), 1713 (s), 1589 (w), 1473 (m), 1461 (m), 1427 (m), 1392 (w), 1375 (m), 1354 (m), 1308 (w), 1277 (br), 1206 (m), 1178 (m), 1155 (m), 1109 (s), 1054 (w), 1030 (w), 1007 (w), 975 (w), 939 (w), 908 (s), 861 (w), 821 (m), 731 (vs), 702 (vs), 648 (w), 609 (m). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (d, J = 7.2 Hz, 3H, 2-CH_3*), 0.98 (d, J = 7.3 Hz, 3H, 2-CH_3), 1.02 (d, J = 6.4 Hz, 3H, 1′-CH_3), 1.03–1.05 (m, 20H, C(CH_3)$_3$, H_a-3, H_a*-3), 1.12 (d, J = 6.3 Hz, 3H, 1′-CH_3),

1.24–1.30 (m, 6H, CH_2CH_3, CH_2CH_3*), 1.54–1.71 (m, 4H, H-3a, H*-3a, H-1, H*-1), 1.89–2.00 (m, 2H, H_b-3, H_b*-3), 2.07–2.22 (m, 4H, H-7a, H*-7a, H-2, H*-2), 2.23 (s, 3H, $COCH_3$), 2.24 (s, 3H, $COCH_3$*), 2.82–2.94 (m, 2H, H-4, H*-4), 3.64–3.72 (m, 2H, H-5, H*-5), 4.02–4.08 (m, 1H, H-1′), 4.08–4.12 (m, 1H, H*-1′), 4.12–4.21 (m, 4H, CH_2CH_3, CH_2CH_3*), 5.62–5.70 (m, 2H, H-7, H*-7), 6.03–6.08 (m, 1H, H-6), 6.24–6.30 (m, 1H, H-6), 7.34–7.45 (m, 12H, *o*-H, *p*-H), 7.64–7.71 (m, 8H, *m*-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4 (CH_2CH_3, CH_2CH_3*), 18.0 (2-CH_3*), 19.28 (2-CH_3), 19.31, 19.4 [$C(CH_3)_3$], 22.2, 24.0 (1′-CH_3, 1′-CH_3*), 27.2, 27.3 [$C(CH_3)_3$], 28.54, 28.56 ($COCH_3$, $COCH_3$*), 32.7, 34.1 (C-2, C-2*), 38.3, 38.5 (C-3, C-3*), 43.2 (C-7a), 44.1, 44.6 (C-3a, C-3a*), 44.7 (C-7a*), 46.76, 46.83 (C-4, C-4*), 51.0, 51.6 (C-1, C-1*), 55.4, 55.5 (C-5, C-5*), 60.7 (CH_2CH_3, CH_2CH_3*), 69.3, 70.7 (C-2, C-2*), 122.5, 123.0 (C-7, C-7*), 127.4, 127.5, 127.6, 127.7 (*o*-C), 129.5, 129.7, 129.75 (*m*-C), 132.5 (C-6, C-6*), 133.5, 133.9, 134.2 (i-C), 134.9 (C-6, C-6*), 135.1 (i-C), 136.0, 136.07, 136.10 (*p*-C), 174.78, 174.84 (CO_2Et), 207.32, 207.39 ($COCH_3$). MS (ESI) *m*/*z* 321.13, 283.15 $[M - C_{18}H_{23}OSi]^+$, 265.14, 231.14, 203.15 $[M - C_{16}H_{19}OSi - C_{14}H_{20}O_2 - H]^+$, 187.15, 145.10, 105.08. HRMS (ESI) obsd 555.2895, calc. for $C_{33}H_{44}O_4SiNa^+$: 555.2901.

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