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Total Synthesis of Cyclic Diterpene Tonantzitlolone Based on a Highly Stereoselective Substrate-Controlled Aldol Reaction and Ring-Closing Metathesis

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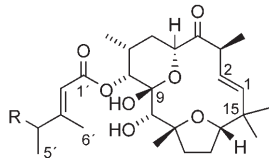
In memory of Jasmin Jakupovic

Abstract: The total synthesis of the cyclic diterpene *ent*-tonantzitlolone (*ent*-**1**) is presented. Key steps for assembling the macrocyclic core structure of **1** are a highly selective aldol reaction and an *E* selective ring-closing metathesis reaction. A detailed investigation of these two steps and the final transformations towards the completion of the synthesis is disclosed.

Keywords: aldol reactions · natural products · ring-closing metathesis · terpenes · total synthesis

Introduction

Recently, we communicated the total synthesis of the antitumor active diterpene tonantzitlolone (**1**) as its enantiomer (*ent*-**1**), thereby elucidating the absolute configuration of the natural product (Figure 1).[1] The new natural compound was first isolated from the endemic Mexican plant *Stillingia sanguinolenta* in 1990 by X. A. Dominguez et al. (Departamento de Quimica, ITESM, Monterrey, Mexico). In a detailed reinvestigation of the same plant, the structures of **1** and a congener **2** (OAc at C-4′ of side chain) were elucidated in collaboration with J. Jakupovic in 1997.[2] Preliminary biological evaluation indicated high activity and selectivity against human breast and kidney cancer cell lines.[3] Interestingly, when PtK_2 potoroo kidney cells were incubated with



tonantzitlolone (**1**): R = H
2: R = OAc

Figure 1. Structures of natural tonantzitlolone (**1**) and its congener **2**.

10 μg mL^{-1} of **1** for one day a high number of mitotic cells (around 20%) showed a monoastral half spindle instead of a normal bipolar spindle apparatus.[4]

Our retrosynthetic analysis is depicted in Scheme 1. The final steps of the synthesis are a dihydroxylation of an olefinic double bond at C-4 and C-5 in **3** which is followed by an esterification of the (*E*)-3-methyl-pent-2-enoic acid thereby introducing the side chain at C-8. The macrocyclisation, one key transformation of the synthesis, is achieved by ring-closing metathesis, therefore an acyclic precursor **4** is required which can be obtained by a substrate-controlled aldol reaction (with *anti*-Felkin–Anh selectivity) of ketone **5** with aldehyde **6**. Tetrahydrofuran **7** is prepared from acyclic diester **8** which originates from methyl geranate **9**, the starting material.

Our synthesis is highlighted by a set of substrate-controlled reactions for introducing the stereogenic centres in the western and the northern part of the molecule. In this full account, we particularly focus on the factors that govern the selectivities of the aldol reaction and the ring-closing meta-

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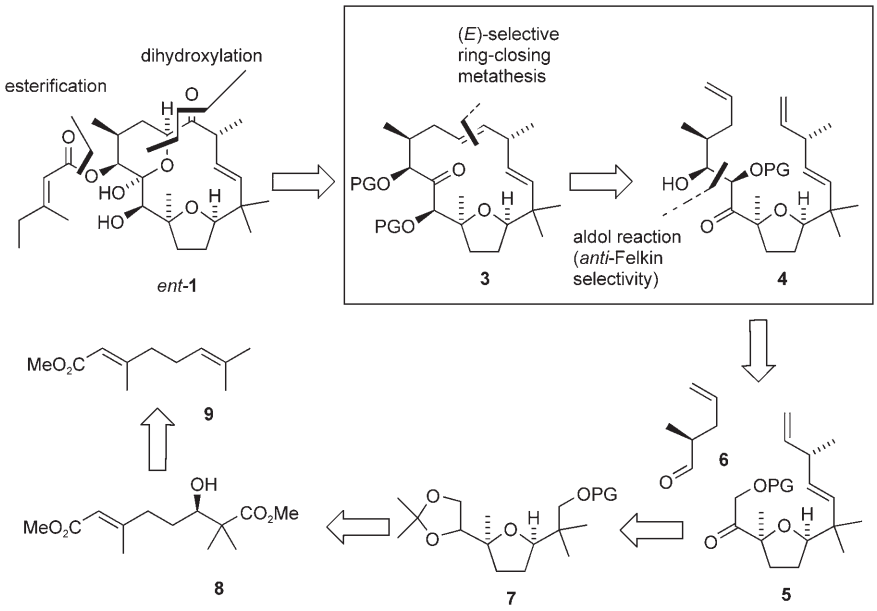


Scheme 1. Retrosynthetic analysis of *ent*-**1** including the key aldol reaction and ring-closing metathesis (RCM). PG = protecting group.

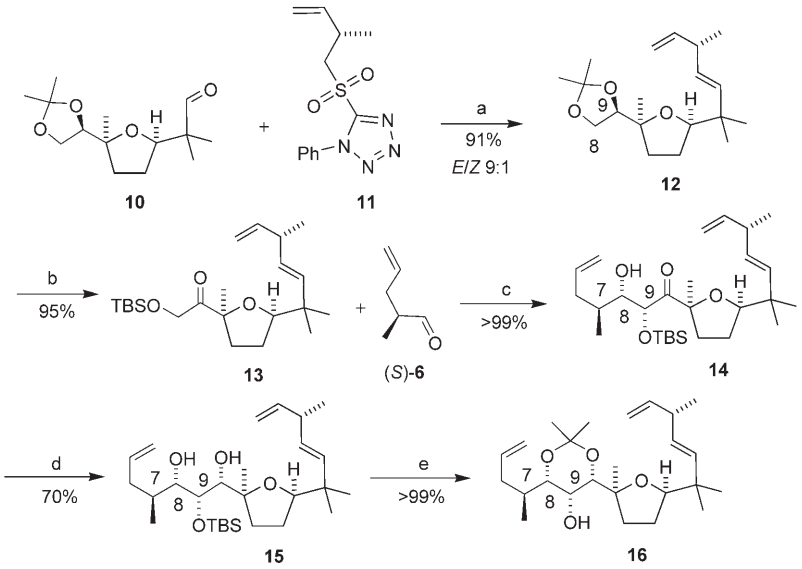
thesis and discuss the late-stage transformations towards the synthetic completion of tonantzitlolone (*ent*-**1**).

Results and Discussion

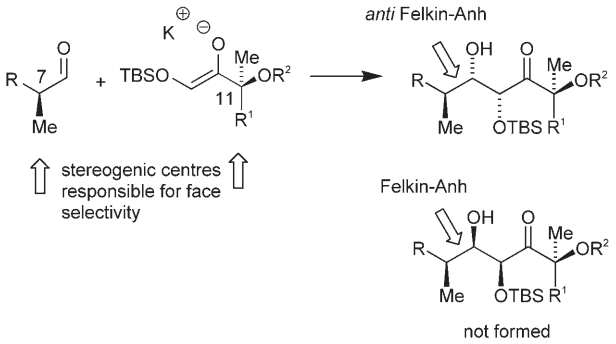
Preparation of the RCM precursor: In our synthetic approach,[1] the macrocyclic core of *ent*-**1** is divided in a more complex south fragment **10** and two smaller northern fragments **11** and **14**. After Julia–Kocienski olefination between **10** and **11**,[5] the resulting diene **12** could be easily transformed to the advanced ketone **13** in three steps (Scheme 2). The *Z* enolate of ketone **13** was then coupled with the aldehyde **6**[6] to furnish the aldol product **14** with a 7,8-*anti*-8,9-*syn* relationship[7] in high yield.[8] Ketone **14** was reduced to the *syn* diol **15** with DIBAL-H and further elaborated to the 1,3-acetonide **16**.[9]

Detailed study of the aldol reaction: Two aspects of the aldol reaction were particularly noteworthy: 1) the reaction proceeded with excellent stereocontrol affording the *anti*-Felkin–Anh product **14**, basically as a single diastereoisomer (Scheme 2)[10] and 2) the base KHMDS was the best choice despite the fact that potassium is not a common counterion in chelation-controlled aldol reactions.[11] The facial differentiation around the aldehyde group cannot be the governing factor to explain the *anti*-Felkin–Anh selectivity at C-7/C-8 as this should lead to the reversed stereochemical result.[12] The reaction of *Z* enolates with α-methyl chiral aldehydes requires additional steric considerations for the transition state, and an excellent model was first introduced by Roush et al. (Scheme 3).[13] For a deeper understanding of the possible transition state of this remarkably substrate-controlled aldol reaction, we studied the roles of the counterion as well as the aldehyde, and additionally altered the relative configuration around the tetrahydrofuran ring.

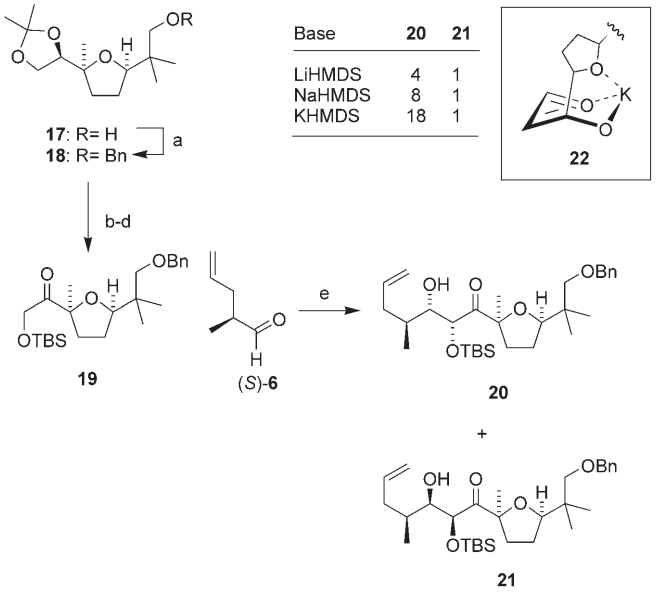
Thus, treatment of α-siloxy ketone **19** (simplified analogue of ketone **13**), prepared by established functional group in-



Scheme 2. Assembly of the fragments to generate RCM-precursor **16** (numbering of positions according to Figure 1): a) LDA, THF, −78 °C, 20 min, **10**, −78 °C to RT, 16 h, Δ, 4 h; b) i) MeOH/H_2O, *p*TsOH, 50 °C, 3 h, 95 + 3.5 % **12**; ii) TBSCl (1.6 equiv), CH_2Cl_2, imidazole, DMAP (cat.), RT, 30 min, 99 %, iii) Dess–Martin periodinane (1.5 equiv), CH_2Cl_2, 0 °C to RT, 2 h, 95 %; c) KHMDS (1.0 equiv), THF, −78 °C, 0.5 h, **6** (ca. 5.0 equiv), 2 h, *dr* > 98:2; d) DIBAL-H (8.0 equiv), CH_2Cl_2, −78 to −30 °C, 4 h; e) i) *p*TsOH (0.4 equiv), 2,2-DMP, RT, 4 h; ii) TBAF (4.4 equiv), THF, RT, 16 h. LDA = lithium diisopropylamide, TBS = *tert*-butyldimethylsilyl, DMAP = 4-dimethylaminopyridine, KHMDS = potassium hexamethyldisilazide, DIBAL-H = diisobutylaluminium hydride, *p*Ts = *p*-toluenesulfonyl, DMP = dimethoxypropane, TBAF = tetra-*n*-butylammonium fluoride.



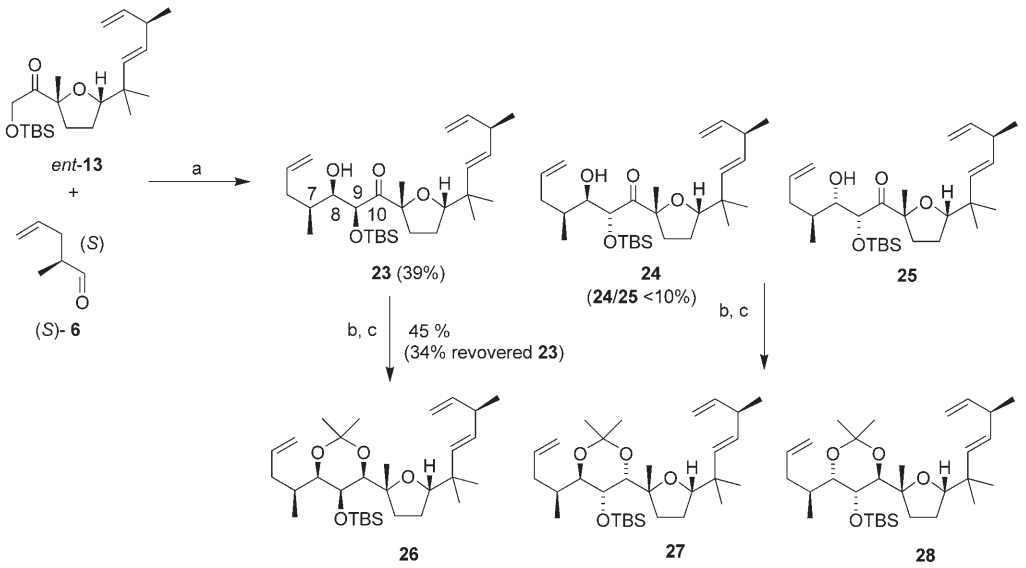
Scheme 3. Stereochemical aspects of the aldol reaction.



Scheme 4. The role of the counter ion on the stereoselectivity of the aldol reaction: a) NaH (2.5 equiv), THF, Δ, 0.5 h, BnBr (1.2 equiv), RT, over night; b) MeOH/H_2O 1:1, *p*TsOH (0.25 equiv), 50 °C, 3 h; c) TBSCl (1.9 equiv), CH_2Cl_2, imidazole, DMAP (cat.), RT, 3 h; d) Dess–Martin periodinane (1.7 equiv), CH_2Cl_2, 0 °C to RT, 6.5 h, 87% over 4 steps; e) HMDS base (1.1 equiv), THF, −78 °C, 0.5 h, (*S*)-**6** (ca. 5.0 equiv), 2 h. HMDS = hexamethyldisilazide.

terconversions from tetrahydrofuran **17**, with bases that differ in the countercation and coupling of the enolate formed with aldehyde (*S*)-**6**, afforded diastereoisomeric aldol products **20** and **21**. The results that are listed in Scheme 4 indicate a decrease in selectivity when the Lewis acidity of the counterion is increased, pointing against a tight and closed transition state. One possible rationale for this unexpected trend can be linked to the size of the cation which becomes part of a chelated Zimmerman–Traxler transition state which includes the oxygen atom of the tetrahydrofuran ring.[14,15]

Secondly, we studied the role of the aldehyde in the aldol reaction by coupling the (*S*)-aldehyde **6** with the enantiomeric tetrahydrofuran *ent*-**13**. Tetrahydrofuran *ent*-**13** was prepared according to the sequence described for **13**.[1] In fact, it has the correct absolute configuration of the natural tonantzitlolone (**1**). Thus, under our established reaction conditions, the aldol reaction yielded three aldol products **23**–**25** of which isomer **23** was separated from the mixture of the other aldol byproducts **24** and **25** (Scheme 5) by column chromatography. As the configuration of the newly formed stereogenic centres at C-8 and C-9 could not unequivocally be determined, we reduced the keto group of the separated fractions and transformed the 1,3-diol moiety into the cyclic isopropylidenes **26**–**28**. At this stage, the two byproducts **27** and **28** could be separated by repeated chromatography so that all three isomers could be analytically inspected in detail. The ^{13}C NMR spectroscopic chemical shifts ($\delta = 29.7$ and 19.1 ppm) of the acetonide methyl groups in **26** revealed the 1,3-*syn* relative configuration.[15,16] NOE contacts and



Scheme 5. Aldol reaction between *ent*-**13** and (*S*)-**6**: a) KHMDS (1.1 equiv), THF, −78 °C, 30 min, (*S*)-**6** (ca. 5.0 equiv), 2 h; b) DIBAL-H (1 M in hexane, 5–10 equiv), CH_2Cl_2, −78 to −30 °C; c) 2,2-DMP, *p*TsOH (0.4 equiv), RT, 4 h.

the values of the coupling constants (J) strongly indicate an all-*syn* relationship between the four stereogenic centres (Figure 2). Although not selective, the aldol addition between aldehyde **6** and the *Z* enolate derived from ketone *ent*-**13** favourably proceeds by a Felkin transition state.

In a similar fashion byproduct **27** was analysed. The ^{13}C NMR spectroscopic chemical shifts ($\delta = 25.9$, 24.8 ppm) of the acetonide methyl groups revealed an *anti* configuration at C-8 and C-10. The values of the coupling constants (J) further support an 8,9-*anti*-9,10-*syn* configuration (Figure 2). Thus, it seems that **27** is the result of a Felkin selective addition of the *E* enolate of ketone *ent*-**13** to the aldehyde (*S*)-**6** followed by an *anti*-selective 1,3-reduction. Equilibration towards the *E*-enolate is not surprising due to a prolonged reaction time necessary for this mismatched transformation while the *anti*-induction can possibly be attributed to solvent influences.[17]

Finally, the second byproduct **28** also results from an *anti* 1,3-reduction as determined from the chemical shifts of the acetonide methyl carbon atoms ($\delta = 26.9$, 24.8 ppm). The ^{1}H NMR coupling constants ($J(8,9) = 3.0$ Hz, $J(9,10) = 6.5$ Hz) indicate the presence of a 8,9-*syn*-9,10-*anti* configuration. As a consequence, the relative configuration between C-7 and C-8 has to be *anti*.[17,18] Thus, acetonide **28** is formed by *anti*-Felkin selective addition of the *Z* enolate of ketone *ent*-**13** to the aldehyde (*S*)-**6** followed by 1,3-*anti*-selective reduction with DIBAL-H.

In addition, further insight into the possible transition states of the aldol reaction were collected by altering the relative configuration around the tetrahydrofuran ring. As outlined in Scheme 6, we synthesized the model ketone **35** by a similar route to the one previously developed.[1] Direct reduction of the Kiyooka aldol product[9] to triol **31** improved the yield from 73 to 90% as this improved protocol minimizes the retroaldol reaction.[19] Protection of the 1,3-diol followed by Sharpless asymmetric epoxidation with (+)-diethyl L-tartrate delivered epoxy alcohol **32**, this time with reduced selectivity ($dr \approx 4:1$).[20] The separation was achieved for the cyclisation products **33** and **34**. Final transformations included protections, deprotection and oxidation which led to the 11,14-*anti* as well as *syn*-configured tetrahydrofurans **35** and **36** which reflects the mediocre selectivity for the Sharpless epoxidation.

When the simplified 11,14-*cis* configured tetrahydrofuran **36** was coupled with aldehyde (*S*)-**6**, the *anti*-Felkin–Anh product **37** was formed, as expected, as a single diastereoisomer (structurally proven as cyclic disiloxane **38**). In contrast, the 11,14-*anti*-configured tetrahydrofuran **35** af-

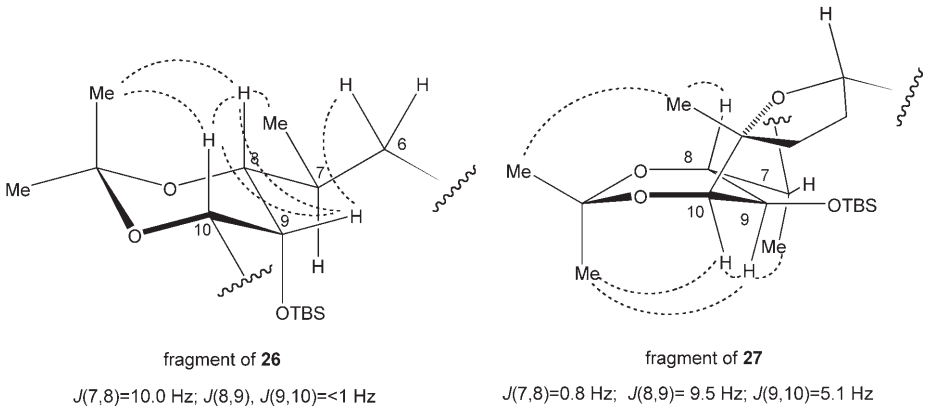
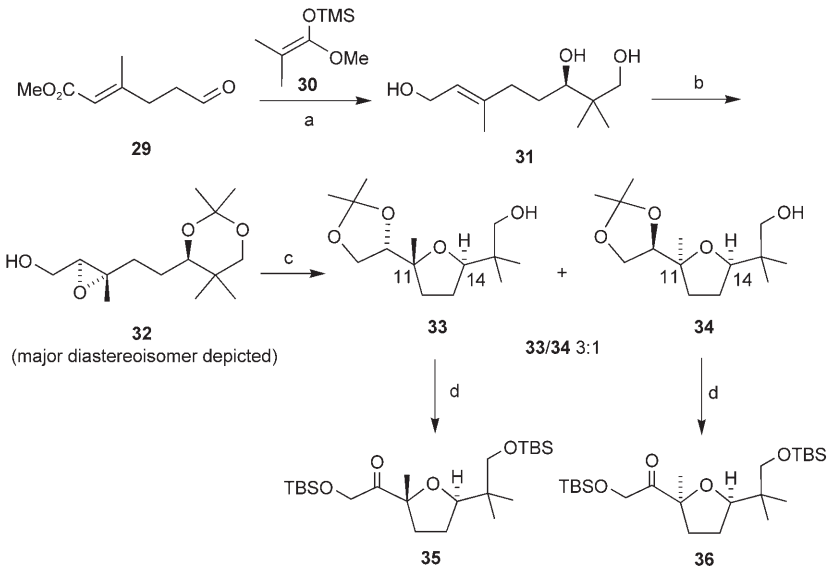


Figure 2. NOE contacts and coupling constants in **26** and **27**.

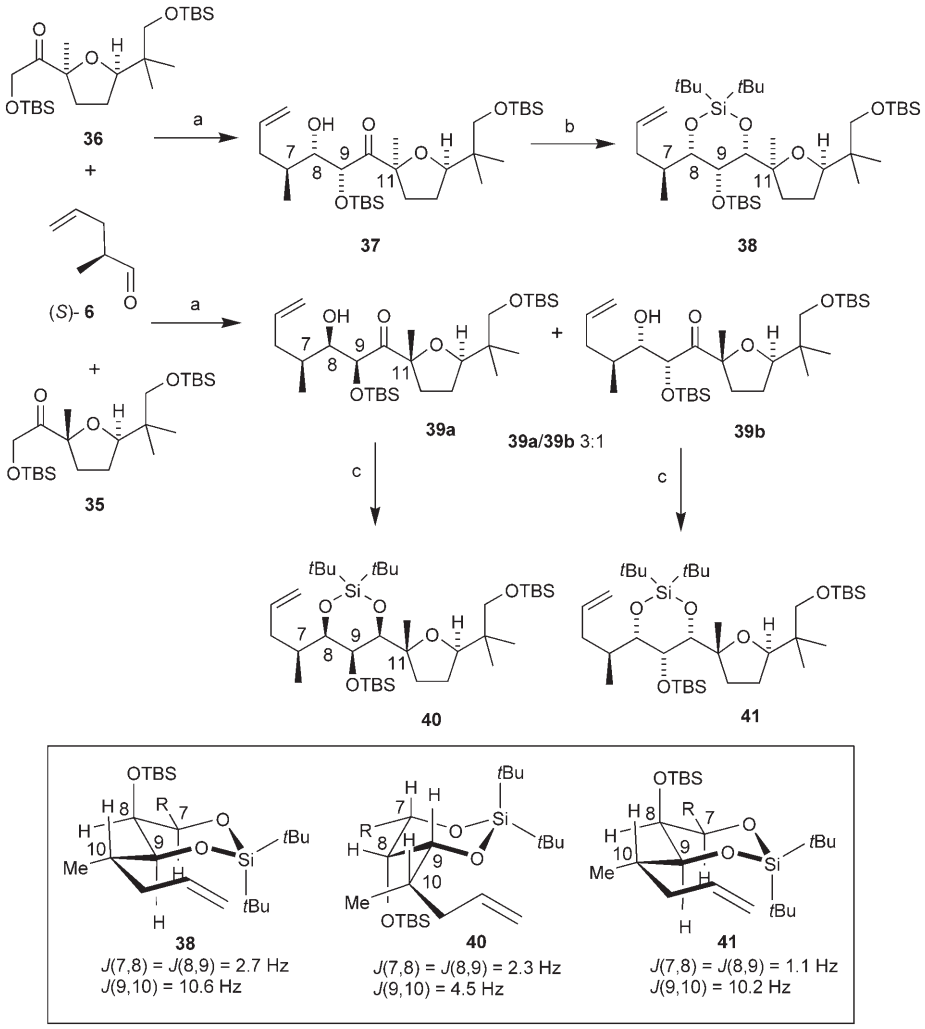


Scheme 6. Synthesis of model ketone **35**: a) i) *N*-Ts-L-valine (1.0 equiv), BH_3·THF (1.0 equiv), CH_2Cl_2, RT, 20 min, −78 °C, **30** (1.5 equiv), **29**, −78 to −30 °C, buffer pH 7, 73%; ii) $LiAlH_4$ (5.0 equiv), Et_2O, 0 °C to RT, overnight, 90%; b) i) *p*TsOH (cat.), 2,2-DMP (5.0 equiv), DMF, RT, 30 min, H_2O, 15 min, K_2CO_3, 95%; ii) 5 mol% $Ti(OiPr)_4$, 6 mol% (+)-diethyl L-tartrate, *t*BuOOH (2.0 equiv), 4 Å MS, −15 °C, CH_2Cl_2, 30 min, −25 °C, allyl alcohol, 10 h, 51%, $dr = 4:1$; c) **32** (mixture of diastereoisomers), $HO(CH_2)_2OH$ (1.2 equiv), 25 mol% *p*TsOH, CH_2Cl_2/THF 18:1, RT, 2 h, then 2,2-DMP, 10 h, 79%, $dr = 3:1$; d) i) MeOH, 20 mol% *p*TsOH, 50 °C, 18 h, 92%; ii) imidazole (3.5 equiv), DMAP (0.2 equiv), TBSCl (2.4 equiv), CH_2Cl_2, RT, 10 h, 85%; iii) Dess–Martin periodinane (2 equiv), CH_2Cl_2, 0 °C to RT, 6 h, 92%.

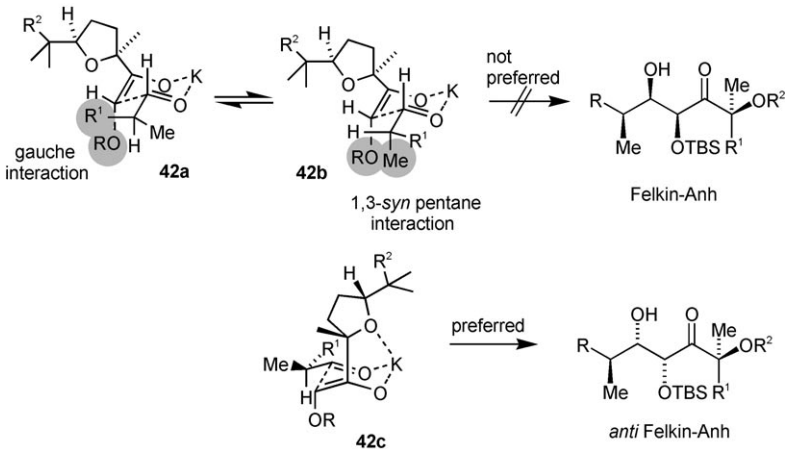
forded a diastereoisomeric mixture of aldol products **39a** and **39b** (3:1) with aldehyde (*S*)-**6** (Scheme 7). For structural elucidation both diastereoisomers were reduced and converted into the dioxasilinanes **40** and **41**. Dioxasilinanes[21] were chosen because acetonide formation proceeded inefficiently. At each stage of the two-step sequence, we checked the diastereoisomeric ratio (after reduction: ~3:1; after protection: ~4:1). Determination of relevant coupling constants[13,22] and NOE in **40** and **41** (contacts between H-7, H-8 and H-9) allowed us to elucidate the configuration of all stereogenic centres. Thus, inversion of configuration at C-11 again led to the preferred Felkin–Anh aldol product **39a**.

Obviously, the enolate moiety and not the aldehyde plays the major role for stereocontrol, because inversion of one stereogenic centre around the tetrahydrofuran ring thereby switching from 11,14-*syn*- to a 11,14-*trans* configuration leads to reversal of the face selectivity during the aldol process. Rationalization of these results is hampered by the fact that very few examples of aldol reactions comprising a *Z* enolate derived from an α-alkoxy ketone and an α-chiral aldehyde can be found in the literature.[12] Additionally, potassium is a very uncommon counterion for these processes. It should be taken into account that it is only a weak Lewis acid and does not necessarily promote closed transition states under standard conditions which is required for the Zimmerman–Traxler one, particularly as THF is a polar solvent with coordinative power. Still, the proposed transition-state model remains feasible and is assured by the high density of oxygen functionalities around the enolate moiety. Hence, by combining the Felkin–Anh rule with the Zimmerman–Traxler model the following transition states for the various aldol reactions can be proposed, which are based on the considerations first described by Roush et al.[13]

When employing the 11,14-*syn* tetrahydrofuran **13** with aldehyde (*S*)-**6** (also applies to tetrahydrofuran **36** and aldehyde (*S*)-**6**), the two Felkin–Anh transition states **42a** and **42b** which are rotamers suffer from 1,3-*syn*-pentane interaction or an unfavourable gauche relationship, respectively (Scheme 8).[23] Both of these interactions are reduced to a minimum in the *anti*-Felkin–Anh transition state **42c** in which potassium additionally chelates the oxygen atom of the tetrahydrofuran ring. Here, the unfavourable interactions present in rotamers **42a** and **42b** are reduced to a minimum for which some evidence has been collected before,[13] albeit in the case presented here the difference in size between R^1 (allyl and methyl) in **42a** and **42c** seems not to be as pronounced as to explain the excellent stereoselectivity of this transformation. A closer view onto the transition state **42c** reveals the methyl substituent at C11 to be a crucial factor, which would point to the axial H-substituent of the aldehyde in similar transition-state conformations of **42a** and **42b** (not depicted in Scheme 8).



Scheme 7. Aldol reaction of diastereoisomeric ketones **35** and **36** with aldehyde (*S*)-**6**: a) KHMDS (1.1 equiv), THF, −78 °C, 0.5 h, (*S*)-**6** (≈5.0 equiv), 15 min for **35** affording **39a**/**39b**: 64% and *dr* = 73:27; and 40 min for **36** affording **37**: 88% and *dr* > 98:2; b) i) DIBAL-H, (1 M in hexane, 5 equiv), CH_2Cl_2, −78 to −30 °C, 5 h, 81% (after reisolation and reuse of the starting materials); ii) $(tBu)_2Si(OTf)_2$, (1.5 equiv), 2,6-lutidine, CH_2Cl_2, RT, 24 h, 96%; c) i) mixture of **39a**/**39b**, Et_2BOMe (1.1 equiv), THF/MeOH 3:1, −78 °C, 15 min, $NaBH_4$ (3.3 equiv), 8 h, 67%, *dr* = 80:20; ii) $(tBu)_2Si(OTf)_2$, (1.5 equiv), 2,6-lutidine, CH_2Cl_2, RT, 24 h, 73%, *dr* = 81:19.



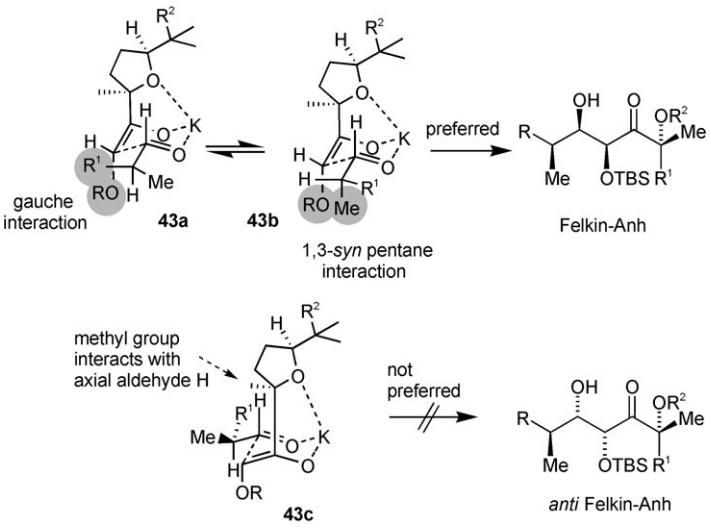
Scheme 8. Possible transition states for the aldol reaction of potassium enolate derived from tetrahydrofuran **13** with aldehyde (*S*)-**6** (matched case).

By switching from **13** to *ent*-**13** and subsequent reaction with aldehyde (S)-**6** under the same conditions, a complex mixture of diastereoisomers was obtained with the Felkin–Anh product **38** (corresponding to a reaction through transition state **43a**) as the main diastereoisomer. This result clearly indicates that the differentiation between Me and R^1 (allyl) in transition states **43c** and **43a** cannot be the governing factor for stereocontrol (vide supra), as this should lead again to a product with *anti*-Felkin–Anh control (corresponding to a reaction through transition state **43c**). Consequently, the C11 methyl/aldehyde-H interaction seems to dominate the stereochemical outcome of this reaction. Considering the low yield of the transformation between *ent*-**13** and (S)-**6**, some contribution of a stronger gauche interaction in **43a** in comparison to **42c** making both transition states (**43a** and **43c**) unlikely cannot be completely neglected.

In the case of the 11,14-*trans* tetrahydrofuran **35** two closed transition states similar to those presented in Schemes 8 and 9 can be drawn, from which again it becomes evident, that the stereochemistry at C-14 has almost no bearing on the selectivity of the aldol reaction.[24]

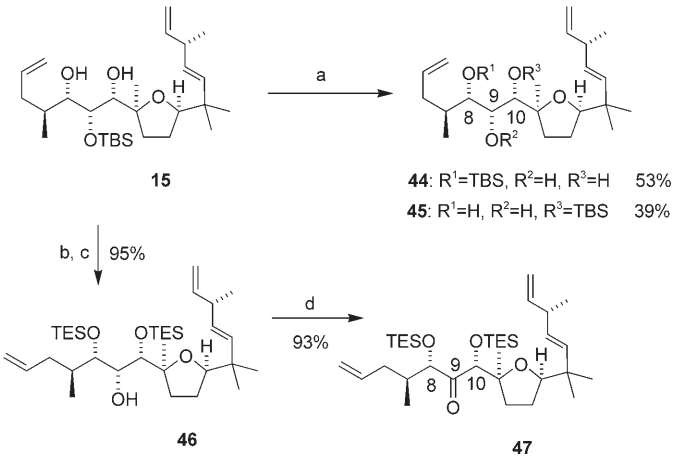
Studies on the stereocontrol of the RCM: To advance the synthesis, oxidation at C-9 of alcohol **16** was necessary which ought to set the stage for the RCM.[25] However, all oxidation procedures tested failed. Additionally, we were unable to develop an orthogonal protecting-group strategy for diol **15**. Under basic conditions, the TBS-group rapidly migrates to the neighbouring hydroxy groups at C-8 and C-10, furnishing regioisomers **44** and **45** (Scheme 10). This observation was exploited for a differentiation strategy. Consequently, desilylation afforded the corresponding triol which in the following was selectively reprotected at C-8 and C-10 with TES-Cl leaving the central hydroxyl group at C-9 in **46** free. In contrast, when TMS-Cl was employed as silylating agent, the discrimination between the three hydroxyl groups was less selective, for which different steric requirements of the two reagents can be made responsible. Alcohol **46** was smoothly converted into the corresponding ketone **47** by using the Dess–Martin reagent.

Our first experimental efforts towards ring closure were conducted with dienes **16**, **27** and **51** (obtained from silyl ether **26**)[26] which all contained an 8,10-acetonide protection and a 11,14-*cis*-disubstituted tetrahydrofuran but differed in the relative configuration between C-7 and C-11 (Scheme 11). The matched-case aldol product **16** afforded macrocycles **49** with pronounced *Z* selectivity (*E*/*Z* $\approx$1:6) when subjected to the RCM with Grubbs II catalyst.[27] This selectivity decreased, when the three positions at C-7, C-9 and C-10 were simultaneously inverted as in diene **27**.[28] Remarkably, when only the position at C-7 is relatively inverted with respect to the rest of the molecule as in the mismatched aldol product **51**, the RCM to macrocycles **52** proceeded with little *E* selectivity.

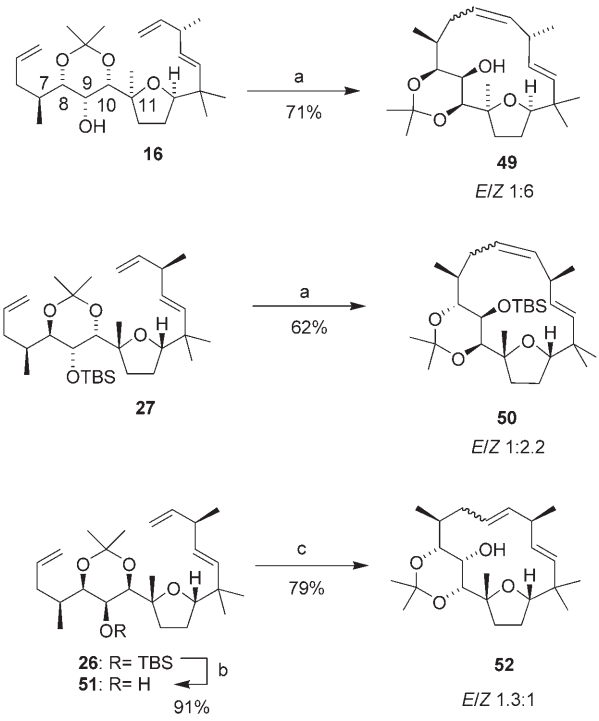


Scheme 9. Possible transition states for the aldol reaction of potassium enolate derived from tetrahydrofuran *ent*-**13** with aldehyde (*S*)-**6** (mismatched case).

We planned to use macrocycle **49** for finishing the total synthesis of tonantzitlolone, but we found that dihydroxylation of the olefinic double bond at C-4/C-5 with OsO_4 proved to be unsuccessful, as only the minor *E* isomer could be converted. We expected that removal of the cyclic acetal should enhance the flexibility of the western chain. Thus, diene **47** afforded the RCM product **53** in excellent yield, but displayed no stereoselectivity (*E*/*Z* $\approx$1:1, Scheme 12). Due to the bulky TES groups, neither the *E* nor the *Z* component of this inseparable mixture could be dihydroxylated

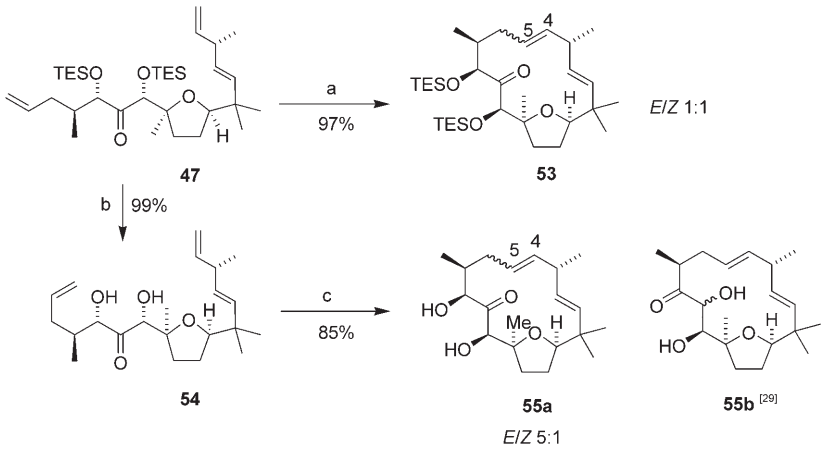


Scheme 10. Differentiation strategy and oxidation of the C-9 position: a) NaH (1.9 equiv), THF, 0 °C, 15 min; b) TBAF (2.3 equiv), THF, RT, 4 h; c) imidazole (6.1 equiv), TES-Cl (5.2 equiv), DMF, RT to 30 °C, 26 h; d) Dess–Martin periodinane (4.2 equiv), CH_2Cl_2, RT, 1.5 h.



Scheme 11. Ring-closing metathesis of acetonides **16**, **27** and **51**: a) Grubbs II (10 mol %), CH_2Cl_2, Δ, 2 h; b) TBAF (5.6 equiv), THF, RT, 19.5 h; c) Grubbs II (10 mol %), CH_2Cl_2, Δ, 5.5 h.

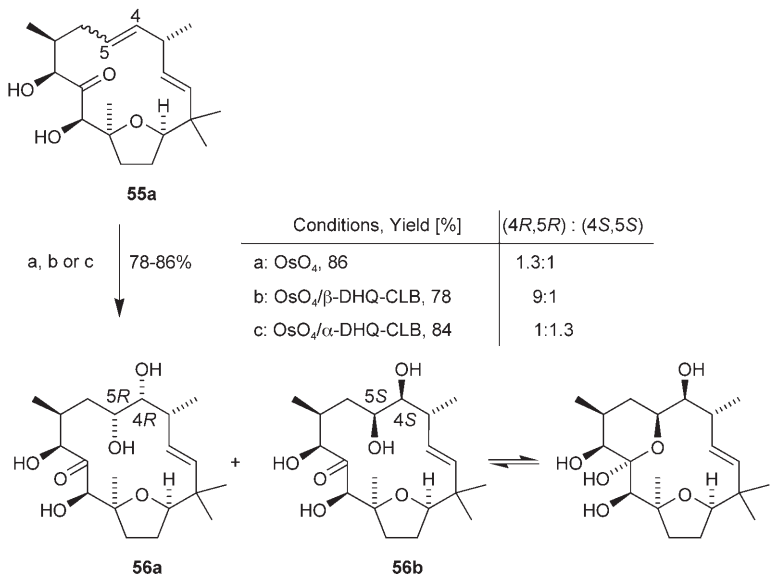
while epoxidation with the smaller reagent *m*CPBA also led to oxidation of the olefinic double bond at C-1/C-2. An important message from this experiment is the observation that formation of an *E*-configured macrocyclisation product has to be envisaged to terminate the synthesis and that the functional and protecting-group pattern in the western half can exert a strong influence on this selectivity. Therefore, we removed the silyl protection and conducted a RCM macrocyclisation with dihydroxy ketone **54**. Indeed, this substrate could be cyclised yielding the macrocycle **55a** with good *E* selectivity in 85% yield ($E/Z \approx 5{:}1$). When basic instead of neutral Al_2O_3 was used during workup, partial tautomerisation of dihydroxy ketone **54** was observed affording one isomeric byproduct **55b** of unknown configuration at C-9.[29] This RCM experiment clearly demonstrates that the degree of flexibility in the western half is of vital importance for the stereochemical outcome of the ring-closing metathesis reaction. This example adds to the increasing number of reports[30] in which subtle changes in the molecular structure of a given precursor or the reaction conditions can have a dramatic effect on the stereochemical outcome of a RCM reaction. Despite the fact that the macrocyclisation is commonly very efficient in terms of yields, the *E*/*Z* selectivity of alkene formation is often low and hard to predict. In particular, examples for the ring-closing metathesis of macrocyclic natural products shed a light on this problem as it became evident that various factors are responsible for the stereochemical outcome of the macrocyclisation process.[31] In the present case, protecting groups and the configuration of several stereogenic centres in the acyclic precursor can dramatically reverse the stereoselectivity of the RCM, even if these governing groups are not closely located to the reaction centre.[32] In the present case, basically almost complete reversal of *E*/*Z* selectivity was achieved by simple functional-group manipulations in related dienes **16** and **54**.[33]



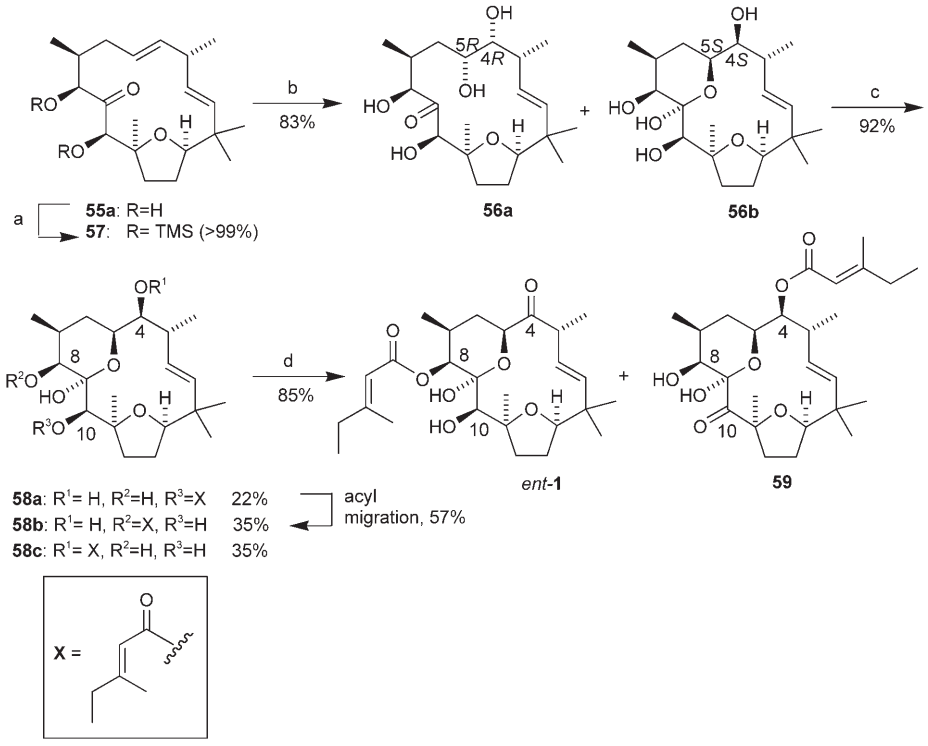
Scheme 12. Ring-closing metathesis of ketones **47** and **54**: a) Grubbs II (13 mol %), CH_2Cl_2, 0 °C, 2 h; b) TBAF (2.7 equiv), THF, 0 °C, 0.5 h; c) Grubbs II (9.5 mol %), CH_2Cl_2, 40 °C, 1.5 h.

Finalization of the synthesis: With macrocycle **55a** in hand, we initiated studies on the direct introduction of the ester side chain at position 8 to avoid additional protection strategies in the western half. We found that only under Yamaguchi conditions could (*E*)-3-methylpent-2-enoic acid[34] be coupled yielding a complex mixture of products. We therefore had to carry out the chemoselective dihydroxylation of the olefinic double bond at C-4 and C-5 first, before introducing the side chain. The dihydroxylation cleanly proceeded at the desired position with slight preference for the undesired (4*R*,5*R*)-diol **56a** under conditions of substrate control (**56a**/**56b** 1.3:1) (Scheme 13).

When the dihydroxylation was carried out under Sharpless conditions[20a] with the β-DHQ-CLB-ligand the (4*R*,5*R*)-diol **56a** (**56a**/**56b** 9:1) was preferentially formed while the α-DHQ-CLB-ligand resembles the mismatched scenario and yielded a mixture of diols **56a** and **56b** (1:1.3).[35] Exploiting again the observation that the choice of functionality in the western part has a strong impact on the stereochemical outcome of reactions around C-4 and C-5 we first formed the protected dihydroxy ketone **57** from the 8,10-diol **55**, which then was treated with Sharpless asymmetric dihydroxylation conditions again by using α-DHQ-CLB as the ligand (Scheme 14).[36] After desilylation of the diastereoisomeric mixture the desired hemiacetal **56b** with improved selectivity (**56a**/**56b** 1:3) was isolated. It is noteworthy that deprotection was required for lactol formation to occur, so that the need for triol differentiation became necessary in the following.[37] As differentiation



Scheme 13. Dihydroxylation of macrocyclic alkene **55a**: a) NMO (2.5 equiv), MSA (3.5 equiv), OsO_4 (6.3 mol%), *t*BuOH/H_2O 2:1, 0°C to RT, 3.5 h, 86%; b) K_2CO_3 (3.4 equiv), $K_3Fe(CN)_6$ (2.7 equiv), MSA (2.3 equiv), OsO_4 (10 mol%), β-DHQD-CLB (22 mol%), *t*BuOH/H_2O 1:1, 0°C, 2 h, 78%, $dr \approx 9:1$; c) K_2CO_3 (3.0 equiv), $K_3Fe(CN)_6$ (3.8 equiv), MSA (3.0 equiv), OsO_4 (4 mol%), α-DHQD-CLB (23 mol%), *t*BuOH/H_2O 1:1, 0°C to RT, 5 h, 84%; NMO = *N*-methylmorpholin-*N*-oxide, MSA = methanesulfonamide, DHQD-CLB = dihydroquinidine *p*-chlorobenzoate.



Scheme 14. Completion of the synthesis: a) NEt_3 (6.9 equiv), TMSCl (4.7 equiv), DMF, 0°C, 1 h, b) i) K_2CO_3 (3.1 equiv), $K_3Fe(CN)_6$ (3.0 equiv), MSA (3.0 equiv), OsO_4 (10 mol%), α-DHQD-CLB (36 mol%), *t*BuOH/H_2O 1:1, 0°C, 2.5 h, ii) TBAF (1.2 equiv), THF, 0°C, 10 min, 83% (2 steps); c) XOH (14.9 equiv), DIC (14.4 equiv), CH_2Cl_2, RT, 1 h, DMAP (1.2 equiv), 28 h; d) TPAP (0.4 equiv), NMO (excess), CH_2Cl_2, RT, 1 h; TMS = trimethylsilyl, DIC = diisopropylcarbodiimide, TPAP = tetraisopropyl perruthenate.

by various protecting-group strategies could not be achieved, direct esterification was tested. Esterification with diisopropyl carbodiimide was the method of choice and yielded a mixture of all possible position isomers (**58a–c**). Gratifyingly, the C-10 ester **58a** quantitatively rearranged to the desired C-8 ester **58b** because of the 8,10-*syn* relationship of the two adjacent hydroxy groups.

Finally, the two resulting esters were oxidized with TPAP/NMO furnishing *ent*-tonantzitlolone (*ent*-**1**),[38] and ketone **59** (derived from **58c**).

Conclusion

We described the first total synthesis of the diterpene tonantzitlolone *ent*-**1** and importantly elucidated its absolute configuration. Important focus was devoted to the aldol reaction of the potassium enolate derived from an α-siloxy ketone with an α-methyl chiral aldehyde in a highly stereocontrolled manner yielding the *anti*-Felkin–Anh product.[39] Factors that may govern this unusual aldol reaction were studied. Additionally, we studied the influence of neighbouring oxygen functionalities and relative configuration of stereogenic centres on the *E*/*Z* selectivity of the key ring-closing metathesis process. These principal studies enabled us to develop a highly stereoselective total synthesis of this compact and highly functionalised macrocyclic diterpene which makes effective use of substrate-controlled reactions. Details on the biological properties and the biological target of tonantzitlolone, its (−)-enantiomer and various derivatives will be reported in a separate account.

Experimental Section

General remarks and starting materials: ^{1}H NMR, ^{13}C NMR, ^{1}H/^{13}C-COSY and NOESY spectra were measured on Avance 200/DPX (Bruker) with 200 MHz (50 MHz), Avance 400/DPX (Bruker) 400 MHz (100 MHz) and Avance 500/DRX (Bruker), respectively, by using tetramethylsilane as the internal standard. If not otherwise noted, $CDCl_3$ and [D_4]MeOH are the solvents for all NMR experiments (reference: $CHCl_3$ = δ = 7.26 ppm, [D_4]MeOH = δ = 3.31 ppm). Multiplicities are described by using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, sext. = sextet, br = broad and ps = pseudo. Chemical shift values of ^{13}C NMR spectra are reported as values in ppm relative to residual $CDCl_3$ (ca. 77.0 ppm) or [D_4]MeOH (ca. 49.0 ppm) as internal standards. The multiplicities refer to the resonances in the off-resonance spectra and were elucidated by using the distortionless enhancement by the polarisation transfer (DEPT) spectral editing technique, with secondary pulses at 90 and 135°. Multiplicities are reported by using the following abbreviations: s = singlet (due to quaternary carbon), d = doublet (methine), q = quartet (methyl) and t = triplet (methylene). Numbering of protons and carbon atoms are commonly related to numbering in tonantzitlolone (**1**). Mass spectra were recorded on a type LCT-spectrometer (Micromass) and on a type VG autospec (Micromass). Ion mass (*m*/*z*) signals are reported as values in atomic mass units followed, in parentheses, by the peak intensities relative to the base peak (100%). Optical rotations [α] were collected on a Polarimeter 341 (Perkin–Elmer) at a wavelength of 589 nm and are given in 10^{-1} deg cm^2 g^{-1}. All solvents used were of reagent grade and were further dried. Reactions were monitored by TLC on silica gel 60 F_{254} (E. Merck, Darmstadt) and spots were detected either by UV-absorption or by charring with H_2SO_4/4-methoxybenzaldehyde in methanol. Preparative column chromatography was performed on silica gel 60 (E. Merck, Darmstadt). For experimental and spectroscopic data of *ent*-**1**, **11**, **12**, **13**, **14**, **15**, **16**, **17**, **29–31**, **46**, **47**, **49**, **54**, **55a**, **56a**,**b**, **57**, **58a–c** and **59** please refer to the Supporting Information of our previous publication.[1]

Aldehyde 10: A flame-dried 10 mL flask was charged with alcohol **17** (205 mg, 0.79 mmol) and dry CH_2Cl_2 (4 mL). Then molecular sieves (4 Å, 120 mg), *N*-methylmorpholine-*N*-oxide (138.5 mg, 1.18 mmol, 1.5 equiv) and tetra-*n*-propylperruthenate (15.3 mg, 0.04 mmol, 5.1 mol%) were added portionwise and the solution was stirred for 2.5 h. After this time, the dark black solution was filtered (5 g of silica gel) and eluted with hexanes/ethyl acetate 8:1. Removal of the solvent under reduced pressure afforded the target aldehyde **10** (184 mg, 0.72 mmol, 91%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97, 1.01 (2s, 6H; $C(CH_3)_2$), 1.11 (s, 3H; $OCCH_3$), 1.27, 1.36 (2s, 6H; $O_2C(CH_3)_2$), 1.59–1.74 (m, 2H; H-12, H-13), 1.81–1.90 (m, 1H; H-13), 1.93–2.01 (m, 1H; H-12), 3.71–3.76 (m, 1H; H-9), 3.89–3.97 (m, 3H; H-9, H-10, H-14), 9.56 ppm (s, 1H; H-1); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.1, 19.6, 21.6 (3q; $C(CH_3)_2$, $OCCH_3$), 25.0, 26.3 (2q; $O_2C(CH_3)_2$), 27.1 (t; C-13), 34.9 (t; C-12), 48.8 (s; C-15), 65.8 (t; C-9), 80.3 (d; C-10), 82.7 (d; C-14), 83.4 (s; C-11), 109.4 (s; $O_2C(CH_3)_2$), 206.3 ppm (d; C-1); IR (ATR): $\tilde{\nu}$ = 2979 (m), 2878 (w), 1725 (s), 1458 (m), 1370 (m), 1211 (m), 1155 (m), 1068 (s), 854 cm^{-1} (s); HRMS-ESI: *m*/*z*: calcd for $C_{14}H_{25}O_4$: 257.1747 $[M+H]^+$; found: 257.1753.

Ketofuran 19: A 10 mL round-bottomed flask was charged with alcohol **17** (157.3 mg, 0.61 mmol) and dry THF (4 mL). NaH (60 mg, 60% suspension, 1.5 mmol, 2.5 equiv) was added and the mixture was heated under refluxing conditions for 30 min. Then, benzyl bromide (90 μL, 0.76 mmol, 1.2 equiv) was added and the solution was stirred overnight at RT. Saturated aqueous NH_4Cl solution was added, and the aqueous layer was separated and extracted with CH_2Cl_2. The combined organic solutions were dried ($MgSO_4$) and concentrated under reduced pressure.

A 100 mL round-bottomed flask was charged with the resulting benzyl ether **18** and with 30 mL of MeOH/H_2O 1:1. After addition of *p*TsOH (25 mg, 0.15 mmol, 0.25 equiv) the solution was warmed to 50°C for 3 h and then cooled to RT. The reaction was stopped by addition of saturated aqueous $NaHCO_3$ solution and the mixture was extracted with ethyl acetate. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure.

A flame-dried 25 mL round-bottomed flask was charged with the crude diol (~0.61 mmol) and dry CH_2Cl_2 (10 mL). Imidazole (100 mg, 1.47 mmol, 2.4 equiv) was added, followed by TBSCl (170 mg, 1.13 mmol, 1.9 equiv) and 4-DMAP (10 mg, 0.08 mmol, 0.1 equiv). After 3 h, the reaction was quenched by addition of saturated aqueous NH_4Cl solution. The aqueous layer was separated and extracted with CH_2Cl_2, and the combined organic solutions were dried ($MgSO_4$) and concentrated under reduced pressure.

A 50 mL round-bottomed flask was charged with the crude alcohol and CH_2Cl_2 (15 mL). The solution was cooled to 0°C, then Dess–Martin periodinane (340 mg, 0.8 mmol, 1.3 equiv) was added and the reaction mixture was warmed to RT and stirred for 6.5 h. During that time two additional portions (50 mg) of Dess–Martin periodinane were added. Then the reaction was terminated by addition of saturated aqueous $NaHCO_3$/$Na_2S_2O_3$ solution. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic solutions were dried ($MgSO_4$) and concentrated under reduced pressure. Flash-column chromatography (hexanes/ethyl acetate 40:1) afforded the desired ketone **19** (221.7 mg, 0.53 mmol, 87% over 4 steps) as an oil. $[\alpha]_D^{23} = -35.9$ (c = 1.07 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, CH_2Cl_2 = 5.3 ppm): δ = 0.13 (2s, 6H; $Si(CH_3)_2tBu$), 0.97, 0.99, 1.36 (3s, 9H; $C(CH_3)_2$, $OCCH_3$), 0.97 (s, 9H; *t*Bu), 1.61–1.70 (m, 1H; H-12), 1.79–1.88 (m, 2H; H-13), 2.16–2.24 (m, 1H; H-12), 3.17, 3.25 (2d, J = 8.8 Hz, 2H; H-1), 3.98–4.03 (m, 1H; H-14), 4.43, 4.47 (2d, J = 12.4 Hz, 2H; $PhCH_2$), 4.58, 4.63 (2d, J = 19.5 Hz, 2H; H-9), 7.28–7.40 ppm (m, 5H; Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ = −5.4, −5.3 (2q; $Si(CH_3)_2$), 18.6 (s, *t*Bu), 20.4, 21.4, 24.2 (3q, $C(CH_3)_2$; $OCCH_3$), 25.9 (q; *t*Bu), 26.0 (t; C-13), 36.2 (t; C-12), 37.6 (s; C-15), 66.5 (t; C-9), 73.3, 77.4 (t, C-1; $PhCH_2$), 83.5 (d; C-14), 87.6 (s; C-11), 127.4, 127.4, 128.3, (d;

Ph), 138.8, (s; Ph), 211.6 ppm (s; C-10); HRMS-ESI: *m/z*: calcd for $C_{24}H_{40}O_4SiNa$: 443.2594 $[M+Na]^+$; found: 443.2596.

Standard procedure for the aldol reaction 19→20/21: The preparation of aldehyde (*S*)-**6** started from the corresponding alcohol which was dissolved in CH_2Cl_2 ($c=0.15$ M). The solution was cooled to 0°C and Dess–Martin periodinane (1.2 equiv) was added. The mixture was warmed to RT and stirred for 1 h. After this time the reaction was terminated by addition of aqueous $Na_2S_2O_3/NaHCO_3$ solution and stirred for an additional hour. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic solutions were dried ($MgSO_4$) and cautiously concentrated ($p>600$ mbar).

A 25 mL round-bottomed flask was charged with ketone **19** and with dry THF ($c=0.04$ M). The solution was cooled to −78°C, before the HMDS-base (as a solution, 1.1 equiv) was introduced dropwise. After 30 min (in the case of LiHMDS and NaHMDS the solution was warmed to −20°C for that time and then recooled to −78°C), the crude aldehyde **6** in dry THF was added and the solution was stirred for 2 h. The reaction was then quenched carefully by addition of MeOH, followed by saturated aqueous NH_4Cl solution. The flask was warmed up to RT in a cold bath, then the aqueous layer was separated and extracted with MTBE. The combined organic solutions were dried ($MgSO_4$), concentrated and filtered over a short column of silica (hexanes/ethyl acetate 40:1). The product ratio **20**:**21** was determined by HPLC-ESI (for Li: 4:1, Na: 8:1 and K: 18:1).

Aldol products 23: A 25 mL round-bottomed flask was charged with ketone *ent*-**13** (60.6 mg, 0.16 mmol) and dry THF (3.6 mL). The solution was cooled to −78°C, before KHMDS (0.25 mL, 0.66 M in toluene, 1.1 equiv) was introduced dropwise. After 30 min, crude aldehyde **6** (about 1.2 mmol) in dry THF (0.4 mL) was added and the solution was stirred for 2 h. The reaction mixture was carefully hydrolysed by addition of MeOH followed by saturated aqueous NH_4Cl solution. The flask was slowly warmed to RT in the cold bath, then the aqueous layer was separated and extracted with MTBE. The combined organic solutions were dried ($MgSO_4$) and concentrated. Flash chromatography (hexanes/ethyl acetate 40:1) furnished the desired aldol product **23** (30 mg, 0.063 mmol, 39%) as a colourless oil and as an inseparable mixture of the two diastereoisomers **24** and **25** which were directly employed in the reduction/protection sequence that followed. Compound **23**: $[\alpha]_D^{23}=+42.6$ ($c=0.99$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=-0.02$, 0.09 (2s, 6H; Si(CH_3)$_2$), 0.93 (s, 9H; *t*Bu), 1.01, 1.04 (2s, 6H; C(CH_3)$_2$), 1.02 (d, $J=6.4$ Hz, 3H; CHCH_3), 1.07 (d, $J=6.9$ Hz, 3H; CHCH_3), 1.35 (s, 3H; OCCH_3), 1.46–1.55 (m, 1H; H-13), 1.74–1.92 (m, 5H; H-12 ×2, H-13, H-6, H-7), 2.04 (br d, $J=10.7$ Hz, 1H; 8-O*H*), 2.33 (dddd, $J=13.2$, 6.3, 3.3, 1.6 Hz, 1H; H-6), 2.81 (sext. td, $J=6.7$, 1.4, 0.8 Hz, 1H; H-3), 3.80 (dd, $J=8.0$, 6.7 Hz, 1H; H-14), 3.90 (br t, $J=9.4$ Hz, 1H; H-8), 4.93 (ddd, $J=10.3$, 1.7, 1.2 Hz, 1H; H-5), 4.96 (ddd, $J=17.2$, 1.7, 1.6 Hz, 1H; H-5), 5.00–5.07 (m, 2H; H-4′ ×2), 5.10 (d, $J=1.3$ Hz, 1H; H-9), 5.36 (dd, $J=15.9$, 6.6 Hz, 1H; H-2), 5.45 (dd, $J=15.9$, 0.8 Hz, 1H; H-1), 5.76 (ddd, $J=17.2$, 10.3, 6.4 Hz, 1H; H-4), 5.77 ppm (dddd, $J=16.5$, 10.6, 7.6, 6.3 Hz, 1H; H-5′); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-5.1$, −4.1 (2q; Si(CH_3)$_2$), 16.6 (q; CHCH_3), 18.6 (s; *t*Bu), 20.3 (q; CHCH_3), 24.2, 24,3, 24.4 (3q; OCCH_3, C-(CH_3)$_2$), 25.8 (t; C-13), 26.0 (q; *t*Bu), 36.7 (d; C-7), 37.4 (t; C-12), 38.2 (t; C-6), 39.0 (s; C-15), 40.7 (d; C-3), 75.0 (d; C-8), 76.3 (d; C-9), 86.5 (d; C-14), 88.7 (s; C-11), 112.9 (t; C-5), 116.4 (t; C-4′), 132.4 (d; C-2), 134.9 (d; C-1), 136.9 (d; C-5′), 143.2 (d; C-4), 212.8 ppm (s; C-10); IR (ATR): $\tilde{\nu}=$ 3558 (w), 3078 (w), 2960 (m), 2929 (m), 2857 (m), 1727 (s), 1639 (m), 1462 (m), 1388 (m), 1363 (m), 1253 (m), 1160 (m), 1101 (m), 1043 (s), 1000 (m), 976 (s), 910 (s), 836 (s), 777 (s), 676 (m), 613 cm^{-1} (w); HRMS-ESI: *m/z*: calcd for $C_{30}H_{53}NO_4SiNa$: 542.3642 $[M+Na+MeCN]^+$; found: 542.3642.

Protected triol 26: A 5 mL round-bottomed flask was charged with aldol product **23** (10.8 mg, 23 μmol) and anhydrous CH_2Cl_2 (1.1 mL) and cooled to −78°C, before DIBAL-H (0.2 mL, 1 M in hexane, 8.7 equiv) was added. After 22 h, the reaction mixture was warmed to −30°C and was then quenched with H_2O (0.2 mL). After reaching RT, saturated aqueous Na/K tartrate solution was added and stirring was continued for 1 h. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic solutions were dried ($MgSO_4$) and concentrated. Flash chromatography (hexanes/ethyl acetate 40:1→10:1) delivered the corresponding diol (5.1 mg, 11 μmol, 48%) as an oil, along with recovered starting material **23** (4.9 mg, 10 μmol, 43%). $[\alpha]_D^{23}=-13.7$ ($c=0.54$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.14$, 0.16 (2s, 6H; Si(CH_3)$_2$), 0.91 (s, 9H; *t*Bu), 0.96, 1.03 (2s, 6H; C(CH_3)$_2$), 0.98 (d, 3H, $J=6.5$ Hz; CHCH_3), 1.08 (d, $J=6.9$ Hz, 3H; CHCH_3), 1.21 (s, 3H; OCCH_3), 1.57–1.70 (m, 2H; H-12, H-13), 1.74–1.89 (m, 3H; H-6, H-7, H-13), 2.03–2.10 (m, 1H; H-12), 2.18–2.25 (m, 1H; H-6), 2.64 (d, $J=7.5$ Hz, 1H; 8-O*H*), 2.78 (d, $J=5.1$ Hz, 1H; 10-O*H*), 2.83 (br sext., $J=6.5$ Hz, 1H; H-3), 3.30 (dt, $J=2.4$, 7.1 Hz, 1H; H-8), 3.47 (t, $J=5.1$ Hz, 1H; H-10), 3.71 (dd, $J=$ 8.5, 6.4 Hz, 1H; H-14), 3.83 (dd, $J=5.6$, 2.6 Hz, 1H; H-9), 4.94 (ddd, $J=$ 10.0, 1.7, 1.4 Hz, 1H; H-5), 4.97 (ddd, $J=17.1$, 1.7, 1.4 Hz, 1H; H-5), 5.00–5.06 (m, 2H; H-4′ ×2), 5.36 (dd, $J=15.8$, 6.3 Hz, 1H; H-2), 5.44 (dd, $J=15.8$, 0.7 Hz, 1H; H-1), 5.77 (dddd, $J=16.9$, 10.3, 7.4, 6.5 Hz, 1H; H-5′), 5.78 ppm (ddd, $J=17.1$, 10.4, 6.6 Hz, 1H; H-4); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-4.4$, −3.3 (2q; Si(CH_3)$_2$), 15.1 (q; CHCH_3), 18.7 (s; *t*Bu), 20.2 (q; CHCH_3), 21.9 (q; OCCH_3), 24.7, 24.7 (2q; C(CH_3)$_2$), 26.4 (q; *t*Bu), 27.2 (t; C-13), 35.4 (d; C-7), 35.5 (t; C-12), 38.5 (t; C-6), 39.0 (s; C-15), 40.6 (d; C-3), 73.9 (d; C-8), 73.9 (d; C-10), 77.0 (d; C-9), 84.1 (s; C-11), 85.6 (d; C-14), 112.9 (t; C-5), 116.5 (t; C-4′), 132.8 (d; C-2), 134.7 (d; C-1), 136.9 (d; C-5′), 143.3 ppm (d; C-4); HRMS-ESI: *m/z*: calcd for $C_{28}H_{52}O_4SiNa$: 503.3533 $[M+Na]^+$; found: 503.3533.

*p*TsOH (6.3 mg, 37 μmol, 0.4 eq) was added to the diol (41.4 mg, 86 μmol), obtained as described above, dissolved in 2,2-dimethoxypropane (2.2 mL). After 4 h, the reaction was stopped by addition of saturated aqueous $NaHCO_3$ solution. The solution was transferred to a separating funnel and extracted twice with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Gel filtration (hexanes/ethyl acetate 80:1) afforded the desired product **26** (37.6 mg, 72 μmol; 84%) as a colourless oil. $[\alpha]_D^{23}=-2.1$ ($c=1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.13$ (s, 6H; Si(CH_3)$_2$), 0.88 (d, 3H, $J=6.5$ Hz; CHCH_3), 0.91 (s, 9H; *t*Bu), 0.95, 0.99 (2s, 6H; C(CH_3)$_2$), 1.08 (d, $J=$ 6.8 Hz, 3H; CHCH_3), 1.22 (s, 3H; OCCH_3), 1.39, 1.46 (2s, 6H; O_2C-(CH_3)$_2$), 1.53–1.77 (m, 4H; H-6, H-12 ×2), H-13), 1.86–1.97 (m, 2H; H-7, H-13), 2.21–2.27 (m, 1H; H-6), 2.81 (sext. q, $J=6.8$, 1.1 Hz, 1H; H-3), 3.19 (d, $J=10.0$ Hz, 1H; H-8), 3.51 (s, 1H; H-10), 3.77 (dd, $J=8.2$, 4.9 Hz, 1H; H-14), 3.83 (s, 1H; H-9), 4.94 (ddd, $J=10.4$, 1.7, 1.4 Hz, 1H; H-5), 4.97 (ddd, $J=17.2$, 1.6, 1.4 Hz, 1H; H-5), 5.00–5.05 (m, 2H; H-4′ ×2), 5.30 (dd, $J=15.9$, 6.5 Hz, 1H; H-2), 5.42 (dd, $J=15.9$, 1.0 Hz, 1H; H-1), 5.76 (dddd, $J=16.6$, 10.7, 8.5, 5.9 Hz, 1H; H-5′), 5.78 ppm (ddd, $J=$ 17.2, 10.4, 6.7 Hz, 1H; H-4); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-2.0$, −1.2 (2q; Si(CH_3)$_2$), 15.3 (q; CHCH_3), 19.1 (q; O_2C(CH_3)$_2$), 19.3 (s; *t*Bu), 20.3 (q; CHCH_3), 21.5 (q; OCCH_3), 24.0, 24.9 (2q; C(CH_3)$_2$), 26.5 (q; *t*Bu), 26.6 (t; C-13), 29.7 (q; O_2C(CH_3)$_2$), 31.5 (d; C-7), 34.00 (t; C-12), 37.1 (t; C-6), 39.7 (s; C-15), 40.7 (d; C-3), 66.2 (d; C-9), 79.2 (d; C-8), 80.8 (d; C-10), 84.5 (s; C-11), 85.1 (d; C-14), 99.4 (s; O_2C(CH_3)$_2$), 112.7 (t; C-5), 116.8 (t; C-4′), 131.6 (d; C-2), 135.7 (d; C-1), 136.2 (d; C-5′), 143.5 ppm (d; C-4); IR (ATR): $\tilde{\nu}=2976$ (s), 2932 (m), 2859 (s), 1639 (w), 1463 (m), 1381 (m), 1257 (m), 1199 (m), 1121 (s), 1091 (s), 1027 (w), 936 (w), 912 (m), 861 (w), 835 (m), 804 (w), 773 (m), 696 cm^{-1} (w); HRMS-ESI: *m/z*: calcd for $C_{31}H_{56}O_4SiNa$: 543.3846 $[M+Na]^+$; found: 543.3846.

Protected triols 27 and 28: Acetonides **27** (14.6 mg, 28 μmol, 41%) and **28** (6.6 mg, 13 μmol, 19%) were obtained from a mixture of hydroxyketones **24** and **25** by performing the reduction/protection sequence described for hydroxyketone **23** after subsequent separation by flash-column chromatography (hexanes/ethyl actetate 150:1).

Compound 27: $R_f=0.68$ (petroleum ether/ethyl acetate 10:1); $[\alpha]_D^{23}=$ +3.3 ($c=1.07$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.08$, 0.09 (2s, 6H; Si(CH_3)$_2$), 0.86 (d, 3H, $J=6.8$ Hz; CHCH_3), 0.90 (s, 9H; *t*Bu), 0.93, 0.96 (2s, 6H; C(CH_3)$_2$), 1.06 (d, $J=6.9$ Hz, 3H; CHCH_3), 1.22 (s, 3H; OCCH_3), 1.32 (d, $J=0.5$ Hz, 3H; O_2C(CH_3)$_2$), 1.46 (d, $J=0.5$ Hz, 3H; O_2C(CH_3)$_2$), 1.48–1.81 (m, 4H; H-12 ×2, H-13 ×2), 2.04 (dddt, $J=13.5$, 8.8, 7.1, 1.3 Hz, 1H; H-6), 2.18 (ddddd, $J=13.5$, 7.3, 6.6, 1.3, 1.2 Hz, 1H; H-6), 2.47 (ddqdd, $J=7.9$, 7.0, 6.8, 0.9, 0.7 Hz, 1H; H-7), 2.80 (sext. q, $J=$ 6.7, 1.2 Hz, 1H; H-3), 3.72 (t, $J=6.8$ Hz, 1H; H-14), 3.76 (d, $J=5.1$ Hz, 1H; H-10), 4.18 (dd, $J=9.5$, 0.8 Hz, 1H; H-8), 4.21 (dd, $J=9.5$, 5.1 Hz, 1H; H-9), 4.93 (ddd, $J=10.4$, 1.7, 1.3 Hz, 1H; H-5), 4.94–4.99 (m, 1H; H-5), 4.95–5.04 (m, 2H; H-4′ ×2), 5.29 (dd, $J=15.9$, 6.7 Hz, 1H; H-2),

5.40 (dd, $J=15.9$, 0.9 Hz, 1H; H-1), 5.77 (ddd, $J=17.2$, 10.4, 6.5 Hz, 1H; H-4), 5.80 ppm (dddd, $J=17.1$, 10.3, 7.1, 6.6 Hz, 1H; H-5′); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-4.2$, −3.1 (2q; $Si(CH_3)_2$), 12.6 (q; $CHCH_3$), 18.9 (s; *t*Bu), 20.3 (q; $CHCH_3$), 21.5 (q; $OCCH_3$), 24.2, 25.0 (2q; $C(CH_3)_2$), 25.0, 27.1 (2q; $O_2C(CH_3)_2$), 25.4 (t; C-13), 26.5 (q; *t*Bu), 33.6 (d; C-7), 39.0 (t; C-12), 39.3 (s; C-15), 39.7 (t; C-6), 40.7 (d; C-3), 72.5 (d; C-8), 80.5 (d; C-9), 82.8 (d; C-10), 84.0 (s; C-11), 86.8 (d; C-14), 106.3 (s; $O_2C(CH_3)_2$), 112.7 (t; C-5), 115.8 (t; C-4′), 131.9 (d; C-2), 135.3 (d; C-1), 138.2 (d; C-5′), 143.9 ppm (d; C-4); HRMS-ESI: *m/z*: calcd for $C_{31}H_{56}O_4SiNa$: 543.3846 $[M+Na]^+$; found: 543.3799.

Compound 28: $R_f=0.58$ (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.08$, 0.11 (2s, 6H; $Si(CH_3)_2$), 0.91 (s, 9H; *t*Bu), 0.95 (d, $J=6.9$ Hz, 3H; $CHCH_3$), 0.97, 1.00 (2s, 6H; $C(CH_3)_2$), 1.07 (d, $J=6.9$ Hz, 3H; $CHCH_3$), 1.17 (s, 3H; $OCCH_3$), 1.33, 1.46 (2s, 6H; $O_2C(CH_3)_2$), 1.52–1.58 (m, 1H; H-13), 1.66–1.91 (m, 4H; H-6, H-12 ×2, H-13), 1.95–2.06 (m, 1H; H-7), 2.62–2.68 (m, 1H; H-6), 2.81 (sext. q, $J=6.8$, 1.1 Hz, 1H; H-3), 3.72 (t, $J=7.0$ Hz, 1H; H-14), 3.97 (d, $J=6.5$ Hz, 1H; H-10), 4.22 (dd, $J=6.5$, 3.0 Hz, 1H; H-9), 4.25 (dd, $J=3.0$, 1.5 Hz, 1H; H-8), 4.93 (ddd, $J=10.4$, 1.7, 1.3 Hz, 1H; H-5), 4.96 (ddd, $J=17.1$, 1.7, 1.6 Hz, 1H; H-5), 4.91–5.01 (m, 2H; H-4′ ×2), 5.31 (dd, $J=15.9$, 6.9 Hz, 1H; H-2), 5.49 (dd, $J=15.9$, 1.1 Hz, 1H; H-1), 5.78 (ddd, $J=17.1$, 10.4, 6.5 Hz, 1H; H-4), 5.82 ppm (dddd, $J=17.1$, 10.1, 8.2, 6.1 Hz, 1H; H-5′); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-4.3$, −3.5 (2q; $Si(CH_3)_2$), 17.7 (q; $CHCH_3$), 18.4 (s; *t*Bu), 20.3 (q; $CHCH_3$), 21.7 (q; $OCCH_3$), 24.1, 24.9 (2q; $C(CH_3)_2$), 24.8, 26.9 (2q; $O_2C(CH_3)_2$), 26.0 (t; C-13), 26.2 (q; *t*Bu), 36.0 (d; C-7), 36.4 (t; C-6), 38.3 (t; C-12), 39.3 (s; C-15), 40.6 (d; C-3), 73.7 (d; C-8), 83.3 (d; C-10), 83.6 (s; C-11), 84.0 (d; C-9), 86.0 (d; C-14), 106.8 (s; $O_2C(CH_3)_2$), 112.6 (t; C-5), 114.9 (t; C-4′), 131.6 (d; C-2), 135.6 (d; C-1), 139.4 (d; C-5′), 143.6 ppm (d; C-4); HRMS-ESI: *m/z*: calcd for $C_{31}H_{56}O_4SiNa$: 543.3846 $[M+Na]^+$; found: 543.3846.

Epoxyalcohols 32a and 32b: A flame-dried three-neck 250 mL round-bottomed flask equipped with a pressure equalised dropping funnel was charged with powdered molecular sieves (4 Å, 910 mg) and dry CH_2Cl_2 (45 mL). The solution was cooled to −15 °C, and then $Ti(iPrO)_4$ (157 μL, 0.56 mmol) was added, followed by (−)-diethyl L-tartrate (131 mg, 0.67 mmol) in dry CH_2Cl_2 (5 mL) and *tert*-butyl hydroperoxide (3.91 mL, 22.28 mmol, 5.5 M in CH_2Cl_2). After 30 min, the suspension was cooled to −25 °C before the allylic alcohol (2.7 g, 11.14 mmol) dissolved in dry CH_2Cl_2 (70 mL) was introduced dropwise by means of a dropping funnel. The reaction was stirred for 10 h at −25 °C and then filtered through a pad of Celite. The filtrate was mixed with H_2O (25 mL) and warmed to RT. Then a mixture of aqueous NaOH solution (30%, 30 mL) saturated with NaCl was added and the mixture was vigorously stirred for 1 h. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (hexanes/ethyl acetate 3:1) afforded a 4:1 mixture of the two diastereoisomeric epoxides **32a** and **32b** in 51% yield as a colourless oil. The mixture was directly employed for the next step. Selected analytical data were collected and signals labelled with * refer to the minor diastereoisomer **32b**. Numbering of protons and carbon atoms are according to IUPAC nomenclature; ^{1}H NMR (400 MHz, [D$_4$]MeOH, TMS = 0 ppm): $\delta=0.70$*, 0.98* (2s, 6H; $C(CH_3)_2$), 0.72, 0.99 (2s, 6H; $C(CH_3)_2$), 1.28 (s, 3H; CH_3 at C-3), 1.28* (s, 3H; CH_3 at C-3), 1.36 (2s, 6H; CH_3 acetonide), 1.35, −1.41 (m, 2H; 4-H), 1.50, −1.59 (m, 1H; 5-H), 1.80, −1.89 (m, 1H; 5-H′), 2.96 (dd, 1H, $J=6.7$, 4.2 Hz; 2-H), 2.99* (dd, 1H, $J=6.6$, 4.2 Hz; 2-H), 3.26 (d, 1H, $J=11.4$ Hz; 8-H), 3.44 (dd, 1H, $J=9.7$, 1.8 Hz; 6-H), 3.57 (d, 1H, $J=11.4$ Hz; 8-H′), 3.67 (dd, 1H, $J=12.1$, 6.7 Hz; 1-H′), 3.82 ppm (dd, 1H, $J=12.1$, 4.2 Hz; 1-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=16.8$, 18.3 (2q; $C(CH_3)_2$), 19.0, 19.1* (2q; CH_3 at C-3), 22.0, 29.8 (2q; methyl acetonide), 21.9*, 29.7* (2q; methyl acetonide), 24.5* (t; C-5), 24.8 (t; C-5), 33.0* (t; C-4), 33.04 (t; C-4), 34.7* (s; C-7), 35.6 (s; C-7), 60.5* (s; C-3), 61.1* (t; C-1), 61.5 (s; C-3), 61.6 (t; C-1), 62.4* (d; C-2), 63.3 (d; C-2), 72.2 (t; C-8), 77.0* (d; C-6), 77.5 (d; C-6), 98.8*, 98.8 ppm (s; C-9).

Tetrahydrofurans 33 and 34: A 100 mL round-bottomed flask was charged with epoxides **32a** and **32b** (904 mg, 3.45 mmol) and dry CH_2Cl_2 (37 mL). A solution of ethylene glycol (256 mg, 4.14 mmol) in dry CH_2Cl_2/THF (48 mL, 10:1) was added, followed by dry *p*TsOH (119 mg, 0.89 mmol). After 2 h, complete conversion of the starting material was observed, before 2,2-dimethoxypropane (7 mL) was introduced. The solution was stirred for 10 h and then terminated by addition of saturated aqueous $NaHCO_3$ solution. The aqueous layer was separated and extracted with methyl *tert*-butylmethyl ether (5 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (hexanes/ethyl acetate 50:1) enabled us to separate both alcohols and gave **33** (535 mg, 2.07 mmol) and **34** (170 mg, 0.66 mmol) in an overall yield of 79%.

Compound 33: $[\alpha]_D^{23}=-2.2$ ($c=1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.82$ (s, 3H; $C(CH_3)_2$), 0.87 (s, 3H; $C(CH_3)_2$), 1.14 (s, 3H; $OC(CH_3)$), 1.32, 140 (2brs, 6H; CH_3 acetonide), 1.66 (m, 1H; 12-H), 1.80 (m, 2H; 13-H), 1.94 (ddd, 1H, $J=9.8$, 7.7, 3.8 Hz; 12-H′), 3.17 (m, 2H; 1-H), 3.47 (dd, 1H, $J=12.6$, 10.9 Hz; 14-H), 3.70 (dd, 1H, $J=8.2$, 6.6 Hz; 10-H), 3.85 (dd, 1H, $J=9.6$, 5.8 Hz; 11-H), 3.97 ppm (dd, 1H, $J=8.2$, 6.8 Hz; 10-H′); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=18.4$ (s; $OCCH_3$), 22.6, 22.9 (2q; $C(CH_3)_2$), 25.2, 26.4 (2q; CH_3 acetonide), 27.0 (t; C-13), 33.9 (t; C-12), 37.3 (s; C-15), 66.0 (t; C-9), 73.0 (t; C-1), 81.2 (d; C-14), 83.5 (s; C-11), 88.8 (d; C-10), 109.5 ppm (s; $OC(CH_3)_2$); IR (ATR): $\tilde{\nu}=$ 3445 (br w), 2968 (m), 2873 (m), 1456 (w), 1369 (m), 1260 (m), 1210 (m), 1155 (m), 1041 (s), 898 (w), 854 cm^{-1} (m); HRMS-ESI: *m/z*: calcd for $C_{14}H_{26}O_4Na$: 281.1729 $[M+Na]^+$; found: 281.1722.

Physical and analytical details for compound **34** are described in our previous communication.[1]

Furanyl ketone 35: A 100 mL round-bottomed flask was charged with acetonide **33** (434 mg, 1.68 mmol) and MeOH (20 mL). After addition of *p*TsOH (63 mg, 0.34 mmol; 0.2 equiv), the solution was warmed to 50 °C for 18 h and then cooled to RT. The reaction was terminated by addition of saturated aqueous $NaHCO_3$ solution and the organic phase was removed under reduced pressure. The aqueous phase was extracted with ethyl acetate. The combined organic phases were dried (Na_2SO_4) and the crude product was purified by flash-column chromatography (ethyl acetate/MeOH 100:1) to provide the desired triol (338 mg, 1.55 mmol; 92%) as an oil. $[\alpha]_D^{23}=+1.3$ ($c=1$ in $CHCl_3$); ^{1}H NMR (400 MHz, [D$_4$]MeOH): $\delta=0.85$, 0.86 (2s, 6H; $C(CH_3)_2$), 1.11 (s, 3H; $OCCH_3$), 1.61 (m, 1H; 12-H), 1.80 (m, 2H; 13-H), 2.09 (m, 1H; 12-H′), 3.32 (m, 2H; 1-H), 3.46 (m, 1H; 14-H), 3.57 (d, 1H, $J=6.8$ Hz; 8-H), 3.78 (d, 1H, $J=8.2$ Hz; 9-H′), 3.97 ppm (dd, 14H, $J=8.2$, 6.8 Hz; 10-H); ^{13}C NMR (100 MHz, [D$_4$]MeOH): $\delta=19.2$ (q; $C(CH_3)_2$), 21.6 (q; $C(CH_3)_2$), 23.3 (q; $OCCH_3$), 27.2 (t; C-13), 35.0 (t; C-12), 38.7 (s; $C(CH_3)_2$), 64.3 (t; C-9), 70.9 (t; C-1), 78.7 (d; C-14), 85.1 (s; $OCCH_3$), 85.8 ppm (d; C-10); HRMS-ESI: *m/z*: calcd for $C_{11}H_{22}O_4Na$: 241.1416 $[M+Na]^+$; found: 241.1409.

Imidazole (140 mg, 2.09 mmol; 3.5 equiv), followed by *tert*-butyldimethylsilyl chloride (216 mg, 1.43 mmol; 2.4 equiv) and 4-DMAP (7 mg, 0.12 mmol; 0.2 equiv) was added to a 20 mL round-bottomed flask charged with the deprotected triol (130 mg, 0.59 mmol) and dry CH_2Cl_2 (5 mL). After 10 h, the reaction was stopped by addition of saturated aqueous NH_4Cl solution. The aqueous layer was extracted once with CH_2Cl_2, and then the combined organic solutions were dried (Na_2SO_4) and concentrated under reduced pressure. Gel filtration over silica gel (hexanes/ethyl acetate 10:1) afforded the TBS-protected alcohol (223 mg, 0.5 mmol, 85%) as a colourless oil. $[\alpha]_D^{23}=-4.7$ ($c=1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.01$, 0.07 (2s, 12H; $Si(CH_3)_2$ ×2), 0.79, 0.82 (2s, 6H; $C(CH_3)_2$, 2-Me), 0.88, 0.89 (2s, 18H; *t*Bu ×2), 1.10 (brs, 3H; $OCCH_3$), 1.58 (m, 1H; 12-H), 1.74 (m, 2H; 13-H), 2.04 (ddd, 1H, $J=18.5$, 11.8, 9.3 Hz; 12-H′), 3.34, 3.28 (2d, 2H, $J=9.4$ Hz; 1-H), 3.56 (m, 1H; 9-H), 3.58 (dd, 1H, $J=16.7$, 7.2 Hz; 14-H), 3.73 (dd, 1H, $J=9.4$, 3.1 Hz; 9-H′), 3.78 ppm (t, 1H, $J=9.4$, 6.6 Hz; 10-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-5.4$, −5.2 (4q; $Si(CH_3)_2$ ×2), 18.4 (2s; *t*Bu ×2), 19.5, 21.0 (2q; $C(CH_3)_2$), 23.2 (q; $OCCH_3$), 26.1 (2s; *t*Bu), 26.4 (t; C-13), 34.3 (t; C-12), 38.3 (s; $C(CH_3)_2$), 64.1 (t; C-9), 70.0 (t; C-1), 77.1 (d; C-14), 83.2 (s; $OCCH_3$), 84.4 ppm (d; C-10); HRMS-ESI: *m/z*: calcd for $C_{23}H_{50}O_4Si_2Na$: 469.3145 $[M+Na]^+$; found: 469.3146.

A 100 mL round-bottomed flask was charged with the TBS-protected alcohol (36 mg, 81 μmol) described above which was dissolved in dry CH_2Cl_2 (20 mL). The solution was cooled to 0 °C, then Dess–Martin periodinane (60 mg, 162 μmol, 2.0 equiv) was added. After addition, the reaction mixture was warmed to RT and stirred for 6 h, before saturated

aqueous $NaHCO_3$ and $Na_2S_2O_3$ solutions were added. The aqueous layer was separated and extracted once with CH_2Cl_2. The combined organic solutions were dried (Na_2SO_4) and concentrated under reduced pressure. Flash-column chromatography (hexanes/ethyl acetate 100:1) afforded the desired ketone **35** (35 mg, 75 μmol, 92%). $[\alpha]_D^{23} = +1.2$ ($c = 1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.02$, 0.07 (2s, 12H; $Si(CH_3)_2$ ×2), 0.79, 0.83 (2s, 6H; $C(CH_3)_2$), 0.88, 0.90 (2s, 18H; *t*Bu ×2), 1.28 (brs, 3H; $OCCH_3$), 1.72 (m, 3H; 12-H, 13-H), 2.13 (m, 1H; 12-H′), 3.26, 3.42 (2d, 2H, $J = 9.3$ Hz; 1-H), 3.78 (t, 1H, $J = 7.4$ Hz; 14-H), 4.72, 4.66 ppm (2d, 2H, $J = 19.4$ Hz; 9-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -5.0$, −4.7 (4q; $Si(CH_3)_2$ ×2), 18.8, 19.1 (2s; *t*Bu ×2), 20.0, 21.3 (2q; $C(CH_3)_2$), 25.4 (q; $OCCH_3$), 26.4 (t; C-13), 26.4, 26.5 (2q; *t*Bu), 36.0 (t; C-12), 38.7 (s; *C*-$(CH_3)_2$), 66.6 (t; C-9), 70.2 (t; C-1), 85.4 (d; C-14), 88.0 (s; $OCCH_3$), 214.3 ppm (s; C-10); HRMS-ESI: *m/z*: calcd for $C_{23}H_{48}O_4Si_2Na$: 467.2989 $[M+Na]^+$; found: 467.2981.

Furanyl ketone 36: Acetonide **34** (418 mg, 1.62 mmol) was treated by the same method as that for the of deprotection acetonides described for the sequence **33**→**35** to yield the corresponding triol (292 mg, 1.34 mmol; 83%) as a colourless oil. $[\alpha]_D^{23} = +26.2$ ($c = 1$ in $CHCl_3$); ^{1}H NMR (400 MHz, [D$_4$]MeOH): $\delta = 0.88$, 0.89 (s, 6H; $C(CH_3)_2$), 1.15 (s, 3H; $OCCH_3$), 1.61 (m, 1H; 12-H), 1.76 (m, 2H; 13-H), 2.08 (m, 1H; 12-H′), 3.33 (m, 2H; 1-H), 3.48 (t, 1H, $J = 8.4$ Hz; 14-H), 3.57 (d, 1H, $J = 8.8$ Hz; 9-H), 3.73 (d, 1H, $J = 6.0$ Hz; 9-H′), 3.87 ppm (dd, 1H, $J = 8.8$, 6.0 Hz; 10-H); ^{13}C NMR (100 MHz, [D$_4$]MeOH): $\delta = 20.0$ (p; $OCCH_3$), 21.7, 21.8 (2q; $C(CH_3)_2$), 27.1 (t; C-13), 36.0 (t; C-12), 38.9 (s; $C(CH_3)_2$), 64.1 (t; C-9), 70.6 (t; C-1), 78.3 (d; C-14), 84.8 (d; C-10), 85.0 ppm (s; $OCCH_3$); HRMS-ESI: *m/z*: calcd for $C_{11}H_{22}O_4Na$: 241.1416 $[M+Na]^+$; found: 241.1411.

This triol (200 mg, 0.92 mmol) was subjected to the procedure for the silylation described for the sequence **33**→**35** to yield the corresponding alcohol (339 mg, 0.76 mmol; 83%) as a colourless oil.

$[\alpha]_D^{23} = -2.5$ ($CHCl_3$ in $c = 1$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.01$, 0.06 (2s, 12H; $Si(CH_3)_2$ ×2), 0.79, 0.81 (2s, 6H; $C(CH_3)_2$), 0.80, 0.88 (2s, 18H; *t*Bu ×2), 1.13 (brs, 3H; $OCCH_3$), 1.55 (m, 1H; 12-H), 1.72 (m, 2H; 13-H), 2.03 (m, 1H; 12-H′), 3.37, 3.33 (2d, 2H, $J = 9.3$ Hz; 1-H), 3.49 (m, 1H; 14-H), 3.60 (dd, 1H, $J = 10.2$, 7.2 Hz; 9-H), 3.75 (dd, 1H, $J = 10.2$, 3.6 Hz; 9-H′), 3.80 ppm (dd, 1H, $J = 7.2$, 3.6 Hz; 10-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -5.4$, −5.2 (4q; $Si(CH_3)_2$ ×2), 18.5 (2s; *t*Bu ×2), 19.7, 21.1 (2q; $C(CH_3)_2$), 21.9 (q; $OCCH_3$), 26.1 (2q; *t*Bu), 26.4 (t; C-13), 34.7 (t; C-12), 38.3 (s; $C(CH_3)_2$), 63.9 (t; C-9), 70.0 (t; C-1), 76.9 (d; C-14), 82.0 (d; C-10), 83.2 ppm (s; $OCCH_3$); HRMS-ESI: *m/z*: calcd for $C_{23}H_{50}O_4Si_2Na$: 469.3145 $[M+Na]^+$; found: 469.3139.

This alcohol (126 mg, 0.28 mmol) was treated by the same method as that for the oxidation described for isomer **33**→**35** to yield ketone **36** (110 mg, 0.25 mmol; 89%) as a colourless oil. $[\alpha]_D^{23} = -17.4$ ($c = 1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.02$, 0.08 (2s, 12H; $Si(CH_3)_2$ ×2), 0.83, 0.85 (2s, 6H; $C(CH_3)_2$), 0.88, 0.91 (2s, 18H; *t*Bu ×2), 1.29 (brs, 3H; $OCCH_3$), 1.72 (m, 3H; 12-H, 13-H), 2.12 (m, 1H; 12-H′), 3.30, 3.41 (2d, 2H, $J = 9.2$ Hz; 1-H), 3.79 (t, 1H, $J = 7.4$ Hz; 14-H), 4.73, 4.63 ppm (2d, 2H, $J = 19.6$ Hz; 9-H); ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = -5.4$, −5.2 (4q; $Si(CH_3)_2$), 18.4, 18.7 (2s; *t*Bu ×2), 19.8, 21.0 (2q; $C(CH_3)_2$), 24.2 (q; $OCCH_3$), 25.9, 26.0 (4q; *t*Bu), 26.0 (t; C-13), 36.4 (t; C-12), 38.4 (s; *C*-$(CH_3)_2$), 66.6 (t; C-9), 70.0 (t; C-1), 83.3 (d; C-14), 87.6 (s; $OCCH_3$), 211.8 ppm (s; C-10); HRMS-ESI: *m/z*: calcd for $C_{23}H_{48}O_4Si_2Na$: 467.2989 $[M+Na]^+$; found: 467.2979.

Aldol products 39a and 39b: A 50 mL round-bottomed flask was charged with ketone **35** (79 mg, 178 μmol) and dry THF (8 mL). The solution was cooled to −78°C, before KHMDS (392 μL, 1.1 equiv, 0.5 M in toluene) was introduced dropwise. After 30 min, the aldehyde **6** in dry THF (5 mL) was added and the solution was stirred for another 15 min. The reaction was then stopped by dropwise addition of pH 7 phosphate buffer under vigorous stirring. The flask was warmed to RT in the cold bath, then the aqueous layer was separated and extracted with MTBE (3×10 mL). The combined organic solutions were dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (hexanes/ethyl acetate 50:1) furnished an inseparable mixture (3:1) of two diastereoisomeric aldol products **39a** and **39b*** (62 mg, 114 μmol, 64%) as a colourless oil. $[\alpha]_D^{23} = +1.2$ ($c = 1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.02$, 0.09 (2s, 12H; $Si(CH_3)_2$ ×2), 0.78, 0.86 (2s, 6H; $C(CH_3)_2$), 0.83 (d, 3H, $J = 6.1$ Hz; CH_3CH), 0.89, 0.92 (2s, 18H; *t*Bu ×2), 1.27 (s, 3H; $OCCH_3$, 6-Me), 1.72–1.97 (m, 6H; CH_3–C*H*, CH_2CH=, 12-H, 13-H), 2.54 (m, 1H; CH_2CH=), 3.29, 3.41 (2d, 2H, $J = 9.4$ Hz; 1-H), 3.78–3.93 (m, 3H; 14-H, 8-H), 4.88* (d, 1H, $J = 1.0$ Hz; 9-H), 4.9 (d, 1H, $J = 1.3$ Hz; 9-H), 5.05 (m, 2H; $=CH_2$), 5.78 ppm (m, 1H; −CH=); ^{13}C NMR (100 MHz, [D$_6$]benzene = 128.1 ppm): $\delta = -5.3$, −5.1 (4q, $Si(CH_3)_2$ ×2), 15.8 (q; CH_3CH), 15.8* (q; CH_3CH), 18.5, 18.8 (2s; *t*Bu ×2), 18.5, 18.9 (2s, *t*Bu ×2), 20.3, 20.8 (q; $C(CH_3)_2$), 25.9 (t; C-13), 26.1, 26.2 (2q; *t*Bu ×2), 26.8 (q; $OCCH_3$), 35.7 (t; C-12), 36.8* (d; CH_3CH), 36.8 (d; CH_3CH), 37.7* (t; CH_2CH=), 37.8 (t, CH_2CH=), 38.8 (s; $C(CH_3)_2$), 70.4 (t; C-1), 75.2 (d; C-8), 75.5* (d; C-8), 75.9* (d; C-9), 77.0 (d; C-9), 86.2* (d; C-14), 86.3 (d; C-14), 88.7 (s; $OCCH_3$), 88.9* (s; $OCCH_3$), 116.5 (t; $=CH_2$), 116.7* (t; $=CH_2$), 137.3* (d; −CH=), 137.5 (d; −CH=), 212.3 (s; C-10), 213.3* ppm (s; C-10); HRMS-ESI: *m/z*: calcd for $C_{29}H_{58}O_5Si_2Na$: 565.3721 $[M+Na]^+$; found: 565.3723.

Aldol product 37: A 50 mL round-bottomed flask was charged with ketone **36** (92 mg, 241 μmol) and dry THF (10 mL). The solution was cooled to −78°C, before KHMDS (530 μL, 265 μmol, 1.1 equiv, 0.5 M in toluene) was introduced dropwise. After 30 min, aldehyde **6** in dry THF (5 mL) was added and the solution was stirred for another 40 min. The reaction was terminated by addition of saturated aqueous NH_4Cl solution. The aqueous layer was separated and extracted with MTBE (3× 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Flash-column chromatography (hexanes/ethyl acetate 20:1) afforded the desired product **37** (115 mg, 212 μmol; 88%) as a colourless oil. $[\alpha]_D^{23} = -21.8$ ($c = 1$ in $CHCl_3$); ^{1}H NMR (400 MHz, [D$_6$]benzene, $C_6H_6 = 7.16$ ppm): $\delta = 0.05$, 0.09 (2s, 12H; $Si(CH_3)_2$ ×2), 0.86, 0.94 (2s, 6H; $C(CH_3)_2$), 0.89 (d, 3H, $J = 11.3$ Hz; CH_3CH), 0.98, 1.01 (2s, 18H; *t*Bu ×2), 1.41 (s, 3H; $OCCH_3$), 1.57–2.20 (m, 6H; CH_3CH, CH_2CH=, 12-H, 13-H), 2.72 (m, 1H; CH_2CH=), 3.33, 3.48 (2d, 2H, $J = 9.2$ Hz; 1-H), 3.72 (t, 1H, $J = 6.1$ Hz; 14-H), 3.81 (d, 1H, $J = 8.9$, 6.3 Hz; 8-H), 4.93 (m, 1H; 9-H), 5.23 (m, 2H; CH_2=), 5.90 ppm (m, 1H; −CH=); ^{13}C NMR (100 MHz, [D$_6$]benzene = 128.1 ppm): $\delta = -5.3$, −5.1 (4q; $Si(CH_3)_2$ ×2), 16.3 (q; CH_3CH), 18.5, 18.9 (2s; *t*Bu ×2), 19.5, 21.2 (q; $C(CH_3)_2$), 24.9 (q; $OCCH_3$), 25.5 (t; C-13), 26.1, 26.2 (2q; *t*Bu ×2), 36.7 (t; C-12), 37.8 (d; CH_3CH), 38.2 (t; CH_2CH=), 38.5 (s; *C*-$(CH_3)_2$), 70.1 (t; C-1), 75.3 (d; C-8), 77.2 (d; C-9), 83.1 (d; C-14), 88.9 (s; $OCCH_3$), 116.6 (t; CH_2=), 137.4 (d; −CH=), 212.0 ppm (s, C-10); HRMS-ESI: *m/z*: calcd for $C_{29}H_{58}O_5Si_2Na$: 565.3721 $[M+Na]^+$; found: 565.3713.

General procedure for silylation of 1,3-diols: A round-bottomed flask was charged with the diol (1 equiv) and dry CH_2Cl_2 (0.1 mmol mL^{-1}). 2,6-Lutidine (3 equiv) was added, followed by di-*tert*-butylsilyl ditriflate (1.5 equiv). After stirring for 24 h at RT the reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic solutions were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Flash-column chromatography afforded the desired silinanes as colourless oils.

Dioxasilinane 38: A 50 mL round-bottomed flask was charged with aldol product **37** (27 mg, 49 μmol)) and anhydrous CH_2Cl_2 (10 mL). The mixture was then cooled to −78°C, before DIBAL-H (150 μL, 147 μmol, 3 equiv) was added. Additional DIBAL-H (100 μL, 2 equiv) was added after 2 h. After 5 h, the reaction mixture was allowed to warm to −30°C and was then hydrolysed with water (0.25 mL) and aqueous NaOH (4 M, 0.25 mL). Na_2SO_4 was added and the mixture was filtered. The residue was washed and the combined organic solutions were concentrated under reduced pressure. Flash-column chromatography delivered the diol (111 mg, 21 μmol, 42%), as an oil, along with recovered starting material (13 mg, 23 μmol, 49%). $[\alpha]_D^{23} = -9.8$ ($c = 1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.03$, 0.13, 0.17 (3s, 12H; $Si(CH_3)_2$), 0.82, 0.84 (2s, 6H; $C(CH_3)_2$), 0.84 (d, $J = 6.8$ Hz, 3H; CH_3CH), 0.89, 0.91 (2s, 18H; *t*Bu ×2), 1.19 (s, 3H; $OCCH_3$), 1.60 (dt, $J = 12.4$, 8.3 Hz; H-12), 1.70–1.85 (m, 3H; H-13, H-13, H-7), 1.96 (dtt, $J = 13.7$, 8.3, 1.0 Hz, 1H; H-6), 2.15 (ddd, $J = 12.4$, 8.8, 4.0 Hz, 1H; H-12), 2.50 (dddt, $J = 13.7$, 6.2, 3.2, 1.6 Hz, 1H; H-6), 2.72 (d, $J = 8.9$ Hz, 1H; 8-O*H*), 2.85 (d, $J = 3.8$ Hz, 1H; 10-O*H*), 3.17 (td, $J = 9.2$, 0.5 Hz, 1H; H-8), 3.32 (d, $J = 9.4$ Hz, 1H; H-1), 3.38 (d, $J = 9.4$ Hz, 1H; H-1), 3.48 (dd, $J = 6.8$, 3.8 Hz, 1H; H-10), 3.80

(dd, $J=6.8$, 0.5 Hz, 1H; H-9), 3.83 (dd, $J=9.4$, 6.3 Hz, 1H; H-14), 4.99–5.07 (m, 2H; H-4 ×2), 5.79 ppm (dddd, $J=16.9$, 10.4, 8.3, 6.2 Hz, 1H; H-5); ^{13}C NMR (400 MHz, $CDCl_3$): $\delta=-5.4$, −5.4, −4.6, −3.3 (4q; Si(CH_3)$_2$ ×2), 15.9 (q; CH_3CH), 18.5, 18.8 (2s; *t*Bu ×2), 20.0, 21.2 (2q; C(CH_3)$_2$), 21.6 (q; OCCH_3), 26.1, 26.3 (2q; *t*Bu ×2), 27.1 (t; C-13), 35.6 (t; C-12), 35.6 (d; C-7), 37.3 (t; C-6), 38.3 (s; C-15), 70.0 (t; C-1), 73.8 (d; C-9), 74.1 (d; C-8), 77.5 (d; C-10), 82.0 (d; C-14), 83.5 (s; C-11), 116.3 (t; C-4), 137.4 ppm (d; C-5); HRMS-ESI: *m/z*: calcd for $C_{29}H_{60}O_5Si_2Na$: 567.3877 $[M+Na]^+$; found: 567.3878.

This diol (11 mg, 21 μmol) was treated by the same method as that described in the general procedure for the silylation of 1,3-diols to yield silinane **38** (14 mg, 20 μmol, 96%) as a colourless oil. $[\alpha]_D^{23}=-6.2$ ($c=1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.03$, 0.03 (2s, 6H; Si(CH_3)$_2$), 0.12 (s, 3H; Si(CH_3)$_2$), 0.14 (s, 3H; Si(CH_3)$_2$), 0.85, 0.91 (2s, 6H; C(CH_3)$_2$), 0.99 (d, 3H, $J=6.9$ Hz; CH_3CH), 0.88, 0.91 (2s, 18H; *t*Bu ×2), 1.01, 1.06 (2, 18H; *t*Bu ×2), 1.27 (s, 3H; OCCH_3), 1.49–1.64 (m, 2H; H-12, H-13), 1.71–1.81 (m, 2H; H-13, CH_2CH=), 1.85–1.98 (m, 2H; H-12, CH_3CH), 2.69–2.76 (m, 1H; CH_2CH=), 3.32 (d, 1H, $J=9.5$ Hz; H-1), 3.50 (d, 1H, $J=9.5$ Hz; H-1), 3.94 (d, 1H, $J=8.9$ Hz; H-8), 3.97–4.07 (m, 2H; H-9, H-14), 4.35 (d, 1H, $J=4.6$ Hz; H-10), 4.94–5.04 (m, 2H; CH_2=), 5.79 ppm (dddd, 1H, $J=17.1$, 10.1, 8.5, 5.6 Hz, −CH=); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-5.4$, −5.3, −4.5, −2.0 (4q; Si(CH_3)$_2$ ×4), 15.2 (q; CH_3CH), 18.4, 18.5 (2s; *t*Bu ×2), 19.9, 21.2 (2q; C(CH_3)$_2$), 20.9, 21.4 (2s; *t*Bu ×2), 22.5 (q; OCCH_3), 26.0 (t; C-13), 26.0, 26.3 (2q; *t*Bu ×2), 27.9, 28.4 (2q; *t*Bu ×2), 34.3 (t; C-12), 36.4 (d; CH_3CH), 38.4 (t; CH_2CH=), 38.5 (s; C(CH_3)$_2$), 70.1 (t; C-1), 69.7 (d; C-10), 70.8 (d; C-8), 80.5 (d; C-9), 81.5 (d; C-14), 85.0 (s; OCCH_3), 116.2 (t; CH_2=), 137.2 ppm (d, −CH=); HRMS-EI: *m/z*: calcd for $C_{37}H_{76}O_5Si_3$: 684.5001 $[M]^+$; found: 684.5004.

Dioxasilinanes 40 and 41: A mixture of both diastereoisomeric ketones **39a** and **39b** (21 mg, 38 μmol) in a mixture of THF/MeOH (7 mL, 3:1) was cooled to −78°C. Et_2BOMe (6 μL, 42 μmol, 1.1 equiv) in THF (1 mL) was then added and the reaction mixture was stirred for 15 min, before adding $NaBH_4$ (4.7 mg, 125 μmol, 3.3 equiv) suspended in 5 mL THF. After stirring for 8 h, the reaction mixture was warmed to 0°C and hydrolysed by dropwise addition of an aqueous solution of AcOH (1N, 10 mL). The mixture was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Purification by column chromatography (hexanes/ethyl acetate 50:1) yielded both diols (14 mg, 26 μmol, 67%) as a colourless oil. The data labelled with * refer to the minor diastereoisomer. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.01$–0.17 (m, 12H; Si(CH_3)$_2$ ×2), 0.79, 0.86 (2s, 6H; C(CH_3)$_2$), 0.82 (d, 3H, $J=6.4$ Hz; CH_3CH), 0.88–0.92 (4s, 18H; *t*Bu ×2), 1.26 (s, 3H; OCCH_3), 1.50–2.00 (m, 6H; 12-H, 13-H, CH_3CH, CH_2–CH=), 2.62 (m, 1H; CH_2–CH=), 3.26, 3.36 (m, 2H; 1-H), 3.59 (m, 1H; 9-H), 3.65 (t, 1H, $J=4.3$ Hz; 14-H), 3.79 (dd, 1H, $J=11.1$, 3.2 Hz; 8-H), 4.0 (d, 1H, $J=3.5$ Hz; 10-H), 4.99 (m, 2H; =CH_2), 5.78 ppm (m, 1H; −CH=); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-5.4$, −5.2 (4q; Si(CH_3)$_2$ ×2), 15.5* (q; CH_3CH), 15.8 (q; CH_3CH), 18.4, 18.5 (2s; *t*Bu ×2), 18.5*, 18.6* (2s; *t*Bu ×2), 19.6, 19.7 (q; C(CH_3)$_2$, 25.9 (t; C-13), 26.0, 26.1 (2q; *t*Bu ×2), 26.3 (q; OCCH_3), 26.4* (q; OCCH_3), 30.5 (t; C-12), 30.6* (t; C-12), 34.3* (d; CH_3CH), 34.4 (d; CH_3CH), 36.8* (t; CH_2–CH=), 36.9 (d; CH_2–CH=), 38.9 (s; C(CH_3)$_2$), 70.0 (t; C-1), 75.4 (d; C-8), 75.4* (d; C-8), 77.1* (d; C-9), 77.2 (d; C-9), 83.2* (d; C-10), 83.3 (d; C-10). 84.4 (t; C-14), 84.5* (d; C-14), 88.7 (s; OCCH_3), 88.9* (s; OCCH_3), 116.9* (t; CH_2=), 115.9 (t; CH_2=), 125.7* (d; CH=), 130.0 ppm (d; CH=); HRMS-ESI: *m/z*: calcd for $C_{29}H_{60}O_5Si_2Na$: 567.3877 $[M+Na]^+$; found: 567.3879.

A mixture of both diastereoisomeric diols (14 mg, 26 μmol) was treated by the same method as that for the silylation to yield a mixture of silinanes **40** and **41** (4:1, 13 mg, 19 μmol, 73%) as a colourless oil.

Compound 40: $[\alpha]_D^{20}=-2.0$ ($c=1$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=0.01$, (2s, 6H; Si(CH_3)$_2$), 0.09 (s, 6H; Si(CH_3)$_2$), 0.79, 0.86 (2s, 6H; C(CH_3)$_2$), 0.81 (d, 3H, $J=10.9$ Hz; CH_3CH), 0.88–0.90 (2s, 18H; *t*Bu ×2), 1.00–1.07 (2s, 18H; *t*Bu ×2), 1.18 (s, 3H; OCCH_3), 1.56–2.20 (m, 6H; 13-H, 12-H, CH_3CH, CH_2–CH=), 2.67 (m, 1H; CH_2–CH=), 3.29, 3.38 (m, 2H; 1-H), 3.56 (dd, 1H, $J=2.3$, 4.5 Hz; 8-H), 3.67 (dd, 1H, $J=10.5$, 3.7 Hz; 14-H), 3.83 (dd, 1H, $J=2.3$, 2.2 Hz; 9-H), 3.96 (d, 1H, $J=2.2$ Hz; 10-H), 4.99 (m, 2H; CH_2=), 5.77 ppm (m, 1H; CH=); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-5.4$, −5.1 (4q; Si(CH_3)$_2$ ×2), 14.3 (q; CH_3CH), 18.4, 18.5 (2s; *t*Bu ×2), 19.7, 19.9 (2s; *t*Bu ×2), 20.3, 20.5 (q; C(CH_3)$_2$), 26.0 (t; C-13), 26.0, 26.1 (2q; *t*Bu), 26.4 (q; OCCH_3), 27.1, 27.3 (2q; *t*Bu ×2), 29.9 (t; C-12), 34.4 (t; C–CH_3CH), 38.4 (t; CH_2–CH=), 38.5 (s; C(CH_3)$_2$), 70.1 (t; C-1), 75.4 (d; C-8), 77.4 (d; C-9), 83.7 (d; C-10). 84.8 (d; C-14), 86.2 (s; OCCH_3), 115.9 (t; CH_2=), 130.0 ppm (d; CH=); HRMS-EI: *m/z*: calcd for $C_{37}H_{76}O_5Si_3$: 684.5001 $[M]^+$; found: 684.5002.

Compound 41: $[\alpha]_D^{20}=-7.7$ ($c=1$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=0.01$–0.15 (4s, 12H; Si(CH_3)$_2$ ×2), 0.78, 0.87 (2s, 6H; C(CH_3)$_2$), 0.84 (d, 3H, $J=6.4$ Hz; CH_3CH), 0.86–0.91 (2s, 18H; *t*Bu ×2), 1.00–1.07 (2s, 18H; *t*Bu ×2), 1.16 (s, 3H; OCCH_3), 1.50–2.20 (m, 6H; 13-H, 12-H, CH_3CH, CH_2–CH=), 2.55 (m, 1H; CH_2–CH=), 3.27, 3.37 (m, 2H; 1-H), 3.57 (dd, 1H, $J=10.2$, 1.1 Hz; 8-H), 3.66 (dd, 1H, $J=10.6$, 3.3 Hz; 14-H), 3.83 (dd, 1H, $J=1.1$, 1.1 Hz; 9-H), 4.02 (d, 1H, $J=1.1$ Hz; 10-H), 4.99 (m, 2H; CH_2=), 5.78 ppm (m, 1H; CH=); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-5.4$, −5.1 (4q; Si(CH_3)$_2$ ×2), 15.6 (q; CH_3CH), 18.4, 18.5 (2s; *t*Bu ×2), 20.1, 20.4 (2s, *t*Bu ×2), 20.3, 20.5 (2q; C(CH_3)$_2$), 26.0 (t; C-13), 26.0, 26.1 (2q; *t*Bu ×2), 26.2 (q; OCCH_3), 27.4, 27.6 (2q; *t*Bu ×2), 29.8 (t; C-12), 34.3 (d; CH_3CH), 38.3 (t; CH_2–CH=), 38.5 (s; C-(CH_3)$_2$), 70.1 (t; C-1), 75.4 (d; C-8), 77.4 (d; C-9), 83.5 (d; C-10), 84.9 (d; C-14), 86.0 (s; OCCH_3), 116.9 (t; CH_2=), 125.7 ppm (d; CH=); HRMS-EI: *m/z*: calcd for $C_{37}H_{76}O_5Si_3$: 684.5001 $[M]^+$; found: 684.5004.

9,10-Dihydroxy-8-*O*-(*tert*-butyldimethylsilyl)ether 44 and 8,9-dihydroxy-10-*O*-(*tert*-butyldimethylsilyl)ether 45: TBS-ether **15** (19 mg, 39 μmol) in THF (1 mL) was added to a suspension of washed NaH (60% in paraffin oil, 3 mg, 75 μmol, 1.9 equiv) in THF (1 mL) at 0°C. The reaction mixture was stirred at this temperature for 15 min until aqueous NH_4Cl (0.5 mL) was added. Direct purification by column chromatography over silica gel (petroleum ether/ethyl acetate 40:1) afforded the two regioisomeric TBS ethers **44** (10 mg, 20.8 μmol, 53%) and **45** (7.5 mg, 15.6 μmol, 39%) as colourless oils.

Compound 44: TLC: $R_f=0.44$ (petroleum ether/ethyl acetate 10:1); $[\alpha]_D^{23}=+12.0$ ($c=1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.09$, 0.12 (2s, 6H; Si(CH_3)$_2$), 0.92 (s, 9H; *t*Bu), 0.96, 1.03 (2s, 6H; C(CH_3)$_2$), 0.98 (d, $J=6.9$ Hz, 3H; CH_3CH), 1.09 (d, $J=6.9$ Hz, 3H; CH_3–CH), 1.21 (s, 3H; OCCH_3), 1.46–1.60 (m, 1H; CH_3CH at C-7), 1.62–1.84 (m, 3H; H-7, H-13 ×2), 1.86–1.97 (m, 1H; CH_2–CH= at C-6), 2.08–2.22 (m, 2H; H-6, H-12), 2.69 (d, $J=9.4$ Hz, 1H; 10-OH), 2.83 (ps hex., $J=6.7$ Hz, 1H; H-3), 3.20 (d, $J=2.5$ Hz, 1H; 9-OH), 3.31 (d, $J=9.4$ Hz, 1H; H-10), 3.64 (dd, $J=6.6$, 2.5 Hz, 1H; H-8), 3.71 (dd, $J=8.5$, 6.5 Hz, 1H; H-14), 3.88 (dd, $J=6.6$, 2.5 Hz, 1H; H-9), 4.90–5.04 (m, 4H; H-5, H-4′), 5.36 (dd, $J=16.0$, 6.3 Hz, 1H; H-2), 5.45 (d, $J=16.0$ Hz, 1H; H-1), 5.79 (ddd, $J=17.1$, 10.4, 6.6 Hz, 1H; H-4), 5.70–5.80 ppm (m, 1H; H-5′); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-4.5$, −3.9 (2q; Si(CH_3)$_2$), 17.3, 20.0, 23.5, 24.3, 24.7 (5q; OCCH_3, $CHCH_3$ ×2, C(CH_3)$_2$), 18.5 (s; *t*Bu), 26.2 (q; SiC-(CH_3)$_3$), 27.0 (t; C-13), 34.4 (t; C-12), 35.5 (t; C-6), 35.9 (d; C-7), 38.9 (s; C-15), 40.5 (d; C-3), 71.2 (d; C-9), 74.4 (d; C-10), 78.0 (d; C-8), 86.1 (s; C-11), 86.2 (d; C-14), 112.7 (t; C-5), 115.5 (t; C-4′), 132.5 (d; C-2), 134.7 (d; C-1), 138.0 (d; C-5′), 143.2 ppm (d; C-4); IR (ATR): $\tilde{\nu}=3479$ (brs), 3077 (w), 2960 (s), 2930 (s), 2857 (m), 1731 (w), 1639 (w), <1462 (m), 1414 (w), 1387 (m), 1362 (w), 1251 (m), 1088 (s), 1060 (m), 993 (w), 912 (m), 888 (w), 836 (m), 777 (m), 673 cm^{-1} (w); HRMS-ESI: *m/z*: calcd for $C_{28}H_{52}O_4SiNa$: 503.3533 $[M+Na]^+$; found: 503.3540.

Compound 45: TLC: $R_f=0.24$ (petroleum ether/ethyl acetate 10:1); ^{1}H NMR (200 MHz, $CDCl_3$, $CHCl_3$): $\delta=0.15$, 0.20 (2s, 6H; Si(CH_3)$_2$), 0.92 (s, 9H; *t*Bu), 0.96, 0.98 (2s, 6H; C(CH_3)$_2$), 0.99 (d, $J=6.8$ Hz, 3H; CH_3CH), 1.07 (d, $J=6.9$ Hz, 3H; CH_3CH), 1.16 (s, 3H; OCCH_3), 1.36–1.76, 1.80–2.07 (m, 6H; H-6, H-7, H-12, H-13), 2.23–2.39 (m, 1H; H-6), 2.71–2.90 (m, 1H; H-3), 2.87 (d, $J=4.3$ Hz, 1H; 8-OH), 3.09 (d, $J=7.7$ Hz, 1H; 9-OH), 3.31 (dd, $J=9.5$, 5.3 Hz, 1H; H-8), 3.51 (ddd, $J=7.7$, 5.3, 2.1 Hz, 1H; H-9), 3.62 (d, $J=2.1$ Hz, 1H; H-10), 3.75 (dd, $J=8.1$, 5.8 Hz, 1H; H-14), 4.88–5.10 (m, 4H; H-5, H-4′), 5.32 (dd, $J=15.9$, 5.9 Hz, 1H; H-2), 5.45 (d, $J=15.9$, 1H; H-1), 5.67–5.90 ppm (m, 2H; H-4, H-5′); IR (ATR): $\tilde{\nu}=3482$ (br, m), 3077 (w), 2959 (s), 2930 (s), 2859 (m), 1639 (w), 1463 (m), 1385 (m), 1251 (m), 1110 (m), 1082 (w), 1027 (m), 993 (m), 911 (m), 836 (m), 780 (m), 683 cm^{-1} (w).

Macrocyclic silyl ether 50: A 10 mL round-bottomed flask was charged with TBS alcohol **27** (2.9 mg, 5.57 μmol) and dry CH_2Cl_2 (2 mL). Grubbs

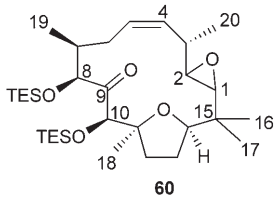
II catalyst (0.5 mg, 0.6 μmol) was added in dry CH_2Cl_2 (1 mL) and the solution was refluxed under nitrogen for 4.5 h and then concentrated. Flash chromatography over silica gel (hexanes/ethyl acetate 20:1) afforded the desired product **50** (1.7 mg, 3.44 μmol, 62%), as a mixture of *E*/*Z* isomers (*E*/*Z* 1:2.2). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.83$ (s, 3H; H-17), 0.87 (d, $J = 6.8$ Hz, 3H; H-19), 0.87 (s, 3H; H-16), 0.89 (s, 9H; Si-$(CH_3)_2t$Bu), 1.13 (d, $J = 7.0$ Hz, 3H; H-20), 1.16 (s, 3H; H-18), 1.32 (s, 3H; $O_2C(CH_3)_2$), 1.47 (s, 3H; $O_2C(CH_3)_2$), 3.00 (ddq, $J = 8.3$, 7.0, 5.6 Hz, 1H; H-3), 3.71 (d, $J = 5.7$ Hz, 1H; H-10), 4.10 (dd, $J = 9.9$, 1.4 Hz, 1H; H-8), 4.19 (dd, $J = 9.9$, 5.7 Hz, 1H; H-9), 5.38 (d, $J = 16.1$ Hz, 1H; H-1), 5.43 (dd, $J = 16.1$, 5.5 Hz, 1H; H-2), 5.45 (dt, $J = 11.2$, 8.2 Hz, 1H; H-5), 5.55 ppm (dd, $J = 11.2$, 8.4 Hz, 1H; H-4); HRMS-EI calcd for $C_{29}H_{52}O_4Si$: 492.3635 $[M]^+$; found: 492.3636.

Trienol 51: A 5 mL round-bottomed flask was charged with TBS alcohol **26** (16.5 mg, 32 μmol) and THF (1 mL). TBAF·3H$_2$O (56 mg, 0.18 mmol, 5.6 equiv) was added in THF (0.5 mL) and the solution was stirred for 19.5 h. Silica gel was added and the mixture was concentrated. A gel filtration over silica gel (hexanes/ethyl acetate 40:1) afforded the desired product **51** (11.6 mg, 29 μmol, 91%) as a colourless oil. $[\alpha]_D^{23} = -14.6$ ($c = 0.9$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): 0.94 (d, $J = 6.5$ Hz, 3H; H-19), 0.99 (s, 3H; H-17), 1.00 (s, 3H; H-16), 1.06 (d, $J = 6.8$ Hz, 3H; H-20), 1.26 (s, 3H; H-18), 1.37 (s, 3H; $O_2C(CH_3)_2$), 1.45 (s, 3H; $O_2C(CH_3)_2$), 1.52 (ddd, $J = 11.9$, 8.4, 7.9 Hz, 1H; H-12), 1.68–1.77 (m, 2H; H-13 ×2), 1.88 (dtt, $J = 13.6$, 8.5, 0.9 Hz, 1H; H-6), 2.03 (dddq, $J = 9.6$, 8.5, 6.5, 3.8 Hz, 1H; H-7), 2.09 (ddd, $J = 11.9$, 8.0, 6.0 Hz, 1H; H-12), 2.35 (dddt, $J = 13.6$, 5.8, 3.8, 1.9 Hz, 1H; H-6), 2.81 (sext. q, $J = 6.9$, 1.2 Hz, 1H; H-3), 3.25 (d, $J = 9.6$ Hz, 1H; H-8), 3.47 (d, $J = 1.0$ Hz, 1H; H-10), 3.71 (dd, $J = 8.2$, 6.8 Hz, 1H; H-14), 3.83 (dt, $J = 2.7$, 1.4 Hz, 1H; H-9), 4.08 (d, $J = 2.7$ Hz, 1H; 9-O*H*), 4.91 (dt, $J = 10.4$, 1.6 Hz, 1H; H-5), 4.95 (dt, $J = 17.1$, 1.6 Hz, 1H; H-5), 4.98–5.08 (m, 2H; H-4′ ×2), 5.28 (dd, $J = 15.7$, 7.2 Hz, 1H; H-2), 5.50 (dd, $J = 15.7$, 1.0 Hz, 1H; H-1), 5.78 (ddd, $J = 17.1$, 10.4, 6.5 Hz, 1H; H-4), 5.80 ppm (dddd, $J = 17.0$, 10.2, 8.4, 5.8 Hz, 1H; H-5′); ^{13}C NMR (100 MHz, $CDCl_3$): 15.8 (q; C-19), 19.1 (q; $O_2C(CH_3)_2$), 20.4 (q; C-20), 23.4 (q; C-17), 23.8 (q; C-16), 24.6 (q; C-18), 27.1 (t; C-13), 29.9 (q; $O_2C(CH_3)_2$), 32.7 (d; C-7), 35.4 (t; C-12), 36.4 (t; C-6), 39.2 (s; C-15), 40.7 (d; C-3), 63.6 (d; C-9), 75.6 (d; C-10), 77.4 (d; C-8), 84.9 (s; C-11), 87.0 (d; C-14), 99.0 (s; $O_2C(CH_3)_2$), 112.5 (t; C-5), 116.2 (t; C-4′), 131.4 (d; C-2), 136.2 (d; C-1), 136.9 (d; C-5′), 143.6 ppm (d; C-4); IR: $\tilde{\nu} =$ 3473 (m), 2964 (m), 2930 (w), 2871 (m), 1639 (m), 1456 (m), 1377 (m), 1259 (m), 1201 (m), 1169 (m), 1091 (m), 1059 (w), 1024 (m), 983 (s), 909 (s), 861 (m), 813 (m), 721 (w), 667 (w), 642 cm^{-1} (w); HRMS-ESI: *m*/*z*: calcd for $C_{25}H_{42}O_4Na$: 429.2981 $[M+Na]^+$; found: 429.2523.

Macrocyclic alcohol 52: A 25 mL round-bottomed flask was charged with alcohol **51** (6.4 mg, 15.7 μmol) and dry CH_2Cl_2 (4 mL). Grubbs II catalyst (1.4 mg, 1.6 μmol) was added in dry CH_2Cl_2 (3 mL) and the solution was heated under refluxing conditions under nitrogen for 5.5 h and then concentrated under reduced pressure. Flash chromatography over silica gel (hexanes/ethyl acetate 40:1) afforded the desired product **52** (4.7 mg, 12.4 μmol, 79%) as a mixture of *E*/*Z* isomers (*E*/*Z* 1.3:1). The *E* isomer was isolated by flash chromatography over silica gel (hexanes/ethyl acetate 100:1). $[\alpha]_D^{23} = -14.5$ ($c = 0.94$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): 0.91, 1.10 (2s, 6H; $C(CH_3)_2$), 0.92 (d, $J = 6.1$ Hz, 3H; $CHCH_3$), 1.00 (d, $J = 6.8$ Hz, 3H; $CHCH_3$), 1.19 (s, 3H; $OCCH_3$), 1.31 (ddd, $J =$ 12.5, 11.6, 8.2 Hz, 1H; H-12), 1.39 (s, 3H; $O_2C(CH_3)_2$), 1.40 (s, 3H; O_2C-$(CH_3)_2$), 1.57–1.70 (m, 2H; H-13 ×2), 1.82–1.95 (m, 3H; H-6, H-7, 9-O*H*), 2.22 (dt, $J = 13.3$, 2.7 Hz, 1H; H-6), 2.52 (ddd, $J = 12.6$, 8.4, 1.5 Hz, 1H; H-12), 2.78–2.87 (m, 1H; H-3), 3.27 (d, $J = 9.2$ Hz, 1H; H-8), 3.50 (d, $J = 1.0$ Hz, 1H; H-10), 3.53 (dd, $J = 10.6$, 5.1 Hz, 1H; H-14), 4.07 (d, $J = 10.9$ Hz, 1H; H-9), 5.30 (ddd, $J = 15.2$, 9.5, 2.5 Hz, 1H; H-4), 5.37 (dd, $J = 16.0$, 5.8 Hz, 1H; H-2), 5.49 (ddd, $J = 15.2$, 10.1, 2.7 Hz, 1H; H-5), 5.57 ppm (dd, $J = 16.0$, 1.4 Hz, 1H; H-1); ^{13}C NMR (100 MHz, $CDCl_3$): 19.2 (q; $O_2C(CH_3)_2$), 19.4 (q; C-19), 21.5 (q; C-20), 24.6 (q; C-17), 27.5 (q; C-16), 28.1 (t; C-13), 28.6 (q; C-18), 30.1 (q; $O_2C(CH_3)_2$), 32.9 (t; C-12), 33.0 (d; C-7), 38.3 (s; C-15), 38.7 (t; C-6), 40.9 (d; C-3), 63.2 (d; C-9), 77.6 (d; C-10), 80.8 (d; C-8), 82.3 (s; C-11), 86.6 (d; C-14), 99.4 (s; $O_2C(CH_3)_2$), 130.1 (d; C-5), 132.9 (d; C-1), 133.4 (d; C-2), 133.9 ppm (d; C-4); IR: $\tilde{\nu} = 3528$ (w), 2962 (m), 2923 (m), 2866 (m), 1453 (m), 1380 (m), 1297 (w), 1260 (m), 1201 (m), 1156 (m), 1060 (s), 1027 (m), 1003 (m), 966 (s), 923 (w), 885 (m), 854 (m), 805 (m), 718 cm^{-1} (m); HRMS-ESI: *m*/*z*: calcd for $C_{25}H_{41}NO_4Na$: 442.2933 $[M+Na]^+$; found: 442.2920.

Macrocyclic 8,10-*O*-(triethylsilyl) ether 53: Grubbs II catalyst (10 mg, 11.8 μmol, 12.5 mol%, $c = 0.0038$ M) was added to a solution of acyclic 8,10-bis-silylated ketone **49** (56 mg, 94 μmol) in absolute CH_2Cl_2 (25 mL) at 0°C. After 2 h, the solution was saturated with air, filtered over neutral Al_2O_3 and concentrated. Column chromatography (petroleum ether/ethyl acetate 60:1) afforded the two inseparable (*E*/*Z* 1:1) macrocycles **53** (51.5 mg, 91 μmol; 97%) as colourless oils. TLC: $R_f = 0.65$ (petroleum ether/ethyl acetate 40–60:1); the interpretation of the ^{1}H NMR spectra was hampered due to line broadening for which we make a slow conformational equilibrium of the macrocycle responsible; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 5.05$, 5.11, 6.79, 6.90, 15.58, 21.74, 24.58, 25.88, 26.22, 28.08, 29.68, 30.63, 32.24, 33.81, 37.78, 41.74, 78.69, 85.65, 85.69, 86.33, 87.25, 128.82, 132.30, 132.84, 133.70, 135.25, 136.37 ppm (all observed signals of the mixture are listed as detected and are not comprehensive. Characteristically, no CH_2 signals were detected with the DEPT-135 method reflecting the absence of terminal olefins); HRMS-ESI: *m*/*z*: calcd for $C_{32}H_{60}O_4Si_2Na$: 587.3928 $[M+Na]^+$; found: 587.3957. Further analytical evidence for the macrocyclic product **53** was collected from the derivative **60** collected after *m*CPBA oxidation (unknown configuration around the oxirane ring).

The inseparable metathesis products **53** (39 mg, 69 μmol) were dissolved in CH_2Cl_2 (1.2 mL) and added to a suspension of *m*CPBA (43 mg, 174 μmol; 2.5 equiv) in CH_2Cl_2 (3 mL) at −20°C. After 2 h, the mixture was warmed to 10°C and a saturated aqueous $NaHCO_3$ solution (3 mL), a saturated aqueous $Na_2S_2O_3$ solution (3 mL) and CH_2Cl_2 (10 mL) were added. The layers were separated and the aqueous phase was twice extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. GC analysis of the crude product (39 mg) revealed three main products, of which only macrocycle **60** (4 mg, 6.9 μmol, 10%) could be isolated by flash-column chromatography (hexanes/ethyl acetate 40:1) as a colourless oil. TLC: $R_f = 0.23$ (petroleum ether/ethyl acetate 40:1); $[\alpha]_D^{23} = -16.1$ ($c = 0.4$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.55$–0.63 (m, 9H; $Si(CH_2CH_3)_3$, H-19), 0.64–0.72 (m, 6H; $Si(CH_2CH_3)_3$), 0.90–1.04 (m, 21H; $Si(CH_2CH_3)_3$ ×2, H-18), 1.11 (d, $J = 7.0$ Hz, 3H; H-20), 1.17, 1.25 (2s, 6H; H-16, H-17), 1.26–1.40, 1.60–1.80 (m, 7H; H-6, H-7, H-12, H-13), 2.49 (d, $J = 2.5$ Hz, 1H; H-1), 2.79 (d, $J = 2.5$ Hz, 1H; H-2), 2.91–3.01 (m, 1H; H-3), 3.58 (dd, $J = 10.7$, 4.5 Hz, 1H; H-14), 4.06 (br s, 1H; H-10), 5.04 (br s, 1H; H-8), 5.20 (t, $J =$ 11.1 Hz, 1H; H-4), 5.33 ppm (dt, $J = 11.1$, 3.3 Hz, 1H; H-5); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 5.0$, 5.1 (t; $Si(CH_2CH_3)_3$), 6.8, 6.9 (q; Si-$(CH_2CH_3)_3$), 15.2 (q; C-18), 18.7 (q; C-19), 19.9 (q; C-20), 26.8, 27.1 (q; C-16, C-17), 29.7, 30.6, 30.9, 32.5, 36.1, 41.1, 58.3 (d; C-1), 59.6 (d; C-2), 77.2 (d; C-8), 78.3 (d; C-10), 85.7 (d; C-14), 86.6 (s; C-11), 129.8 (d; C-5), 130.7 ppm (d; C-4). C-3, 6, 7, 12, 13 and 15 could not be assigned precisely, C-9 was not detected; IR (ATR): $\tilde{\nu} = 2958$ (s), 2912 (w), 2877 (s), 1724 (m), 1458 (m), 1415 (w), 1384 (m), 1325 (w), 1297 (w), 1239 (m), 1124 (s), 1101 (s), 1054 (w), 1005 (m), 975 (w), 921 (m), 896 (m), 872 (w), 846 (m), 808 (m), 795 (m), 744 (s), 687 cm^{-1} (w); HRMS-ESI: *m*/*z*: calcd for $C_{32}H_{60}O_5Si_2Na$: 603.3877 $[M+Na]^+$; found: 603.3865.



60

Macrocyclic 8-keto-9,10-diol (55b): Experimental details for the synthesis of the target olefin **55a** are described in our previous communication.[1] When the workup was conducted according to the procedure described above for triethylsilylated macrocycles **53**, with the exception that basic

instead of neutral Al_2O_3 was employed, partial tautomerisation towards **55b** was observed.

Compound 55b: TLC: $R_f = 0.13$ (petroleum ether/ethyl acetate 10:1); $[\alpha]_D^{23} = +48.2$ ($c = 1.0$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.88$, 1.05 (2 s, 6H; H-16, H-17), 1.03 (d, $J = 6.7$ Hz, 3H; H-20), 1.09 (s, 3H; H-18), 1.17 (d, $J = 7.0$ Hz, 3H; H-19), 1.74–1.95 (m, 4H; H-6, H-12 ×2, H-13), 1.97–2.09 (m, 2H; H-6, H-13), 2.47–2.57 (m, 1H; H-7), 2.67–2.80 (m, 2H; H-3, 8-OH), 3.54 (brs, 1H; 10-OH), 3.81 (dd, $J = 8.0$, 3.0 Hz, 1H; H-14), 4.35 (brs, 1H; H-8), 4.57 (brs, 1H; H-10), 5.16–5.24 (m, 1H; H-5), 5.27 (dd, $J = 15.4$ Hz, 7.9 Hz, 1H; H-2), 5.33 (d, $J = 15.4$ Hz, 1H; H-1), 5.40 ppm (dd, $J = 15.5$, 8.8 Hz, 1H; H-4); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.4$ (q; C-19), 21.0 (q; C-18), 21.3 (q; C-20), 24.2, 25.7 (q; C-16, C-17), 26.7 (t; C-13), 32.3 (t; C-12), 34.6 (t; C-6), 39.6 (s; C-15), 40.3 (d; C-7), 42.0 (d; C-3), 77.9 (d; C-8), 81.8 (d; C-10), 85.4 (s; C-11), 88.2 (d; C-14), 127.8 (d; C-2), 132.7 (d; C-5), 133.8 (d; C-1), 137.2 (d; C-4), 212.4 ppm (s; C-9); IR (ATR): $\tilde{\nu} = 3477$ (br), 2961 (m), 2930 (w), 2871 (m), 1707 (m), 1454 (m), 1374 (m), 1327 (m), 1239 (m), 1156 (w), 1121 (m), 1074 (m), 1059 (s), 1024 (s), 982 (s), 910 (w), 883 (w), 829 (w), 769 (w), 726 (w), 666 cm^{-1} (w); HRMS-ESI: m/z: calcd for $C_{20}H_{32}O_4Na$: 359.2198 $[M+Na]^+$; found: 359.2202.

Macrocyclic tetrols 56a/56b: Procedure A: NMO (15 mg, 128 μmol, 2.5 equiv) and MSA (17 mg, 179 μmol, 3.5 equiv) were added to a solution of olefin **55a** (17 mg, 50.5 μmol) in *t*BuOH (2 mL) and H_2O (1 mL). Then the solution was cooled to 0 °C and a solution of OsO_4 in *t*BuOH (2.5 wt %, 40 μL, 32.4 mg, 3.2 μmol, 6.3 mol %) was added dropwise. The solution was slowly warmed to RT and after 3.5 h, terminated by addition of $Na_2S_2O_3 \cdot 5H_2O$ (46 mg, 185 μmol, 3.7 equiv). After 10 min, the aqueous layer was separated and extracted twice with CH_2Cl_2. The combined organic solutions were dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash-column chromatography (hexanes/EtOAc 1:1) afforded the inseparable mixture (1.3:1) of tetraols **56a** and **56b** (16 mg, 43.2 μmol, 86 %) as a colourless oil. TLC: $R_f = 0.16$ (petroleum ether/ethyl acetate 1:1); $[\alpha]_D^{20} = +38.8$ ($c = 1.0$ in $CHCl_3$); IR (ATR): $\tilde{\nu} =$ 3335 (s, br), 2964 (m), 2929 (m), 2871 (m), 1716 (m), 1455 (m), 1386 (m), 1326 (s), 1154 (s), 1098 (w), 1052 (m), 1025 (s), 991 (s), 914 (w), 878 (w), 827 (w), 764 (w), 667 cm^{-1} (w); HRMS-ESI: m/z: calcd for $C_{20}H_{34}O_6Na$: 393.2253 $[M+Na]^+$; found: 393.2258.

Compound 56a: ^1H NMR (500 MHz, $[D_4]$MeOH): $\delta = 0.91$, 1.17 (2s, 6H; H-16, H-17), 1.04 (d, $J = 7.0$ Hz, 3H; H-20), 1.03–1.10 (m, 1H; H-6), 1.07 (d, $J = 7.0$ Hz, 3H; H-19), 1.29 (s, 3H; H-18), 1.57 (ddd, $J = 12.5$, 8.7, 6.7 Hz, 1H; H-12), 1.80–1.93 (m, 2H, H-6; H-13), 1.96–2.08 (m, 1H; H-13), 2.13–2.30 (m, 3H; H-3, H-7, H-12), 3.15 (dd, $J = 7.6$, 2.4 Hz, 1H; H-4), 3.37 (ddd, $J = 10.9$, 7.6, 1.7 Hz, 1H; H-5), 3.75 (dd, $J = 8.7$, 6.8 Hz, 1H; H-14), 4.46 (brs, 2H; H-8, H-10), 5.47 (dd, $J = 15.9$, 8.6 Hz, 1H; H-2), 5.53 ppm (d, $J = 15.9$ Hz, 1H; H-1); ^{13}C NMR (125 MHz, $[D_4]$MeOH): $\delta = 18.4$ (q; C-19), 19.5 (q; C-20), 25.6 (q; C-18), 27.2–27.6 (q, q, t; C-16, C-17, C-13), 33.2 (t; C-12), 34.1 (t; C-6), 36.3 (d; C-7), 39.5 (s; C-15), 41.9 (d; C-3), 73.3 (d; C-5), 76.2 (d; C-8), 78.7 (d; C-10), 79.5 (d; C-4), 85.4 (s; C-11), 88.3 (d; C-14), 130.6 (d; C-2), 136.9 (d; C-1), 212.1 ppm (s; C-9).

Compound 56b: ^1H NMR (500 MHz, $[D_4]$MeOH): $\delta = 0.90$, 1.12 (2s, 6H; H-16, H-17), 1.04 (d, $J = 6.6$ Hz, 3H; H-20), 1.08 (d, $J = 6.9$ Hz, 3H; H-19), 1.22 (s, 3H; H-18), 1.45–1.68 (m, 2H; H-6, H-12), 1.83–1.95 (m, 1H; H-13), 1.92–2.06 (m, 1H; H-13), 2.08–2.19 (m, 3H; H-6, H-7, H-12), 2.28–2.37 (m, 1H; H-3), 3.26 (dd, $J = 10.2$, 1.4 Hz, 1H; H-4), 3.57 (pst, $J = 7.0$ Hz, 1H; H-5), 3.71 (dd, $J = 8.4$, 6.1 Hz, 1H; H-14), 4.28 (brs, 1H; H-10), 4.55 (d, $J = 2.2$ Hz, 1H; H-8), 5.23 (dd, $J = 15.8$, 9.6 Hz, 1H; H-2), 5.56–5.50 ppm (m, 1H; H-1); ^{13}C NMR (125 MHz, $[D_4]$MeOH): $\delta = 18.1$ (q; C-19), 19.2 (q; C-20), 24.8 (q; C-18), 26.0, 27.2–27.6 (q, q, t; C-16, C-17, C-13), 33.9 (t; C-12), 34.1 (t; C-6), 35.9 (d; C-7), 39.5 (s; C-15), 41.7 (d; C-3), 72.0 (d; C-5), 75.8 (d; C-4), 77.1 (d; C-10), 78.7 (d; C-8), 85.1 (s; C-11), 88.1 (d; C-14), 133.6 (d; C-2), 136.9 (d; C-1), 210.4 ppm (s; C-9).

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[1] C. Jasper, R. Wittenberg, M. Quitschalle, J. Jakupovic, A. Kirschning, *Org. Lett.* **2005**, *7*, 479–482.
[2] a) X. A. Dominguez, H. V. Sanchez, E. G. Gomez Lopez, G. Dräger, E. Kunst, A. Kirschning, F. Tsichritzis, F. Jeske, J. Jakupovic, unpublished results; b) F. Jeske, PhD Thesis, TU Berlin (Germany), **1997**.
[3] J. Jakupovic, F. Sasse, unpublished results.
[4] We are indebted to Dr. Florenz Sasse, Gesellschaft für Biotechnologische Forschung, Braunschweig (Germany), for performing biological tests with tonantzitlolone and derivatives.
[5] P. R. Blakemore, *J. Chem. Soc. Perkin Trans. 1* **2002**, 2563–2585 and references therein.
[6] a) D. A. Evans, M. D. Ennis, D. J. Mathre, *J. Am. Chem. Soc.* **1982**, *104*, 1737–1739; b) D. A. Evans, S. L. Bender, J. Morris, *J. Am. Chem. Soc.* **1988**, *110*, 2506–2526. Because of its volatility, aldehyde **6** was used in excess to ensure complete conversion of the enolate moiety.
[7] Throughout the text and the graphics the numbering of carbon atoms in substructures correspond to the numbering used for tonantzilolone.
[8] Elucidation of the absolute configuration was not possible before ring-closing metathesis reaction and formation of a macrocycle of type **3** had been conducted (see also reference [1]).
[9] S.-i. Kiyooka, H. Kuroda, Y. Shimasaki, *Tetrahedron Lett.* **1986**, *27*, 3009–3012. Elucidation of the 8,10-*syn* relationship in **15** was achieved by NMR spectroscopic analysis of the acetonide **16** (see references [1, 15 and 16] and discussion of the following section).
[10] Schinzer and co-workers disclosed a related aldol reaction as part of the total syntheses of epothilones A and B with identical preference for the *anti*-Felkin–Anh selectivity: a) D. Schinzer, A. Bauer, O. M. Böhm, A. Limberg, M. Cordes, *Chem. Eur. J.* **1999**, *5*, 2483–2491; b) D. Schinzer, A. Bauer, J. Schieber, *Chem. Eur. J.* **1999**, *5*, 2483–2491.
[11] In our first synthetic endeavour, we tested other enolisation protocols (LDA, Bu_2BOTf/Et_3N, Cy_2BCl/Et_3N, $TiCl_4/(iPr_2)EtN$ and Me_2AlCl/Et_3N), which all proved to be insufficient: R. Wittenberg, H. Monenschein, G. Dräger, C. Beier, G. Jas, C. Jasper, A. Kirschning, *Tetrahedron Lett.* **2004**, *45*, 4457–4460.
[12] a) A. Mengel, O. Reiser, *Chem. Rev.* **1999**, *99*, 1191–1223.
[13] a) W. R. Roush, *J. Org. Chem.* **1991**, *56*, 4151–4157; b) C. Gennari, S. Vieth, A. Comotti, A. Vulpetti, J. M. Goodmann, I. Paterson, *Tetrahedron* **1992**, *48*, 4439–4458.
[14] Addition of 18-crown-6 to a potassium enolate led to reduced diastereoselectivity (10:1). Crown ethers have cavities with different space which are able to size-select cations. To some extent chelate **22** resembles a cavity of a crown ether.
[15] D. A. Evans, D. L. Rieger, J. R. Gage, *Tetrahedron Lett.* **1990**, *31*, 7099–7100.
[16] S. D. Rychnovsky, B. Rogers, G. Yang, *J. Org. Chem.* **1993**, *58*, 3511–3515.
[17] In their original communication Kiyooka et al. reported on the non-selectivity of the 1,3-*syn* reduction with DIBAL-H in CH_2Cl_2 while the use of THF assures a high level of selectivity (see reference [9]). When we first applied this protocol, CH_2Cl_2 proved to be the best choice. However, reduction of hydroxyketones **23**–**25** most likely did not display the same solvent dependence.
[18] Note: The 7,8-*syn*-8,9-*syn* aldol product **23** is reduced *syn* selectively by DIBAL-H. This means that **28** cannot have a 7,8-*syn*-8,9-*syn*-9,10-*anti* configuration.
[19] All aldol products described in this report tended to undergo retro-aldol reaction.

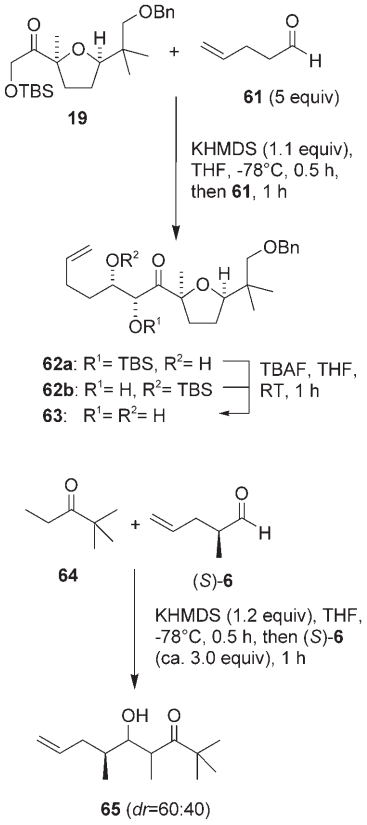
[20] a) H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483–2547; b) Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, K. B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.

[21] In related contexts the di-*tert*-butylsiloxy group has been utilised before: a) K.-M. Chen, G. E. Hardtmann, K. Prasad, O. Repic, M. J. Shapiro, *Tetrahedron Lett.* **1987**, *28*, 155–158; b) I. Paterson, J. G. Cumming, R. A. Ward, S. Lamboley, *Tetrahedron* **1995**, *51*, 9393–9412; c) D. A. Evans, S. W. Kaldor, T. K. Jones, J. Clardy, T. J. Stout, *J. Am. Chem. Soc.* **1990**, *112*, 7001–7031.

[22] I. Paterson, M. V. Perkins, *Tetrahedron* **1996**, *52*, 1811–1834.

[23] R. W. Hoffmann, *Angew. Chem.* **2000**, *112*, 2134–2150; *Angew. Chem. Int. Ed.* **2000**, *39*, 2054–2070.

[24] The dominant stereochemical role of the enolate compared to the aldehyde is also ideally supported by two related model reactions in which we used 1) simplified achiral aldehyde **61** and 2) simplified ketone **64**. Silyl migration after aldol reaction led to isomeric ketones **62a** and **62b** which both gave dihyroxy ketone **63** upon desilylation. Basically no other diastereoisomer was detected in the crude reaction mixtures while the second aldol reaction between **64** and (*S*)-**6** yielded the two diastereomeric products **65** in a 3:2 ratio, as was judged from the ^{1}H NMR spectra (refer also to reference [13a]).



[25] Reviews on alkene metathesis including ring-closing metathesis (RCM): a) M. Schuster, S. Blechert, *Angew. Chem.* **1997**, *109*, 2124–2145; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2036–2056; b) A. Fürstner, *Top. Catal.* **1997**, *4*, 285–299; c) S. K. Armstrong, *J. Chem. Soc. Perkin Trans. 1* **1998**, 371–388; d) R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413–4450; e) A. Fürstner, *Angew. Chem.* **2000**, *112*, 3140–3172; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012–3043; f) T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18–29; g) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4564–4601; *Angew. Chem. Int. Ed.* **2005**, *44*, 4490–4527.

[26] Syntheses of macrocycles **48** and **50** were also used to further support elucidation of the relative stereochemistry of **25** and **26**.

[27] Hoveyda-type catalysts turned out not to be suited for this RCM.

[28] Dienes **16** and **27** are enantiomeric in the furan part and at C-3. Because focus is directed to the stereotetrade between C-7 and C-10 relative changes between **16** and **27** are highlighted for this part relative to the furan moiety.

[29] The NMR spectroscopic data for **55b** clearly show an *E* configuration at C-4/C-5 ($J(4,5) > 15$ Hz).

[30] A short overview can be found in J. Prunet, *Angew. Chem.* **2003**, *115*, 2932–2936; *Angew. Chem. Int. Ed.* **2003**, *42*, 2826–2830.

[31] a) K. Nakashima, R. Ito, M. Sono, M. Tori, *Heterocycles* **2000**, *53*, 301–314; b) A. Fürstner, K. Radkowski, *Chem. Commun.* **2001**, 671–672; c) A. Fürstner, T. Dierkes, O. R. Thiel, G. Blanda, *Chem. Eur. J.* **2001**, *7*, 5286–5298; d) A. Fürstner, K. Radkowski, C. Wirtz, R. Goddard, C. Lehmann, R. Mynott, *J. Am. Chem. Soc.* **2002**, *124*, 7061–7069; e) E. A. Couladouros, A. P. Mihou, E. A. Bouzas, *Org. Lett.* **2004**, *6*, 977–980.

[32] Switches in stereoselectivity for the RCM macrocyclisation exerted by a remote substituent were described for the syntheses of epothilone and salicylhalamides A and B: a) D. Meng, D.-S. Su, A. Balog, P. Bertinato, A. J. Sorensen, S. J. Danishefsky, Y.-H. Zheng, T.-C. Chou, L. He, S. B. Horwitz, *J. Am. Chem. Soc.* **1997**, *119*, 2733–2734; b) A. Fürstner, O. R. Thiel, G. Blanda, *Org. Lett.* **2000**, *2*, 3731–3734. However, for both natural product projects a reliable prediction of the stereochemical outcome of the RCM could not be given.

[33] Besides the increased flexibility of the western fragment in **16** compared to **54**, also the presence of functional groups with coordinative properties for metal complexes (such as the Grubbs II catalyst) in dihydroxy ketone **55** can be made responsible for the observed selectivity.

[34] a) H. E. Zimmerman, J. D. Robbins, R. D. McKelvey, C. J. Samuel, L. R. Sousa, *J. Am. Chem. Soc.* **1974**, *96*, 4630–4643; b) W. Oppolzer, J.-P. Barras, *Helv. Chim. Acta* **1987**, *70*, 1666–1675.

[35] It needs to be noted that the stereochemical outcome of the asymmetric dihydroxylation is reversed to the prediction given by the Sharpless mnemonic. Asymmetric induction with the commercially available dihydroxylation kit (AD-mix) did not result in any conversion. Dihydroxylation product **56a** was only present in the open form, while diastereoisomer **56b** was also present in the lactol form.[36]

[36] The high chemoselectivity of the dihydroxylation manifests itself both in the complete differentiation of the two olefinic double bonds and by the reisolation of pure *Z*-configured 4,5-alkene after the oxidation.

[37] Not surprisingly, lactol formation only occurs with the desired dihydroxylation product **56b**, and not with **56a**, which does not display the required stereochemical topolgy. Interestingly, this lactol formation of **56b** is only complete when **56a** is removed, although no intermolecular phenomenona/interactions of the mixture could be determined.

[38] Optical rotations for *ent*-tonantzitlolone (*ent*-**1**) was determined to be $[\alpha]_D^{20} = -119$ ($c = 0.06$ in $CHCl_3$) (tonantzitlolone **1**: $[\alpha]_D^{20} = +134$ ($c = 0.25$ in $CHCl_3$)). Apart from these facts all spectroscopic data (NMR, IR, MS) were in full accordance with those of the authentic material.

[39] Lithium enolates tend to form dimers which may also prevent formation of transition states that involve coordination by the furan oxygen atom.

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