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Transannular Diels-Alder Studies on the Asymmetric Synthesis of (+)-Maritimol

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Abstract

Assembly of 13-membered TCC macrocyclic trienes are described and their transannular Diels-Alder reaction are investigated as a model study for the asymmetric synthesis of the ABC-ring system of (+)-maritimol. Albeit the original expectations that the *pro*-3(*S*)- and 4(*R*)-functionalities induce perfect absolute and relative control in the strategic step has not been fully met, a position at *pro*-12(*R*) complying with these requirements is recognized.

Keywords: asymmetric synthesis, Diels-Alder reactions, macrocycles, transannular reactions.

1. Introduction

One of the most powerful tools that emerged recently in polycyclic chemistry is the Transannular Diels-Alder (TADA) strategy.[1] Fundamental synthetic and computational studies show that high relative stereocontrol of the forming TADA tricyclic product can be predicted and achieved by controlling the double bonds geometry.[2] Moreover, the conformation of the TADA transition state can be successfully influenced by appropriately placed chiral substituents on the macrocycle leading to absolute stereocontrol. It follows that the perfect accord of these two parameters in the TADA substrate can introduce a new level of stereocontrol by inducing four new chiral centers in the strategic step. Since in the past decade, the degree and diversity of control in double bond formation and acyclic chiral induction improved dramatically, the tools for

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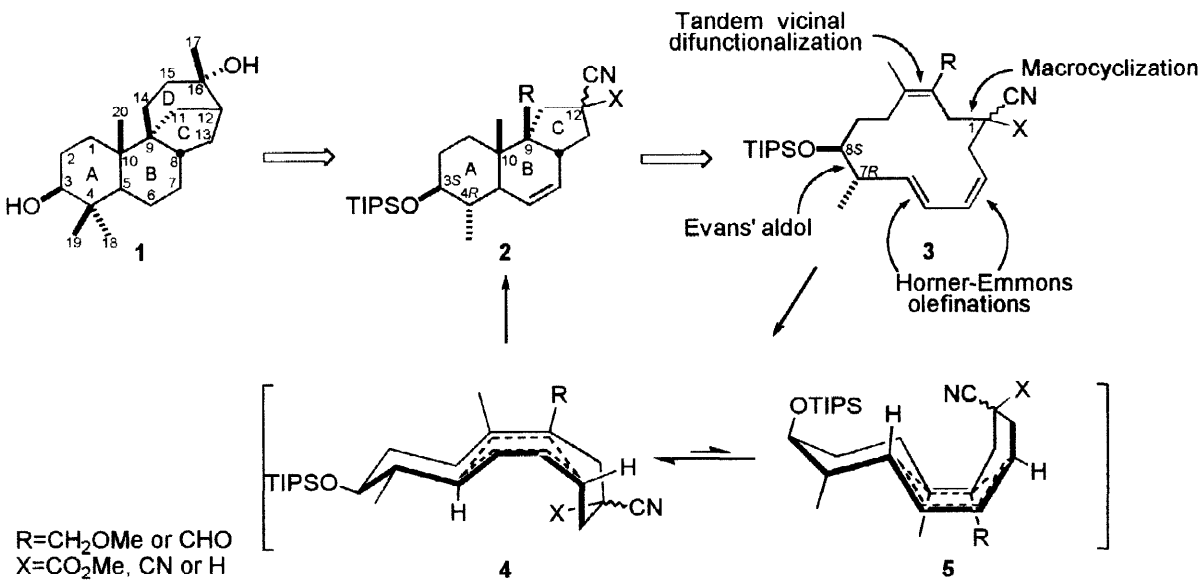
the investigation of this strategy have become widely available. Thus, the stage is set to test the scope and limitations as well as the practical implementations of TADA strategy. To this end, certain natural products, among them (+)-maritimol (**1**)[3] isolated from *Stemodia maritima* L. (Scrophulariaceae) used as a Caribbean folk medicine for treatment of venereal diseases was selected as a target. Diterpene **1** represents a real synthetic challenge[4] with its unique tetracyclic stemodane framework (a *trans*-decalin (ring A/B) fused to a bicyclo[3.2.1]octane (ring C/D) system), which requires the construction of seven chiral centers, especially the two adjacent quaternary carbons at C-9 and C-10 (**Scheme 1**). On the other hand, from a synthetic point of view, its tricyclic A.B.C[6.6.5] *trans,syn,cis* (TSC) ring system correlates well with our previous fundamental model studies demonstrating the stereospecific transformation of 14- and 15-membered *trans,cis,cis* (TCC) macrocyclic trienes into the corresponding A.B.C.[6.6.6][5] and [6.6.7][6] TSC-tricycles. Accordingly, the requisite TSC-tricycle **2** is potentially available by an extension of these model studies to the 13-membered TCC macrocyclic triene **3**. Furthermore, using an appropriately functionalized tetrasubstituted dienophile, the C-9 functionality obtained, together with the C-12 functionality, a remainder of the former macrocyclization connector, could serve later as a foothold for the construction of ring D as it had been demonstrated in an earlier successful synthesis.[7] Moreover, examination of the transition states of TADA shows that of the four hypothetical possibilities, only the two *endo*-states should be considered as the alternative two *exo*-states are conformationally restricted.[1] A quasi 1,3-diequatorial alignment of the *pro*-3(*S*)-oxygen- and the *pro*-4(*R*)-methyl functionalities in the *endo* transition state **4** is expected to be favored over a *quasi* triaxial alignment of these and the additional *pro*-10-methyl groups in the competing transition state **5**, thus, inducing the desired absolute stereocontrol leading to key



Scheme 1

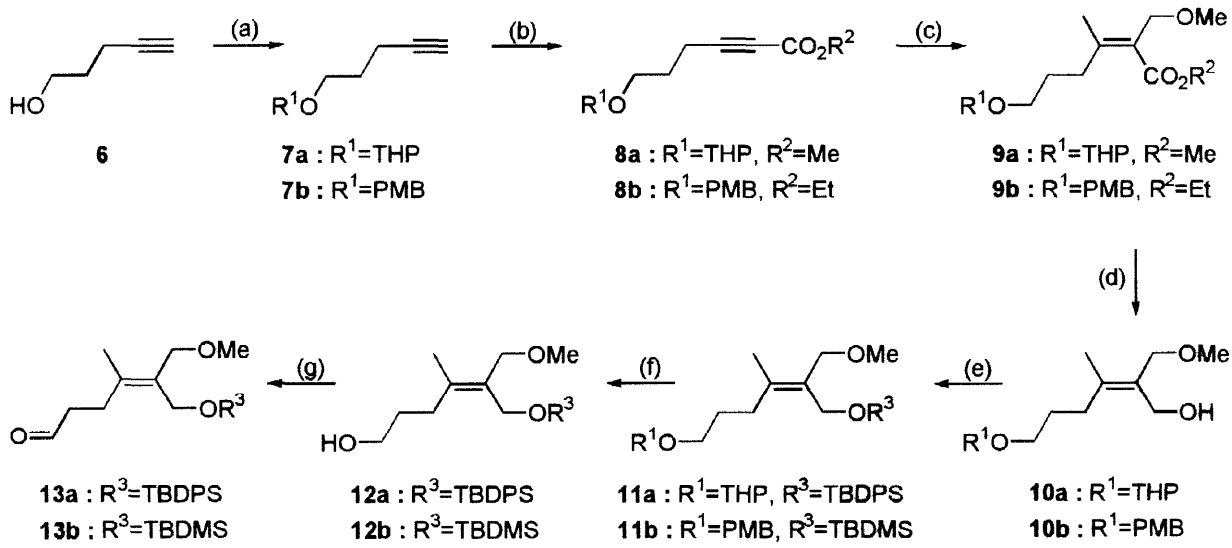
intermediate **2**. In addition, the *anti* arrangement of these substituents can be routinely acquired via an enantioselective Evans' aldol methodology and this strategy promises an easy access to the final 4-*gem*-dimethyl system of ring A in maritimol (**1**). To realize all the above requirements, a linear synthesis was designed to assemble the key macrocycle **3**. An acetylenic ester tandem vicinal difunctionalization mastered in our laboratory[8] was used to deliver the appropriately functionalized tetrasubstituted dienophile. This was followed by an Evans' aldol reaction[9] to introduce the necessary chirality. Two Horner-Emmons olefinations[10,11] furnished the correct diene system and the sequence was concluded by the macrocyclization via a cyanoester or a malononitrile connector[12] followed by some functional group modifications.

In this paper, we report the synthesis of the key macrocycles, our results on their TADA reaction testing the presuppositions outlined above and the conclusions of these model studies.

2. Results and Discussion

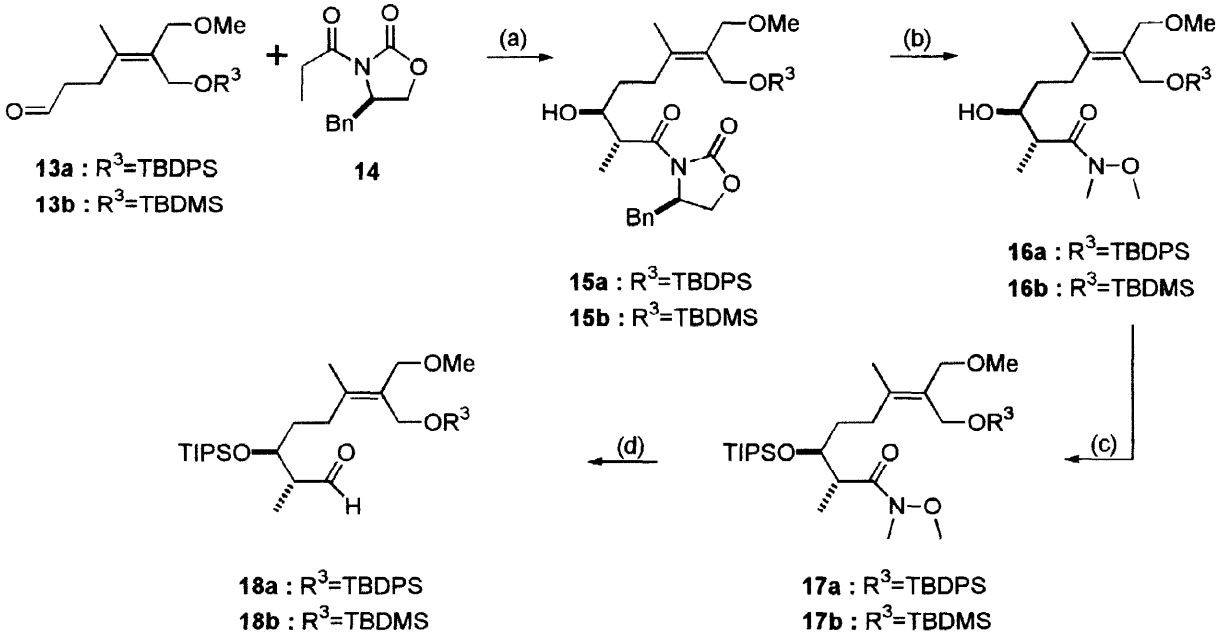
2.1. Synthesis of TCC Macrocyclic Trienes:

Preparation of the tetrasubstituted dienophile and introduction of the chirality presented a synthetic challenge by itself due to an inevitably intensive protective group manipulation. Two sequences, Route A and Route B were carried out (**Scheme 2** and **3**).



Scheme 2: Route A: (**a**) DHP, CSA (90%). (**b**) *n*-BuLi then $ClCO_2Me$ (86%). (**c**) Me_2CuLi then MOMI. (**d**) DIBAL-H (83% over 2 steps). (**e**) TBDPSCl, imidazole. (**f**) PPTS (89% over 2 steps). (**g**) $(COCl)_2$, DMSO then Et_3N (93%). **Route B:** (**a**) NaH, PMBCl, $(n\text{-}Bu)_4NI$ (95%). (**b**) *n*-BuLi then $ClCO_2Et$ (83%). (**c**) Me_2CuLi then MOMI (87%). (**d**) DIBAL-H (90%). (**e**) TBDMSCl, imidazole. (**f**) DDQ (73% over 2 steps). (**g**) $(COCl)_2$, DMSO then Et_3N (93%).

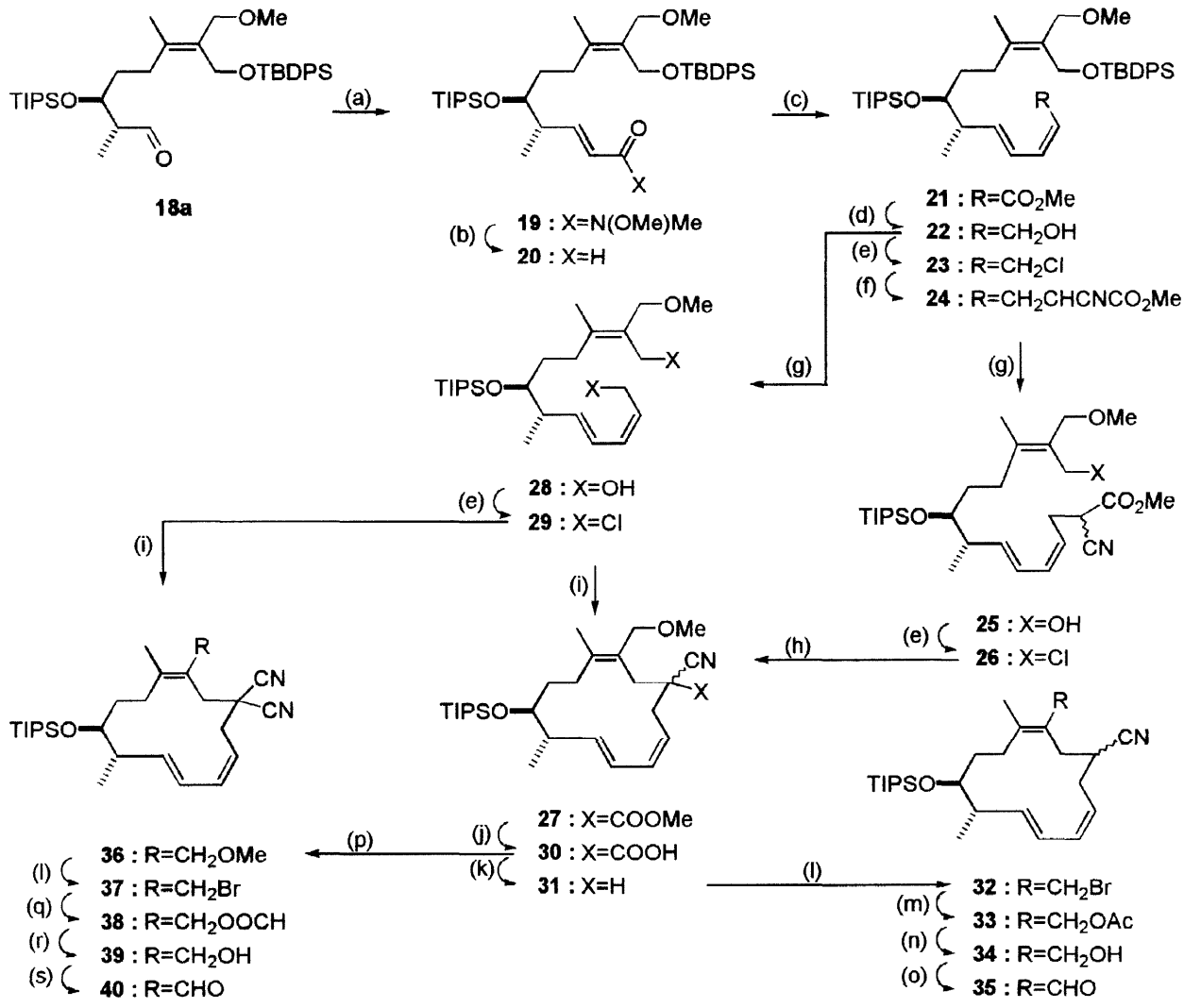
In Route A, a tetrahydropyranyl (THP) protection of pentynol (**6**) under standard conditions with dihydropyran (DHP) and camphorsulfonic acid (CSA), then quenching the lithium acetylide of **7a** with methyl chloroformate furnished acetylene ester **8a**. It was subjected to organocupration and the intermediate vinyl cuprate was quenched with iodomethyl methylether (MOMI) to give the tetrasubstituted olefin **9a** with a Z/E ratio of 20:1.[6] This mixture was separated after reduction to isolate allyl alcohol **10a** in 83% yield over 2 steps. Sequential protection as *tert*-butyldiphenylsilyl (TBDPS) ether **11a**, deprotection of the THP ether with pyridinium *para*-toluenesulfonate (PPTS) to primary alcohol **12a** and its Swern oxidation[13] provided aldehyde **13a** as a substrate for the Evans' aldol reaction[9] with chiral imide **14**.[14] The aldol product **15a** was transamidated using Weinreb's technique[15], then secondary alcohol **16a** was protected as triisopropylsilyl (TIPS) ether **17a**, diisobutylaluminum hydride (DIBAL-H) reduction of which gave aldehyde **18a** in a yield of 33% over the 11-step sequence.



Scheme 3: Route A: (a) *n*-Bu_2BOTf, Et_3N (74%). (b) $HN(OCH_3)CH_3 \cdot HCl$, $AlMe_3$ (94%). (c) 2,6-lutidine, TIPSOTf (89%). (d) DIBAL-H (99%). **Route B:** (a) *n*-Bu_2BOTf, Et_3N (82%, 99% corr.). (b) $HN(OCH_3)CH_3 \cdot HCl$, $AlMe_3$ (94%). (c) 2,6-lutidine, TIPSOTf (94%). (d) DIBAL-H (96%).

Route B paralleled route A starting with *p*-methoxybenzyl (PMB) ether **7b**. The same sequence was used to get tetrasubstituted allyl alcohol **10b** with a Z/E ratio of 9:1 and an isolated yield of 87% in the tandem difunctionalization of acetylene ester **8b**. Here, deprotection of PMB with dichlorodicyanobenzoquinone (DDQ) offered the opportunity to protect allyl alcohol **10b** with the less acid resistant *tert*-butyldimethylsilyl (TBDMS) ether in **11b** to conclude the sequence from primary alcohol **12b** to aldehyde **18b** as in Route A with a yield of 35% over the 11 steps. For further progression, aldehyde **18a** was selected because of the excellent stereocontrol

achieved in the tandem difunctionalization.† The *Z,E*-diene system was completed in three steps with two Horner-Emmons olefinations (**Scheme 4**). Thus, an olefination with N-methoxy-N-methyl-carbamoylmethylphosphonate[10] delivered the *trans* double bond in amide **19** with 86:14 selectivity and 86% isolated yield. Then, following a DIBAL-H reduction to aldehyde **20**, a second olefination with Still's phosphonate[11] gave the *cis* double bond in ester **21** with 30:1 selectivity and 89% isolated yield. Preparation for the macrocyclization was made as follows: DIBAL-H ester reduction of **21** to alcohol **22** and a subsequent chlorination with triphenylphosphine/hexachloroacetone (PPh_3/HCA) system[16] to allylic chloride **23** gave the electrophile



Scheme 4: (a) NaH, $(EtO)_2POCH_2CON(Me)OMe$. (b) DIBAL-H (99%). (c) $KN(TMS)_2$, $(CF_3CH_2O)_2POCH_2CO_2Me$, 18-Crown-6. (d) DIBAL-H (98%). (e) PPh_3, HCA. (f) NaOMe, $CNCH_2CO_2Me$ (82% over 2 steps). (g) PTSA, MeOH (h) Syringe pump addition to Cs_2CO_3 in MeCN (81%). (i) Syringe pump addition of admixtured **29** and connector to Cs_2CO_3 in MeCN. (j) NaOH in THF (97%). (k) Cu_2O (cat.) reflux in MeCN, Argon (85%). (l) Me_2BBr. (m) NaOAc in DMF. (n) K_2CO_3 in MeOH (79% over 3 steps). (o) TPAP, NMO (87%). (p) ClCOOEt, Et_3N then NH_3 then Cl_3CCOCl, Et_3N. (q) HCO_2Na in DMF. (r) HCl in THF (65% over 3 steps). (s) Dess-Martin periodinane (85%).

† However, **18b** is also to be used in a synthesis of (+)-aphidicolin, details of which are going to be published in due course.

for the alkylation of connector methyl cyanoacetate. Here, a large excess of connector was necessary to suppress bis-alkylation. However, even with 30-fold excess, still 3% of bis-alkylated product was observed. Selective deprotection of TBDPS in cyanoester **24** to alcohol **25** with *para*-toluenesulfonic acid (PTSA) in methanol (86%) and chlorination as above (95%) gave precursor **26** for macrocyclization. This step was accomplished under high dilution conditions (c_{final}=2 mM) with a 10 hour syringe pump addition of chloride **26** to a suspension of 5 eq. Cs_2CO_3 in acetonitrile at 70°C to give macrocycle **27** as an 1:1 epimeric mixture in 81% yield.

The observation that the second alkylation competes successfully with the first one at the connector coupling stage, led us to develop a novel double alkylation macrocyclization methodology, as alcohol **22** afforded ready access to diol **28** then dichloride **29** as described above. Accordingly, slow addition of a mixture of dichloride **29** and methyl cyanoacetate to a suspension of Cs_2CO_3 in acetonitrile at 70°C gave the same macrocycle **27** in 53% yield.[12]The final modifications on **27** consisted in a decarboxylation[17] via acid **30** to the 1:1 epimeric mixture of cyanide **31** (82% yield), deprotection of the methoxy group via a three step sequence involving Me_2BBr cleavage[18] to bromide **32**, substitution to acetate **33** and basic hydrolysis to alcohol **34** (79% yield) to conclude with a tetrapropylammonium perrhuthenate/N-methyl-morpholine N-oxide (TPAP/NMO) oxidation[19] to produce aldehyde **35** (87% yield).

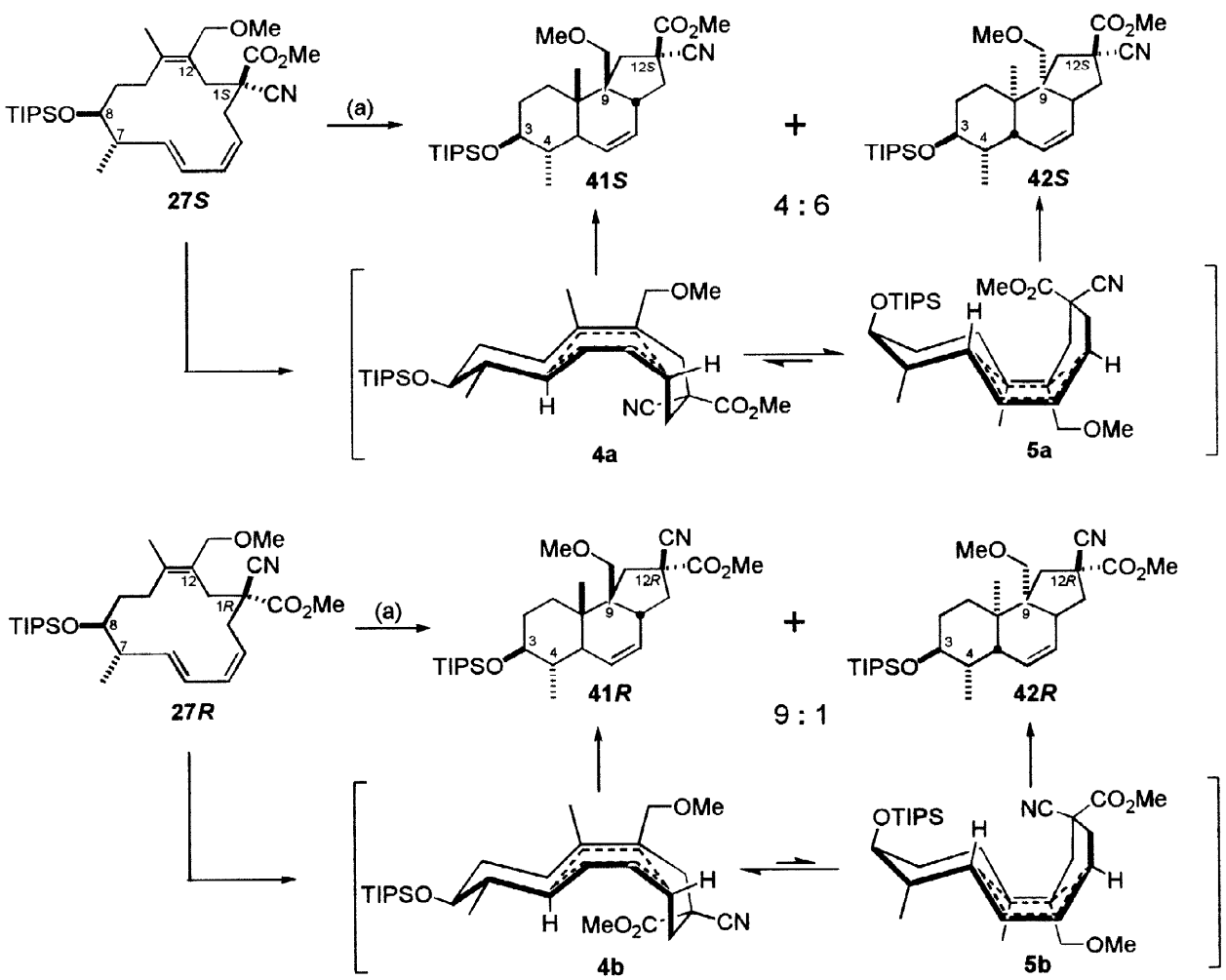
The double alkylation macrocyclization methodology described above worked even better with malononitrile to produce the enantiopure dinitrile macrocycle **36** in 73% combined yield from diol **28**.[12] Macrocycle **36** was also obtained from acid **30** via its amide[20] in 83% overall yield from **27**. Final conversion of the methoxy group to an aldehyde was performed slightly differently from the protocol described for aldehyde **35**. Here, the same Me_2BBr cleavage[18] of the methoxide afforded bromide **37**, however, it was transformed to formate **38**, acidic hydrolysis of which afforded the extremely base sensitive alcohol **39** in 65% overall yield. Final oxidation to aldehyde **40** was made using the non-basic Dess-Martin periodinane method[21] in 85% yield.

2.2. Transannular Diels-Alder Studies:

For these investigations, macrocycles **27**, **35** and **40** were selected. While the first macrocycle could undergo Diels-Alder reaction only with thermal activation, the other two having a conjugated dienophile offer an opportunity for Lewis acid catalyzed reactions to decrease the activation barrier thus the reaction temperature in order to improve selectivity.

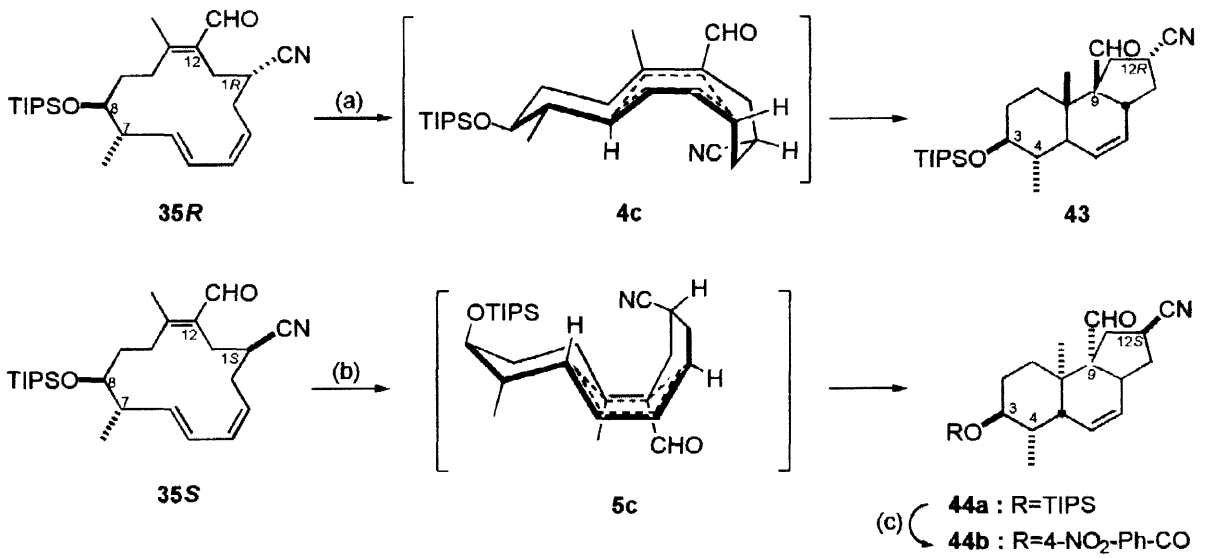
Preliminary thermal experiments conducted on epimeric macrocycles **27** at 230°C showed the formation of four tricyclic products. For correct evaluation of the reaction, the separation of the epimeric macrocycles became inevitable. Though hard, they could be separated by chromatography and, to our delight, the more polar one, termed **27*R*** after the absolute configuration at C-1, gave crystals good enough for X-ray analysis to determine its structure

unambiguously (**figure 1**). The results of the Diels-Alder experiments are summarized in **Scheme 5**. Accordingly, a pair of tricycles were formed from both epimeric substrates **27*S*** and **27*R*** with a different ratio. After separation of the products from both reactions, thorough inspection of their ^{1}H NMR spectra revealed a structural cross correlation between those pairs. A lower (7 Hz) coupling constant of the C-4 methyl and the broad high field multiplets of 3-H (~3.3 ppm) and 5-H (~1.8 ppm) in isomers **41** over the respective higher (8 Hz) coupling constant and the narrow low field multiplets (~3.8 ppm) and (3.0 ppm) in isomers **42** confirmed a 3,4-*trans*-diequatorial arrangement in the formers over a 3,4-*trans*-diaxial arrangement in the latters. The total skeletal diastereoselective excess of the expected tricycle **41** was about 30%. It is clear that, under a thermal activation, the *pro*-3 and *pro*-4 functionalities do not induce enough control in the TADA reaction through the equilibrium of transition states **4** and **5**, the decisive factor is, in fact, the bulkier CO_2Me-group at the *pro*-12 position which prefers to end up in an *anti*-position with the *pro*-9 functionality.



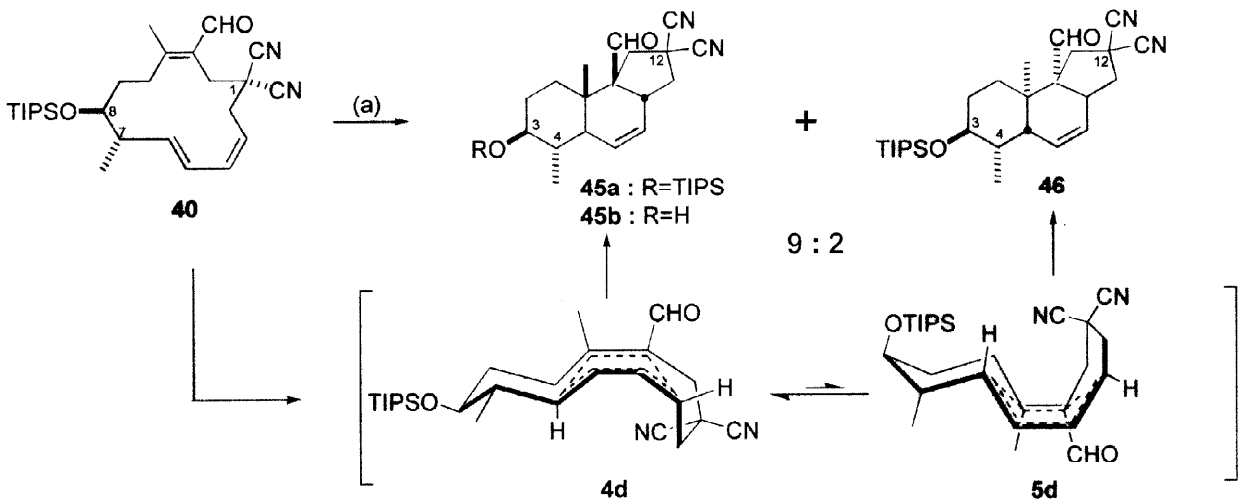
Scheme 5: (a) 230°C, 3 hours, PhMe, sealed tube.

The next model studies were conducted under Lewis acid catalyzed conditions. A 1:1 epimeric mixture of macrocyclic aldehydes **35** show a clean transformation to a 1:1 mixture of two tricycles in a Lewis-acid catalyzed TADA at 0°C. However, according to their ^{1}H NMR spectra, these compounds, instead of being epimers, are structural isomers showing the characteristics of isomers **41** and **42**. It was verified by repeating the experiment with separated epimers **35*R*** and **35*S*** to obtain clean tricycles **43** and **44a**, respectively (**Scheme 6**). Moreover, by changing the silyloxy group in **44a** to 4-nitrobenzoate, the crystalline **44b** was obtained, X-ray analysis of which confirmed its structure unambiguously (**figure 2**). Though the difference in the activation temperature of epimers **35*R*** and **35*S*** reflects the conformational expectations outlined in the introduction, now it is perfectly clear that the original *pro*-3(*S*)- and 4(*R*)-functionalities intended to induce selectivity in the TADA reaction not only cannot enforce enough control but their influence is totally overruled by the *pro*-12 functionality. On the other hand, a position for excellent control has just been located there.



Scheme 6: (a) 5eq. Me_2AlCl, CH_2Cl_2, -40°C, 2 hours. (b) same as (a) at 0°C. (c) Bu_4NF then 4-NO_2-PhCOCl, pyr.

The undisturbed influence of the *pro*-3(*S*)- and 4(*R*)-functionalities upon selectivity control can be weighed by the reaction of 1,1-dicyano-macrocycle **40** symmetrized at the *pro*-12 position. Though with long reaction period, the best ratio of **45** and **46** (9:2 or 63% d.e.) was achieved at 0°C. After a week, the conversion was 98%, however, selective deprotection of the equatorial silyloxy group also occurred to isolate **45b** and **46** (**Scheme 7**). Monitoring the reaction did not reveal any change in the ratio of Σ**45/46**, i.e., the diastereoselective excess remained constant to demonstrate an equal controlling effect of both the protected and the unprotected 8(*S*)-alcohol.



Scheme 7: (**a**) 5eq. $SnCl_4$, CH_2Cl_2, 0°C, 7 days.

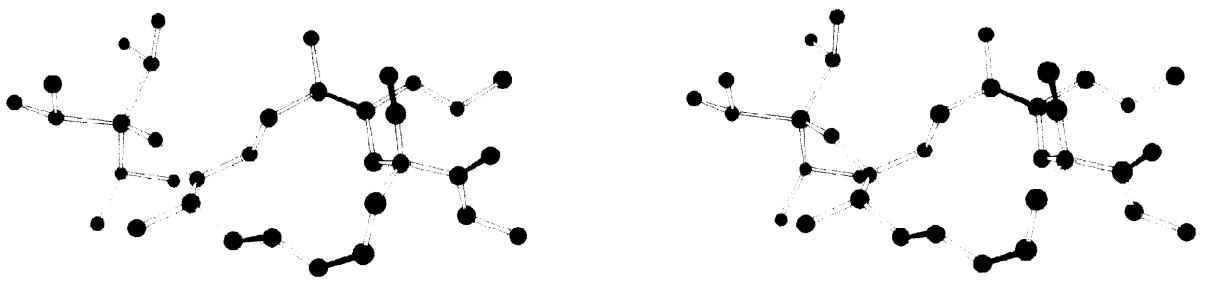


Figure 1: X-ray structure of macrocycle **27*R*** in stereoview.

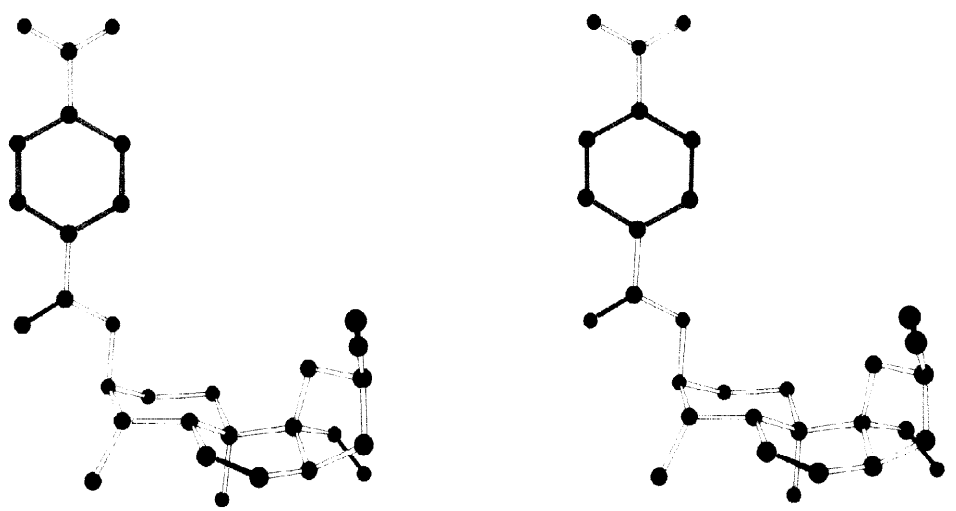


Figure 2: X-ray structure of tricycle **44b** in stereoview.

3. Conclusion

With macrocycles **27**, the bulkier COOMe group at *pro*-12 ends up preferably *anti* to the C-9 substituent in the TADA products. This result is somewhat surprising as the bulkier COOMe prefers to be "inside" the boat-like conformation (**5a** and **4b** being preferred over **4a** and **5b**,

respectively) at the transition state level. This tendency is even more pronounced when the COOMe group is replaced by a hydrogen, since the nitrile group is found exclusively *anti* to the formyl group in the TADA products of macrocycles **35**. With macrocycle **40**, there is not an overwhelming preference for the diequatorial transition state **4d**. This could be explained if the "*chair-boat*" transition state **5d** for ring AB can be replaced by a "*boat-boat*" transition state with two quasi equatorial substituents at *pro*-C-3 and C-4. Indeed, there may be no large energy difference between a chair-like or a boat-like ring A conformation at the transition state level. A possible explanation of these results would be that there is a steric or electrostatic repulsion between *syn* aligned *pro*-C-9 and C-12 substituents at the transition state level. However, attempts to obtain theoretical support for this assumption by molecular modeling at the transition state level have not been successful.

From the view of the asymmetric total synthesis of (+)-maritimol, it appears clear now that only one chiral center at the *pro*-C-12 position on the macrocycle is sufficient to obtain complete stereochemical control. We are presently working in this direction while trying, at the same time, to conceive a more convergent synthetic route.

4. Experimental

Reactions were performed under nitrogen or argon atmosphere with flame-dried glassware. All solvents were dried and distilled shortly before use: tetrahydrofuran (THF), ether (Et_2O) from sodium/benzophenone ketyl; benzene, acetonitrile, dichloromethane, dimethylsulfoxide (DMSO) and toluene from calcium hydride; methanol from magnesium/iodine. Most amines were dried over calcium hydride and distilled, hexachloroacetone was also distilled. Cesium carbonate was flame-dried under reduced pressure before use. All other starting materials and reagents were obtained commercially and used as such or purified by standard means. All solvents and reagents purified or dried were stored under nitrogen. Thin-layer chromatography were carried out on precoated glass plates with silica gel 60F-250 (Merck). Materials were detected by visualization under an ultraviolet lamp and by dipping into a solution of phosphoceric acid (10% in ethanol) followed by heating on a hot plate. For flash chromatography, Merck Kieselgel silica gel 60 (230-400 Mesh) was used. Aqueous work-ups were carried out with either ether, hexane, ethyl acetate (EtOAc) washed with reasonable quantity of brine or, with dichloromethane washed with water. All organic solutions were dried over $MgSO_4$ and evaporated under reduced pressure.

The optical rotation ($[\alpha]_D$) values were obtained with a Perkin-Elmer 141 polarimeter. The infrared (IR) spectra were recorded on a ν-scale in cm^{-1}, on a Perkin-Elmer 1600 FT-IR spectrometer. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Bruker AC-300 instrument. For ^1H NMR, the following abbreviations were used: br broad; s singlet; d

doublet; t triplet; q quartet; qn quintet and m multiplet. Chemical shifts are reported in ppm δ units, relative to $CHCl_3$ (7.26 ppm) or benzene (7.15 ppm) as internal standards. Proton decoupled ^{13}C NMR spectra used $CDCl_3$ (77.00 ppm) or benzene-d_6 (126.00 ppm) as internal standards. When necessary, decoupling experiments and 2D techniques were applied. Mass spectra (MS) were obtained on a VG Micromass ZAB-2F instrument. Crystallographic analyses were performed on an Enraf-Nonius CAD-4 diffractometer (Mo Kα radiation; λ=0.70930 Å).

5-(Tetrahydropyranyl)oxy-1-pentyne (7a): To a solution of 4-pentynol (**6**) (35.3 g, 0.42 mol) and camphorsulfonic acid (9.96 g, 4.20 mmol) in CH_2Cl_2 (1.0 L), 3,4-dihydro-*2H*-pyrane (51.0 mL, 542 mmol) was added dropwise at 0°C. The mixture was stirred overnight. A Na_2CO_3 solution (250 mL, sat.) was added and the resulting mixture was stirred for an additional 15 min. After an aqueous work-up with CH_2Cl_2, the crude product was purified by chromatography (5% EtOAc in hexane) to afford acetal **7a** (63.5 g, 90%) as a colorless oil. IR (film): 3298, 2944, 2871, 2118, 1441. ^1H NMR ($CDCl_3$): 4.50 (1H, t, J=3.5 Hz, OC<u>H</u>O), 3.75 (2H, m, C<u>H</u>$_2$OTHP), 3.40 (2H, m, C<u>H</u>$_2$O), 2.21 (2H, td, J=7.0, 2.5 Hz, C<u>H</u>$_2$C≡), 1.87 (1H, t, J=2.5 Hz, ≡C<u>H</u>), 1.60 (8H, m, 4xC<u>H</u>$_2$). ^{13}C NMR ($CDCl_3$): 98.3, 83.5, 68.3, 65.3, 61.6, 30.3, 28.4, 25.2, 19.2, 15.0. MS (*m/z*): 167 $(M-H)^+$. HR-MS, calcd for $C_{10}H_{16}O_2$ $(M-H)^+$: 167.1072; found: 167.1074.

5-(*p*-Methoxybenzyl)oxy-1-pentyne (7b): To a solution of 4-pentynol (**6**) (27.92 mL, 0.3 mol) in THF (1.5 L), NaH (13.13 g, 300 mmol, 60% dispersion in oil) was added at 0°C. The mixture was allowed to warm to 22°C. After 30 min stirring, *para*-methoxybenzyl chloride (40.48 mL, 299 mmol) and Bu_4NI (4.42 g, 11.9 mmol) were added. The milky white emulsion was refluxed for 2h, then upon cooling, a saturated NH_4Cl solution (500 mL) was added. The phases were separated. After an aqueous work-up with ether, a slush of the crude product and wet silica (200 mL) in 20% EtOAc in hexane (500 mL) was vigorously stirred for 30 min at 22°C to destroy the excess of the reagent then $MgSO_4$ was added. The mixture was filtered through a silica plug and eluted with EtOAc. The filtrate was evaporated and purified by chromatography (20% EtOAc in hexane) to afford ether **7b** (57.6 g, 95%) as a pale yellow oil. IR (film): 3294, 2936, 2858, 1612, 1512. ^1H NMR ($CDCl_3$): 7.28-7.25 and 6.89-6.87 (2x2H, m, *p*-CH_3O<u>Ph</u>), 4.44 (2H, s, ArC<u>H</u>$_2$O), 3.81 (3H, s, ArOC<u>H</u>$_3$), 3.55 (2H, t, J=6.5 Hz, OC<u>H</u>$_2$), 2.31 (2H, td, J=6.5, 3.0 Hz, C<u>H</u>$_2$C), 1.94 (1H, t, J=3.0 Hz, C<u>H</u>), 1.82 (2H, qn, J=6.5 Hz, C<u>H</u>$_2$CH$_2$O). NMR ($CDCl_3$): 159.2, 130.6, 129.3, 113.8, 84.0, 72.6, 68.4, 55.3, 28.7, 15.3. MS (*m/z*): 204 $(M)^+$. HR-MS, calcd for $C_{13}H_{16}O_2$ $(M)^+$: 204.1150; found: 204.1154.

Methyl 6-(tetrahydropyranyl)oxy-2-hexynoate (8a): To a solution of acetal **7a** (63.5 g, 378 mmol) in THF (2 L), butyllithium (1.6 M in hexane, 236 mL, 378 mmol) was added dropwise *via* canula at -78°C. The mixture was stirred at -78°C for 30 min, at -20°C for 75 min then methyl

chloroformate (90.0 mL, 1.15 mole) was added. It was stirred for 30 min at -20°C then allowed to slowly warm up to 22°C over 90 min. NH_4Cl solution (300 mL, sat.) was added and the major part of the volatiles were evaporated. After an aqueous work-up with ether, the crude product was purified by chromatography (10 to 15% EtOAc in hexane) to afford **8a** (73.5 g, 86%) as a pale yellow oil. IR (film): 2947, 2872, 2237, 1716, 1437, 1258, 1033. ^1H NMR ($CDCl_3$): 4.59 (1H, t, J=3.5 Hz, OC<u>H</u>O), 3.85 (2H, m, C<u>H</u>$_2$OTHP), 3.76 (3H, s, OC<u>H</u>$_3$), 3.55-3.40 (2H, m, C<u>H</u>$_2$O), 2.47 (2H, t, J=7.0 Hz, C<u>H</u>$_2$C), 1.87 (2H, q, J=7.0 Hz, C<u>H</u>$_2$CH$_2$OTHP), 1.80-1.45 (6H, m, 3xC<u>H</u>$_2$). ^{13}C NMR ($CDCl_3$): 153.2, 98.0, 88.3, 72.4, 64.7, 61.3, 51.7, 30.0, 27.3, 24.9, 18.8, 14.9. MS (*m/z*): 225 $(M-H)^+$. HR-MS calcd for $C_{12}H_{18}O_4$ $(M-H)^+$: 225.1127; found: 225.1106.

Ethyl 6-(*p*-methoxybenzyl)oxy-2-hexynoate (8b): The previous procedure was followed with ether **7b** (1.21 g, 5.92 mmol), THF (42 mL), butyllithium (4.80 mL, 6.51 mmol, 1.36 M in hexane) and ethyl chloroformate (1.70 mL, 17.8 mmol). Chromatography (15 to 20% EtOAc in hexane) afforded **8b** (1.37 g, 83%) as a pale yellow oil. IR (film): 3397 (br), 2938, 2862, 2234, 1708, 1256. ^1H NMR ($CDCl_3$): 7.25 and 6.87 (2x2H, m, *p*-CH_3O<u>Ph</u>), 4.43 (2H, s, ArC<u>H</u>$_2$O), 4.21 (2H, q, J=7.0 Hz, OC<u>H</u>$_2$CH$_3$), 3.80 (3H, s, ArOC<u>H</u>$_3$), 3.53 (2H, t, J=6.5 Hz, OC<u>H</u>$_2$), 2.45 (2H, t, J=6.5 Hz, C<u>H</u>$_2$C≡), 1.85 (2H, qn, J=6.5 Hz, C<u>H</u>$_2$), 1.30 (3H, t, J=7.0 Hz, CH$_2$C<u>H</u>$_3$). ^{13}C NMR ($CDCl_3$): 158.9, 153.3, 130.0, 128.9, 113.5, 88.3, 72.3, 67.6, 61.4, 54.8, 27.5, 15.2, 13.7. MS (*m/z*): 276 $(M)^+$. HR-MS, calcd. for $C_{16}H_{20}O_4$ $(M)^+$: 276.1361; found: 276.1354.

(*Z*)- and (*E*)-Methyl 2-methoxymethyl-3-methyl-6-(tetrahydropyranyl)oxy-2-hexenoate (9a): To a suspension of CuI (13.2 g, 69.3 mmol, 99,99%) in THF (600 mL), MeLi (98.0 mL, 137 mmol, 1.4 M in ether) was added dropwise *via* canula at 0°C. The mixture was stirred at 0°C for 15 min. After the dissolution of the yellow precipitate formed, a precooled solution of acetylenic ester **8a** (5.5 g, 68.5 mmol) in THF (170 mL) was added *via* canula at -78°C. The mixture was stirred for 100 min at -78°C and MOMI (13.8 mL, 158 mmol) was added dropwise. The temperature was kept at -78°C for an additional 30 min, then the cooling bath was replaced by an ice bath. After another 60 min stirring at 0°C, NH_4Cl solution (500 mL, sat.), ether (500 mL) and NH_4OH (5mL, cc.) were added. Following an aqueous work-up with ether, crude **9a** (19.5 g) was used in the next step without any characterization and further purification.

(*E*)-2-Methoxymethyl-3-methyl-6-(tetrahydropyranyl)oxy-2-hexenol (10a): To a solution of crude ester **9a** (19.5 g, 68.1 mmol) in an 1:1 mixture of hexane/CH_2Cl_2, DIBAL-H (204 mL, 204 mmol, 1 M in hexane) was added dropwise *via* canula over 25 min at -78°C. The mixture was stirred at -78°C for 1 h, then MeOH (70 ml) was slowly added. It was warmed up to 22°C with further 30 min stirring. Ether (1.4 L) was added then the resulting slush was poured into an Erlenmeyer flask containing brine (70 mL). After stirring for 15 min, $MgSO_4$ (120 g) was added.

After stirring for 10 min, it was filtered under vacuum, washed with EtOAc and evaporated. The ^{1}H NMR spectra of the crude material indicated an *E/Z* olefin ratio of 20:1. Chromatography (25 to 50% EtOAc in hexane) afforded **10a** (14.6 g, 83% for 2 steps) as a pale yellow oil. IR (CH_2Cl_2): 3603, 3464, 2945, 1660, 1454. ^{1}H NMR ($CDCl_3$): 4.54 (1H, m, OC<u>H</u>O), 4.25 and 4.15 (2H, 2d, J=12 Hz, C<u>H</u>$_2$OH), 4.08 (2H, s, C<u>H</u>$_2$OCH$_3$), 3.85 and 3.70 (2H, 2m, C<u>H</u>$_2$OTHP), 3.45 (2H, m, C<u>H</u>$_2$OCHO), 3.35 (3H, s, OC<u>H</u>$_3$), 2.62 (1H, s, O<u>H</u>), 2.30 (2H, m, C<u>H</u>$_2$C(CH$_3$)=), 1.75 (4H, m, 2xC<u>H</u>$_2$), 1.76 (3H, s, C(CH$_3$)=), 1.60-1.45 (4H, m, 2xC<u>H</u>$_2$). ^{13}C NMR ($CDCl_3$): 137.4, 130.4, 98.9, 71.3, 66.2, 62.6, 60.7, 58.0, 30.6, 30.3, 27.8, 25.2, 19.7, 17.9. MS (*m/z*): 259 $(M+H)^+$, 276 $(M+NH_4)^+$. HR-MS, calcd for $C_{14}H_{26}O_4$ $(M+H)^+$: 259.1909; found: 259.1904.

(*Z*)- and (*E*)-ethyl 3-methyl-6-(*p*-methoxybenzyl)oxy-2-methoxymethyl-2-hexenoate (9b): The procedure to prepare **9a** was applied with CuI (2.419 g, 12.65 mmol, 99.99%), THF (120 mL), MeLi (17.98 mL, 25.17 mmol, 1.4 M in ether), ester **8b** (3.478 g, 12.69 mmol) in THF (15 mL + 2x7 mL rinse) and MOMI (2.44 mL, 28.7 mmol). ^{1}H NMR spectra of the crude product indicated a *Z/E* olefin ratio of 9:1. An analytical sample **9b** was purified by chromatography (7 to 20% EtOAc in hexane) affording a pale yellow oil for characterization. IR (film): 3401.5 (br), 2978, 1711.0 (br), 1247.0, 1094.5. ^{1}H NMR ($CDCl_3$): 7.22-7.23 and 6.88-6.85 (2x2H, 2m, *p*-CH$_3$O<u>Ph</u>), 4.42 (2H, s, ArC<u>H</u>$_2$O), 4.20 (2H, q, J=7.0 Hz, OC<u>H</u>$_2$CH$_3$), 4.15 (2H, s, C<u>H</u>$_2$OCH$_3$), 3.80 (3H, s, ArOC<u>H</u>$_3$), 3.46 (2H, t, J=6.5 Hz, PMBOC<u>H</u>$_2$), 3.31 (3H, s, CH$_2$OC<u>H</u>$_3$), 2.41 (2H, t, J=8.0 Hz, C<u>H</u>$_2$C(CH$_3$)=), 2.04 (3H, s, C(C<u>H</u>$_3$)=, (*E*)-isomer), 1.89 (3H, s, C(C<u>H</u>$_3$)=, (*Z*)-isomer), 1.86-1.73 (2H, m, C<u>H</u>$_2$), 1.27 (3H, t, J=7.0 Hz, CH$_2$C<u>H</u>$_3$). ^{13}C NMR ($CDCl_3$): 168.5, 159.1, 151.3, 130.6, 129.1, 126.0, 113.6, 72.6, 69.8, 69.1, 60.2, 57.9, 55.2, 33.3, 28.4, 19.8, 14.2. MS (*m/z*): 304 $(M)^+$. HR-MS, calcd. for $C_{19}H_{28}O_5$ $(M)^+$: 304.167; found: 304.1671.

(*E*)-3-Methyl-6-(*p*-methoxybenzyl)oxy-2-methoxymethyl-2-hexenol (10b): The procedure to prepare **10a** was applied to reduce a crude mixture of **9b** (29.87 g, 88.8 mmol) in a mixture of hexane (400 mL) and CH_2Cl_2 (800 mL) with DIBAL-H (270 mL, 266 mmol, 1.0 M in CH_2Cl_2). Chromatography (20 to 60% EtOAc in hexane) afforded **10b** (23.62 g, 90%) as a pale yellow oil. IR (film): 3442 (br), 2931, 2865, 1512, 1247. ^{1}H NMR ($CDCl_3$): 7.25 and 6.87 (2x2H, 2m, *p*-CH$_3$O<u>Ph</u>), 4.42 (2H, s, ArC<u>H</u>$_2$O), 4.20 (2H, s(br), C<u>H</u>$_2$OH), 4.07 (2H, s, C<u>H</u>$_2$-OCH$_3$), 3.80 (3H, s, ArOC<u>H</u>$_3$), 3.42 (2H, t, J=6.0 Hz, C<u>H</u>$_2$OPMB), 3.34 (3H, s, CH$_2$OC<u>H</u>$_3$), 2.52 (1H, s, O<u>H</u>), 2.26 (2H, t, J=7.5 Hz, C<u>H</u>$_2$C(CH$_3$)=), 1.75 (3H, s, C(C<u>H</u>$_3$)=), 1.70 (2H, m, C<u>H</u>$_2$-CH$_2$O). ^{13}C NMR ($CDCl_3$): 159.1, 137.7, 130.2, 130.1, 129.2, 113.6, 72.3, 71.7, 68.8, 61.0, 58.1, 55.1, 30.4, 27.9, 18.0. MS (*m/z*): 294 $(M)^+$. HR-MS, calcd for $C_{17}H_{26}O_4$ $(M)^+$: 294.1831; found: 294.1827.

(*Z*)-1-(*tert*-Butyldiphenylsilyl)oxy-2-methoxymethyl-3-methyl-6-(tetrahydropyranyl)oxy-2-hexene (11a): A solution of *tert*-butylchlorodiphenylsilane (14.4 g, 52.4 mmol) in CH_2Cl_2 (40

mL) was cannulated into a solution of allyl alcohol **10a** (8.46 g, 32.8 mmol), imidazole (3.79 g, 55.7 mmol) and dimethylaminopyridine (200 mg, 1.64 mmol) in CH_2Cl_2 (130 mL) over 25 min at 22°C. After stirring for 1 h, $NaHCO_3$ (75 mL, sat.) was added. After stirring this mixture for 15 min, then an aqueous work-up with CH_2Cl_2, the crude product was passed through a silica plug and eluted with 50% EtOAc in hexane. The filtrate was evaporated to afford alcohol **11a** as a pale yellow oil to be used in the next step without characterization and any further purification.

(*Z*)-6-(*tert*-Butyldiphenylsilyl)oxy-5-methoxymethyl-4-methyl-4-hexenol (12a): Pyridinium *p*-toluene-sulfonate (PPTS) (840 mg, 3.28 mmol) was added to a 2-propanol (180 mL) solution of the previous alcohol **11a** at 65°C. After 6h stirring, it was cooled to 22 °C for quenching with $NaHCO_3$ (1 g). The solution was then allowed to stir for another 15 min. The volatiles were evaporated, then EtOAc/hexane (150 ml, 3:7) was added. The salts were filtered off and washed with the same solution. The filtrate was evaporated to near dryness and then chromatographied (20 to 40% EtOAc in hexane) to afford alcohol **12a** (12.0 g, 89% for 2 steps) as a pale yellow oil. IR (film): 3423, 3069, 2932, 1660, 1467, 1106. ^{1}H NMR ($CDCl_3$): 7.70 and 7.40 (4H+6H, 2m, ArH), 4.25 (2H, s, CH_2OSi), 3.97 (2H, s, CH_2OCH_3), 3.50 (2H, t, J=6.0 Hz, CH_2OH), 3.22 (3H, s, OCH_3), 2.09 (2H, t, J=7.5 Hz, $CH_2C(CH_3)$=), 1.77 (3H, s, $C(CH_3)$=), 1.68 (1H, s, OH), 1.60-1.50 (2H, m, CH_2CH_2OH), 1.06 (9H, s, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$): 138.6, 135.5, 133.5, 129.5, 129.4, 127.4, 69.3, 61.7, 61.0, 57.6, 30.8, 30.1, 26.7, 19.1, 18.1. MS (*m/z*): 413 $(M+H)^+$, 430 $(M+NH_4)^+$. HR-MS, calcd for $C_{25}H_{36}O_3Si$ $(M+H)^+$: 413.2512; found: 413.2508.

(*Z*)-1-(*tert*-Butyldimethylsilyl)oxy-2-methoxymethyl-3-methyl-6-(*p*-methoxybenzyl)oxy-2-hexene (11b): The procedure to prepare **11a** was applied for the protection of alcohol **10b** (5.67 g, 19.3 mmol) in THF (400 mL) with imidazole (6.56 g, 96.3 mmol) and *tert*-butylchlorodimethylsilane (11.61 g, 77.0 mmol). A 10 mg sample was purified by chromatography (40% EtOAc in hexane) for characterization to afford **11b** as a pale yellow oil. IR (film): 3452 (br), 2931, 2867, 1250. ^{1}H NMR ($CDCl_3$): 7.25 and 6.87 (2x2H, 2d, J=8.5 Hz, *p*-CH_3OPh), 4.42 (2H, s, $ArCH_2O$), 4.21 (2H, s, CH_2OSi), 4.00 (2H, s, CH_2OCH_3), 3.79 (3H, s, $ArOCH_3$), 3.42 (2H, t, J=6.5 Hz, $PMBOCH_2$), 3.29 (3H, s, CH_2OCH_3), 2.22 (2H, t, J=7.5 Hz, $CH_2C(CH_3)$=), 1.78 (3H, s, $C(CH_3)$=), 1.71 (2H, qn, J=6.5 Hz, CH_2), 0.90 (9H, s, $C(CH_3)_3$), 0.07 (6H, s, $Si(CH_3)_2$). ^{13}C NMR ($CDCl_3$): 159.0, 138.0, 130.6, 130.0, 129.0, 113.6, 72.3, 69.5, 69.1, 60.0, 57.6, 55.1, 30.8, 28.5, 25.9, 25.6, 18.4, -5.42. MS (*m/z*): 376 $(M-CH_2OH)^+$, 351 $(M-C_4H_9)^+$. HR-MS, calcd. for $C_{23}H_{40}O_4Si$ $(M-C_4H_9)^+$: 351.1991; found: 351.1997.

(*Z*)-6-(*tert*-Butyldimethylsilyl)oxy-5-methoxymethyl-4-methyl-2-hexenol (12b): A solution of crude alcohol **11b** in CH_2Cl_2 (190 mL) and water (10 mL) was added with DDQ (4.81 g, 21.2 mmol). It was stirred for 4h, then a saturated $NaHCO_3$ solution (20 mL) was added. The phases

were separated, the organic one was dried, evaporated and the crude product was directly purified by column chromatography (20 to 50% EtOAc in hexane) to afford **12b** (4.08 g, 73% for two steps) as a pale yellow oil. IR (film): 3440.2 (br), 2928.1, 1255.1, 1062.3 (br), 836.4. ^{1}H NMR ($CDCl_3$): 4.21 (2H, s, $C\underline{H}_2OSi$), 3.97 (2H, s, $C\underline{H}_2OCH_3$), 3.54 (2H, t, J=6.5 Hz, $C\underline{H}_2OH$), 3.29 (3H, s, $OC\underline{H}_3$), 2.31 (2H, t, J=6.5 Hz, $C\underline{H}_2C(CH_3)$=), 1.76 (3H, s, $C(C\underline{H}_3)$=), 1.68 (2H, qn, J=6.5 Hz, $C\underline{H}_2$), 0.90 (9H, s, $C(C\underline{H}_3)_3$), 0.09 (6H, s, $Si(C\underline{H}_3)_2$). ^{13}C NMR ($CDCl_3$): 138.9, 129.9, 69.6, 60.8, 60.1, 57.6, 30.2, 30.0, 25.9, 18.3 17.9, -5.5. MS (*m/z*): 243 $(M\text{-}CH_2OCH_3)^+$, 241 $(M\text{-}C_4H_9)^+$. HR-MS, calcd. for $C_{15}H_{22}O_3Si$ ($M\text{-}CH_2OCH_3$): 243.1780; found: 243.1775.

(*Z*)-6-(*tert*-Butyldiphenylsilyl)oxy-5-methoxymethyl-4-methyl-4-hexenal (13a): A solution of DMSO (4.80 mL, 68.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a CH_2Cl_2 (120 mL) solution of oxalyl chloride (2.85 mL, 32.6 mmol) at -78°C. It was stirred at -78°C for 1h, then a solution of alcohol **12a** (11.7 g, 28.4 mmol) in CH_2Cl_2 (25 mL) was added dropwise *via* canula. The resulting mixture was stirred for an hour at -78°C, then triethylamine (19.4 mL, 139 mmol) was added. Stirring was continued for 15 min at -78°C and 45 min at 22 °C. Water (40 ml) was added and the phases were separated. Following an aqueous work-up with CH_2Cl_2, the crude product was passed through silica (150 mL) and eluted with 30% EtOAc in hexane (750 mL) to afford aldehyde **13a** (11.5 g, 99%) as a pale yellow oil after evaporation. IR ($CHCl_3$): 3072, 3009, 2931, 2859, 1723, 1428. ^{1}H NMR ($CDCl_3$): 9.63 (1H, s, $C\underline{H}O$), 7.68 and 7.40 (4H+6H, 2m, Ar$\underline{H}$), 4.23 (2H, s, $C\underline{H}_2OSi$), 4.02 (2H, s, $C\underline{H}_2OCH_3$), 3.27 (3H, s, $OC\underline{H}_3$), 2.45-2.20 (4H, m, $2xCH_2$), 1.76 (3H, s, $C(C\underline{H}_3)$=), 1.05 (9H, s, $C(C\underline{H}_3)_3$). ^{13}C NMR ($CDCl_3$): 201.6, 136.6, 135.6, 133.6, 130.9, 129.6, 127.6, 69.5, 61.1, 57.9, 42.6, 26.8, 26.6, 19.2, 18.2. MS (*m/z*): 353 $(M\text{-}C_4H_9)^+$. HR-MS, calcd for $C_{25}H_{34}O_3Si$ $(M\text{-}C_4H_9)^+$: 353.1573; found: 353.1568.

(*Z*)-6-(*tert*-Butyldimethylsilyl)oxy-5-methoxymethyl-4-methyl-4-hexenal (13b): The former Swern oxidation was applied to oxidize alcohol **12b** (8.92 g, 30.9 mmol) in CH_2Cl_2 (30 mL+ 2x10 ml rinse) with DMSO (5.27 mL, 74.2 mmol) activated with oxalyl chloride (3.26 mL, 34.0 mmol) in CH_2Cl_2 (150 mL) and quenched with triethylamine (21.6 mL, 155 mmol). Chromatography (20 to 40% EtOAc in hexane) afforded **13b** (8.24 g, 93%) as a pale yellow oil. IR (film): 2955, 2820, 1727, 1255, 1062, 837. ^{1}H NMR ($CDCl_3$): 9.72 (1H, s, $C\underline{H}O$), 4.13 (2H, s, $C\underline{H}_2OSi$), 3.92 (2H, s, $C\underline{H}_2OCH_3$), 3.23 (3H, s, $OC\underline{H}_3$), 2.51-2.39 (4H, m, $C\underline{H}_2C\underline{H}_2CHO$), 1.72 (3H, s, $C(C\underline{H}_3)$=), 0.84 (9H, s, $C(C\underline{H}_3)_3$), 0.01 (6H, s, $Si(C\underline{H}_3)_2$). ^{13}C NMR ($CDCl_3$): 201.5, 136.4, 130.9, 69.3, 60.1, 57.7, 42.7, 26.5, 25.8, 18.2, -5.6. MS (*m/z*): 255 $(M\text{-}OCH)^+$, 241 $(M\text{-}CH_2OCH_3)^+$. HR-MS, calcd. for $C_{15}H_{30}O_3Si$ $(M\text{-}OCH_3)^+$: 255.1780; found: 255.1775.

(*Z*)-[3(2*R*,3*S*),4R]-3-[8-(*tert*-Butyldiphenylsilyl)oxy-3-hydroxy-7-methoxymethyl-2,6-dimethyl-6-octenoyl]-4-benzyl-2-oxazolidinone (15a): To a solution of **14** (4.40 g, 18.9 mmol) in

CH_2Cl_2 (70 mL), dibutylboron triflate (5.45 mL, 21.7 mmol) was added dropwise over 10 min at 0°C. Et_3N (3.42 mL, 24.5 mmol) was added over 12 min then the resulting mixture was cooled to -78°C. A -78°C precooled solution of aldehyde **13a** (8.13 g, 19.8 mmol) in CH_2Cl_2 (15 mL) was added dropwise *via* canula. After stirring for 2h, phosphate buffer (20 mL, pH:7) and methanol (65 mL) were added at -78°C. The temperature was allowed to warm to 0°C over 20 min then a 2:1 mixture (60 mL) of methanol and 30% H_2O_2 was added dropwise. After 30 min stirring at 0°C, the volatiles were evaporated. Following an aqueous work-up with ether, the crude product was chromatographied (25 to 50% EtOAc in hexane) to afford **15a** (9.44 g, 74%) as a thick colorless oil. $[\alpha]^{27}_D$: -34.0° (c: 1.00, $CHCl_3$). IR ($CHCl_3$): 3541, 3013, 2932, 2361, 1781, 1688, 1428, 1384, 1225. ^{1}H NMR ($CDCl_3$): 7.75-7.15 (15H, m, ArH), 4.70-4.60 (1H, m, (Bn)CH), 4.28 (2H, AB m, CH_2OSi), 4.16 (2H, d, J=5.0 Hz, (Bn)CHCH_2O), 4.01 and 3.93 (2H, 2d, J=10.5 Hz, CH_2OCH_3), 3.85-3.75 (1H, m, CHOH), 3.67 (1H, m, CH(CH_3)), 3.23 (1H, dd, J=15.0, 3.5 Hz, HCHPh), 3.21 (3H, s, OCH_3), 3.01 (1H, d, J=3.5 Hz, OH), 2.78 (1H, dd, J=15.0, 9.5 Hz, HCHPh), 2.30-2.05 (2H, m, -$CH_2C(CH_3)$=), 1.78 (3H, s, C(CH_3)=), 1.60-1.35 (2H, m, CH_2CHOH), 1.21 (3H, d, J=7.0 Hz, CH(CH_3)), 1.06 (9H, s, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$): 176.9, 152.8, 138.5, 135.6, 135.0, 133.6, 129.9, 129.5, 129.3, 128.9, 127.5, 127.3, 70.7, 69.3, 66.0, 61.1, 57.8, 55.0, 42.5, 37.7, 32.3, 30.5, 26.9, 19.1, 18.3, 11.1. MS (*m/z*): 644 $(M+H)^+$, 661 $(M+NH_4)^+$. HR-MS, calcd for $C_{38}H_{49}NO_6Si$ $(M-C_4H_9)^+$: 586.2625; found: 586.2617.

(*Z*)-[3(2*R*,3*S*),4*R*]-3-[8-(*tert*-Butyldimethylsilyl)oxy-3-hydroxy-7-methoxymethyl-2,6-dimethyl-6-octenoyl]-4-benzyl-2-oxazolidinone (15b): The previous Evans' aldol protocol was applied to a solution of oxazolidinone **14** (9.69g, 41.6 mmol) in CH_2Cl_2 (100 mL), dibutylboron triflate (12.0 mL, 47.8 mmol), Et_3N (7.53 mL, 54.0 mmol) and a solution of aldehyde **13b** (12.5 g, 43.7 mmol) in CH_2Cl_2 (50 mL). The crude product was purified by chromatography (20 to 40% EtOAc in hexane) to afford **15b** (18.17 g, 84%, 99% corrected after recovery of unreacted **13b**) as a thick pale yellow oil. $[\alpha]^{25}_D$: -49.0° (c: 2, $CHCl_3$). IR (film): 3446.1 (br), 2930, 1780, 1695, 1459, 1383, 1248, 1210, 1090. ^{1}H NMR ($CDCl_3$): 7.36-7.19 (5H, m, ArH), 4.70-4.63 (1H, m, (Bn)CH), 4.29 (1H, d, J=11.0 Hz, HCHOSi), 4.23-4.15 (2H, m, (Bn)CHCH_2O), 4.19 (1H, d, J=11.0 Hz, HCHOSi), 4.03 (1H, d, J=11.0 Hz, $HCHOCH_3$), 3.95 (1H, d, J=11.0 Hz, $HCHOCH_3$), 3.84-3.77 (1H, m, CH(OH)), 3.80-3.71 (1H, m, CH(CH_3)), 3.61 (1H, m, OH), 3.30 (3H, s, OCH_3), 3.25 (1H, dd, J=13.5, 3.5 Hz, HCHPh), 2.78, (1H, dd, J=13.5, 9.5 Hz, HCHPh), 2.49 (1H, dt, J=13.5, 9.0 Hz, $HCHC(CH_3)$=), 2.18 (1H, ddd, J=13.5, 7.5, 5.5 Hz, $HCHC(CH_3)$=), 1.79 (3H, s, C(CH_3)=), 1.64-1.56 (2H, m, CH_2CHOH), 1.25 (3H, d, J=7.0 Hz, CH(CH_3)), 0.91 (9H, s, $C(CH_3)_3$), 0.10 (6H, s, $Si(CH_3)_2$). ^{13}C NMR ($CDCl_3$): 176.7, 152.9, 138.8, 135.1, 130.1, 129.4, 128.9, 127.3, 70.2, 69.6, 66.0, 60.1, 57.8, 55.1, 42.9, 37.7, 32.1, 30.4, 29.9, 18.4, 10.1, 11.7, -5.4. MS (*m/z*): 520 $(M)^+$, 488 $(M-OCH_3)^+$. HR-MS, calcd. for $C_{28}H_{45}O_6NSi$ $(M)^+$: 520.3094; found: 520.3083.

(*Z*)-(2*R*,3*S*)-8-(*tert*-Butyldiphenylsilyl)oxy-3-hydroxy-*N*-methoxy-7-methoxymethyl-*N*,2,6-trimethyl-6-octenamide (16a): Me_3Al (37.4 mL, 74.8 mmol, 2.0 M in toluene) ***(CAUTION: Pyrophoric)*** was added dropwise to a stirred CH_2Cl_2 (165 mL) suspension of *N,O*-dimethylhydroxylamine hydrochloride (7.34 g, 75.2 mmol) at 0°C. It was stirred for 2h at 22°C then cooled to -20°C. A solution of **15a** (22.7 g, 35.3 mmol) in CH_2Cl_2 (55 mL) was added dropwise *via* canula. It was allowed to warm up to 22°C and the stirring was allowed to continue for an additional 4.5 h. It was poured in a vigorously stirred tartaric acid solution (1.0 M, 215 mL) at 0°C. Stirring was maintained for 1h at 22°C, then the phases were separated. Following an aqueous work-up with CH_2Cl_2, the crude product was purified by chromatography (45% to 65% EtOAc in hexane) to afford 17.5 g alcohol **16a** (94%) as a white solid. $[\alpha]^{25}_D$ -10.1° (c 1.00, $CHCl_3$). IR ($CHCl_3$): 3455, 3067, 2935, 1636, 1466. ^1H NMR ($CDCl_3$): 7.75-7.65 and 7.45-7.35 (4H+6H, 2m, ArH), 4.31 and 4.22 (2H, 2d, J=11.5 Hz, CH_2OSi), 4.02 and 3.91 (2H, 2d, J=10.5 Hz, CH_2OCH_3), 3.85 (1H, s, OH), 3.69 (1H, m, CHOH), 3.62 (3H, s, $NOCH_3$), 3.20 (3H, s, CH_2OCH_3), 3.17 (3H, s, NCH_3), 2.85-2.70 (1H, m, $CH(CH_3)$), 2.30-2.00 (2H, m, $CH_2C(CH_3)$=), 1.78 (3H, s, $C(CH_3)$=), 1.65-1.50 and 1.45-1.30 (2H, 2m, $CH_2CH(OH)$), 1.11 (3H, d, J=7.0 Hz, $CH(CH_3)$), 1.05 (9H, s, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$): 138.9, 135.7, 133.7, 129.5, 127.6, 71.0, 69.4, 61.4, 61.1, 57.8, 39.2, 32.7, 32.0, 30.6, 26.9, 19.2, 18.3, 11.0. MS (*m/z*): 528 $(M+H)^+$, 496 $(M-OCH_3)^+$. HR-MS, calcd for $C_{30}H_{45}NO_5Si$ $(M+H)^+$: 528.3145; found: 528.3142.

(*Z*)-(2*R*,3*S*)-8-(*tert*-Butyldimethylsilyl)oxy-3-hydroxy-*N*-methoxy-7-methoxymethyl-*N*,2,6-trimethyl-6-octenamide (16b): The previous Weinreb's procedure was applied to a suspension of *N,O*-dimethylhydroxylamine hydrochloride (6.68 g, 68.4 mmol) in CH_2Cl_2 (140 mL) with Me_3Al (34.2 mL, 68.4 mmol, 2.0 M in toluene) and a solution of **15b** (16.94 g, 32.6 mmol) in CH_2Cl_2 (85 mL). Chromatography (45 to 65% EtOAc in hexane) afforded **16b** (12.31 g, 94%) as a pale yellow oil. $[\alpha]^{25}_D$: -23.9° (c: 2, CH_2Cl_2). IR (film): 3450, 2933, 1654, 1463, 1254. ^1H NMR ($CDCl_3$): 4.29 and 4.17 (2H, 2d, J=11.0 Hz, CH_2OSi), 4.02 and 3.92 (2H, 2d, J=11.0 Hz, CH_2OCH_3), 3.69-3.64 (1H, m, CH(OH)), 3.68 (3H, s, $NOCH_3$), 3.29 (3H, s, OCH_2CH_3), 3.18 (3H, s, NCH_3), 2.92-2.80 (1H, m, $CH(CH_3)$), 2.48 (1H, dt, J=13.0, 8.0 Hz, $HCHC(CH_3)$=), 2.14 (1H, dt, J=13.0, 6.5 Hz, $HCHC(CH_3)$=), 1.77 (3H, s, $C(CH_3)$=), 1.58-1.50 (2H, m, $CH_2CH(OH)$), 1.18 (3H, d, J=7.0 Hz, $CH(CH_3)$), 0.90 (9H, s, $C(CH_3)_3$), 0.09 (6H, s, $Si(CH_3)_2$). ^{13}C NMR ($CDCl_3$): 139.1, 129.9, 70.7, 69.6, 61.5, 60.1, 57.8, 40.1, 32.5, 32.0, 30.5, 26.0, 18.5, 18.1, -5.3. MS (*m/z*): 356 $(M-C_2H_7O)^+$, 346 $(M-C_4H_9)^+$. HR-MS, calcd. for $C_{20}H_{41}O_5Si$ $(M-C_2H_7O)^+$: 356.2257 and for $(M-C_4H_9)^+$: 346.2050; found: 356.2266 and 346.2042, respectively.

(*Z*)-(2*R*,3*S*)-8-(*tert*-Butyldiphenylsilyl)oxy-*N*-methoxy-7-methoxymethyl-*N*,2,6-trimethyl-3-(triisopropylsilyl)oxy-6-octenamide (17a): To a solution of alcohol **16a** (5.00 g, 9.48 mmol) in CH_2Cl_2 (250 mL), 2,6-lutidine (4.50 mL, 38.6 mmol) and triisopropylsilyl triflate (5.78 mL,

21.5 mmol) were added at 0°C. After 10 min, the cooling bath was removed and the stirring was continued for an additional 30 min. The excess of the triflate was destroyed with methanol (7.5 mL) and NH_4Cl (50 mL, sat.). After an aqueous work-up with CH_2Cl_2, the crude product was purified by chromatography (15% EtOAc in hexane) to afford amide **17a** (5.77 g, 89%) as a colorless oil. $[\alpha]^{25}_D$: +18.5° (c: 1.00, $CHCl_3$). IR (film): 3069, 2939, 2865, 1665, 1464. ^1H NMR ($CDCl_3$): 7.75-7.65 and 7.45-7.35 (4H+6H, 2m, ArH), 4.28 (2H, AB-d, CH_2OTBDPS), 4.15-4.05 (1H, m, CH(OTIPS)), 4.05 (2H, s, CH_2OCH_3), 3.42 (3H, s, $N(OCH_3)$), 3.26 (3H, s, CH_2OCH_3), 3.00 (3H, s, $N(CH_3)$), 2.85-2.75 (1H, m, $CH(CH_3)$), 2.10-1.90 (2H, m, $CH_2C(CH_3)$=), 1.75 (3H, s, $C(CH_3)$=), 1.60-1.40 (2H, m, CH_2CH(OTIPS)), 1.09 (3H, d, J=7.0 Hz, $CH(CH_3)$), 1.03 (9H, s, $C(CH_3)_3$), 1.01 (21H, s, TIPS). ^{13}C NMR ($CDCl_3$): 137.8, 135.5, 133.9, 129.5, 127.6, 73.5, 69.0, 61.1, 61.0, 57.8, 40.2, 34.7, 32.0, 29.4, 26.8, 19.3, 18.4, 18.2, 13.0, 12.8. MS (*m/z*): 640 (M-$C_3H_7)^+$. HR-MS, calcd for $C_{39}H_{65}NO_5Si_2$ (M-$C_3H_7)^+$: 640.3853; found: 640.3848.

(*Z*)-(2*R*,3*S*)-8-(*tert*-Butyldimethylsilyl)oxy-*N*-methoxy-7-methoxymethyl-*N*,2,6-trimethyl-3-(triisopropylsilyl)oxy-6-octenamide (17b): The previous procedure was applied to protect hydroxyamide **16b** (559 mg, 1.38 mmol) in CH_2Cl_2 (6 mL) with 2,6-lutidine (657 μL, 5.68 mmol) and triisopropylsilyl triflate (856 μL, 3.19 mmol). Chromatography (20% EtOAc in hexane) afforded **17b** (733 mg, 94%) as a colorless oil. $[\alpha]^{25}_D$: +17.6° (c: 1.83, CH_2Cl_2). IR (film): 2941, 2865, 1665, 1463, 1253. ^1H NMR ($CDCl_3$): 4.21-4.15 (1H, m, CH(OTIPS)), 4.19 (2H, s, CH_2OTBDMS), 3.97 (2H, s, CH_2OCH_3), 3.68 (3H, s, $N(OCH_3)$), 3.28 (3H, s, CH_2OCH_3), 3.16 (3H, s, $N(CH_3)$), 3.02-2.92 (1H, m, $CH(CH_3)$), 2.23-2.04 (2H, m, $CH_2C(CH_3)$=), 1.75 (3H, s, $C(CH_3)$=), 1.65-1.55 (2H, m, CH_2CH(OTIPS)), 1.20 (3H, d, J=7.0 Hz, $CH(CH_3)$), 1.07 (21H, s, TIPS), 0.89 (9H, s, $C(CH_3)_3$), 0.06 (6H, s, $Si(CH_3)_2$). ^{13}C NMR ($CDCl_3$): 137.9, 129.7, 73.8, 68.9, 61.3, 60.1, 57.8, 40.5, 34.9, 32.2, 29.5, 26.0, 18.5, 18.3, 18.3, 13.4, 13.2, -5.3. MS (*m/z*): 516 (M-$C_3H_7)^+$. HR-MS, calcd. for $C_{29}H_{61}O_5Si_2$ (M-$C_3H_7)^+$: 516.3540; found: 516.3535.

(*Z*)-(2*R*,3*S*)-8-(*tert*-Butyldiphenylsilyl)oxy-7-methoxymethyl-2,6-dimethyl-3-(triisopropylsilyl)oxy-6-octenal (18a): To a solution of amide **17a** (16.4 g, 24.0 mmol) in THF (250 mL), DIBAL-H (72.0 mL, 72.0 mmol, 1.0 M in CH_2Cl_2) was added dropwise over 0.5h at -78°C. It was stirred for 1h, then acetone (4 mL) was added. Stirring was continued for an additional 5 min at -78°C, then the mixture was poured in a vigorously stirred mixture of hexane (170 mL) and tartaric acid (260 mL, 1M). After 1 h of stirring and an aqueous work-up with ether, the crude product was passed through a plug of silica and eluted with a 40% EtOAc in hexane. Evaporation afforded aldehyde **18a** (14.9 g, 99%) as a colorless oil to be used in the next step without delay. $[\alpha]^{25}_D$: -8.3° (c: 1.00, $CHCl_3$). IR (film): 3069, 2940, 1729, 1661, 1464. ^1H NMR ($CDCl_3$): 9.73 (1H, s, CHO), 7.75-7.65 and 7.45-7.35 (4H+6H, 2m, ArH), 4.22 (2H, s, CH_2OTBDPS), 4.15

(1H, m, C<u>H</u>(OTIPS)), 4.04 (2H, s, C<u>H</u>$_2$OCH$_3$), 3.28 (3H, s, OC<u>H</u>$_3$), 2.24 (1H, qd, J=7.0 Hz, 3.0 Hz, C<u>H</u>(CH$_2$)CHO), 1.90-1.80 (2H, m, C<u>H</u>$_2$C(CH$_3$)=), 1.76 (3H, s, C(C<u>H</u>$_3$)=), 1.55-1.45 (2H, m, C<u>H</u>$_2$(OTIPS), 1.04 (9H, s, C(C<u>H</u>$_3$)$_3$), 0.98 (21H, s, TIPS), 0.92 (3H, d, J=7.0 Hz, CH(C<u>H</u>$_3$)CHO). ^{13}C NMR ($CDCl_3$): 205.0, 137.3, 135.6, 133.7, 130.0, 129.6, 127.6, 72.6, 69.1, 61.0, 57.9, 50.6, 33.4, 30.7, 26.8, 19.3, 18.5, 18.1, 12.7, 6.9. MS (*m/z*): 581 (M-C_3H_7)$^+$, 567 (M-C_4H_9)$^+$. HR-MS, calcd for $C_{37}H_{60}O_4Si_2$ (M-C_3H_7)$^+$: 581.3482; found: 581.3478.

(*Z*)-(2*R*,3*S*)-8-(*tert*-Butyldimethylsilyl)oxy-7-methoxymethyl-2,6-dimethyl-3-(triisopropylsilyl)oxy-6-octenal (18b): The previous procedure was applied to reduce amide **17b** (435 mg, 0.78 mmol) in THF (6.9 mL) with DIBAL-H (2.6 mL, 3.89 mmol, 1.5 M in toluene). Chromatography (20% EtOAc in hexane) afforded **18b** (374 mg, 96%) as a pale yellow oil. $[\alpha]^{25}_D$ -17.6° (c: 2, CH_2Cl_2). IR (film): 2943, 2865, 1729, 1464. ^{1}H NMR ($CDCl_3$): 9.85 (1H, s, C<u>H</u>O), 4.31 (1H, td, J=6.5, 3.0 Hz, C<u>H</u>(OTIPS)), 4.17 (2H, s, C<u>H</u>$_2$OTBDMS), 3.98 (2H, s, C<u>H</u>$_2$OCH$_3$), 3.30 (3H, s, OC<u>H</u>$_3$), 2.51 (1H, qd, J=7.0, 3.0 Hz, C<u>H</u>(CH$_3$)CHO), 2.22-2.00 (2H, m, C<u>H</u>$_2$C(CH$_3$)=), 1.78 (3H, s, C(C<u>H</u>$_3$)=), 1.72-1.55 (2H, m, C<u>H</u>$_2$CH(OTIPS)), 1.09 (3H, d, J=7.0 Hz, CH(C<u>H</u>$_3$)CHO), 1.05 (21H, s, TIPS), 0.90 (9H, s, C(C<u>H</u>$_3$)$_3$), 0.07 (6H, s, Si(C<u>H</u>$_3$)$_2$). ^{13}C NMR ($CDCl_3$): 205.2, 137.4, 130.3, 73.0, 69.1, 60.1, 57.9, 51.0, 33.4, 30.8, 26.0, 18.6, 18.2, 12.8, 7.4, -5.3. MS (*m/z*): 457 (M-C_3H_7)$^+$, 443 (M-C_4H_9)$^+$. HR-MS, calcd. for $C_{27}H_{56}O_4Si_2$ (M-C_3H_7)$^+$: 457.3169; found: 457.3160.

2(*Z*),8(*Z*)- and 2(*E*),8(*Z*)-(4*R*,5*S*)-10-(*tert*-Butyldiphenylsilyl)oxy-*N*-methoxy-9-methoxymethyl-*N*,4,8-trimethyl-5-(triisopropylsilyl)oxy- 2,8-decadienamide (19): NaH (1.20 g, 31.2 mmol, 60% dispersion in oil) was slowly added to a stirred THF (240 mL) solution of diethyl (N-methoxy-N-methylcarbamoylmethyl)phosphonate (7.47 g, 31.2 mmol) at 0°C. After 30 min stirring, a solution of aldehyde **18a** (14.9 g, 23.9 mmol) in THF (25mL) was added by canula. Upon removing the ice bath, the stirring was continued for 2.5 hours at 22 °C, then the reaction was quenched with NH_4Cl (100 mL, sat.). Following an aqueous work-up with ether, the crude product was purified by chromatography (20 to 30% EtOAc in hexane) to separate the isomers to yield 14.60g **19(*E*)** (86%) and 2.33g **19(*Z*)** (14%) as pale yellow oils. **19*(E)*:** $[\alpha]^{25}_D$: -4.5° (c: 1, $CHCl_3$). IR (film): 3070, 2940, 2865, 1740, 1667, 1636, 1463, 1381. ^{1}H NMR ($CDCl_3$): 7.75-7.35 (10H, m, Ar<u>H</u>), 7.07 (1H, dd, J=15.5 Hz, 7.0 Hz, (CH$_3$)CHC(<u>H</u>)=), 6.33 (1H, d, J=15.5 Hz, C=C(<u>H</u>)C=O), 4.22 (2H, s, CH$_2$OTBDPS), 4.03 (2H, s, C<u>H</u>$_2$OCH$_3$), 3.70 (1H, m, C<u>H</u>OTIPS), 3.66 (3H, s, N(OC<u>H</u>$_3$)), 3.27 (3H, s, CH$_2$OC<u>H</u>$_3$), 3.23 (3H, s, N(C<u>H</u>$_3$)), 2.45-2.35 (1H, m, (CH$_3$)C<u>H</u>C(H)=), 2.05-1.85 (2H, m, C<u>H</u>$_2$C(CH$_3$)=), 1.74 (3H, s, C(CH$_3$)=), 1.45-1.35 (2H, m, C<u>H</u>$_2$CHOTIPS), 1.04 (9H, s, C(CH$_3$)$_3$), 1.00 (21H, s, TIPS), 0.92 (3H, d, J=7.0 Hz, CH(C<u>H</u>$_3$). ^{13}C NMR ($CDCl_3$): 166.9, 150.4, 138.3, 135.6, 133.8, 129.5, 127.5, 118.0, 76.0, 69.2, 61.5, 61.0, 57.8, 41.5, 33.0, 32.3, 31.0, 26.8, 19.3, 18.5, 18.2, 13.6, 12.9. MS (*m/z*): 666 (M-C_3H_7)$^+$.

HR-MS, calcd. for $C_{38}H_{60}NO_5Si_2$ $(M-C_3H_7)^+$: 666.4010; found: 666.4003. **19(*Z*):** $[\alpha]^{25}_D$: +43.9° (c: 1, $CHCl_3$). IR (film): 3048, 2941, 2816, 1658, 1463, 1254. ^1H NMR ($CDCl_3$): 7.55 (10H, m, ArH), 6.20-6.15 (2H, m, CH=CH), 4.24 (2H, s, $CH_2OTBDPS$), 4.03 (2H, s, CH_2OCH_3), 3.77 (1H, m, CHOTIPS), 3.66 (3H, s, $N(OCH_3)$), 3.60-3.50 (1H, m, $(CH_3)CHCH=$), 3.25 (3H, s, CH_2OCH_3), 3.18 (3H, s, $N(CH_3)$), 2.10-1.90 (2H, m,$CH_2C(CH_3)=$), 1.76 (3H, s, $C(CH_3)=$), 1.60-1.40 (2H, m, $CH_2CHOTIPS$), 1.04 (9H, s, $C(CH_3)_3$), 0.98 (21H, s, TIPS), 0.88 (3H, d, J=7.0Hz, $CH(CH_3)$). ^{13}C NMR ($CDCl_3$): 167.2, 151.5, 138.3, 135.6, 133.9, 129.4, 129.3, 127.5, 116.5, 75.9, 69.0, 61.4, 61.0, 57.7, 36.4, 33.8, 32.1, 30.7, 26.9, 19.3, 18.8, 18.2, 13.3, 12.9. MS (*m/z*): 666 $(M-C_3H_7)^+$. HR-MS, calcd. for $C_{38}H_{60}NO_5Si_2$ $(M-C_3H_7)^+$: 666.4010; found: 666.4003.

2(*E*),8(*Z*)-(4*R*,5*S*)-10-(*tert*-Butyldiphenylsilyl)oxy-9-methoxymethyl-4,8-dimethyl-5-(triisopropylsilyl)oxy-2,8-decadienal (20): This aldehyde was prepared the same way as aldehyde **18a** in 99% yield as a pale yellow oil and used without delay in the next step. **20:** $[\alpha]^{25}_D$: -10.2° (c: 1, $CHCl_3$). IR (film) : 3071, 2942, 2865, 1694, 1635, 1463. ^1H NMR ($CDCl_3$): 9.46 (1H, d, J=8.0 Hz, CHO), 7.75-7.35 (10H, m, ArH), 6.96 (1H, dd, J=15.5, 6.0 Hz, $(CH_3)CHC(H)=$), 6.04 (1H, dd, J=15.5, 8.0 Hz, $C=C(H)CHO$), 4.22 (2H, s, $CH_2OTBDPS$), 4.02 (2H, s, CH_2OCH_3), 3.73 (1H, m, CHOTIPS), 3.28 (3H, s, OCH_3), 2.55-2.45 (1H, m, $(CH_3)CHC(H)=$), 1.93 (2H, m, $CH_2C(CH_3)=$), 1.75 (3H, s, $C(CH_3)=$), 1.45-1.35 (2H, m, $CH_2CHOTIPS$), 1.04 (9H, s, $C(CH_3)_3$), 1.01 (21H, s, TIPS), 0.92 (3H, d, J=7.0 Hz, $CH(CH_3)$). ^{13}C NMR ($CDCl_3$): 193.78, 161.10, 137.62, 135.49, 133.61, 132.12, 129.73, 129.47, 127.47, 75.52, 69.04, 60.94, 57.84, 41.67, 32.75, 30.87, 26.73, 19.16, 18.44, 18.06, 12.70. MS (*m/z*): 593 $(M-C_4H_9)^+$. HR-MS, calcd. for $C_{35}H_{53}O_4Si_2$ $(M-C_4H_9)^+$: 593.3482; found: 593.3475.

Methyl 2(*Z*),4(*E*),10(*Z*)-(6*R*,7*S*)-12-(*tert*-butyldiphenylsilyl)oxy-11-methoxymethyl-6,10-dimethyl-7-(triisopropylsilyl)oxy-2,4,10-dodecatrienoate (21): A solution of potassium bistrimethylsilyl amide (5.72 mL, 2.86 mmol, 0.5 M in toluene) was added dropwise to a stirred THF (40 mL) solution of bis (2,2,2-trifluoroethyl) methoxycarbonylmethylphosphonate (947 mg, 2.97 mmol) and 18-Crown-6 (3.27 g, 12.4 mmol) at -78°C. After an hour stirring at -78°C, a solution of aldehyde **20** (1.49 g, 2.29 mmol) in THF (15 mL) was cannulated to the reagent. It was stirred for 2.5 h then, after allowing it to warm to 22 °C, the reaction was quenched with NH_4Cl (40 mL, sat.). Following an aqueous work-up with ether, the crude product was purified by chromatography (7% EtOAc in hexane) to yield 1.44 g (89%) ester **21** (*Z*/*E* ratio 30:1) as a pale yellow oil. $[\alpha]^{25}_D$: -8.6° (c: 1, $CHCl_3$). IR (film): 3071, 2943, 2890, 1719, 1463, 1112. ^1H NMR ($CDCl_3$): 7.75-7.25 (11H, m, ArH and $HC=CHHC=CHCO_2CH_3$), 6.51 (1H, dd, J=11.5, 11.5 Hz, $HC=CHCO_2CH_3$), 6.17 (1H, dd, J=15.5, 7.0 Hz, $HC=CHHC=CHCO_2CH_3$), 5.56 (1H, d, J=11.5 Hz, $HC=CHCO_2CH_3$), 4.22 (2H, s, $CH_2OTBDPS$), 4.03 (2H, s, CH_2OCH_3), 3.72 (3H, s, CO_2CH_3), 3.65 (1H, m, CHOTIPS), 3.27 (3H, s, OCH_3), 2.40 (1H, m, $CH(CH_3)$), 1.95-1.85 (2H,

m, $C\underline{H}_2C(CH_3)$=), 1.74 (3H, s, $C(C\underline{H}_3)$=), 1.45-1.30 (2H, m, (TIPSO)CHC$\underline{H}_2$), 1.04 (9H, s, $C(C\underline{H}_3)_3$), 0.99 (21H, s, TIPS), 0.91 (3H, d, J = 7.0 Hz, $CH(C\underline{H}_3)$). ^{13}C NMR (CDCl): 166.9, 148.4, 145.7, 138.3, 135.6, 133.8, 129.5, 127.6, 126.0, 115.2, 76.3, 69.1, 61.0, 57.9, 51.0, 41.7, 33.0, 31.0, 26.9, 19.3, 18.6, 18.2, 13.5, 12.9. MS (*m/z*): 706 $(M)^+$, 675 $(M\text{-}OCH_3)^+$. HR-MS, calcd. for $C_{39}H_{59}O_5Si_2$ $(M\text{-}C_3H_7)^+$: 663.3901; found: 663.3894.

2(*Z*),4(*E*),10(*Z*)-(6*R*,7*S*)-12-(*tert*-butyldiphenylsilyl)oxy-11-methoxymethyl-6,10-dimethyl-7-(triisopropylsilyl)oxy-2,4,10-dodecatrienol (22): DIBAL-H (4.6 mL, 4.65 mmol, 1.0 M in CH_2Cl_2) was added dropwise to a CH_2Cl_2 (20 mL) solution of ester **21** (1.31 g, 1.85 mmol) at -78°C. After 1h stirring, the excess reagent was destroyed with methanol (2.5 mL). Sodium tartrate (25 mL, sat.) was added, then it was allowed to warm to 22°C in 1 h. Following an aqueous work-up with CH_2Cl_2, chromatography (20-40% EtOAc in hexane) afforded 1.23 g (98%) alcohol **22** as a colorless oil. $[\alpha]^{25}_D$: -1.2° (c: 1, $CHCl_3$). IR (film): 3398, 2939, 2865, 1656, 1464. ^{1}H NMR ($CDCl_3$): 7.75-7.35 (10H, m, Ar$\underline{H}$), 6.21 (1H, dd, J=15.0, 11.0 Hz, CH-HC=C$\underline{H}$), 6.01 (1H, dd, J=11.0, 11.0Hz, $\underline{H}$C=CHCH$_2$OH), 5.81 (1H, dd, J=15.0, 7.0 Hz, CH-$\underline{H}$C=CH), 5.48 (1H, dt, J=11.0, 7.0 Hz, HC=C$\underline{H}$CH$_2$OH), 4.26 (2H, d, J=7.0 Hz, C$\underline{H}_2$OH), 4.23 (2H, s, C$\underline{H}_2$OTBDPS), 4.03 (2H, s, C$\underline{H}_2$OCH$_3$), 3.62 (2H, m, C$\underline{H}$OTIPS), 3.27 (3H, s, CH$_2$-OC$\underline{H}_3$), 2.30 (1H, m, C$\underline{H}$(CH$_3$)), 2.0-1.90 (2H, m, C$\underline{H}_2$C(CH$_3$)=), 1.75 (3H, s, C(CH$_3$)=), 1.45-1.30 (3H, m, C$\underline{H}_2$CHOTIPS and O$\underline{H}$), 1.04 (9H, s, C(CH$_3$)$_3$), 1.00 (21H, s, TIPS), 0.88 (3H, d, J = 7.0 Hz, CH(C$\underline{H}_3$)). ^{13}C NMR ($CDCl_3$): 139.8, 138.5, 135.5, 133.8, 131.1, 129.5, 129.4, 127.5, 127.4, 124.0, 76.5, 69.1, 61.0, 58.7, 57.8, 41.5, 32.9, 30.9, 26.8, 19.2, 18.5, 18.2, 14.1, 12.9. MS (*m/z*): 647 $(M\text{-}OCH_3)^+$. HR-MS, calcd. for $C_{37}H_{57}O_4Si_2$ $(M\text{-}C_4H_9)^+$: 621.3795; found: 621.3801.

Methyl 4(*Z*),6(*E*),12(*Z*)-(8*R*,9*S*)-14-(*tert*-butyldiphenylsilyl)oxy-2-cyano-13-methoxy-methyl-8,12-dimethyl-9-(triisopropylsilyl)oxy-4,6,12-tetradecatrienoate (24): To a stirred THF (50 mL) solution of alcohol **22** (2.81 g, 4.14 mmol), PPh_3 (1.56 g, 5.95 mmol) and, after cooling to -40 °C, HCA (900 μL, 5.93 mmol) was added. After another 15 min stirring at -40 °C, the reaction was allowed to rewarm. By this time, chloride **23** was formed. It was then cannulated into a preformed solution of sodium methyl cyanoacetate made by a dropwise addition of a solution of sodium methoxide (37.0 mL, 162 mmol, 25% in MeOH) to a solution of methyl cyanoacetate (14.7 mL, 167 mmol) in MeOH (60 mL) and THF (80 mL) at 23 °C followed by 30 min stirring. After 3h stirring at 23 °C, the reaction was quenched with NH_4Cl (75 mL, sat.) at 0 °C. Following the evaporation of the bulk of the solvents and an aqueous work-up with ether, the crude product was purified by chromatography (30% EtOAc in hexane) to yield 2.58 g (82% over two steps) epimeric cyanoester **24** as a pale yellow oil. IR (film): 2942, 2865, 2250, 1754, 1654, 1463. ^{1}H NMR ($CDCl_3$): 7.75-7.30 (10H, m, Ar$\underline{H}$), 6.20-6.05 (2H, m, HC=C$\underline{H}$C$\underline{H}$=CH) 5.90-5.80 (1H, m, CH-$\underline{H}$C=CH), 5.30-5.20 (1H, m, HC=C$\underline{H}$CH$_2$), 4.23 (2H, s, C$\underline{H}_2$OTBDPS), 4.03

($C\underline{H}_2OCH_3$), 3.80 (3H, s, $CO_2C\underline{H}_3$), 3.63 (1H, m, C<u>H</u>OTIPS), 3.52 (1H, t, J=7.0 Hz, C<u>H</u>(CN)), 3.27 (3H, s, $CH_2OC\underline{H}_3$), 2.78 (2H, m, C<u>H</u>$_2$CH(CN)), 2.30 (1H, m, C<u>H</u>(CH_3)), 2.00-1.90 (2H, m, $C\underline{H}_2C(CH_3)$=), 1.75 (3H, s, $C(CH_3)$=), 1.45-1.30 (2H, m, CH(OTIPS)C<u>H</u>$_2$), 1.04 (9H, s, $C(C\underline{H}_3)_3$), 1.00 (21H, s, TIPS), 0.88 (3H, d, J=7.0 Hz, $CH(C\underline{H}_3)$). ^{13}C NMR ($CDCl_3$): 166.1, 140.7, 138.4, 135.6, 133.8, 133.5, 129.5, 127.6, 123.5, 120.9, 116.1, 76.5, 69.2, 61.0, 57.9, 53.4, 41.6, 37.4, 32.9, 31.0, 28.0, 26.8, 19.3, 18.6, 18.2, 14.1. MS (*m/z*): 647 $(M\text{-}C_3H_7)^+$. HR-MS, calcd. for $C_{41}H_{60}NO_5Si_2$ $(M\text{-}C_4H_9)^+$: 702.4010; found: 702.4005.

Methyl 4(*Z*),6(*E*),12(*Z*)-(8*R*,9*S*)-2-cyano-14-hydroxy-13-methoxymethyl-8,12-dimethyl-9-(triisopropylsilyl)oxy-4,6,12-tetradecatrienoate (25): PTSA (363 mg, 1.91 mmol) was added to a MeOH (50 ml) solution of silylether **24** (1.45 g, 1.91 mmol) at 23 °C. After 4 h stirring, $NaHCO_3$ (193 mg, 2.3 mmol) was added. Solvents were evaporated. An aqueous work-up with EtOAc, chromatography (0 to 40% EtOAc in hexane) afforded 250 mg (17%) silylether **24** and 715 mg (72%, 86% corrected) alcohol **25** as a pale yellow oil. IR (film): 3450, 2944, 2251, 1751, 1656. ^{1}H NMR ($CDCl_3$): 6.35-6.10 (2H, m, HC=C<u>H</u>C<u>H</u>=CHCH$_2$) 5.90 (1H, m, <u>H</u>C=CHCH=CHCH$_2$), 5.35-5.25 (1H, m, HC=C<u>H</u>CH$_2$), 4.16 (2H, d, J=1 Hz, C<u>H</u>$_2$OH), 4.05 ($C\underline{H}_2OCH_3$), 3.80 (3H, s, $CO_2C\underline{H}_3$), 3.76 (1H, m, C<u>H</u>OTIPS), 3.58 (1H, m, C<u>H</u>(CN)), 3.34 (3H, s, $CH_2OC\underline{H}_3$), 2.85-2.75 (2H, m, C<u>H</u>$_2$CH(CN)), 2.47 (1H, m, C<u>H</u>(CH_3)), 2.30-2.00 (2H, m, $C\underline{H}_2C(CH_3)$=), 1.74 (3H, s, $C(CH_3)$=), 1.60-1.40 (2H, m, CH(OTIPS)C<u>H</u>$_2$), 1.06 (9H, s, $C(C\underline{H}_3)_3$), 1.06 (21H, s, TIPS), 1.02 (3H, d, J = 7.0 Hz, $CH(C\underline{H}_3)$). ^{13}C NMR ($CDCl_3$): 166.2, 140.4, 138.4, 133.4, 129.1, 123.6, 121.1, 116.1, 76.3, 71.9, 61.5, 58.3, 53.5, 41.9, 41.8, 37.4, 33.2, 30.6, 30.5, 28.0, 18.5, 18.2, 14.9, 14.7, 13.0. MS (*m/z*): 489 $(M\text{-}CH_3OH)^+$. HR-MS, calcd. for $C_{28}H_{47}NO_4Si$ $(M\text{-}CH_3OH)^+$: 489.3274; found: 489.3285.

Methyl 4(*Z*),6(*E*),12(*Z*)-(8*R*,9*S*)-14-chloro-2-cyano-13-methoxymethyl-8,12-dimethyl-9-(triisopropylsilyl)oxy-4,6,12-tetradecatrienoate (26): PPh_3 (731 mg, 2.79 mmol) and HCA (420 mg, 2.77 mmol) was sequentially added to a stirred CH_2Cl_2 (10 mL) solution of alcohol **25** (1.32 g, 2.53 mmol) at -40 °C. After 15 min stirring, the mixture was warmed to 22 °C. The crude product was purified directly by chromatography (0-25% EtOAc in hexane) to yield 1.30 g (95%) chloride **26** as a pale yellow oil used without delay for macrocyclization.

Methyl 3(*Z*),5(*E*),11(*Z*)-(1ξ,7*R*,8*S*)-1-cyano-12-methoxymethyl-7,11-dimethyl-8-(triisopropylsilyl)oxy-3,5,11-cyclotridecatrienecarboxylate (27): A solution of chloride **26** (360 mg, 667 μmol) in MeCN (10 mL) was syringe pumped over 10 h into a stirred MeCN (400 mL) suspension of Cs_2CO_3 (1.12 g, 3.44 mmol) at 70°C. Following 2 h stirring, the bulk of the solvent was stripped, the residue was dissolved in hexane/ether (100 mL, 1:1) then water (30 mL) was added. Following an usual work-up, chromatography (0-20% EtOAc in hexane) afforded 272 mg

(81%) macrocycle **27** as a 1:1 mixture of epimers. It was separated for characterization and model studies. **27*S*:** $[\alpha]^{28}_D$: +59.2° (c: 1, $CHCl_3$). IR ($CDCl_3$): 2946, 2868, 2244, 1742, 1463. ^1H NMR ($CDCl_3$): 6.55 (1H, m, 5-H), 6.50-6.35 (1H, m, 4-H), 5.60 (1H, m, 3-H), 5.49 (1H, dd, J=15.0, 10.0 Hz, 6-H), 3.93 (2H, s, CH_2OCH_3), 3.78 (3H, s, CO_2CH_3), 3.62 (1H, m, 8-H), 3.25 (3H, s, CH_2OCH_3), 3.01 (1H, m, 2-H_A), 2.93 and 2.50 (2H, 2d, J=15.0 Hz, 13-H_2), 2.58 (1H, dd, J=13.0, 7.0 Hz, 2-H_B), 2.45-2.30 (1H, m, 7-H), 2.19 and 2.02 (2H, 2td, J=13.0, 4.0 Hz, 10-H_2), 1.73 (3H, s, 11-CH_3), 1.65-1.50 and 1.45-1.30 (1H, m, 9-H_2), 1.13 (3H, d, J=6.5 Hz, 7-CH_3, 1.08 (21H, s, TIPS). ^{13}C NMR ($CDCl_3$): 169.8, 139.7, 138.0, 135.1, 126.2, 125.3, 122.2, 120.0, 77.6, 69.8, 58.0, 53.3, 47.4, 45.5, 36.8, 36.4, 34.9, 29.2, 19.4, 18.8, 18.5, 13.1. MS (*m/z*): 503 $(M)^+$, 460 $(M-C_3H_7)^+$. HR-MS, calcd. for $C_{29}H_{49}NO_4Si$ $(M)^+$: 503.3431; found: 503.3427. **27*R***: $[\alpha]^{28}_D$: +79.2° (c: 1, $CHCl_3$). IR (film): 2948, 2250, 1743, 1225. ^1H NMR ($CDCl_3$): 6.51 (1H, m, 5-H), 6.42 (1H, m, 4-H), 5.70 (1H, m, 6-H), 5.43 (1H, m, 3-H), 3.90 (2H, AB-d, CH_2OCH_3), 3.82 (3H, s, CO_2CH_3), 3.80 (1H, m, 8-H), 3.19 (3H, s, CH_2OCH_3), 3.00-2.90 (1H, m, 2-H_A), 2.79 and 2.61 (2H, 2d, J=15.0 Hz, 13-H_2), 2.69 (1H, dd, J=13.5, 7.5 Hz, 2-H_B), 2.55-2.40 (1H, m, 7-H), 2.34 and 1.99 (2H, 2td, J=13.0, 4.0 Hz, 10-H_2), 1.74 (3H, s, 11-CH_3), 1.70-1.55 and 1.35-1.20 (2H, 2m, 9-H_2), 1.10 (24H, s, 7-CH_3 and TIPS). ^{13}C NMR($CDCl_3$): 169.9, 138.7, 137.6, 134.5, 125.9, 125.3, 121.9, 119.4, 76.2, 70.8, 57.8, 53.3, 47.9, 44.0, 36.2, 34.5, 32.8, 28.1, 19.2, 18.2, 17.5, 12.8. MS (*m/z*): 503 $(M)^+$. HR-MS, calcd. for $C_{29}H_{49}NO_4Si$ $(M)^+$: 503.3431; found: 503.3427.

2(*Z*),4(*E*),10(*E*)-(6*R*,7*S*)-11-methoxymethyl-6,10-dimethyl-7-(triisopropylsilyl)oxy-2,4,10-dodecatrien-1,12-diol (28): The same procedure as for allyl alcohol **25** was used to deprotect silylether **22**. Chromatography (25-60% EtOAc in hexane) afforded diol **28** in 72% (91% corr.) yield (21% silylether **22** was recovered). Diol **28:** $[\alpha]^{25}_D$: - 5.7° (c:1 ,$CHCl_3$). IR (film): 3363, 2942, 2866, 1654, 1463, 1382. ^1H NMR ($CDCl_3$): 6.47 (1H, dd, J=15.0, 11.0 Hz, CH-HC=CH), 6.08 (1H, t, J=11.0 Hz, HC=$CHCH_2$), 5.74 (1H, dd, J=15.0, 8.5 Hz, CH-HC=CH), 5.56 (1H, m, HC=$CHCH_2$), 4.39 (1H, dd, J=13.0, 8.5 Hz, CH=$CHCH_A$), 4.20-4.00 (5H, m, CH=$CHCH_B$, CH_2OH and CH_2OCH_3), 3.75 (1H, m, CH(OTIPS)), 3.34 (3H, s, OCH_3), 2.50-2.40 (1H, m, $CH(CH_3)$), 2.33 and 2.05 (2H, 2td, J=13.0, 4.5 Hz, $CH_2C(CH_3)$=), 2.25 (2H, s, 2xOH), 1.74 (3H, s, $C(CH_3)$=), 1.70-1.55 and 1.50-1.35 (2H, 2m, CH(OTIPS)CH_2), 1.08 (21H, s, TIPS), 1.06 (3H, d, J=7.0 Hz, $CH(CH_3)$). ^{13}C NMR ($CDCl_3$): 139.0, 138.7, 130.8, 128.8, 128.3, 124.4, 76.0, 72.2, 61.6, 58.2, 42.6, 33.8, 29.0, 18.5, 18.3, 16.6, 12.9. MS (*m/z*): 441 $(M+H)^+$, 458 $(M+NH_4)^+$. HR-MS, calcd. for $C_{25}H_{49}O_4Si$ $(M+H)^+$: 441.3400; found: 441.3412, and calcd. for $C_{25}H_{52}NO_4Si$ $(M+NH_4)^+$: 458.3665; found: 458.3661.

Methyl 3(*Z*),5(*E*),11(*Z*)-(1ξ,7*R*,8*S*)-1-cyano-12-methoxymethyl-7,11-dimethyl-8-(triisopropylsilyl)oxy-3,5,11-cyclotridecatrienecarboxylate (27) (via dialkylation from diol **28**)**:** To a stirred solution of diol **28** (11.8 mg, 27.3 μmol) in 500 μL CH_2Cl_2, PPh_3 (15.8 mg, 2.2 eq) and

HCA (9.1 μL, 2.2 eq) was added at -78°C. The temperature was allowed to warm up to 22°C in 15 min then the mixture was adsorbed on a plug of silica having been washed with 50% ether in hexane. The plug was eluted fast with hexane to get rid of the chloroacetones then with 50% ether in hexane. Fractions of dichloride **29** were collected and evaporated to use immediately for the macrocyclization as follows. A mixture of dichloride **29** and methyl cyanoacetate (33 μL, 1.2 eq, 1 M solution in MeCN) in MeCN (3 mL) was injected by syringe pump over 22 min into a suspension of Cs_2CO_3 (89 mg, 10 eq) in acetonitrile (30 mL) at 70-75 °C. The same work-up as for the stepwise reaction furnished 8.0 mg (58%) identical epimeric mixture of macrocycle **27**.

3(*Z*),5(*E*),11(*Z*)-(1ξ,7*R*,8*S*)-12-methoxymethyl-7,11-dimethyl-8-(triisopropylsilyl)oxy-3,5, 11-cyclotridecatrienecarbonitrile (31): To a stirred solution of 1:1 epimeric mixture of ester **27** (342 mg, 680 μmol) in THF (10 mL), a NaOH solution (2.72 mL, 2.72 mmol, 1M) was added. It was stirred for 17h at 50°C. Upon cooling, it was acidified with HCl (3.0 mL, 3.0 mmol, 1M), then a usual work-up with CH_2Cl_2 (50 mL) furnished an 1:1 mixture of epimeric acid **30** (323 mg, 97%) as a white foam which was decarboxylated by having been refluxed in deoxygenated MeCN (15 mL) with Cu_2O (9 mg, 63 mmol) for 24h under Argon. Upon cooling, this suspension was filtered through a pad of silica and washed with 40% EtOAc in hexane. After evaporation of this solution, a purification with chromatography (10% EtOAc in hexane) furnished an 1:1 epimeric mixture of nitrile **31** (248 mg, 82% over 2 steps) as a white foam. **31:** IR (film): 2942, 2866, 2237, 1653, 1464. ^{1}H NMR ($CDCl_3$): 6.40-6.15, 5.80-5.70 and 5.60-5.40 (2H+0.5H+1.5H, 3m, vinyl protons), 4.13 and 3.92 (2H, 2d, J=11.0 Hz, $C\underline{H}_2OCH_3$) or 3.99 (2H, AB-d, $C\underline{H}_2OCH_3$), 3.78 or 3.62 (1H, m, 8-H), 3.32 (3H, s, $OC\underline{H}_3$), 1.74 or 1.73 (3H, 2s, 11-CH_3), 1.15-1.05 (24 H, 7-$C\underline{H}_3$ and TIPS). ^{13}C NMR ($CDCl_3$): 139.1, 138.1, 137.5, 137.1, 132.7, 132.0, 128.2, 127.0, 126.5, 126.1, 125.9, 124.8, 123.1, 122.9, 77.0, 75.3, 72.4, 71.8, 57.9, 46.1, 44.0, 36.0, 35.1, 34.1, 33.2, 31.8, 31.0, 30.6, 30.4, 26.9, 18.7, 18.5, 18.4, 18.1, 13.6, 13.3. MS (*m/z*): 445 $(M)^+$, 402 $(M-C_3H_7)^+$. HR-MS, calcd. for $C_{27}H_{47}NO_2Si$ $(M)^+$: 445.3376; found: 445.3383.

3(*Z*),5(*E*),11(*Z*)-(1ξ,7*R*,8*S*)-12-hydroxymethyl-7,11-dimethyl-8-(triisopropylsilyl)oxy-3,5, 11-cyclotridecatrienecarbonitrile (34): To a stirred solution of 1:1 epimeric mixture of ether **31** (82 mg, 184 μmol) in CH_2Cl_2 (20 mL), Me_2BBr (734 μL, 734 μmol, 1.0 M in 1,2-dichloroethane) was added at -10°C. After 20 min stirring, the excess reagent was destroyed with a saturated solution of $NaHCO_3$ (10 mL) at -78°C. Following an aqueous work-up with CH_2Cl_2, DMF (4 mL) and dry sodium acetate (151 mg, 1.84 mmol) were added to the evaporated crude bromide **32** and the solution was heated for 6h at 65°C. Upon cooling, following an aqueous work-up with ether, the crude acetate **33** was hydrolyzed in MeOH (3 mL) with anhydrous K_2CO_3 (255 mg, 1.85 mmol) for 3h at 23°C. Following an acidification with a solution of HCl (3.6 mL, 3.6 mmol, 1.0 N) and an aqueous work-up with ether, the crude product was purified by chromatography (20%

EtOAc in hexane) to furnish 1:1 epimeric mixture of alcohol **34** (62.7 mg, 79% from **31**) as a colorless oil. IR ($CDCl_3$): 3610(br), 2960, 2868, 2249, 1652, 1464. ^{1}H NMR ($CDCl_3$): 6.35-6.15, 5.85-5.75 and 5.65-5.45 (2H+0.5H+1.5H, 3m, vinyl protons), 4.31 and 4.21 (2H, 2d, J=12.5 Hz, $C\underline{H}_2OH$) or 4.24 (2H, s, $C\underline{H}_2OH$), 3.80 or 3.60 (1H, m, 8-$\underline{H}$), 1.75 or 1.74 (3H, s, 11-$C\underline{H}_3$), 1.15-1.05 (24 H, m, 7-$C\underline{H}_3$ and TIPS). ^{13}C NMR ($CDCl_3$): 138.3, 137.2, 136.8, 132.3, 131.7, 130.0, 129.9, 126.6, 125.5, 124.2, 123.1, 76.6, 74.7, 63.0, 62.2, 45.8, 43.6, 35.8, 35.20, 33.78, 33.19, 31.39, 31.17, 30.29, 30.16, 26.60, 18.25, 17.74, 13.15, 12.89. MS (*m/z*): 431 $(M)^+$, 388 $(M-C_3H_7)^+$. HR-MS, calcd. for $C_{26}H_{45}NO_2Si$ $(M)^+$: 431.3219; found: 431.3215.

3(*Z*),5(*E*),11(*Z*)-(1ξ,7*R*,8*S*)-12-formyl-7,11-dimethyl-8-(triisopropylsilyl)oxy-3,5,11-cyclotridecatrienecarbonitrile (35): To a stirred solution of an 1:1 epimeric mixture of alcohol **34** (58.2 mg, 135 μmol) in CH_2Cl_2 (5 mL), NMO (20.5 mg, 1.3 eq), molecular sieve (100 mg, 4Å) and TPAP (3.3 mg, 7% eq) were added at 0°C. After 20 min stirring at 22°C, the bulk of the solvent was stripped, then the resulting suspension was purified directly by chromatography (40% ether in hexane) to isolate 15.4 mg (27%) **35*S***, 14.2 mg (25%) **35*R*** and 21.6 mg (37%) of the mixture of **35*S*** and **35*R*** as colorless oils. These aldehydes needed to be used without delay in the next step. **35*S*:** ^{1}H NMR ($CDCl_3$): 10.15 (1H, s, C$\underline{H}$O), 6.35-6.25, 5.78-5.68, 5.62-5.50 (2H+1H+1H, 3m, vinyl protons), 3.91-3.85 (1H, m, 8-$\underline{H}$), 2.215 (3H, s, 11-$C\underline{H}_3$), 1.13 (3H, d, J=6.8 Hz, 7-$C\underline{H}_3$), 1.11 (21H, s, TIPS). ^{13}C NMR ($CDCl_3$): 190.4, 162.0, 136.4, 133.9, 131.8, 126.4, 125.7, 121.4, 74.7, 43.6, 33.3, 32.9, 30.7, 29.4, 27.0, 18.3, 18.2, 17.9, 13.1. MS (*m/z*): 429 $(M)^+$, 386 $(M-C_3H_7)^+$. HR-MS, calcd. for $C_{26}H_{43}NO_2Si$ $(M)^+$: 429.3063; found: 429.3072. **35*R*:** ^{1}H NMR ($CDCl_3$): 10.13 (1H, s, C$\underline{H}$O), 6.49-6.25, 5.63-5.50 (2H+2H, 2m, vinyl protons), 3.72-3.64 (1H, m, 8-$\underline{H}$), 2.21 (3H, s, 11-$C\underline{H}_3$), 1.16 (3H, d, J=6.6 Hz, 7-$C\underline{H}_3$, 1.12 (21H, s, TIPS). ^{13}C NMR (C_6D_6): 188.2, 157.5, 134.9, 132.7, 130.1, 124.9, 123.7, 119.4, 74.9, 44.0, 33.5, 30.2, 28.9, 28.0, 25.0, 17.0, 16.8, 15.8, 11.6. MS (*m/z*): 429 $(M)^+$, 386 $(M-C_3H_7)^+$. HR-MS, calcd. for $C_{26}H_{43}NO_2Si$ $(M)^+$: 429.3063; found: 429.3072.

3(*Z*),5(*E*),11(*Z*)-(7*R*,8*S*)-12-methoxymethyl-7,11-dimethyl-8-(triisopropylsilyl)oxy-3,5,11-cyclotridecatrienedicarbonitrile (36) (via double alkylation from diol **28**)**:** Diol **28** (499 mg, 1.132 mmol) was transformed into dichloride **29** as described for the preparation of **27** via double alkylation macrocyclization. Then a solution of dichloride **29** and malononitrile (600 mg, 8 eq) in MeCN (10 mL) was syringe pumped over 3 hour to a stirred suspension of Cs_2CO_3 (3.690 g, 10 eq) in MeCN (550 mL) at 70°C. After an additional hour of stirring, the bulk of MeCN was evaporated, hexane/ether (100 mL, 50%) were added, washed with dil. HCl and brine, dried and evaporated. The crude product was purified by chromatography (20% ether in hexane) to isolate 389 mg (73%) macrocycle **36** as a pale yellow oil. **36:** $[\alpha]^{20}_D$: +80.5° (c:2 ,$CHCl_3$). IR (film): 2941, 2867, 2371, 1461, 1107. ^{1}H NMR ($CDCl_3$): 6.53-6.40 (2H, m, 4-$\underline{H}$, 5-$\underline{H}$) 5.70-5.55 (2H,

m, 3-H, 6-H), 4.06 (2H, AB-d, CH_2OCH_3), 3.74 (1H, ddd, J=8.3, 6.1, 2.2 Hz, 8-H), 3.38 (3H, s, OCH_3), 3.08 (1H, dd, J=13.4, 10.2 Hz, 2-H_A), 2.91 (1H, dd, J=13.4,6.9 Hz, 2-H_B), 2.89 (1H, d, J=14.9 Hz, 13-H_A), 2.56 (1H, d, J=14.9 Hz, 13-H_B), 2.40 (1H, m, 7-H), 2.23 (1H, td, J=13.3, 4.5 Hz, 10-H_A), 2.02 (1H, td, J=13.3, 4.0 Hz, 10-H_B), 1.77 (3H, s, 11-CH_3), 1.61 (1H, tt, J=14.0, 4.5 Hz, 9-H_A), 1.27 (1H, m, 9-H_B), 1.12 (3H, d, J=6.7 Hz, 7-CH_3), 1.09 (21H, s, TIPS). ^{13}C NMR ($CDCl_3$): 140.0, 138.8, 135.9, 125.1, 124.9, 120.1, 116.9, 115.9, 76.1, 70.2, 58.1, 44.7, 37.3, 36.5, 34.7, 34.1, 28.3, 19.4, 18.2, 18.0, 12.9. MS (*m/z*): 470 $(M)^+$, 427 $(M-C_3H_7)^+$. HR-MS, calcd. for $C_{28}H_{46}N_2O_2Si$ $(M)^+$: 470.3328; found: 470.3337.

3(*Z*),5(*E*),11(*Z*)-(7*R*,8*S*)-12-methoxymethyl-7,11-dimethyl-8-(triisopropylsilyl)oxy-3,5,11-cyclotridecatrienedicarbonitrile (36) (from macrocycle **27**): Ester **27** (256 mg, 509 μmol) was saponified to acid **30** by the procedure applied for the preparation of **31**. Ethyl chloroformate (74 μL, 1.5 eq) was added to a stirred mixture of crude acid **30**, THF (5 mL) and Et_3N (143 μL, 2 eq) at -40°C. The mixture was stirred for 30 min at -5°C then cooled back to -40°C to condense about 5 mL NH_3 (*l*) in it. The mixture was allowed to warm to 22°C in an hour to let the excess of NH_3 evaporate. Following an aqueous work-up with CH_2Cl_2, the dry crude amide was dissolved in CH_2Cl_2 then Et_3N (180 μL, 2.5 eq) and trichloroacetyl chloride (86 μL, 1.5 eq) were added at 0°C. After 2h stirring, the reaction was quenched with 2 drops of cc. NH_4OH. Following an aqueous work-up with CH_2Cl_2, the crude product was purified by the same way as in the previous procedure to give 200 mg (83% over 4 steps) identical macrocycle **36**.

3(*Z*),5(*E*),11(*Z*)-(7*R*,8*S*)-12-hydroxymethyl-7,11-dimethyl-8-(triisopropylsilyl)oxy-3,5,11-cyclotridecatrienedicarbonitrile (39): To a stirred solution of ether **36** (131 mg, 278 μmol) in CH_2Cl_2 (35 mL), Me_2BBr (1.08 mL, 4 eq, 1.0 M in 1,2-dichloroethane) was added at -10°C. After 15 min stirring, the excess reagent was destroyed with a saturated solution of $NaHCO_3$ (5 mL) at -40°C. Following an aqueous work-up with CH_2Cl_2, DMF (5 mL) and dry sodium formate (183 mg, 10 eq) were added to the dry crude bromide **37** and the solution was heated for 3h at 50°C. Upon cooling, following an aqueous work-up with ether, the crude formate **38** was hydrolyzed in THF (20 mL) with HCl (4 mL, 1M) for 3 days at 22°C. Following an aqueous work-up with ether, the crude product was purified with chromatography (20% to 30% Et_2O in hexane) to furnish 83 mg (65% over 3 steps) alcohol **39** as a colorless oil. **39:** $[\alpha]^{20}_D$: +83° (c:2, $CHCl_3$). IR (film): 3524(br), 2944, 2867, 2248, 1459. ^1H NMR ($CDCl_3$): 6.55-6.40 (2H, m, 4-H, 5-H), 5.72-5.56 (2H, m, 3-H, 6-H), 4.37 (2H, s, CH_2OH), 3.75 (1H, ddd, J=8, 6 and 2 Hz, 8-H), 3.09 (1H, dd, J=13.5,10.1 Hz, 2-H_A), 2.94 (1H, d, J=15.0 Hz, 13-H_A), 2.93 (1H, dd, J=15.0, 13.4 Hz, 2-H_B), 2.62 (1H, d, J=15.0 Hz, 13-H_B), 2.41 (1H, m, 7-H), 2.21 (1H, td, J=13.3, 4.5 Hz, 10-H_A), 2.02 (1H, td, J=13.3, 4.1 Hz, 10-H_B), 1.80 (3H, s, 11-CH_3), 1.61 (1H, tt, J=14.1, 4.5 Hz, 9-H_A), 1.27 (1H, m, 9-H_B), 1.12 (3H, d, J=6.7 Hz, 7-CH_3), 1.09 (21H, s, TIPS). ^{13}C NMR ($CDCl_3$):

140.6, 138.9, 136.0, 126.6, 125.0, 119.9, 116.9, 115.9, 76.1, 60.2, 44.7, 37.0, 36.4, 34.0, 28.4, 19.2, 18.2, 17.9, 12.9. MS (*m/z*): 456 $(M)^+$, 413 $(M\text{-}C_3H_7)^+$. HR-MS, calcd. for $C_{27}H_{44}N_2O_2Si$ $(M)^+$: 456.3172; found: 456.3182.

3(*Z*),5(*E*),11(*Z*)-(7*R*,8*S*)-12-formyl-7,11-dimethyl-8-(triisopropylsilyl)oxy-3,5,11-cyclotridecatrienedicarbonitrile (40): To a stirred solution of alcohol **39** (204 mg, 447 μmol) in CH_2Cl_2 (10 mL), Dess-Martin periodinane (284 mg, 1.5 eq) was added at 0°C. After a stirring period of 20 min at 22°C, the reaction was quenched with cc. $Na_2S_2O_3$ (5 mL). After an aqueous work-up with CH_2Cl_2, the crude product was purified by chromatography (10% to 30% Et_2O in hexane) to afford 173 mg (85%) aldehyde **40** as a pale yellow oil. **40:** $[\alpha]^{20}_D$: +184° (c:2, $CHCl_3$). IR (film): 2943, 2867, 2249, 1665, 1621, 1463. ^1H NMR ($CDCl_3$): 10.17 (1H, s, C<u>H</u>O), 6.57-6.44 (2H, m, 4-<u>H</u>, 5-<u>H</u>) 5.69-5.59 (2H, m, 3-<u>H</u>, 6-<u>H</u>), 3.75 (1H, ddd, J=8.7, 4.3, 2.1 Hz, 8-<u>H</u>), 3.09 (1H, dd, J=13.4, 10.6 Hz, 2-$\underline{H}_A$), 2.93 (1H, dd, J=13.4, 6.4 Hz, 2-$\underline{H}_B$), 2.79 (1H, d, J=15.0 Hz, 13-$\underline{H}_A$), 2.65 (1H, d, J=15.0 Hz, 13-$\underline{H}_B$), 2.56 (1H, td, J=13.1, 4.6 Hz, 10-$\underline{H}_A$), 2.38 (1H, m, 7-<u>H</u>), 2.30 (3H, s, 11-C$\underline{H}_3$), 2.24 (1H, td, J=13.1, 3.5 Hz, 10-$\underline{H}_B$), 1.66 (1H, tt, J=14.0, 4.0 Hz, 11-$\underline{H}_A$), 1.33 (1H, m, 11-$\underline{H}_B$), 1.15 (3H, d, J=6.5 Hz, 13-C$\underline{H}_3$), 1.11 (21H, s, TIPS). ^{13}C NMR ($CDCl_3$): 190.6, 164.1, 138.3, 135.7, 132.5, 125.5, 120.6, 116.6, 115.4, 75.5, 44.7, 38.0, 34.2, 33.9, 32.3, 29.7, 19.4, 18.3, 18.2, 13.0. MS (*m/z*): 454 $(M)^+$, 411 $(M\text{-}C_3H_7)^+$. HR-MS, calcd. for $C_{27}H_{42}N_2O_2Si$ $(M)^+$: 454.3015; found: 454.3019.

Methyl (9*R*,10*S*,12*S*)-12-cyano-14-methoxy-3β-(triisopropylsilyl)oxy-15,17,19-trinor-14,16-seco-5α,8β-stemod-6-en-16-oate (41*S*) and Methyl (9*S*,10*R*,12*S*)-12-cyano-14-methoxy-3β-(triisopropylsilyl)oxy-15,17,19-trinor-14,16-seco-5β,8α-stemod-6-en-16-oate (42*S*): A solution of macrocycle **27*S*** (64.0 mg, 127 μmol) in toluene (2.0 mL) was heated for 3 h in a sealed tube at 230°C to produce a 4:6 mixture (^1H NMR) of tricycle **41*S*** and **42*S***. These were separated and purified by chromatography (10% EtOAc in hexane) to isolate tricycle **41*S*** (22.0 mg, 34.4%) as a colorless oil and tricycle **42*S*** (34.2 mg, 53.4%) as a white foam. Tricycle **41*S*:** $[\alpha]^{28}_D$: -88.8° (c: 1, $CHCl_3$). IR ($CHCl_3$): 2945, 2892, 2240, 1746, 1461. ^1H NMR ($CDCl_3$): 5.78 (1H, dm, J = 10.5 Hz, 7-<u>H</u>) and 5.53 (1H, dt, J=10.5, 3.0 Hz, 6-<u>H</u>), 3.81 (3H, s, $CO_2C\underline{H}_3$), 3.44 and 3.26 (2H, 2d, J = 9.5 Hz, $C\underline{H}_2OCH_3$), 3.33-3.23 (1H, m, 4-<u>H</u>), 3.24 (3H, s, $CH_2OC\underline{H}_3$), 2.81 (1H, dd, J=13.5, 8.0 Hz, 13-$\underline{H}_A$), 2.65 (1H, m, 8-<u>H</u>), 2.44 (2H, AB-d, 11-$\underline{H}_2$), 2.11 (1H, d, J=13.5 Hz, 13-$\underline{H}_B$), 1.90-1.50 and 1.20-1.10 (5H+1H, 2m, 5-<u>H</u>, 4-<u>H</u>, 2-$\underline{H}_2$ and 1-$\underline{H}_2$), 1.14 (3H, d, J=6.5 Hz, 4-C$\underline{H}_3$), 1.07 (21H, s, TIPS), 0.94 (3H, s, 10-C$\underline{H}_3$). ^{13}C NMR ($CDCl_3$): 170.1, 130.0, 128.6, 121.8, 77.6, 76.2, 58.8, 54.4, 53.6, 46.2, 44.0, 43.5, 40.4, 39.6, 38.4, 37.7, 32.2, 31.1, 18.3, 16.7, 15.8, 12.9. MS (*m/z*): 460 $(M\text{-}C_3H_7)^+$. HR-MS, calcd. for $C_{26}H_{42}NO_4Si$ $(M\text{-}C_3H_7)^+$: 460.2883; found: 460.2879. Tricycle **42*S*:** $[\alpha]^{28}_D$: -47.3°(c:1, $CHCl_3$). IR (film): 2944, 2890, 2241, 1748, 1462. ^1H NMR ($CDCl_3$): 5.40-5.30 (2H, m, 6-<u>H</u> and 7-<u>H</u>), 3.85-3.80 (1H, m, 3-<u>H</u>),

3.73 (3H, s, CO_2CH_3), 3.47 and 3.41 (2H, AB-d, J=9.5 Hz, CH_2OCH_3), 3.35 (3H, s, CH_2OCH_3), 2.90 (1H, m, 5-H), 2.80-2.65 (2H, m, 11-H_A and 13-H_A), 2.63 (1H, m, 8-H), 2.37 (2H, d, J = 14.0 Hz, 11-H_B and 13-H_B), 1.95 (1H, m, 4-H), 1.85-1.30 (4H, m, 2-H_2, 1-H_2), 1.05 (21H, s, TIPS), 0.94 (3H, d, J=8.0 Hz, 4-CH_3), 0.92 (3H, s, 10-CH_3). ^{13}C NMR ($CDCl_3$): 170.0, 130.0, 122.3, 76.0, 71.4, 58.8, 55.5, 53.4, 45.6, 43.9, 41.1, 40.9, 39.7, 38.4, 34.0, 27.3, 25.0, 18.1, 16.8, 15.3, 12.2. MS (*m/z*): 460 $(M-C_3H_7)^+$. HR-MS, calcd. for $C_{26}H_{42}NO_4Si$ $(M-C_3H_7)^+$: 460.2883; found: 460.2879.

Methyl (9*R*,10*S*,12*R*)-12-cyano-14-methoxy-3β-(triisopropylsilyl)oxy-15,17,19-trinor-14,16-seco-5α,8β-stemod-6-en-16-oate (41*R*) and Methyl (9*S*,10*R*,12*R*)-12-cyano-14-methoxy-3β-(triisopropylsilyl)oxy-15,17,19-trinor-14,16-seco-5β,8α-stemod-6-en-16-oate (42*R*): A solution of macrocycle **27*R*** (31.0 mg, 61.6 μmol) in toluene (2.0 mL) was heated for 3 h in a sealed tube at 230°C to produce a 9:1 mixture (^1H NMR) of tricycle **41*R*** and **42*R***. These were separated and purified by chromatography (5 to 10% EtOAc in hexane) to obtain tricycle **41*R*** (23.4 mg, 75.5%) as a white foam and tricycle **42*R*** (2.6 mg, 8.4%) as a colorless oil. Tricycle **41*R*:** $[\alpha]^{28}_D$: -73.1° (c: 1, $CHCl_3$). IR ($CHCl_3$): 2945, 2867, 2241, 1745. ^1H NMR ($CDCl_3$): 5.60 (1H, dm, J=10.0 Hz, 7-H), 5.35 (1H, dt, J=10.0, 3.0 Hz, 6-H), 3.78 (3H, s, CO_2CH_3), 3.49 and 3.37 (2H, 2d, J=9.5 Hz, CH_2OCH_3), 3.34 (3H, s, CH_2OCH_3), 3.33-3.23 (1H, m, 3-H), 2.78 (1H, dd, J=13.5, 8.5 Hz, 13-H_A), 2.59 and 2.37 (2H, 2d, J=14.0 Hz, 11-H_2), 2.53 (1H, m, 8-H), 2.32 (1H, d, J=13.5 Hz, 13-H_B), 1.85-1.45 and 1.25-1.10 (5H+1H, 2m, 5-H, 4-H, 2-H_2 and 1-H_2), 1.09 (3H, d, J=6.5 Hz, 4-CH_3), 1.07 (21H, s, TIPS), 0.92 (3H, s, 10-CH_3). ^{13}C NMR ($CDCl_3$): 170.0, 129.9, 127.4, 122.0, 77.5, 76.1, 58.8, 54.6, 53.6, 45.5, 43.4, 43.2, 41.3, 38.5, 38.3, 38.0, 32.2, 31.0, 18.3, 16.6, 15.9, 12.9. MS (*m/z*): 472 $(M-OCH_3)^+$, 460 $(M-C_3H_7)^+$. HR-MS, calcd. for $C_{26}H_{42}NO_4Si$ $(M-C_3H_7)^+$: 460.2883; found: 460.2887. Tricycle **42*R*:** ^1H NMR ($CDCl_3$): 5.60-5.45 (2H, m, 6-H and 7-H), 3.87-3.82 (1H, m, 3-H), 3.81 (3H, s, CO_2CH_3), 3.42 and 3.28 (2H, 2d, J=9.5 Hz, CH_2OCH3), 3.24 (3H, s, CH_2OCH_3), 3.06 (1H, m, 5-H), 2.73 (1H, dd, J=13.0, 8.0 Hz, 13-H_A), 2.70 (1H, m, 8-H), 2.55 and 2.44 (2H, 2d, J=15.0 Hz, 11-H_2), 2.12 (1H, d, J=13.0 Hz, 13-H_B), 2.05-1.20 (5H, m, 4-H, 2-H_2, 1-H_2), 1.07 (21H, s, TIPS), 0.97 (3H, d, J=7.0 Hz, 4-CH_3), 0.95 (3H, s, 10-CH_3).

(9*R*,10*S*,12*R*)-14-oxo-3β-(triisopropylsilyl)oxy-15,17,19-trinor-14,16-seco-5α,8β-stemod-6-en-16-nitrile (43): Me_2AlCl (150 μL, 5 eq, 1M in CH_2Cl_2) was added to a stirred CH_2Cl_2 (5 mL) solution of macrocycle **35*R*** (12.9 mg, 30 μmol) at -40°C under Argon atmosphere. After two hours at this temperature, the reaction was quenched with $NaHCO_3$ (2 mL, 1M). After an aqueous work-up with ether, the product is filtered through a plug of silica to afford 12.8 mg (100%) tricycle **43** as a colorless oil. **43:** $[\alpha]^{24}_D$: -129.3° (c:1, $CHCl_3$). IR ($CHCl_3$): 3026, 2945, 2867, 2241, 1716, 1463. ^1H NMR ($CDCl_3$): 9.74 (1H, s, CHO), 5.73 (1H, d, J=10.5 Hz, 7-H),

5.66 (1H, dt, J=10.5, 3.0 Hz, 6-H), 3.31 (1H, ddd, J=4.9, 9.6, 10.7 Hz, 3-H), 3.08 (1H, m, 8-H), 2.58 (1H, m, 12-H), 2.46 (1H, dd, J=13.1, 7.9 Hz, 11-H_A), 2.20 (1H, m, 13-H_A), 1.97 (1H, dd, J=13.1, 9.2 Hz, 11-H_B), 1.90-1.70 (3H, m, 5-H, 13-H_B, 2-H_A), 1.68-1.35 (4H, m, 4-H, 2-H_B, 1-H_2), 1.14 (3H, d, J=6.2 Hz, 4-CH_3), 1.07 (21H, s, TIPS), 1.02 (3H, s, 10-CH_3). ^{13}C NMR (CD_2Cl_2): 205.1, 130.0, 126.8, 122.8, 77.6, 65.0, 43.4, 38.6, 38.4, 37.9, 35.4, 32.4, 31.5, 30.9, 25.1, 18.4, 16.8, 15.8, 13.2. MS (*m/z*): 386 $(M-C_3H_7)^+$. HR-MS, calcd. for $C_{26}H_{43}NO_2Si$ $(M-C_3H_7)^+$: 386.2515; found: 386.2522.

(9*S*,10*R*,12*S*)-14-oxo-3β-(triisopropylsilyl)oxy-15,17,19-trinor-14,16-seco-5β,8α-stemod-6-en-16-nitrile (44a): The same procedure was applied as for the preparation of **43** but at 0°C instead of -40°C to afford 12.2 mg (95%) tricycle **44a** as a colorless oil. **44a:** $[\alpha]^{24}_D$: +86.6° (c: 1, $CHCl_3$). IR ($CHCl_3$): 3020, 2944, 2866, 2242, 1716, 1464, 1046. ^{1}H NMR ($CDCl_3$): 9.73 (1H, s, CHO), 5.66 (1H, dt, J=10.0, 3.5 Hz, 6-H), 5.44 (1H, dm, J=10.0 Hz, 7-H), 3.90-3.86 (1H, m, 3-H), 3.15 (1H, m, 8-H), 2.95 (1H, m, 5-H), 2.61-2.51 (1H, m, 12-H), 2.41 (1H, dd, J=13.5, 8.0 Hz, 11-H_A), 2.30-1.32 (8H, m, in the order of 13-H_A, 11-H_B, 4-H, 1-H_A, 2-H_A, 13-H_B, 2-H_B, 1-H_B), 1.07 (21H, s, TIPS), 0.98 (3H, s, 10-CH_3), 0.96 (3H, d, J = 8.0 Hz, 4-CH_3). ^{13}C NMR (CD_2Cl_2): 205.4, 130.3, 129.7, 122.8, 71.7, 66.0, 41.1, 38.9, 38.1, 35.4, 34.4, 32.0, 27.7, 25.0, 24.9, 18.3, 18.1, 15.2, 12.7. MS (*m/z*): 386 $(M-C_3H_7)^+$. HR-MS, calcd. for $C_{26}H_{43}NO_2Si$ $(M-C_3H_7)^+$: 386.2515; found: 386.2522.

(9*S*,10*R*)-12-cyano-14-oxo-3β-(triisopropylsilyl)oxy-15,17,19-trinor-14,16-seco-5β,8α-stemod-6-en-16-nitrile (46) and (9*R*,10*S*)-12-cyano-3β-hydroxy-14-oxo-15,17,19-trinor-14,16-seco-5α,8β-stemod-6-en-16-nitrile (45b): To a stirred solution of macrocycle **40** (172 mg, 378 μmol) in CH_2Cl_2 (10 mL), $SnCl_4$ (2.27 mL, 6 eq, 1M in CH_2Cl_2) was added at -78°C. After a 7 days reaction with occasional stirring at 0°C, the reaction was quenched with $NaHCO_3$ (4 mL, 2M) at -78°C. After an aqueous work-up with CH_2Cl_2, ^{1}H NMR spectra shows >98% conversion with a ratio of **46/45b** = 2:9. Chromatography (30% to 100% Et_2O in hexane) afforded 28 mg (16%) **46** and 82 mg (72%) **45b** as colorless oils. Tricycle **46:** $[\alpha]^{24}_D$: +107° (c: 1.8, $CHCl_3$). IR ($CHCl_3$): 2944, 2867, 2250, 1721, 1464. ^{1}H NMR ($CDCl_3$): 9.81 (1H, s, CHO), 5.64-5.58 44 (1H, m, 6-H and 7-H), 3.91-3.87 (1H, m, 3-H), 3.40-3.34 (1H, m, 8-H), 3.04-2.98 (1H, m, 5-H), 2.91 (1H, d, J=15.2 Hz, 11-H_A), 2.75 (1H, d, J=15.2 Hz, 11-H_B), 2.42 (1H, d, J=13.7 Hz, 13-H_A), 2.29 (1H, dd, J=13.7 and 7.3 Hz, 13-H_B), 2.13-2.03 (1H, m, 4-H), 1.83 (2H, AB-d, 2-H_A and 1-H_A), 1.68-1.57 (1H, m, 2-H_B), 1.30-1.20 (1H, m, 1-H_B), 1.08 (21H, s, TIPS), 1.06 (3H, s, 10-CH_3), 0.97 (3H, d, J=7.8 Hz, 4-CH_3). ^{13}C NMR ($CDCl_3$): 202.9, 133.1, 127.1, 116.7, 116.6, 70.9, 66.0, 42.1, 40.6, 39.7, 39.2, 38.7, 33.8, 31.6, 27.3, 24.3, 18.1, 17.6, 14.9, 12.2. MS (*m/z*): 411 $(M-C_3H_7)^+$. HR-MS, calcd. for $C_{24}H_{35}N_2O_2Si$ $(M-C_3H_7)^+$: 411.2468; found: 411.2471. Tricycle **45b:** $[\alpha]^{24}_D$: -202° (c: 2, $CHCl_3$). IR ($CHCl_3$): 3516, 3275(br), 2934, 2256, 1712, 1455.

^{1}H NMR ($CDCl_3$): 9.84 (1H, s, C<u>H</u>O), 5.90 (1H, dd, J=10.2, 1.7 Hz, 7-<u>H</u>), 5.67 (1H, dt, J=10.2, 3.1 Hz, 6-<u>H</u>), 3.31 (1H, m, 8-<u>H</u>), 3.18 (1H, ddd, J=10.8, 9.8, 5.1 Hz, 3-<u>H</u>), 3.02 (1H, d, J=14.9 Hz, 11-<u>H</u>$_A$), 2.55 (1H, d, J=14.9 Hz, 11-<u>H</u>$_B$), 2.42 (1H, dd, J=13.9, 1.3 Hz, 13-<u>H</u>$_A$), 2.29 (1H, dd, J=13.9, 7.3 Hz, 13-<u>H</u>$_B$), 1.93-1.85 (1H, m, 4-<u>H</u>), 1.78 (1H, ddd, J=11.4, 3.1, 1.7 Hz, 5-<u>H</u>), 1.65-1.28 (4H, m, 2-<u>H</u>$_2$, 1-<u>H</u>$_2$)1.16 (3H, d, J=6.2 Hz, 4-C<u>H</u>$_3$), 1.12 (3H, s, 10-CH_3). ^{13}C NMR ($CDCl_3$): 202.7, 129.6, 127.0, 116.7, 116.3, 75.6, 65.1, 43.0, 41.7, 39.5, 38.2, 38.1, 36.8, 31.9, 31.4, 29.6, 16.3, 15.0. MS (*m/z*): 251 $(M-H_2O-CHO)^+$, 280 $(M-H_2O)^+$, 411 $(M)^+$. HR-MS, calcd. for $C_{18}H_{22}N_2O_2$ $(M)^+$: 298.1681; found: 298.1688.

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