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Synthetic studies on the sarcodictyins: synthesis of fully functionalized cyclization precursors

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Abstract—A strategy featuring a key retrosynthetic disconnection at the C2–C3 position was applied to the total synthesis of the common diterpenoid tricyclic skeleton of sarcodictyins and eleutherobin. Fully functionalized cyclization precursors were accessed via a brief and convergent route, making use of unprecedented synthetic transformations.

1. Introduction

Since FDA approval for the use of Taxol® (paclitaxel) **1** (Fig. 1) in the chemotherapeutic treatment of ovarian cancer in 1992, this compound has become the drug of choice for many solid tumors and it has proven to be particularly effective at treating recurrent tumors as well as those unresponsive to previous first line therapies. The mode of action of Taxol is characterized by suppression of microtubule dynamics via unnatural promotion of tubulin polymerization and over-stabilization of microtubules.[1] Its exceptional activity is however accompanied by a number of side effects and limitations, which narrow its scope and applicability in therapeutic programs.

In recent years, a number of natural compounds were isolated that possess a mode of action similar to that of Taxol.[2] Among these, the marine diterpenoids sarcodictyin A, B (**2**, **3**) were isolated in 1987 by Pietra et al. from the Mediterranean stoloniferan coral *Sarcodictyon roseum*.[3] Eight years later, Fenical et al. reported isolation of the diterpene glycoside **4**, named eleutherobin, from an *Eleutherobia* species of soft coral found near Bennet's Shoul in Western Australia.[4,5] While possessing the same carbon skeleton of the sarcodictyins, eleutherobin contains a β-linked 2-*O*-acetyl-D-arabinopyranose unit instead of the alkyl ester of the other members of the family.

The similarity in the terpenoid structure of sarcodictyins and eleutherobin has suggested their inclusion in a common family. It can be expected that the synthetic strategies devised for one member of the family would require only minor variation to be adapted for the synthesis of the others, which differ only for variation in appendages or side chains. This was indeed the case in Nicolaou's synthesis of sarcodictyins,[6,7] which was completed in 1997. Also Danishefsky et al. have devised an elegant approach to the tricyclic skeleton of this class of compounds, which culminated in the total synthesis of eleutherobin **4**.[8]

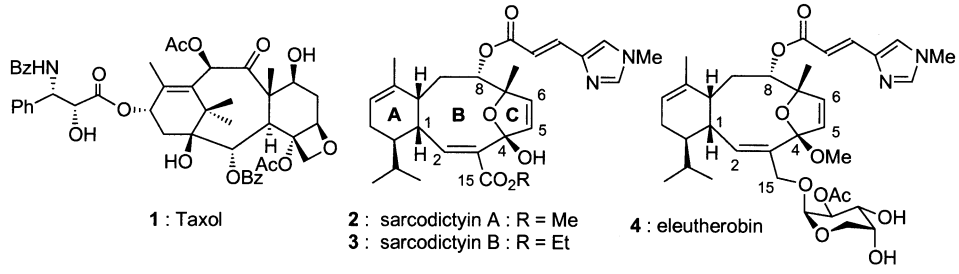

Figure 1.

Keywords: sarcodictyins; epoxidation; Wittig reaction; total synthesis.

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The present paper reports studies towards the implementation of a new synthetic strategy to the sarcodictyins, featuring a key disconnection at the C2–C3 double bond.[9]

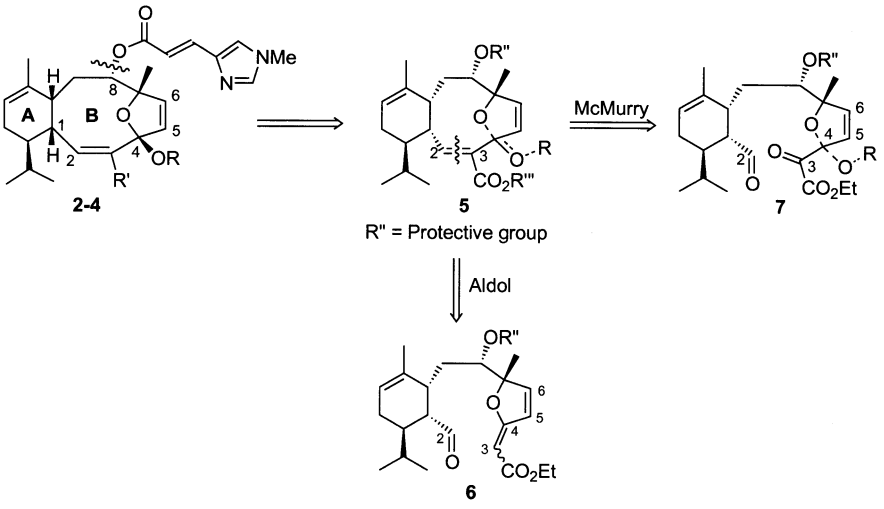
2. Results and discussion

2.1. Retrosynthetic analysis

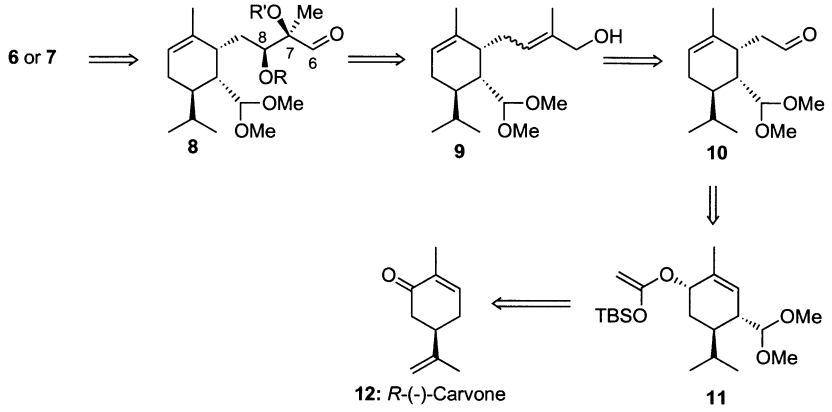
The feature that characterizes all the members of the sarcodictyins family is the central tricyclic skeleton, comprizing a six (ring A), nine (ring B) and five (ring C) membered ring. The latter is easily recognized as an internal hemiacetal system (methyl acetal in the case of eleutherobin). The scission of the acetal bond and retrosynthetic disconnection of the *N*-methylurocanic appendage leads to a simplified target **5** (Scheme 1) which comprises all the elements necessary to give access to the natural compound(s). In the design of a synthetic route to the sarcodictyins, we directed our efforts towards this key tricyclic structure, a potential convergence point for all members of the sarcodictyins family.

Upon examination of the simplified target **5**, we selected the C2–C3 double bond as the most promising site for ring closure, with retrosynthetic analysis revealing an aldehyde or masked aldehyde in the C2 position. The complementary C3 reactive site could bear a nucleophilic character, as in intermediate **6**, suggesting an acid-catalyzed aldol type reaction as key cyclization event. Alternatively, the C3 position could constitute the carbonyl partner for application of a titanium catalyzed reductive (McMurry) coupling at the cyclization stage, as evident in precursor **7**.

For both substrates **6** and **7**, introduction of the C3–C5 portion can be achieved via a Wittig type olefination reaction in a single convergent step (Scheme 2). The two oxygenated stereogenic centres C7 and C8 may be regarded as the result of a Sharpless asymmetric epoxidation/epoxide opening sequence on allylic alcohol **9**. The precursor aldehyde **10** is accessed via an original Claisen type rearrangement strategy from silyl ketene acetal **11**. This in turn originates from the natural compound *R*-(−)-carvone **12**. This inexpensive compound is commercially available from the chiral pool,



Scheme 1. Key retrosynthetic disconnections.



Scheme 2. Retrosynthetic analysis of the cyclization precursors.

and was selected as starting material and source of absolute stereocontrol in this synthetic scheme.

2.2. Synthesis of the six-membered ring

The six membered ring portion of the sarcodictyins contains three adjacent stereogenic centres of the six present in the terpenoidic sector of the molecules. The stereoselective generation of this substitution pattern by synthesis would most likely be complex and cumbersome. The use of *R*-(−)-carvone **12**, which allows control over the absolute stereochemistry of the whole synthetic process was therefore an intriguing possibility. This choice was mainly determined by the availability of a method (through iron catalyzed formation of the dienolate)[10] to functionalize the γ position of the ring (with respect to the carbonyl group) which would become the C1 stereocentre of the target structure.

Accordingly, **12** was first hydrogenated selectively at the exocyclic (less substituted) double bond with Wilkinson's catalyst,[11] to give dihydrocarvone **13**, which was then subjected to deprotonation with the combination MeMgBr/$FeCl_3$ (Scheme 3). The resulting dienolate anion was trapped with trimethylsilyl chloride in the presence of DMPU, to form the corresponding dienoxysilane **14**. When this was exposed to trimethylorthoformate in the presence of $BF_3{\cdot}Et_2O$, formylation in the γ position was achieved to give **15** with complete regio- and stereo-selectivity, albeit in modest yield (30–45%).[10] The use of different Lewis acid catalysts and conditions did not lead to any significative improvement in the yield of this reaction, which however occurs at a very early stage in the synthesis.

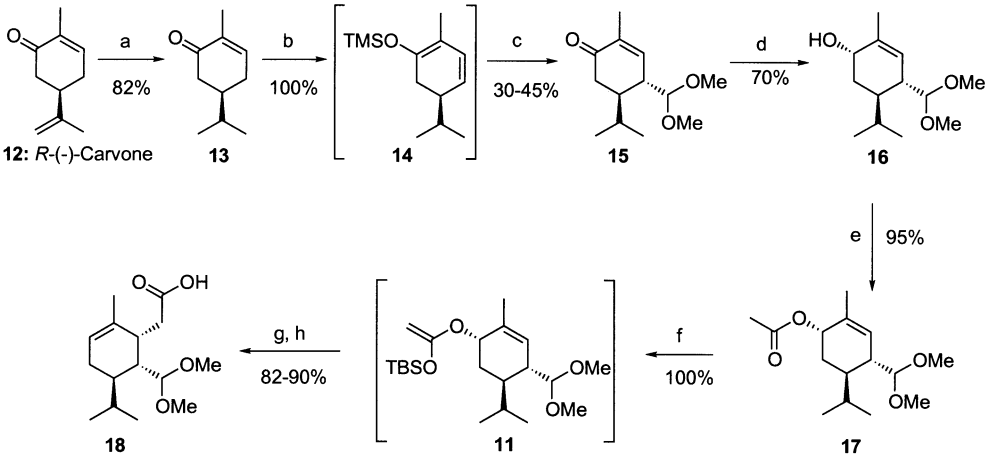
The pseudo-axial alcohol **16** was accessed in good yield by application of lithium tri-*sec*-butylborohydride (L-Selectride®)[12] at low temperature (pseudo-axial/pseudo-equatorial≥95:5 diastereomeric ratio). As a matter of interest, reduction with lithium aluminium hydride provided, as expected, the reverse stereochemistry (pseudo-equatorial/pseudo-axial=90:10 diastereomeric ratio).[13]

Alcohol **16** was acetylated to afford the allyl ester **17** as substrate for Ireland–Claisen rearrangement.[14] After extensive experimentation, the ketene *t*-butyldimethylsilyl acetal **11** could be accessed using $LiN(TMS)_2$ as base and *t*-butyldimethylsilylchloride as trapping agent in the presence of DMPU.[14b,15] This was isolated and redissolved in xylene. Rearrangement occurred in 5–7 h upon heating to 190°C in sealed vials or in a high pressure reactor. The intermediate silyl ester was hydrolyzed to afford the corresponding acid **18** (82–90%). This intermediate not only possesses the same stereochemical arrangement of the six membered ring A in the natural products (see Scheme 1), but also the most adequate functional groups for completion of the synthesis.

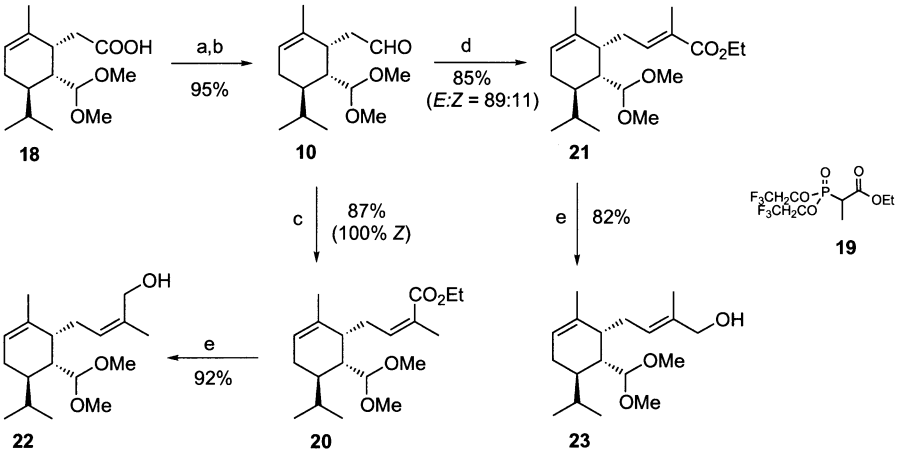
The absolute and relative stereochemistry of structure **18** is secured by: (a) the configuration of the enantiomerically pure starting material; (b) the directing influence of the isopropyl group over the γ-formylation reaction, which forces the dimethylacetal group to be introduced *anti* to the isopropyl substituent; (c) the reduction of the α,β-unsaturated ketone to the axial alcohol, granted by L-Selectride®; (d) the stereospecificity of the Ireland–Claisen rearrangement. The stereochemical assignment was further secured by the convergence with the compounds (**22** and **23**) prepared by Magnus and coworkers via a completely different route.[16]

2.3. Formation of the C7 and C8 stereocentres by Sharpless asymmetric epoxidation (SAE)

Acid **18** was converted to aldehyde **10** through a simple and high yielding reduction–reoxidation sequence (Scheme 4). A Horner–Emmons reaction was then applied for the obtainment of either the *Z* or the *E* trisubstituted double bond. In the first case, phosphonate **19** developed by Still and Gennari was applied using $KN(TMS)_2$/18-crown-6 as base.[17] This combination yielded the *Z* ester **20** in good yield and with complete stereocontrol. The opposite stereochemistry (ester **21**) was obtained in a 9:1 ratio using triethylphosphonopropionate and NaH at room temperature in DME.[18] Both esters were easily reduced to the corresponding allylic alcohols **22** and **23** with lithium aluminium hydride.



Scheme 3. Synthesis of the six membered ring. *Reagents and conditions*: (a) H_2, $(Ph_3P)_3RhCl$, C_6H_6, rt, 5–12 h; (b) MeMgBr, $FeCl_3$ (1.5%), TMSCl, TEA, DMPU, Et_2O, −20°C to rt, 20 h; (c) $(MeO)_3CH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78°C to rt, 1.5 h; (d) L-Selectride®, THF, −78°C, 40 min; (e) Ac_2O, TEA, DMAP, CH_2Cl_2, rt, 3 h; (f) $LiN(TMS)_2$, TBSCl, DMPU, THF, −78°C to rt, 45 min; (g) xylenes, 190°C, 5 h; (h) i. NaOH, 3 h; ii. HCl.



Scheme 4. *Reagents and conditions*: (a) $LiAlH_4$ (2 molar equiv.), Et_2O, rt, 50 min; (b) Dess–Martin Periodinane (DMP), CH_2Cl_2, rt, 30 min; (c) **19**, $KN(TMS)_2$, 18-c-6, THF, −78°C, then aldehyde **10**, 1 h; (d) triethylphosphonopropionate, NaH, DME, rt, then aldehyde **10**; 1 h; (e) $LiAlH_4$, Et_2O, rt, 1 h.

The bias of the preexisting stereogenic centres towards epoxidation in substrates **22** and **23** could not be foreseen. Moreover, epoxide opening could imply inversion at the tertiary or secondary position. For these reasons, we decided to explore the generation of all possible stereoisomeric epoxides by employing both (−)- and (+)-diethyltartrate (DET) on both the *Z* and *E* allylic alcohols.[19,20] The results are reported in detail in Table 1 and Scheme 5.

The *Z* substrate **22** exerted a strong stereochemical bias upon epoxidation. In particular, reaction with (−)-DET was a completely mismatched case, yielding as major isomer the same compound **24** obtained in the reaction with (+)-DET. The *E* alkene **23** was much more prone to reagent control, and good diasteroisomeric excess for epoxides **26** and **27** were obtained with (+)- or (−)-diethyltartrate, respectively. In the latter case, a peculiar by-product **28** was also formed, in which the dimethyl acetal in the south chain is involved.[21]

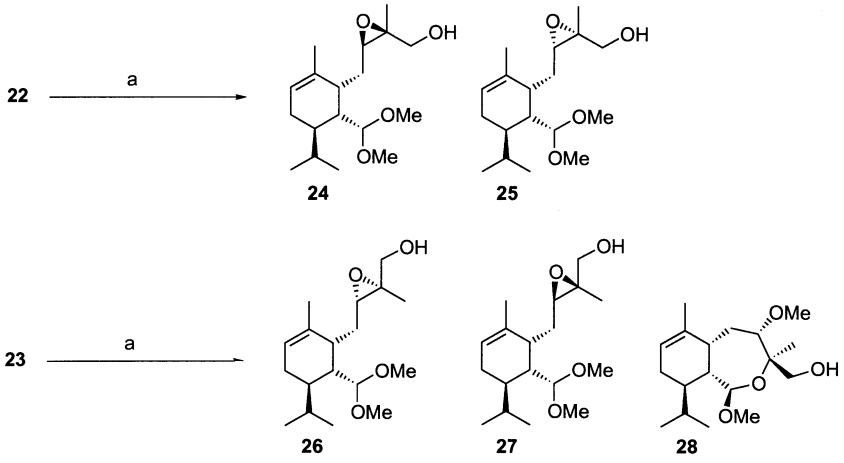
Table 1. Summary of the results obtained from SAE

Ligand	(+)-DET		(−)-DET	
Substrate	**22**	**23**	**22**	**23**
Yield (%)[a]	60 (25)	95 (59)	89 (72)	65 (34)
d.r.	9:1	10:1	55:45	>95:5
Major product[b,c]	**24** (7*S*,8*R*)	**26** (7*S*,8*S*)	**24** (7*S*,8*R*)	**27** (7*R*,8*R*)
By-products[d]	–	–	–	**28** (15)

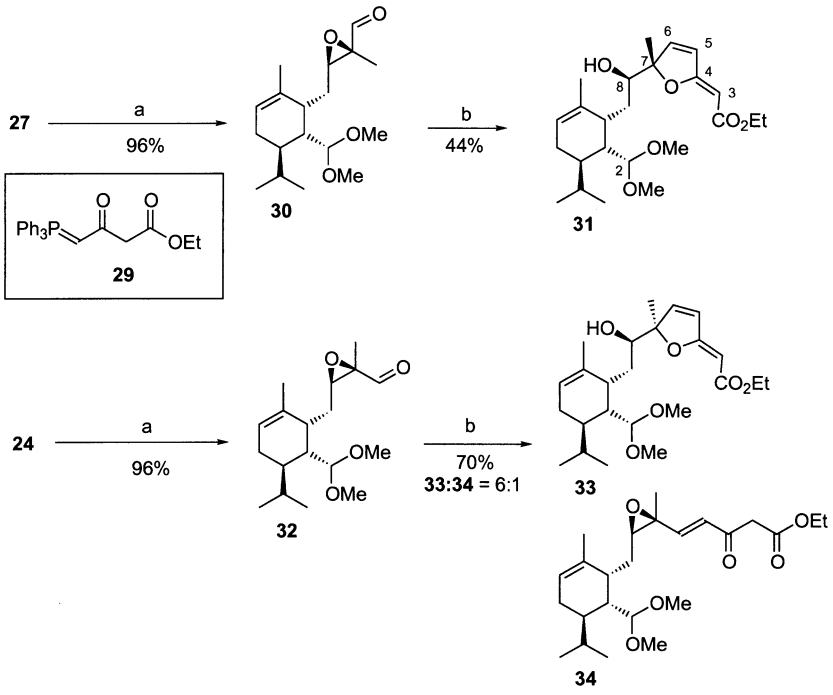
[a] Yields are normalized to the amount of starting material recovered, reported in parenthesis.
[b] Absolute configuration of the stereocentres is reported in parenthesis.
[c] Sarcodictyin numbering.
[d] Yield in parenthesis.

Installation of the 7*S*,8*S* stereochemistry present in the natural targets would require either opening at the secondary (C8) position of epoxide **24** or opening at the tertiary (C7) position of epoxide **25** with inversion of configuration. The first option was soon demonstrated to be impractical, since all attempts to perform a titanium-promoted regioselective opening[22] on epoxide **24** resulted in decomposition of the substrate or, at best, in formation of bicyclic acetals analogous to the by-product **28** observed in one of the SAEs.[21] Examination of the alternative opening at the tertiary position resulted in an unexpected transformation that considerably abbreviated the planned route.

The reagent (3-ethoxycarbonyl-2-oxopropylidene)triphenyl-



Scheme 5. *Reagents and conditions*: (a) TBHP, DET (12%), $Ti(Oi\text{-}Pr)_4$ (10%), MS, CH_2Cl_2, −20°C, 18 h.



Scheme 6. *Reagents and conditions*: (a) DMP, CH_2Cl_2, rt, 1 h; (b) **29**, $NaN(TMS)_2$, THF, then aldehyde, 0°C, 10 min.

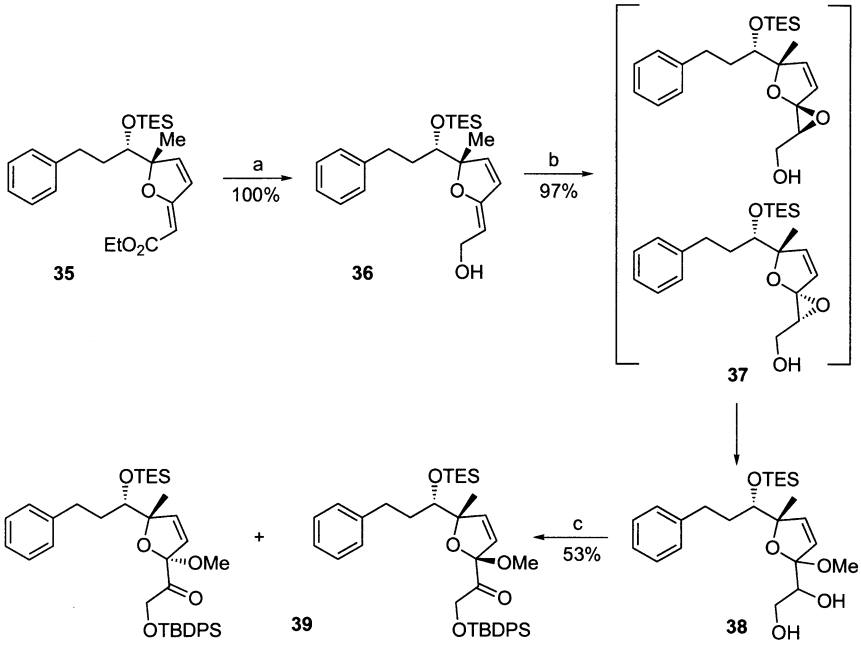
phosphorane **29** can be deprotonated at the activated C3 methylene position by the action of a base. The resulting anionic ylide reacts with aldehydes at the phosphorous-bearing C1 carbon in a Wittig reaction; the formation of the enolate at the β-ketoester unit strongly reduces the ylide stabilization and consequently induces a substantial *Z* selectivity.[23] Use of epoxide **25**, which would yield the correct 7*S*,8*S* stereochemistry (sarcodictyin numbering) was not considered due to the scarce efficiency of the corresponding epoxidation reaction (**25** is always obtained as a minor diastereoisomer, see Table 1). Aldehyde **30**, synthesized by oxidation of epoxide **27**, reacted with phosphorane **29** in the presence of $NaN(TMS)_2$ as base, under anhydrous conditions (Scheme 6): to our surprise and delight, the major product of the reaction was hydrofuran **31**, in which the oxirane ring was opened by intramolecular enolate-oxygen attack at the epoxide tertiary position. Apparently, the proximity of the enolate oxygen to the oxirane ring favors this S_N2 type attack with concurrent ring opening (oxirane) and ring closing (hydrofuran). The reaction is general and can be performed also on other substrates. Aldehyde **32**, for example, derived from epoxide **24**, reacts generating the cyclic product **33** (60%) plus a minor amount of the *trans* isomer **34** (10%) which cannot cyclize.

Installation of the 7*S*,8*S* stereochemistry present in the natural targets would require inversion of the secondary oxygenated stereocentre (C8) of **31** (7*S*,8*R*; sarcodictyin numbering). The enolether moiety present in structure **31** could in principle be involved in an Aldol-type cyclization reaction. Though embedded in a hydrofuran ring, this enolether indeed demonstrated some reactivity: when exposed to Lewis or protic acids a clean isomerization of the C3–C4 double bond (sarcodictyin numbering) was observed. Unfortunately, to date no attempt to induce an intramolecular Aldol-type reaction between the enolether present in **31** (or derivatives protected at the C8 hydroxyl) and either the dimethylacetal or the aldehyde in the 'south' chain was successful. Indeed, the C2 position (sarcodictyin numbering) demonstrated a very poor reactivity in a variety of reactions, probably due to steric hindrance exerted by the isopropyl substituent in the six-membered ring.

2.4. Studies towards application of the McMurry reaction

A metal catalyzed reaction, such as the McMurry reaction,[24] appeared as a very promising alternative for the generation of the disfavored medium-sized ring of the target structures. Accordingly, some preliminary studies were performed to define a synthetic route towards a cyclization precursor bearing two carbonyl groups at the C2 and C3 position (see **7** in Scheme 1). This intermediate appeared as a synthetic elaboration of the enol ether moiety of hydrofuran **31**.

Using a route similar to that illustrated above, compound **35** (ee=75%) was synthesized as a model,[25] and the ester group was reduced with lithium aluminium hydride to the labile alcohol **36** (Scheme 7). In the allylic alcohol **36** the enolether double bond, which is electronically enriched by the geminal oxygen substituent, was selectively oxidized by dimethyldioxirane (DMDO),[26] which is known to selectively oxidize electron-rich double bonds.[27] The preference of DMDO for oxidizing allylic alcohols[28] is not operative here, as the reaction was conducted in MeOH/acetone, a solvent mixture which is known to disrupt the hydrogen-bond interaction between the allylic hydroxyl and the dioxirane.[29] The intermediate epoxides **37** were opened solvolytically in situ to yield the acetal diols **38** as a 1.9:1.6:1 mixture of three diastereoisomers. The primary hydroxyl of these diols was selectively protected with a



Scheme 7. *Reagents and conditions*: (a) $LiAlH_4$, Et_2O, 0°C, 1 h; (b) DMDO, acetone/MeOH, 0°C, 5 min, 1.9:1.6:1.0 d.r.; (c) i. TBDPSCl, Im, CH_2Cl_2, rt, 1 h; ii. DMP, CH_2Cl_2, rt, 2 h, 1.8:1.0 d.r.

sterically encumbered silylating agent (TBDPS), and the secondary hydroxyl was oxidized with Dess–Martin periodinane (DMP)[30] to give the ketones **39** as a mixture of two epimers at the acetal carbon, in a 1.8:1 ratio.

Following these model experiments, a viable route to the generation of a dicarbonyl cyclization precursor was set (cf. **7** in Scheme 1). Studies on the implementation of the sequence on substrate **31** and on the ensuing McMurry cyclization reaction are currently underway.

3. Conclusions

A new retrosynthetic strategy towards the central tricyclic skeleton of the sarcodictyins and eleutherobin was devised, featuring a key cyclization step at the C2–C3 position of the natural targets. Implementation of this strategy in the forward direction allowed a fast and efficient synthesis of the fully functionalized cyclization precursor **31**. A new transformation of epoxyaldehydes was identified in the course of these investigations, which allowed the convergent introduction of the C3–C5 portion of the target with concurrent epoxide opening. Model studies towards the generation of a viable precursor for application of a McMurry cyclization reaction were also performed.

4. Experimental

4.1. General

All reactions were performed in pre-dried glassware, under an inert atmosphere of nitrogen or argon. All commercially available reagents were used without further purification unless otherwise noted. Diethyl ether, THF, benzene, toluene and xylene were distilled from sodium benzophenone ketyl under nitrogen. Acetonitrile, CH_2Cl_2, ethanol, methanol, hexane, TEA, DIPEA, $HN(TMS)_2$, DMPU, NMP were distilled from CaH_2 under nitrogen prior to use. Acetone was distilled from preactivated 4 Å molecular sieves immediately before use.

NMR spectra were measured on a Bruker AC300 (^1H at 300 MHz, ^{13}C at 75 MHz) or a Bruker AC200 (^1H at 200 MHz, ^{13}C at 50 MHz) magnetic resonance spectrometer. Proton NMR spectra are reported as chemical shifts in parts per million (ppm) downfield from tetramethylsilane (0 ppm). The following abbreviations are used to describe spin multiplicity: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, b=broad, dd=doublet of doublets, dt=doublet of triplets, dq=doublet of quartets, ddd=doublet of doublet of doublets. Coupling constants (*J*) are reported in Hertz (Hz). Carbon-13 NMR spectra are reported as chemical shifts in ppm based on the middle peak of chloroform-*d* (77.0 ppm) and were recorded with complete (proton) heterodecoupling. Gas chromatograms were registered on a DANI 6500 instrument, equipped with a flame ionization detector and a capillary column OV1 in fused silica (10 m, 46×250 nm), using H_2 as transport gas.

4.1.1. Dihydrocarvone (13). A two necked 100 mL flask is charged with 3.0 g of *R*-(−)-carvone **12** (20 mmol) and 24 mL of thiophene free benzene. One neck is sealed and the other is fitted with a three way stopcock connected to an atmospheric pressure hydrogenation apparatus and to a vacuum pump. The solution is accurately degassed and purged with hydrogen before adding 350 mg of freshly prepared $(Ph_3P)_3RhCl$ (0.35 mmol). The system is then purged and filled with hydrogen. The reaction is monitored by removing small aliquots of the mixture for GC analysis. The reaction is complete within 5–12 h. The solution is then filtered through a dry column (2 cm diameter) of 40 g of

Florisil (60–100 mesh). The column is eluted with diethyl ether until no product can be detected by TLC analysis, and the combined solvent fractions are concentrated under reduced pressure. Vacuum distillation of the yellow residue through a vigreux column [Bp 110°C (20 mmHg); lit[11] 100–102°C (14 mmHg)] affords 2.51 g of the title compound **13** as a colorless oil (82%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.75–6.70 (1H, m), 2.57–1.80 (5H, m), 1.76–1.74 (3H, m), 1.60–1.50 (1H, m), 0.90 (6H, d, J=6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 153.2, 145.1, 95.6, 41.9, 41.8, 31.9; 29.7, 19.4, 15.5.

4.1.2. (4*R*,5*R*)-4-Dimethoxymethyl-5-isopropyl-2-methyl-cyclohex-2-enone (15). A 250 mL three-necked flask equipped with a three way stopcock and a dropping funnel with pressure equalizer is flame dried under vacuum then flushed with argon. The apparatus is charged with 151 mg (0.93 mmol) of dry $FeCl_3$ and 12 mL of dry Et_2O. The dark suspension is cooled to −20°C and MeMgBr (3.0 M in Et_2O, 24.5 mL, 73.6 mmol) is added dropwise via the dropping funnel over 15 min, while precipitation of a black solid is observed. A solution of 9.2 g (61.3 mmol) of dihydrocarvone **13** in 10 mL of ether is added, and the mixture stirred for 30 min at −20°C. The cooling bath is substituted with an ice/water bath and TMSCl (9.3 mL, 8.0 g, 73.6 mmol), triethylamine (5.7 mL) and dry DMPU (5.7 mL) are added in sequence via the dropping funnel over 30 min. The cooling bath is removed and stirring is maintained at 25°C overnight under an argon atmosphere. After about 12 h, TLC analysis shows no starting material left. Saturated aqueous $NaHCO_3$ (100 mL) is added and the gray suspension is filtered through a short pad of celite, which is accurately washed with diethyl ether. The two phases are separated and the aqueous phase extracted with ether (3×30 mL). The combined organic extracts are washed thoroughly with saturated NaCl (to completely remove DMPU), dried over Na_2SO_4 and the solvent is evaporated under reduced pressure to give *[(5R)-5-isopropyl-2-methyl-cyclohexa-1,3-dienyloxy]-trimethyl-silane* **14** (13.1 g), which is used in the following step with no further purification. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.75 (1H, dd, J=1.5, 9.5 Hz), 5.38 (1H, dd, J=2.7, 9.5 Hz), 2.30–1.20 (7H, m), 0.91 (3H, d, J=6.5 Hz), 0.89 (3H, d, J=6.7 Hz), 0.24 (6H, s), 0.22 (3H, s). The crude silyldienol-ether (from 9.2 g of dihydrocarvone, see preceding preparation) is dissolved in 117 mL of dry dichloromethane and transferred under argon to a flame dried three necked flask equipped with a three way stopcock and a dropping funnel with pressure equalizer. Freshly distilled trimethylorthoformate (8.3 mL, 8.1 g, 76.0 mmol) is added and the solution is cooled to −78°C in a dry ice/acetone bath. $BF_3{\cdot}Et_2O$ (7.2 mL, 8.3 g, 58.5 mmol) is added dropwise via the dropping funnel over 1.5 h. Stirring is maintained at −78°C for 30 min, after which reaction is complete by TLC analysis. Saturated aqueous $NaHCO_3$ (130 mL) is added dropwise at −78°C over 30 min, and temperature is raised to rt over 1 h. The two phases are separated and the aqueous phase is extracted with methylene chloride (3×30 mL). The combined organic extracts are dried over Na_2SO_4 and the solvent is evaporated under reduced pressure. The residue is purified by flash chromatography (hexanes/ethyl acetate 9:1–8:2), yielding 4.18 g of the title compound **15** as a colorless oil (30% overall yield; yields up to 45% have been obtained on smaller scale experiments). $[\alpha]_D^{20}$=+146.4 (c 0.98, EtOAc); ν_{max} (film) 2961, 2834, 1676 (C=O), 1456, 1370, 1105 (C–O), 1074 (C–O) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.77–6.74 (1H, m), 4.45 (1H, d, J=4.7 Hz), 3.44 (6H, s), 2.67–2.60 (1H, m), 2.55 (1H, dd, J=4.7, 16.8 Hz), 2.29 (1H, dd, J=8.6, 16.8 Hz), 2.10–1.80 (2H, m), 1.81–1.79 (3H, m), 0.92 (3H, d, J=8.0 Hz), 0.89 (3H, d, J=8.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 199.3, 143.5, 135.7, 105.4, 55.6, 54.4, 42.2, 41.2, 37.1, 28.2, 20.7, 17.7, 15.5. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.07; H, 9.62.

4.1.3. (1*S*,4*R*,5*R*)-4-Dimethoxymethyl-5-isopropyl-2-methyl-cyclohex-2-enol (16). A flame dried 250 mL flask equipped with a rubber septum is flushed with nitrogen and charged with ketone **15** (1.5 g, 6.63 mmol) and dry THF (130 mL). The solution is cooled to −78°C and L-Selectride® (1.0 M solution in THF, 10 mL, 10 mmol) is added dropwise at −78°C via syringe over 25 min. The reaction is stirred for further 20 min at −78°C and shown to be complete by TLC analysis. The reaction is quenched by adding ethanol (9.0 mL) and water (5.0 mL) at −78°C. Temperature is raised to 0°C over 15 min, then 6.0 M NaOH (10 mL) and 30% hydrogen peroxide (10 mL) are added in sequence. Stirring is maintained at room temperature for 1.0 h. The reaction mixture is transferred to a separatory funnel and the aqueous phase saturated with solid $NaHCO_3$. The two clear phases are separated and the aqueous phase is extracted with Et_2O (5×10 mL). The combined organic extracts are dried over Na_2SO_4 or $MgSO_4$ and the solvent is evaporated under reduced pressure. The residue is purified by flash chromatography (hexanes/ethyl acetate 7:3) yielding the pseudo-axial alcohol **16** as a colorless oil (1.05 g, 70%). $[\alpha]_D^{20}$=+53.9 (c=1.89, EtOAc); ν_{max} (film) 3420 (O–H), 2940, 2815, 1445, 1370, 1145 (C–O), 1110 (C–O), 1070 (C–O) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.57–5.50 (1H, m), 4.30 (1H, d, J=4.5 Hz), 3.98 (1H, bt, J=4.3 Hz), 3.44 (3H, s), 3.41 (3H, s), 2.48–2.36 (1H, m), 1.90–1.50 (4H, m), 1.82 (3H, bs), 0.99 (3H, d, J=6.7 Hz), 0.87 (3H, d, J=6.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.8, 20.6, 21.2, 27.8, 30.6, 35.5, 41.3, 54.7, 56.0, 67.4, 107.1, 123.0, 137.5. Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 69.02; H, 10.54. The pseudo-equatorial alcohol (less than 4% of the crude reaction mixture) was characterized only by ^{1}H NMR spectroscopy (200 MHz, $CDCl_3$): δ 5.62–5.52 (1H, m), 4.26 (1H, d, J=3.7 Hz), 4.22–4.10 (1H, m), 3.41 (3H, s), 3.40 (3H, s), 2.48–2.36 (1H, m), 1.90–1.50 (4H, m), 1.87 (3H, bs), 0.96 (3H, d, J=6.9 Hz), 0.85 (3H, d, J=7.0 Hz).

4.1.4. Acetic acid (1*S*,4*R*,5*R*)-4-dimethoxymethyl-5-isopropyl-2-methyl-cyclohex-2-enyl ester (17). A 100 mL flask equipped with a rubber septum is flushed with nitrogen and charged with alcohol **16** (900 mg, 3.90 mmol) and dry dichloromethane (39 mL). The solution is cooled to 0°C and triethylamine (1.1 mL, 7.89 mmol) and dimethylaminopyridine (DMAP) (0.2 M solution in dry dichloromethane, 1.9 mL, 0.39 mmol) are added, followed by freshly distilled acetic anhydride (0.55 mL, 5.90 mmol). Stirring is maintained at 25°C under a nitrogen atmosphere for 3 h, after which the reaction is complete by TLC analysis. Saturated $NaHCO_3$ is added (35 mL), and after stirring for 15 min, the two phases are separated and the aqueous phase is extracted

with dichloromethane (3×10 mL). The combined organic extracts are dried over Na_2SO_4 and the solvent is evaporated under reduced pressure. The residue is purified by flash chromatography (hexanes/diethyl ether 9:1–8:2), yielding 1.02 g of the title compound **17** as a colorless oil (95%). $[\alpha]_D^{20}$=+58.3 (*c* 0.98, EtOAc); ν_{max} (film) 2957, 2832, 1734 (C=O), 1458, 1372, 1242 (C–O), 1117 (C–O), 1076 (C–O), 1019, 965 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$):δ 5.72–5.65 (1H, m), 5.26 (1H, bt, *J*=4.4 Hz), 4.34 (1H, d, *J*=5.5 Hz), 3.43 (3H, s), 3.39 (3H, s), 2.33–2.31 (1H, m), 2.08 (3H, s), 1.80–1.50 (4H, m), 1.70 (3H, d, *J*=0.6 Hz), 0.94 (3H, d, *J*=7.1 Hz), 0.90 (3H, d, *J*=7.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.1, 20.1, 21.2, 21.4, 27.1, 27.5, 37.1, 41.1, 54.0, 55.3, 70.0, 106.4, 126.2, 133.3, 171.0. Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69. Found: C, 66.71; H, 9.75.

4.1.5. [(1*R*,5*R*,6*R*)-6-Dimethoxymethyl-5-isopropyl-2-methyl-cyclohex-2-enyl]-acetic acid (18). A 500 mL two necked flask is equipped with a magnetic stirring bar, a dropping funnel (with pressure equalizer) and a three way stopcock. The apparatus is flame dried under vacuum, flushed with argon and charged with $HN(TMS)_2$ (7.7 mL, 36.6 mmol) and dry THF (33 mL). The solution is cooled to 0°C, and *n*-BuLi (1.6 M hexanes solution, 21.3 mL, 34.2 mmol) is added dropwise with stirring. The mixture is stirred at 0°C for 30 min, then cooled to −78°C. A solution of the acetate **17** (3.3 g, 12.2 mmol) in THF (40 mL) is added dropwise, and the resulting solution is stirred at −78°C for 30 min. *tert*-Butyl dimethyl silyl chloride (5.5 g, 36.6 mmol) is dissolved in dry DMPU (26 mL) with the aid of a small quantity of THF (2 mL). The resulting solution is added dropwise to the reaction mixture, and stirring is maintained at −78°C for 45 min. After warming to room temperature over 40 min, the mixture is transferred to a separatory funnel with pentane (260 mL) and washed with phosphate buffer solution (3×100 mL) and brine (30 mL). The combined aqueous phases are back extracted with pentane (60 mL) and the combined organic phases are dried (Na_2SO_4) and evaporated. Formation of the silyl ketene acetal **11** can be ascertained by analysis of diagnostic signals in the NMR spectrum of the crude. ^1H NMR (200 MHz, $CDCl_3$): δ (selected signals) 3.31 (1H, d, *J*=2.2 Hz), 3.20 (1H, d, *J*=2.2 Hz). The crude light yellow oil is dissolved in dry xylenes (50 mL) and transferred to a high pressure stainless steel reactor (Ashcroft, 250 mL), equipped with a magnetic stirring bar. The reactor is purged and flushed with argon three times, then warmed to 190°C and stirred for 5 h, after which the reaction is complete by TLC analysis. The solvent is evaporated and the residue is dissolved in THF (35 mL) and treated at room temperature with 2.0 M NaOH (30 mL). Desilylation is complete in about 3 h. The reaction mixture is transferred to a separatory funnel and diethyl ether is added (50 mL) the two phases are separated and the organic phase is extracted with 2.0 M NaOH (2×35 mL). The combined aqueous phases are washed with diethyl ether (2×25 mL), and then carefully acidified to pH 3 with 10% aqueous HCl. The suspension is immediately extracted with diethyl ether (5×40 mL) and the combined organic extracts are dried over Na_2SO_4 and evaporated under reduced pressure to give the title compound **18** (2.7 g, 82%; yields up to 90% have been obtained on smaller scale experiments), which is considered sufficiently pure for following usage with no further purification. $[\alpha]_D^{20}$=+48.6 (*c*=0.81, EtOAc); ν_{max} (CCl_4) 2960, 2825, 1705 (C=O), 1540, 1440, 1390, 1370, 1215, 1110 (C–O), 1075 (C–O), 1005 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.38 (1H, bs), 4.40 (1H, d, *J*=5.6 Hz), 3.39 (3H, s), 3.37 (3H, s), 2.85–2.74 (2H, m), 2.52–2.30 (1H, m), 2.17–2.05 (1H, m), 1.98–1.55 (4H, m), 1.70 (3H, bs), 0.95 (3H, d, *J*=6.6 Hz), 0.86 (3H, d, *J*=6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 179.3, 134.7, 122.0, 106.0, 54.4, 53.2, 39.4, 36.8, 35.6, 34.4, 27.0, 24.3, 21.8, 20.9, 18.1. Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69. Found: C, 67.11; H, 9.91.

4.1.6. [(1*R*,5*R*,6*R*)-6-Dimethoxymethyl-5-isopropyl-2-methyl-cyclohex-2-enyl]-acetaldehyde (10). To a stirred suspension of $LiAlH_4$ (882 mg, 23.24 mmol) in Et_2O (50 mL) under nitrogen at 0°C is added a solution of acid **18** (3.12 g, 11.54 mmol) in Et_2O (40 mL) via cannula. The suspension is warmed to room temperature, stirred for 2 h and then cooled to 0°C. H_2O (0.9 mL), 15% NaOH aq (0.9 mL), H_2O (2.7 mL) and Na_2SO_4 (5.9 g) are added successively and the resulting suspension is stirred at room temperature until powdery solids separate (about 1.5–2 h). The suspension is then filtered, washed with Et_2O, and the filtrate evaporated under reduced pressure, yielding the primary alcohol as a colorless oil (2.91 g, 98%). $[\alpha]_D^{20}$=+86.4 (*c*=1.48, EtOAc); ν_{max} (film) 3380 (OH), 2940, 2815, 1445, 1375, 1180 (C–O), 1150 (C–O), 1110 (C–O), 1070 (C–O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.26 (1H, bs), 4.33 (1H, d, *J*=5.9 Hz), 3.70–3.63 (2H, m), 3.33 (3H, s), 3.32 (3H, s), 2.89 (1H, bs, OH), 2.30–2.25 (1H, m), 2.10–1.60 (7H, m), 1.65 (3H, d, *J*=1.1 Hz), 0.92 (3H, d, *J*=6.8 Hz), 0.83 (3H, d, *J*=6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 137.2, 120.6, 106.9, 62.6, 54.6, 54.5, 40.7, 36.2, 35.8, 33.4, 26.9, 24.3, 22.4, 21.2, 16.5. Anal. Calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01. Found: C, 70.41; H, 10.95. To a stirred suspension of Dess–Martin periodinane (DMP) (7.08 g, 16.69 mmol) in CH_2Cl_2 (60 mL) under nitrogen at room temperature is added a solution of the alcohol (3.12 g, 11.54 mmol) in CH_2Cl_2 (40 mL) via cannula. After 45 min 2 M NaOH aq (70 mL) and Et_2O (70 mL) are added successively and the suspension stirred at room temperature for 30 min. The two layers are separated and the aqueous layer extracted with Et_2O (2×80 mL). The combined organic layers are washed with brine (80 mL), dried (Na_2SO_4) and the solvent evaporated under reduced pressure to give the title aldehyde **10** as a clear oil (2.74 g, 97%). ν_{max} (film): 1720 cm^{-1} (C=O); ^1H NMR (200 MHz, $CDCl_3$): δ 9.72 (1H, bs), 5.38 (1H, bs), 4.32 (1H, d, *J*=4.8 Hz), 3.35 (3H, s), 3.32 (3H, s), 2.83 (1H, bs), 2.74 (1H, dd, *J*=2.5, 9.9 Hz), 2.31–2.19 (1H, m), 2.10–1.60 (5H, m), 1.66 (3H, d, *J*=1.5 Hz), 0.94 (3H, d, *J*=6.8 Hz), 0.84 (3H, d, *J*=6.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$):δ 201.3, 135.2, 121.8, 106.9, 54.8, 54.6, 44.6, 40.5, 35.6, 33.5, 26.6, 24.2, 21.8, 21.1, 16.5. Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 71.03; H, 10.01.

4.1.7. (*Z*)-4-[(1*R*,5*R*,6*R*)-6-Dimethoxymethyl-5-isopropyl-2-methyl-cyclohex-2-enyl]-2-methyl-but-2-enoic acid ethyl ester (20). A solution of phosphonate **19** (155 mg, 0.45 mmol) and 18-crown-6 (148 mg, 0.56 mmol) in THF (3.5 mL) is flushed with nitrogen and cooled to −78°C.

$KN(TMS)_2$ (15% w/v solution in toluene, 0.62 mL, 0.41 mmol) is added, followed by a solution of the aldehyde **10** (94.5 mg, 0.37 mmol) in THF (4.0 mL). The mixture is stirred at −78°C for 1.0 h, after which the reaction is complete by TLC analysis. The reaction is quenched with saturated NH_4Cl (4.5 mL) and the mixture is partitioned between water and Et_2O. Drying (Na_2SO_4) and evaporation of the solvent affords a crude oil, which is purified by flash chromatography (hexanes/ethyl acetate 9:1), yielding the title compound **20** as a colorless oil (110 mg, 87%). ^1H NMR (200 MHz, $CDCl_3$): δ 6.10 (1H, bt, *J*=6.7 Hz), 5.33 (1H, bs), 4.31 (1H, d, *J*=5.8 Hz), 4.18 (2H, q, *J*=7.0 Hz), 3.33 (3H, s), 3.32 (3H, s), 2.91–2.75 (1H, m), 2.67–2.56 (1H, m), 2.39–2.22 (1H, m), 2.04–1.57 (5H, m), 1.94 (3H, bs), 1.66 (3H, bs), 1.23 (3H, t, *J*=7.0 Hz), 0.87 (3H, d, *J*=6.7 Hz), 0.80 (3H, d, *J*=6.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.2, 144.1, 136.3, 125.7, 121.3, 106.8, 59.7, 54.6, 54.0, 40.6, 39.3, 36.5, 30.6, 27.2, 24.4, 22.5, 21.1, 20.7, 17.0, 14.2. Anal. Calcd for $C_{20}H_{34}O_4$: C, 70.97; H, 10.12. Found: C, 71.09; H, 10.42.

4.1.8. (*E*)-4-[(1*R*,5*R*,6*R*)-6-Dimethoxymethyl-5-isopropyl-2-methyl-cyclohex-2-enyl]-2-methyl-but-2-enoic acid ethyl ester (21). To a stirred suspension of sodium hydride (60% dispersion in mineral oil) (519 mg, 12.98 mmol) in DME (60 mL) under nitrogen at room temperature is added triethylphosphonopropionate (3.9 mL, 18.19 mmol). After 10 min the suspension becomes a clear solution which is stirred for a further 20 min and then a solution of aldehyde **10** (2.74 g, 10.77 mmol) in DME (40 mL) is added via cannula. After 1.0 h the reaction is completed by TLC analysis, sat. NH_4Cl aq (20 mL) is added and the suspension partitioned between Et_2O (50 mL) and H_2O (50 mL). The aqueous layer is extracted with Et_2O (3×80 mL), the combined organic layers are washed with brine (80 mL), dried (Na_2SO_4), filtered, the solvent removed and the residue purified by flash chromatography (hexanes/ethyl acetate 9:1) to give a colorless oil which contains the title compound **21** plus the corresponding *Z* isomer **20** (3.10 g, 85%, 89:11 *E*/*Z*), which are separated at a later stage, i.e. after reduction of the ester group. **21**: ν_{max} (film): 1705 (C=O), 1640 (C=C) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 6.92 (1H, bt, *J*=7.0 Hz), 5.36 (1H, bs), 4.31 (1H, d, *J*=5.2 Hz), 4.17 (2H, q, *J*=7.0 Hz), 3.35 (3H, s), 3.34 (3H, s), 2.57–2.32 (3H, m), 2.10–1.60 (5H, m), 1.81 (3H, bs), 1.65 (3H, bs), 1.27 (3H, t, *J*=7.0 Hz), 0.88 (3H, d, *J*=6.7 Hz), 0.79 (3H, d, *J*=6.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.3, 143.6, 136.3, 126.2, 121.7, 101.0, 60.0, 54.9, 54.6, 41.1, 38.6, 35.7, 30.1, 27.0, 24.2, 22.7, 21.1, 16.2, 14.2, 12.3. Anal. Calcd for $C_{20}H_{34}O_4$: C, 70.97; H, 10.12. Found: C, 71.03; H, 10.01.

4.1.9. (*Z*)-4-[(1*R*,5*R*,6*R*)-6-Dimethoxymethyl-5-isopropyl-2-methyl-cyclohex-2-enyl]-2-methyl-but-2-en-1-ol (22). A suspension of lithium aluminium hydride (11 mg, 0.29 mmol) in Et_2O (1.0 mL) is flushed with nitrogen and cooled to 0°C. A solution of ester **20** (98 mg, 0.29 mmol) in Et_2O (2.0 mL) is added dropwise. The cooling bath is removed, and the mixture stirred at room temperature for 1 h. The reaction mixture is diluted by Et_2O, cooled to 0°C and quenched with a few drops of saturated NH_4Cl. Solid Na_2SO_4 (500 mg) is added, and the mixture is stirred for 75 min, then the salts are filtered and washed with Et_2O. The organic filtrates are evaporated under reduced pressure, yielding the title compound **22** as a colorless oil[16] (78 mg, 92%). ν_{max} (film) 3420, 2960 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.40–5.30 (2H, m), 4.32 (1H, d, *J*=5.3 Hz), 4.07 (1H, d, *J*=11.6 Hz), 3.95 (1H, d, *J*=11.6 Hz), 3.36 (3H, s), 3.34 (3H, s), 2.60–2.40 (1H, m), 2.35–2.10 (2H, m), 2.05–1.60 (5H, m), 1.77 (3H, bs), 1.67 (3H, bs), 0.86 (3H, d, *J*=6.5 Hz), 0.77 (3H, d, *J*=6.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 137.1, 134.0, 128.6, 121.2, 107.4, 61.3, 54.8, 54.7, 40.8, 39.2, 35.9, 28.6, 27.1, 24.4, 22.9, 21.9, 21.1, 16.4. Anal. Calcd for $C_{18}H_{32}O_3$: C, 72.93; H, 10.88. Found: C, 73.07; H, 10.64.

4.1.10. (*E*)-4-[(1*R*,5*R*,6*R*)-6-Dimethoxymethyl-5-isopropyl-2-methyl-cyclohex-2-enyl]-2-methyl-but-2-en-1-ol (23). Ester **21** (105 mg, 0.31 mmol) is reduced with lithium aluminium hydride (12 mg, 0.31 mmol) as described above for ester **20**. The crude, containing both the *E* and *Z* allylic alcohols, is purified by flash chromatography (hexanes/ethyl acetate 8:2), yielding the title compound **23** as a colorless oil[16] (67 mg, 72%) and the *Z* allyl alcohol **22** (9.2 mg, 9.9%). **23**: ν_{max} (film) 3380, 2960 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.53 (1H, bt, *J*=6.9 Hz), 5.32 (1H, bs), 4.31 (1H, d, *J*=5.7 Hz), 3.98 (2H, s), 3.34 (6H, s), 2.35–2.20 (3H, m), 2.05–1.65 (5H, m), 1.66 (6H, s), 0.88 (3H, d, *J*=6.7 Hz), 0.79 (3H, d, *J*=6.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$). δ 137.1, 133.7, 127.3, 121.1, 107.0, 69.2, 54.4, 54.2, 40.8, 39.1, 36.3, 28.8, 27.3, 24.4, 22.9, 21.2, 16.7, 13.7. Anal. Calcd for $C_{18}H_{32}O_3$: C, 72.93; H, 10.88. Found: C, 73.04; H, 10.69.

4.1.11. {(2*S*,3*R*)-3-[(1*R*,5*R*,6*R*)-6-Dimethoxymethyl-5-isopropyl-2-methyl-cyclohex-2-enylmethyl]-2-methyl-oxiranyl}-methanol (24). A suspension of powdered 3 Å molecular sieves (50 mg) in dichloromethane (1.0 mL) is cooled to −20°C and treated with (+)-DET (0.2 M solution in dichloromethane, 0.15 mL, 0.030 mmol), $Ti(O\textit{i}\text{-}Pr)_4$ (0.0075 mL, 7.1 mg, 0.025 mmol) and TBHP (5.5 M in nonane, 0.091 mL, 0.5 mmol). The mixture is stirred at −20°C for 25 min, after which a solution of the alcohol **22** (70 mg, 0.24 mmol) in CH_2Cl_2 (1.0 mL) over molecular sieves is added dropwise. The reaction mixture is stirred at −20°C for 18 h, then H_2O (1.0 mL) is added, and the temperature is raised to rt over 30 min. NaOH 30% saturated with NaCl (0.2 mL) is added and the emulsion stirred vigorously until two clear phases separate (about 15 min). The lower organic phase is separated from the upper sieve-containing aqueous phase, which is extracted twice with dichloromethane. The combined organic extracts are dried (Na_2SO_4) and evaporated under reduced pressure. Flash chromatography (hexanes/ethyl acetate 7:3) affords the epoxide (33.6 mg, 45%) as a mixture of the two isomers **24** and **25** (90:10), plus recovered starting material (17.5 mg, 25%). The two isomers can be separated by chromatography with CH_2Cl_2/ethyl ether 8:2. Title compound **24**: ^1H NMR (200 MHz, $CDCl_3$): δ 5.45 (1H, bs), 4.32 (1H, d, *J*=4.5 Hz), 3.62 (1H, d, *J*=12.0 Hz), 3.54 (1H, d, *J*=12.0 Hz), 3.40 (6H, s), 2.97 (1H, dd, *J*=3.4 Hz, *J*=8.9 Hz), 2.53–2.40 (1H, m), 2.20–2.10 (2H, m), 2.10–1.50 (5H, m), 1.77 (3H, d, *J*=1.2 Hz), 1.39 (3H, s), 0.91 (3H, d, *J*=6.6 Hz), 0.80 (3H, d, *J*=6.6 Hz). Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32. Found: C, 69.45; H, 10.12.

4.1.12. {(2*R*,3*S*)-3-[(1*R*,5*R*,6*R*)-6-Dimethoxymethyl-5-isopropyl-2-methyl-cyclohex-2-enylmethyl]-2-methyl-oxiranyl}-methanol (25). Alcohol **22** (50 mg, 0.17 mmol) is epoxidized as described above using (−)-DET (4.2 mg, 0.020 mmol) as chiral ligand. Standard workup and flash chromatography affords the epoxides (13.5 mg, 25%) as a mixture of the two isomers (55:45 in favor of distereoisomer **24**) plus recovered starting material (36 mg, 72%). The two isomers can be separated by flash chromatography with CH_2Cl_2/ethyl ether 8:2. Title compound **25**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.35 (1H, bs), 4.36 (1H, d, J=4.7 Hz), 3.65–3.55 (2H, m), 3.41 (6H, s), 3.02 (1H, dd, J=4.3 Hz, J=8.6 Hz), 2.40–2.30 (1H, m), 1.77 (3H, bs), 2.2–1.5 (7H, m), 1.45 (3H, s), 0.91 (3H, d, J=6.5 Hz), 0.82 (3H, d, J=6.5 Hz).

4.1.13. {(2*S*,3*S*)-3-[(1*R*,5*R*,6*R*)-6-Dimethoxymethyl-5-isopropyl-2-methyl-cyclohex-2-enylmethyl]-2-methyl-oxiranyl}-methanol (26). Alcohol **23** (27 mg, 0.091 mmol) is oxidized using (+)-DET as chiral ligand, as described above. Due to the scale, Ti(O*i*-Pr)$_4$ is added as a solution in CH_2Cl_2 (2.7% v/v). Purification by flash chromatography (hexanes/ethyl acetate 7:3) yields the epoxide (11 mg, 39%) as a mixture of the two isomers (ratio 10:1) plus recovered starting material (16 mg, 59%). The two isomers can be separated by flash chromatography (CH_2Cl_2/ethyl ether 8:2) to give the title compound **26** (major isomer) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.36 (1H, bs), 4.34 (1H, d, J=5.6 Hz), 3.67–3.57 (2H, m), 3.36 (6H, s), 3.23 (1H, dd, J=4.6 Hz, J=7.0 Hz), 2.41–2.38 (1H, m), 2.12–1.60 (7H, m), 1.74 (3H, bs), 1.30 (3H, s), 0.93 (3H, d, J=6.7 Hz), 0.82 (3H, d, J=6.6 Hz).

4.1.14. {(2*R*,3*R*)-3-[(1*R*,5*R*,6*R*)-6-Dimethoxymethyl-5-isopropyl-2-methyl-cyclohex-2-enylmethyl]-2-methyl-oxiranyl}-methanol (27); [(1*R*,3*R*,4*S*,5a*R*,9*R*,9a*R*)-9-isopropyl-1,4-dimethoxy-3,6-dimethyl-1,3,4,5,5a,8,9,9a-octahydro-benzo[*c*]oxepin-3-yl]-methanol (28). Alcohol **23** (20 mg, 0.067 mmol) is oxidized as described above using (−)-DET (1.7 mg, 0.0081 mmol). Due to the scale, Ti(O*i*-Pr)$_4$ is added as a solution in CH_2Cl_2 (2.4% v/v). Purification by flash chromatography (CH_2Cl_2/ethyl ether 85:15–7:3) yields the epoxide **27**[16] (9.1 mg, 43%) as a single isomer, the rearranged product **28**[16] (2.1 mg, 10%) plus recovered starting material (6.8 mg, 34%). **27**: colorless oil;[16] ν_{max} (film) 3450, 2960 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.37 (1H, bs), 4.33 (1H, d, J=5.1 Hz), 3.61–3.40 (2H, m), 3.38 (3H, s), 3.37 (3H, s), 3.24 (1H, dd, J=5.0 Hz, J=7.6 Hz), 2.46–2.30 (1H, m), 2.11–1.49 (7H, m), 1.71 (3H, d, J=1.2 Hz), 1.29 (3H, s), 0.91 (3H, d, J=6.9 Hz), 0.81 (3H, d, J=6.6 Hz); ^{13}C NMR ($CDCl_3$): δ 136.3, 122.1, 106.9, 66.3, 61.6, 60.3, 55.1, 54.6, 41.2, 36.3, 35.3, 28.8, 27.0, 24.0, 22.7, 21.1, 16.0, 14.4. **28**: colorless oil;[16] ν_{max} (film) 3465, 2935 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.38 (1H, bs), 4.51 (1H, d, J=7.1 Hz), 3.59 (2H, s), 3.47 (1H, dd, J=3.4, 11.7 Hz), 3.38 (3H, s), 3.33 (3H, s), 2.20–2.10 (1H, m), 2.10–1.40 (6H, m), 1.71 (3H, s), 1.18 (3H, s), 0.98 (3H, d, J=6.6 Hz), 0.95–0.85 (1H, m), 0.81 (3H, d, J=6.7 Hz); ^{1}H NMR (C_6D_6): δ 5.33 (1H, bs), 4.42 (1H, d, J=7.0 Hz), 3.8–3.6 (2H, m), 3.49 (1H, dd, J=3.2 Hz, J=11.8 Hz), 3.09 (3H, s), 3.07 (3H, s), 2.35 (OH, bs), 2.20 (1H, t, J=7.9 Hz), 2.1–2.0 (1H, m), 2.0–1.2 (8H, m), 1.06 (3H, s), 1.05–0.95 (1H, m), 0.95 (3H, d, J=6.5 Hz), 0.93 (3H, d, J=6.6 Hz).

4.1.15. (2*S*,3*R*)-3-[(1*R*,5*R*,6*R*)-6-Dimethoxymethyl-5-isopropyl-2-methyl-cyclohex-2-enylmethyl)-2-methyl-oxirane-2-carbaldehyde (30). A solution of alcohol **27** (9.0 mg, 0.029 mmol) in CH_2Cl_2 (0.42 mL) is treated with Dess–Martin periodinane (DMP) (18 mg, 0.042 mmol) and the mixture stirred at room temperature for 1.0 h. The reaction mixture is then poured into a separatory funnel containing 1.0 M NaOH (0.3 mL) and Et_2O (1.0 mL). The two phases are separated and the organic phase is washed twice with water, dried (Na_2SO_4) and evaporated to give the title aldehyde **30** (8.5 mg, 96%), which is used in the following step with no further purification. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.88 (1H, s), 5.40 (1H, bs), 4.33 (1H, d, J=4.9 Hz), 3.39 (3H, s), 3.37 (3H, s), 2.41–2.26 (1H, m), 2.24–1.60 (8H, m), 1.69 (3H, s), 1.39 (3H, s), 0.89 (3H, d, J=6.9 Hz), 0.81 (3H, d, J=6.7 Hz).

4.1.16. (*Z*)-{(5*S*)-5-[(1*R*)-2-((1*R*,5*R*,6*R*)-6-Dimethoxymethyl-5-isopropyl-2-methyl-cyclohex-2-enyl)-1-hydroxy-ethyl]-5-methyl-5*H*-furan-2-ylidene}-acetic acid ethyl ester (31). Phosphorane **29** (16.4 mg, 0.042 mmol) is dissolved in THF (0.20 mL) under nitrogen, cooled to 0°C and treated with NaN(TMS)$_2$ (1.0 M solution in THF, 0.033 mL, 0.033 mmol). After stirring for 1.0 h, aldehyde **30** (8.5 mg, 0.027 mmol) is added via cannula as a solution in THF (0.30 mL). The mixture is stirred at 0°C for ~10 min. Water is added (0.30 mL) and the mixture is warmed to room temperature. After diluting with Et_2O and water, the two phases are separated, and the organic phase washed with brine, dried (Na_2SO_4) and evaporated. The crude is purified by flash chromatography (hexanes/acetate 7:3) yielding the cyclic title compound **31** (5.0 mg, 44%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.81 (1H, d, J=5.8 Hz), 6.12 (1H, d, J=5.8 Hz), 5.27 (1H, bs), 4.86 (1H, s), 4.41 (1H, d, J=5.7 Hz), 4.20–4.10 (2H, m), 3.64 (1H, dd, J=9.2 Hz, J=1.6 Hz), 3.39 (3H, s), 3.38 (3H, s), 2.35–2.30 (1H, m), 2.20–1.58 (7H, m), 1.69 (3H, d, J=1.5 Hz), 1.44 (3H, s), 1.25 (3H, t, J=7.0 Hz), 0.93 (3H, d, J=6.8 Hz), 0.83 (3H, d, J=6.6 Hz).

4.1.17. (2*R*,3*R*)-3-[(1*R*,5*R*,6*R*)-6-Dimethoxymethyl-5-isopropyl-2-methyl-cyclohex-2-enylmethyl)-2-methyl-oxirane-2-carbaldehyde (32). Alcohol **24** (11 mg, 0.035 mmol) is oxidized as described above for alcohol **27**. The crude aldehyde **32** (10.5 mg, 96%) is used in the following step with no further purification.

4.1.18. (*Z*)-{(5*R*)-5-[(1*R*)-2-((1*R*,5*R*,6*R*)-6-Dimethoxymethyl-5-isopropyl-2-methyl-cyclohex-2-enyl)-1-hydroxy-ethyl]-5-methyl-5*H*-furan-2-ylidene}-acetic acid ethyl ester (33). Aldehyde **32** (10.5 mg, 0.034 mmol) is exposed to the phosphorane **29** as described above for aldehyde **30**. Purification of the crude by flash chromatography (hexanes/acetate 9:1–6:4) affords the acyclic *trans* isomer **34** (1.4 mg, 10%) (as a mixture of the keto and enol tautomers) and the cyclic title compound **33** (8.6 mg, 60%). **33**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.68 (1H, d, J=5.7 Hz), 6.16 (1H, d, J=5.7 Hz), 5.25 (1H, bs), 4.86 (1H, s), 4.41 (1H, d, J=5.8 Hz), 4.2–4.1 (2H, m), 3.88 (1H, d, J=9.6 Hz), 3.39 (3H, s), 3.38 (3H, s), 2.37–2.28 (1H, m), 2.10–1.40 (7H, m),

1.70 (3H, d, J=1.2 Hz), 1.54 (3H, s), 1.27 (3H, t, J=7.1 Hz), 0.92 (3H, d, J=6.8 Hz), 0.82 (3H, d, J=6.9 Hz). **34**: ^{1}H NMR (200 MHz, $CDCl_3$): δ [(6.81, d, J=17.2 Hz), (6.61, d, J=15.9 Hz), 1H corresponding to keto+enol tautomer]; [(6.35, d, J=15.9 Hz), (6.01, dd, J=17.2, 1.3 Hz), 1H corresponding to keto+enol tautomer]; 5.37 (1H, bs); [(5.08, s), (3.58, s), 2H corresponding to keto+enol tautomer]; 4.30 (1H, d, J=5.2 Hz); 4.18–4.12 (2H, m); 3.38 (6H, s); 3.32–3.21 (1H, m); 2.49–2.28 (1H, m); 2.19–1.62 (7H, m); [(1.50, s), (1.48, s), 3H corresponding to keto+enol tautomer]; 1.33–1.25 (3H, m); 0.89 (3H, d, J=7.7 Hz); 0.81 (3H, d, J=6.6 Hz).

4.1.19. 1-[(5*S*)-2-Methoxy-5-methyl-5-(3-phenyl-1*S*-triethylsilanyloxy-propyl)-2,5-dihydrofuran-2-yl]-ethane diol (38). A solution of ester **35**[25] (171 mg, 0.41 mmol) in Et_2O (5.0 mL) is cooled to 0°C and treated with $LiAlH_4$ (23 mg, 0.63 mmol). The mixture is stirred at 0°C for 1 h, then quenched by diluting with Et_2O saturated with NaOH 6.0 M. Na_2SO_4 is added, and the salts filtered and washed with Et_2O. The solution is evaporated under reduced pressure to give the crude alcohol **36** (152 mg) which is highly unstable and is processed immediately to the following reaction. Crude alcohol **36** (152 mg, 0.41 mmol) is dissolved in dry MeOH (4.4 mL) and cooled to 0°C. A freshly prepared solution of DMDO in acetone (0.0845 M, 5.2 mL, 0.44 mmol) is added dropwise, and the mixture stirred at 0°C for 5 min. DMDO is removed under a stream of nitrogen, then the volatiles are evaporated. The crude, consisting of mixture of three isomers **38** (approx. 1.9:1.6:1) (168 mg, 97%), is pure enough for subsequent transformations. ^{1}H NMR (200 MHz, $CDCl_3$): δ (major isomer) 7.37–7.12 (5H, m), 6.07 (1H, d, J=5.1 Hz), 5.64 (1H, d, J=5.1 Hz), 4.12 (1H, dd, J=4.1 Hz, J=8.3 Hz), 3.86–3.72 (3H, m), 3.22 (3H, s), 3.10–2.90 (1H, m), 2.75–2.60 (1H, m), 2.10–1.95 (2H, m), 1.42 (3H, s), 1.10–0.95 (9H, m), 0.75–0.55 (6H, m). ^{1}H NMR (200 MHz, $CDCl_3$): δ (middle isomer) 7.37–7.12 (5H, m), 6.13 (1H, d, J=5.1 Hz), 5.68 (1H, d, J=5.1 Hz), 4.00–3.66 (4H, m), 3.25 (3H, s), 3.05–2.85 (1H, m), 2.65–2.50 (1H, m), 1.85–1.65 (2H, m), 1.32 (3H, s), 1.10–0.95 (9H, m), 0.75–0.55 (6H, m). ^{1}H NMR (200 MHz, $CDCl_3$): δ (minor isomer) 7.37–7.12 (5H, m), 6.05 (1H, d, J=5.5 Hz), 5.80 (1H, d, J=5.5 Hz), 4.45–4.37 (1H, m), 3.86–3.72 (3H, m), 3.23 (3H, s), 3.10–2.90 (1H, m), 2.75–2.60 (1H, m), 2.10–1.95 (2H, m), 1.41 (3H, s), 1.10–0.95 (9H, m), 0.75–0.55 (6H, m).

4.1.20. 2-(*tert*-Butyl-diphenyl-silanyloxy)-1-[(5*S*)-2-methoxy-5-methyl-5-(3-phenyl-1*S*-triethylsilanyloxy-propyl)-2,5-dihydro-furan-2-yl]-ethanone (39). The crude mixture of isomers **38** (168 mg, 0.40 mmol) obtained with the previous procedure is dissolved in CH_2Cl_2 (4.0 mL) and treated at room temperature with imidazole (68 mg, 1.0 mmol) and TBDPSCl (132 mg, 0.125 mL, 0.48 mmol). After stirring for 1.0 h at room temperature, the mixture is partitioned between CH_2Cl_2 and brine. The organic extracts are dried (Na_2SO_4) and evaporated, and the residue purified by flash chromatography (hexanes/ethyl acetate 9:1), yielding the silylated compound (260 mg, 99%) as a mixture of the three isomers. To a suspension of Dess–Martin periodinane (DMP) (204 mg, 0.48 mmol) in CH_2Cl_2 (1.0 mL), pyridine (38 mg, 0.039 mL, 0.48 mmol) is added, followed by a solution of the protected alcohol mixture (260 mg, 0.40 mmol). The mixture is stirred at room temperature for 2 h, then partitioned between Et_2O and 2.0 M NaOH. The crude is purified by flash chromatography (hexanes/ethyl acetate 95:5) yielding the title compound **39** as a mixture of the two acetal epimers (1.8:1) (140 mg, 53%). **39** (1.8:1 mixture of epimers): $[\alpha]_D^{20}=-16.4$ (c 1.23, EtOAc); ν_{max} (film) 2957, 2878, 1746 (C=O), 1458, 1427, 1242 (C–O), 1113 (C–O), 1067 (C–O), 1047, 1019, 740, 702 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ (major epimer) 7.72–7.15 (15H, m), 6.61 (1H, d, J=4.8 Hz), 5.63 (1H, d, J=4.8 Hz), 4.92 (1H, d, J=18.4 Hz), 4.65 (1H, d, J=18.4 Hz), 3.69 (1H, dd, J=4.1, 7.8 Hz), 3.09 (3H, s), 2.95–2.75 (1H, m), 2.62–2.43 (1H, m), 1.75–1.55 (2H, m), 1.37 (3H, s), 1.10 (9H, s), 0.97 (9H, q, J=7.4 Hz), 0.64 (6H, t, J=7.4 Hz). ^{1}H NMR (200 MHz, $CDCl_3$): δ (minor epimer) 7.72–7.15 (15H, m), 6.61 (1H, d, J=4.8 Hz), 5.69 (1H, d, J=4.8 Hz), 4.77 (2H, bs), 3.71 (1H, dd, J=4.1, 7.8 Hz), 3.12 (3H, s), 2.95–2.75 (1H, m), 2.62–2.43 (1H, m), 1.75–1.55 (2H, m), 1.52 (3H, s), 1.09 (9H, s), 1.2–0.79 (9H, m), 0.71–0.58 (6H, m). Anal. Calcd for $C_{39}H_{54}O_5Si_2$: C, 71.08; H, 8.26. Found: C, 71.14; H, 8.19.

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25. Compound **35** was synthesized from hydrocinnamic aldehyde via the following route: (a) **19**, $KN(TMS)_2$, 18-c-6, THF, −78°C, then hydrocinnamic aldehyde, 1 h (84%); (b) $LiAlH_4$, Et_2O, 0°C to rt, 1 h (88%); (c) TBHP, (−)-DET (12%), $Ti(Oi\text{-}Pr)_4$ (10%), MS, CH_2Cl_2, −20°C, 18 h (96%); (d) DMP, CH_2Cl_2, rt, 15 min (86%); (e) **29**, $NaN(TMS)_2$, THF, then aldehyde, −5°C, 10 min (69% hydrofuran+18% acyclic *trans* isomer as a mixture of the keto and enol tautomers); (f) TESCl, imidazole, CH_2Cl_2, rt, 1.5 h (85%). **35**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.35–7.13 (5H, m), 6.67 (1H, d, J=5.7 Hz), 6.18 (1H, d, J=5.7 Hz), 4.91 (1H, s), 4.18 (2H, q, J=6.7 Hz), 3.90 (1H, dd, J=6.0, 4.7 Hz), 2.89–2.72 (1H, m), 2.69–2.51 (1H, m), 1.72–1.60 (2H, m), 1.52 (3H, s), 1.29 (3H, t, J=6.7 Hz), 1.07–0.96 (9H, m), 0.78–0.63 (6H, m). The enantiomeric excess (ee) of the Sharpless asymmetric epoxidation (Ref. 19) was evaluated by acetylation of the epoxy-alcohol and NMR analysis of the resulting acetate in the presence of the chiral shift reagent Europium tris[3-(hepta-fluoropropylhydroxymethylene)-(+)-camphorate] [$Eu(hfc)_3$], and shown to be 75%. The reference opposite enantiomer was prepared by reaction of the allylic alcohol with TBHP, (+)-DET (12%), $Ti(Oi\text{-}Pr)_4$ (10%), MS, CH_2Cl_2, −20°C, 18 h (92%), while the reference racemic mixture was prepared by reaction of the allylic alcohol with TBHP, vanadyl acetylacetonate [$VO(acac)_2$] (4%), CH_2Cl_2, rt, 30 min (98%).
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