Transannular Diels–Alder/Intramolecular Aldol Tandem Reaction as a Stereocontrolled Route to (+)-Aphidicolin and its Isosteric C8-Epimer[1]

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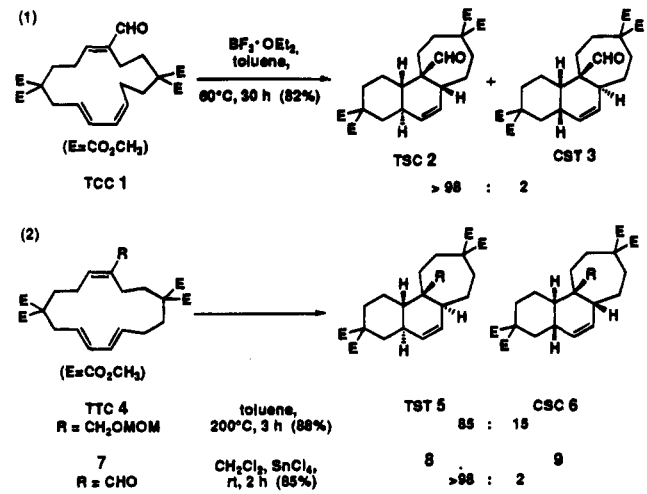
The *trans,syn,cis* A.B.C.[6.6.7] tricyclic subunit of aphidicolin could be derived from the transannular Diels–Alder (TADA) reaction of a *trans,cis,cis* (TCC) cyclopentadecatriene. On the other hand, a *trans,trans,cis* (TTC) isomeric cyclopentadecatriene could lead to the *trans,syn,trans* tricyclic skeleton of aphidicolin's C8-epimer. Interestingly, semiempirical calculations have shown the latter to be isosteric with aphidicolin in respect to the four hydroxyl groups. The required TCC and TTC 15-membered macrocyclic trienes **46** and **59** were synthesized using modern methods of acyclic stereoselection such as an organocopper-based difunctionalization reaction, Evans' asymmetric aldol methodology and Wittig–Horner–Wadsworth reactions. At the end, an efficient macrocyclization protocol served in achieving the synthesis of the desired optically active precursors **46** and **59**. Whereas TCC substrate **46** failed to realize a TADA cycloaddition for steric and conformational reasons, TTC cyclopentadecatrienal **59** led to a stereospecific TADA/aldol tandem reaction. In the first reported example of such a transformation, macrocycle **59** was thermolyzed (toluene, sealed tube, 210 °C, 18 h) in a single operation into tetracyclic product **61** containing six new stereogenic centers. Mechanistic considerations of this impressive conversion along with transition-state modeling are also presented. Further transformations of compound **61** culminating in stereospecific functionalization at C16 were performed by making use of an hydroxyl-directed epoxidation reaction leading to the advanced intermediate **67**. Thus, this exploratory work demonstrates the value of a TADA/aldol route for the synthesis of the titled compounds and analogs thereof.

Introduction

In the recent years, the transannular Diels–Alder (TADA) reaction of macrocyclic trienes has emerged as a powerful transformation with obvious potential in view of synthesizing natural products and analogs.[2] In particular, fundamental studies from our group have revealed the one-step stereospecific conversion of *trans,-cis,cis* (TCC)[3] and *trans,trans,cis* (TTC)[4] cyclopentadecatrienes **1** and **7** to the respective *trans,syn,cis* (TSC) and *trans,syn,trans* (TST) A.B.C[6.6.7] tricyclic products **2** and **8** (Scheme 1). Such structures are closely related to the complex skeleton of (+)-aphidicolin (**10**) (Scheme 2), a potent antibiotic produced by the mold *Cephalosporium aphidicola* Petch.[5] Aphidicolin (**10**) was found to exert its biological action[6,7] through specific inhibition of eucaryotic DNA α-polymerase,[8] thus only attacking proliferating cells. As a result, it shows interesting promise as an antitumoral agent employed in the form of an hydrosoluble prodrug.[9] The structural features of this tetrol include a rather unusual tetracyclic framework with a spiro-fused bicyclo[3.2.1]octane moiety constitut-

Scheme 1



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(6) For its marked activity against Herpes Simplex Type I virus, both *in vitro* and in the rabbit eye: (a) Bucknall, R. A.; Moores, H.; Simms, R.; Hesp, B. *Antimicrob. Agents Chemother.* **1973**, *4*, 294. (b) Ikegami, S.; Taguchi, T.; Ohashi, M.; Oguro, M.; Nagano, H.; Mano, Y. *Nature (London)* **1978**, *275*, 458. For its antitumor activity in the C6 mouse colon and B16 mouse melanosarcoma screens: (c) Douros, J.; Suffness, M. In *New Anticancer Drugs*; Carter, S. K., Sakurai, Y., Eds.; Springer-Verlag: Berlin, 1980; p 29. For its inhibiting action on the growth of leukemic T- and B-lymphocytes: (d) Pedrali-Noy, G.; Belvedere, M.; Crepaldi, T.; Focher, F.; Spedari, S. *Cancer Res.* **1982**, *42*, 3810.

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(8) Ohashi, M.; Taguchi, T.; Ikegami, S. *Biochem. Bioophys. Res. Commun.* **1978**, *82*, 1084.

(9) Poor water solubility and rapid *in vivo* deactivation by liver microsomal oxidase (refs 7b and 10) have been the main hurdle to the development of aphidicolin as an antitutumor agent. However, the 17-glycinate ester hydrochloride salt shows increased solubility in water and is presently in clinical trial in Europe (see note 36 in ref 15): O'Dwyer, P. J.; Moyer, J. D.; Suffness, M.; Plowman, J. *Proceedings of the Seventy-Sixth Annual Meeting of the American Association for Cancer Research;* May 22–25, 1985; Houston, TX; Abstract 1009.

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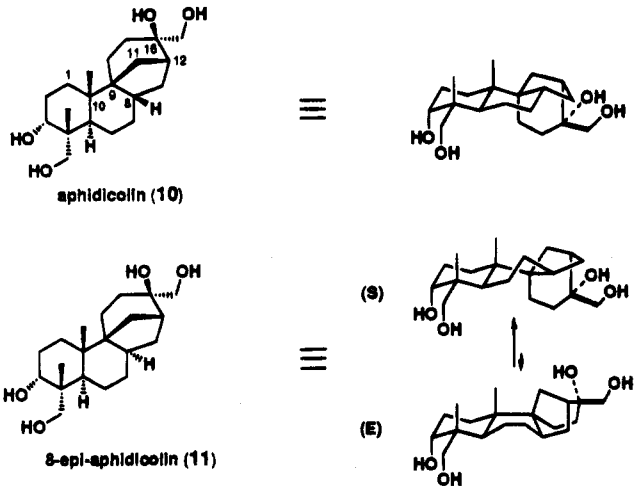
Scheme 2



ing rings C/D. Accordingly, such interesting characteristics have made aphidicolin (**10**) the subject of several synthetic efforts[11-14] culminating in nine total syntheses of which a single one, reported by Holton's group,[11g] was enantioselective. Moreover, most of these approaches faced without ease the difficult issue of elaborating the vicinal diol unit from the corresponding C16 ketone, which offers a poor facial steric bias.[15] Hence, aphidicolin (**10**) (and derivatives thereof) still stands as a challenging synthetic target and is indeed an appealing prototype product to verify the suitability of the TADA strategy as applied to cyclopentadecatrienes.

As shown in Scheme 1 (eq 1), TCC cyclopentadecatrienes can lead to the required TSC A.B.C[6.6.7] tricyclic substructure of aphidicolin (**10**), although with rather rigorous conditions (Lewis acids, 60 °C) caused by the sterically disfavored *trans-cis* diene component.[16] Going to a tetrasubstituted dienophile should further raise the temperature of activation and a functionalized macrocyclic substrate might not survive such a treatment with strong Lewis acids (*vide infra*). On the other hand, TTC model analog (eq 2) can lead with more ease to a TST tricycle which could serve, upon C/D bridging, as a precursor of 8-epiaphidicolin (**11**) (Scheme 2). This analog of **10** is also highly interesting from a pharmaceutical point of view. Whereas **10** embodies a rigid B-ring in chair conformation, molecular model analysis of **11** reveals a high degree of flexibility for the same ring and shows two possible boat conformers S and E (Scheme 2). However, conformer S should be highly favored since it minimizes steric strain between the two adjacent quaternary carbons (C9–C10) through a staggered (S) conformation as opposed to conformer E in which the same carbons are eclipsed (E). As a result, the inversion at C8 of **11** is apparently compensated relative to **10** and the four alcohol functions of both epimers are expected to coincide spatially. Actually, the following molecular modeling experiments corroborated this preliminary analysis. Geometry optimization of aphidicolin (**10**) and its C8-epimer **11** was performed using the semiempirical Hamiltonian AM1.[17] Compound **11** indeed exhibited the S conformation predicted above and graphic superposition with **10** showed a near-perfect fit of the four sets of hydroxyl functions (Figure 1). Therefore, aside from their carbon skeleton, **10** and **11** can be mutually considered as being isosteric. Accordingly, they should exhibit a comparable biological activity knowing that the diol moieties were previously identified as key pharmacophores of aphidicolin.[18]

In this article, we report our first investigations directed toward the enantiocontrolled synthesis of aphidicolin (**10**) and its C8-epimer **11** using the TADA reaction as a central strategy.

Retrosynthetic Approach

Our projected retrosynthetic plan, illustrated on Scheme 3 for aphidicolin (**10**), is also valid for **11** by replacing the diene of *E,Z* geometry by a (*E,E*)-diene. Aphidicolin (**10**) could be formally synthesized from the known C16-keto derivative (*cf.* **12**) through the use of Smith diastereoselective protocol.[15] Generation of the tetrasubstituted thermodynamic enolate of **12**, followed by formaldehyde aldol condensation from the α-face, as observed by Ireland,[11d] would complete the synthesis. Intramolecular enolate alkylation on **13** would create the spiro-fused 5-membered ring expectedly without competition from the 4-membered ring closure. The TSC compound **13** would derive from TCC macrocyclic precursor **14** through a highly diastereoselective TADA reaction proceeding

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(14) For other approaches to the ring system of aphidicolin, see: (a) Nicolaou, K. C.; Zipkin, R. E. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 785. (b) Kametani, T.; Honda, T.; Shiratori, Y.; Mausumoto, H.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1386. (c) Cargill, R. L.; Bushey, D. F.; Dalton, J. R.; Prasad, R. S.; Dyer, R. D.; Bordner, J. *J. Org. Chem.* **1981**, *46*, 3389. (d) Pearson, A. J.; Heywood, G. C.; Chandler, M. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2631. (e) Kelly, R. B.; Sankar Lal, G.; Gowda, G.; Rej, R. N. *Can. J. Chem.* **1984**, *62*, 1930. (f) Iwata, C.; Morie, T.; Maezaki, N.; Shimamura, H.; Tanaka, T.; Imanishi, T. *J. Chem. Soc., Chem. Commun.* **1984**, 930. (g) Koyama, H.; Okawara, H.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1985**, *26*, 2685. (h) Bell, V. L.; Giddings, P. J.; Holmes, A. B.; Mock, G. A.; Raphael, R. A. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1515. Bell, V. L.; Holmes, A. B.; Hsu, S. Y.; Mock, G. A.; Raphael, R. A. *J. Chem. Soc., Perkin Trans 1* **1986**, 1507. (i) White, J. D.; Somers, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 4424. (j) Robichaud, A. J.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2607. (k) Ref. 3.

(15) For a related discussion and a solution to this problem, see: Rizzo, C. J.; Smith, A. B., III. *Tetrahedron Lett.* **1988**, *29*, 2793; *J. Chem. Soc., Perkin Trans. 1* **1991**, 969.

(16) Unfavorable steric repulsions in the reactive S-*cis* conformation make them poorly reactive. For a review, see: Fringuelli, F.; Taticchi, A. Dienes in the Diels–Alder Reaction; Wiley: New York; 1990.

(17) Computational procedure: All the calculations were done at the RHF level. The first input files for MOPAC 6.00 were created by means of SYBYL 6.01 (Tripos Associates, Inc.: 16995 Hanley Rd, Suite 303, St. Louis, MO 63144-2913) for IBM RISC 6000 computers. The gradients of the norm of these draft structures were then fully optimized using EF or TS subroutines. Finally, all the transition structures were characterized by only one negative force constant. The calculations were carried out on IBM RISC 6000 computers.

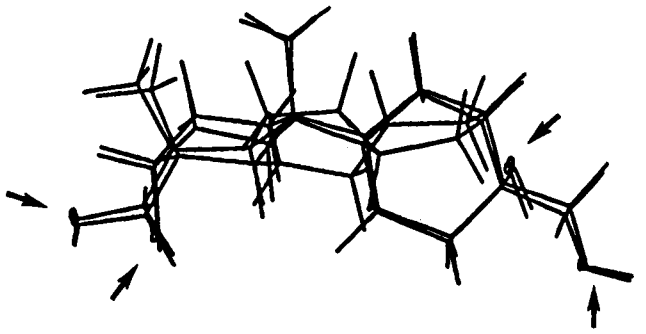
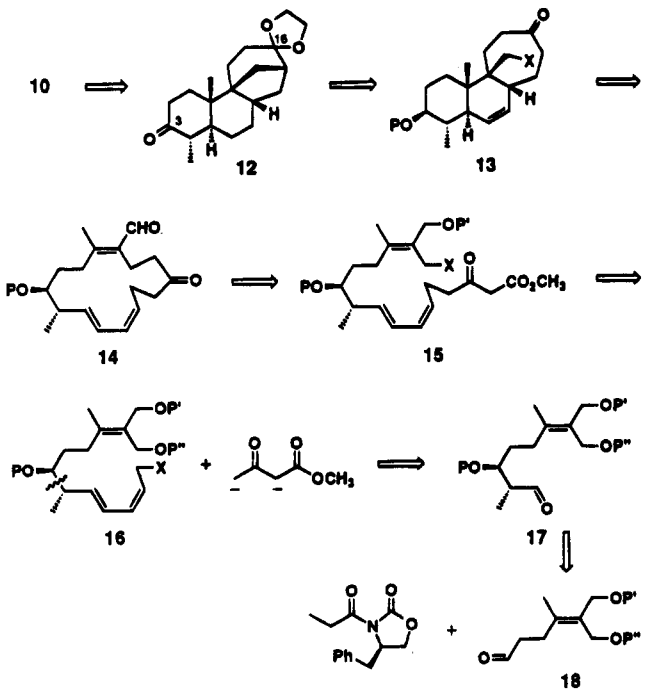


Figure 1. Superposition of geometry-optimized (AM1) **10** and **11** (OH are pointed).

Scheme 3



through an endo approach. The alternative exo approach is not allowed as it would lead to a strained B.C *trans*-diaxial ring junction at transition state level.[3] The configuration of the C4-methyl substituent is foreseen to assure the absolute stereochemistry of **13** by operating an efficient chirality induction process. With a β-alkoxy group as a disguised C3 ketone, incipient ring A in chair conformation should prefer transition state A with C4-methyl in equatorial position (Figure 2). The competing diastereotopic transition state B with the C4-methyl group in axial position is disfavored as it develops a severe 1,3-diaxial interaction with the C10-methyl group. The required macrocycle **14** could then be formed via a mild intramolecular allylic alkylation of β-keto ester **15**, itself made from precursor **16** and methyl acetoacetate dianion. The suggested route to **16** involves Evans' enantioselective aldol methodology[19] and implies stereo-

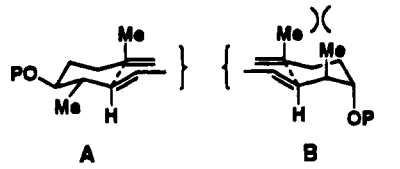
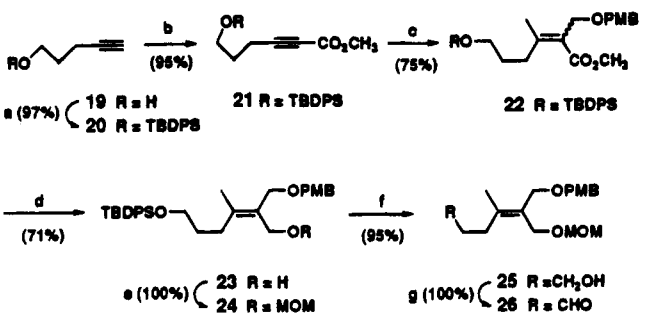


Figure 2. Diastereotopic *endo* transition states.

Scheme 4[a]



[a] (a) Imidazole, TBDPSCl, THF, rt, 1.5 h; (b) nBuLi, THF, −78 °C to −20 °C; then $ClCO_2CH_3$, −20 °C to rt, 2 h; (c) Me_2CuLi, THF, −78 °C, 1 h; then [(*p*-methoxybenzyl)oxy]methyl chloride, −78 °C to 0 °C, 4 h, (*Z*/*E* = 7:1); (d) DIBALH, CH_2Cl_2, −78 °C, 1.5 h, *Z*/*E* chromatographic separation; (e) DIPEA, MOMCl, CH_2Cl_2, rt, 11 h; (f) TBAF, THF, rt, 2 h; (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt, 1 h.

selective diene elongation from aldehyde **17**. At the onset, the strategy requests the apparently difficult task of preparing a tetrasubstituted dienophilic synthon **18** with an acceptable stereoselection.

Results and Discussion

The efficient construction of large carbocycles such as the ones required in this study stands as a considerable challenge by itself.[20] Our work was first directed toward the preparation of a TCC cyclopentadecatriene substrate as a direct TADA approach to the aphidicolin skeleton.

Preparation and Thermolysis of TCC Macrocyclic Trienes 69 and 72. The construction of (*Z*)-tetra-C-substituted α-alkoxymethyl α,β-unsaturated ester **22** (Scheme 4) was achieved using our reported extension[21] of Corey/Siddall methodology of organocopper conjugate addition on acetylenic esters.[22] Thus, substrate **21** was prepared in near-quantitative yields by silylation of 3-butynol (**19**) followed by acetylide acylation of **20** with methyl chloroformate. A selective tandem *cis*-difunctionalization of **21** was then carried out by conjugate addition of lithium dimethyl copper and trapping of the resulting α-carbalkoxy vinylcopper intermediate with [(*p*-methoxybenzyl)oxy]methyl chloride (PMBCl).[23] Thus, pure (*E*)-allylic alcohol **23** was isolated in 53% overall

(18) For biological evaluation of aphidicolin derivatives synthesized by microbial or chemical ways, see refs 6a, 15, and: (a) Ipsen, J.; Fuska, J.; Foskova, A.; Rosazza, J. P. *J. Org. Chem.* **1982**, *47*, 3278. (b) Haraguchi, T.; Oguro, M.; Nagano, H.; Ichihara, A.; Sakamura, S. *Nucleic Acids Res.* **1983**, *11*, 1197. (c) Ipsen, J.; Rosazza, J. P. *J. Nat. Prod.* **1984**, *47*, 497. (d) Ichihara, A.; Oikawa, H.; Hayashi, K.; Hashimoto, M.; Sakamura, S.; Sakai, R. *Agric. Biol. Chem.* **1984**, *48*, 1687. (e) McMurry, J. E.; Webb, T. R. *J. Med. Chem.* **1984**, *27*, 1367. (f) Hiranuma, S.; Shimizu, T.; Yoshioka, H.; Ono, K.; Nakane, H.; Takahashi, T. *Chem. Pharm. Bull.* **1987**, *35*, 1641.

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(22) (a) Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 1851. (b) Siddall, J. B.; Biskup, M.; Fried, J. H. *J. Am. Chem. Soc.* **1969**, *91*, 1853.

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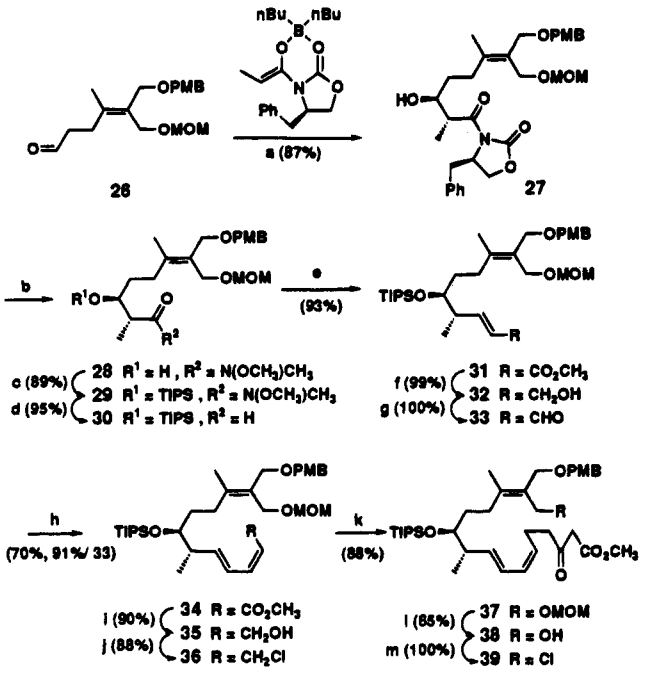
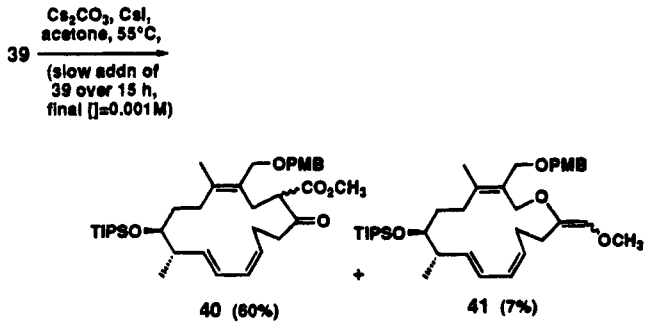
Scheme 5[a]



[a] (a) (*R*)-3-(1-Oxopropyl)-4-benzyl-2-oxazolidinone, nBu_2BOTf, CH_2Cl_2, 0 °C to −78 °C; and then **26**, −78 °C, 2 h; −60 °C, 4 h; (b) $HN(OCH_3)CH_3$ HCl, $AlMe_3$, rt, 4.5 h; (c) 2,6-lutidine, TIPSOTf, CH_2Cl_2, 0 °C to rt, 0.5 h; (d) DIBALH, THF, −90 °C, 1 h; (e) NaH $(EtO)_2P(O)CH_2CO_2CH_3$, THF, 0 °C, 1.5 h; (f) DIBALH, THF, −78 °C, 1.5 h; (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt, 1 h; (h) $(CF_3CH_2O)_2P(O)CH_2CO_2CH_3$, 18-crown-6, $KN(TMS)_2$, THF, −78 °C; then **33**, −78 °C to 0 °C, 4 h; (i) DIBALH, CH_2Cl_2, THF, −78 °C, 1 h; (j) *s*-collidine, LiCl, MsCl, DMF, 0 °C, 5 h; (k) NaH, $CH_3COCH_2CO_2CH_3$, nBuLi, THF, 0 °C; then **36**, 0 °C, 0.5 h; (l) $HCl_{(aq)}$, iPrOH, 55 °C, 10 h; (m) PPh3, $(Cl_3C)_2CO$, rt, 2.5 h.

yield after ester reduction of **22** and chromatographic separation of the 6:1 *E*/*Z* mixture. Etherification with methoxymethyl chloride (MOMCl), desilylation, and Swern oxidation[24] of the resulting alcohol **25** proceeded in 95% combined yield leading to 0.1 mol quantities of aldehyde **26**. A syn-propionate Evans' boron–aldol condensation[19,25] with (*R*)-3-(1-oxopropyl)-4-benzyl-2-oxazolidinone[26] afforded adduct **27** in 87% yield (Scheme 5). At this point, the stereochemical assignment of **27** was made on the sole basis of literature precedents. The oxazolidone-based chiral auxiliary was removed via transamidation according to Weinreb's technique,[27] giving amide **28** on which secondary alcohol protection as a triisopropylsilyl ether gave **29** in 89% combined yield. Then, aldehyde **30** was obtained in 95% yield through a low-temperature (−90 °C) monoreduction of the *N*,*O*-dimethylhydroxylamide function with DIBALH. Diene elaboration from **30** proceeded via a first Horner–Emmons–Wadsworth olefination,[28] giving a 98% combined yield of (*E*,*Z*)-α,β-unsaturated esters **31** (^{1}H NMR ratio: *E*/*Z* = 16:1), mutually separable by silica gel chromatography. The *E* isomer was converted almost quantitatively to enal **33**

Scheme 6



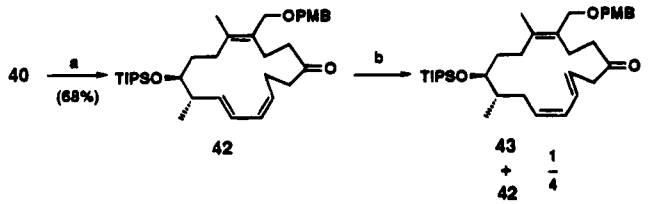
via a DIBALH reduction/Swern oxidation[24] sequence.[29] The second double bond was then introduced in 70% yield (91% based on recuperated **33**) with very high selectivity using Still (*Z*)-variant,[30] affording *E*,*Z* doubly unsaturated ester **34**. The latter was reduced with DIBALH, giving allylic alcohol **35** (90% yield) which was converted in 88% yield to the sensitive allylic chloride **36** using Meyers method.[31] This compound was alkylated without delay with methyl acetoacetate dianion,[32] yielding β-keto ester **37** (88% yield).

Even with extensive attempts under most literature conditions[33] employing various Brønsted and Lewis acids, the allylic MOM ether of **37** could only be cleaved to alcohol **38** with a modest 65% yield (74% based on recuperated **37**) using concentrated aqueous HCl in isopropyl alcohol. Significant amount of side products appeared with prolonged reaction times and seemed to originate from cleavage of the PMB ether. This time, allylic chlorination was better carried out with the hexachloroacetone (HCA)/triphenylphosphine system,[34] affording macrocyclization acyclic substrate **39** (~95% yield, homogeneous on TLC). Intramolecular displacement of the latter employed pseudo-high dilution conditions inspired from our earlier work,[35] using cesium carbonate as a base with added cesium iodide in near refluxing acetone (Scheme 6). Doing so, a 60% two-step yield of desired macrocyclic β-keto ester **40** (1:1 mixture of epimers at C14) was isolated with a minor amount of presumed *O*-alkylation product **41**. The absence of iodide ion resulted in increased proportions of the minor product. No dimerization products were observed, the lacking material being more likely lost through decomposition of the sensitive allylic halide substrate. Although still succeeding, cyclization at room temperature did not help in slowing degradation and raising the yield of **40**. Thus, by virtue of its mildness and truly acceptable yield, the macrocyclization process just described is exceptionnaly efficient considering steric crowding around the allylic chloride brought by the tetrasubstituted alkene.

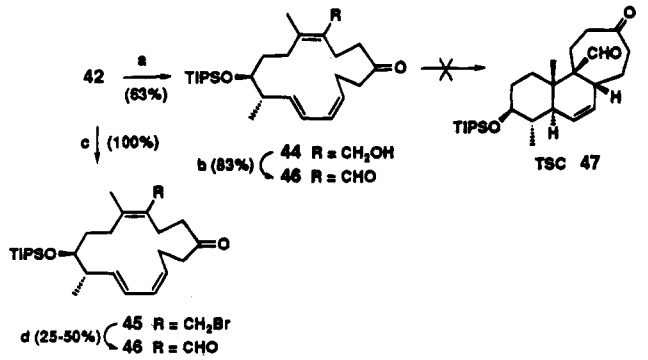
Demethoxycarbonylation of C14 epimers **40** was carried out according to conditions developed by Krapcho[36] (Scheme 7), giving optically pure TCC macrocyclic triene

(24) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
(25) For recent applications of this methodology similar to the following sequence, see: Evans, D. A.; Black, C. *J. Am. Chem. Soc.* **1993**, *115*, 4497 and references therein.
(26) Evans, D. A.; Gage, J. R. *Org. Synth.* **1989**, *68*, 77, 83.
(27) (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *18*, 4171. (b) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989.
(28) Spino, C.; Liu, G.; Tu, N.; Girard, S. *J. Org. Chem.* **1994**, *59*, 5596.
(29) The direct half-reduction of **31** to aldehyde **33** using reported procedures was not successful.
(30) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
(31) Collington, E. W.; Meyers, A. I. *J. Org. Chem.* **1971**, *36*, 3044.
(32) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.
(33) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991; pp 17–20.
(34) Magid, R. M.; Fruchey, O. S.; Johnson, W. L.; Allen, T. G. *J. Org. Chem.* **1979**, *44*, 359.
(35) (a) Baettig, K.; Dallaire, C.; Pitteloud, R.; Deslongchamps, P. *Tetrahedron Lett.* **1987**, *28*, 5249. (b) Baettig, K.; Marinier, A.; Pitteloud, R.; Deslongchamps, P. *Tetrahedron Lett.* **1987**, *28*, 5253.
(36) Krapcho, A. P. *Synthesis* **1982**, *805*, 893.

Scheme 7



Scheme 8[a]

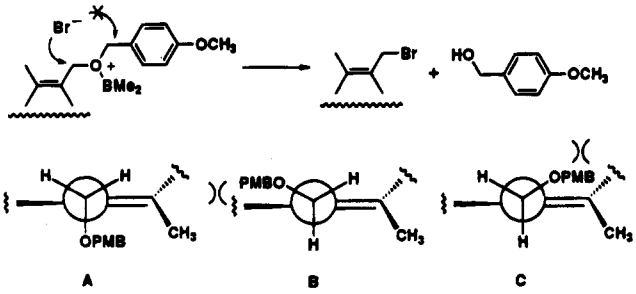


[a] (a) DDQ, 18:1 CH_2Cl_2/H_2O, rt, 50 min; (b) Dess–Martin periodinane, CH_2Cl_2, rt, 1 h; (c) Me_2BBr, CH_2Cl_2, 0 °C, 5 min; (d) $(n\text{-}Bu_4N)_2Cr_2O_7$, $CHCl_3$, 50 °C; or DMSO, Ag_2CO_3, Et_3N, CH_2Cl_2, rt.

42 (68–80% yield) which was fully characterized by standard spectroscopic methods. In particular, ^1H NMR coupling constants and COSY experiments have ascertained the geometrical integrity of the *E,Z* diene component. Attempts to improve the yield of the last tranformation using PhSK/PhSH[37] were fruitless as diene scrambling occurred through inversion of olefins.

Although unpromising owing to recent model studies,[3] thermolysis of unactivated candidate **42** was nevertheless attempted (Scheme 7). No TADA products were indeed observed even under heating at 300 °C in a quartz sealed tube. Instead, **42** was expectedly found to slowly isomerize at 200 °C, giving ca. 20% of CTC macrocycle **43** resulting from a 1,5-sigmatropic hydrogen shift on the diene moiety. Compound **43** was identified on the basis of its ^1H NMR spectra. From now on, our hope of constructing a functionalized TSC A.B.C[6.6.7] tricycle as a direct route to aphidicolin relied on activated analog **46** (Scheme 8), on which Lewis acid catalysis offers several opportunities.[38] However, much to our surprise, formation of alcohol **44** through removal of the allylic *p*-methoxybenzyl protecting group was a problematic issue. To this end, most of the reported methods[39] were tried without success. Among others, hydrogenolytic methods resulted in partial double-bond reduction and electrochemical oxidation failed entirely. Interestingly, upon treatment of **42** at 0 °C with an excess of Guindon's reagent, dimethylboron bromide,[40] substitution occurred cleanly at the allylic site in lieu of the anticipated cleavage at the benzylic methylene group (Scheme 8). Actually, allylic bromide **45** could be formed in less than 5 min at −78 °C!

Scheme 9



We suggest that a conformational effect may account for the apparently anomalous reactivity of **42**. Indeed, the CH_2OPMB moiety of **42** could be virtually frozen in conformation A (Scheme 9) in order to avoid the allylic interactions with the neighboring alkene substituents as in rotamers B and C. Rotamer A with periplanar σ^*(C–O) and π(C–C) bonds is the stereoelectronically favored one toward allylic nucleophilic substitution.[41] Specific cleavage at this site would be explained since the competing PMB–O bond is apparently not subjected to the same conformational constraints. It is noteworthy to mention that a similar theoretical treatment can apply for **39** as well and rationalize for the facile macrocyclization of this crowded allylic chloride. Unfortunately, the obtention of labile bromide **45** remained useless so far. Further transformation to aldehyde **46**, either with *n*-tetrabutylammonium dichromate (TBADC)[42] or Ag_2CO_3-assisted dimethyl sulfoxide oxidative displacement,[43] gave nonreproducible yields in the 25–50% range.

At the end, the key TCC formyl-substituted macrocycle **46** could be obtained via a sluggish alcohol deprotection of **42** (Scheme 8) with DDQ[44] (63% yield). Considerable loss of material ensued from this rather disappointing yield and prior deprotection investigations.[45] Indeed, deprotection of primary allylic PMB ethers with DDQ usually proceed efficiently without complications[46] such as overoxidation. The resulting allylic alcohol **44** was then oxidized to **46** in 83% yield with the Dess–Martin periodinane.[47]

Following the example of macrocyclic triene **42**, earlier model studies were not encouraging for the uncatalyzed thermolysis of **46** to TSC tricycle **47**. Thus, substrate **46** gave no traces of TADA products around 200 °C and self-degraded substantially over 250 °C in a sealed tube. According to model compound **1**, Lewis acid catalysis could be applied with success to the difficult case of macrocycle **46**. However, although the latter resisted to the presence of excess tin tetrachloride or boron trifluoride etherate for a few hours at 100 °C in toluene, no

(37) Holton, R. A.; Kim, H.-B.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, P.D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Sukuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1599.

(38) For a review on existing methods to accelerate Diels–Alder reactions, see: Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741.

(39) See ref 33, pp 47–55.

(40) Guindon, Y.; Yoakim, C.; Morton, H. E. *J. Org. Chem.* **1984**, *49*, 3912.

(41) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; pp 172–174.

(42) Landini, D.; Rolla, F. *Chem. Ind.* **1979**, 213.

(43) (a) Ganem, B.; Boeckman, R. K., Jr. *Tetrahedron Lett.* **1974**, 917. (b) Lavallée, J.-F.; Rej, R.; Courchesne, M.; Nguyen, D.; Attardo, G. *Tetrahedron Lett.* **1993**, *34*, 3519.

(44) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.

(45) Ketone α,β-dehydrogenation should not compete in this case since reaction on the corresponding ethylene ketal gave poor yields as well. The use of pH 7 buffer instead of water did not help further. As excess DDQ was found to be detrimental to the reaction, we suggest that this primary tetrasubstituted allylic alcohol might be prone to overoxidation, going to the acrylic acid.

(46) For a recent example, see: Nicolaou, K. C.; Nadin, A.; Leresche, J. E.; La Greca, S.; Tsuri, T.; Yue, E. W.; Yang, Z. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2187.

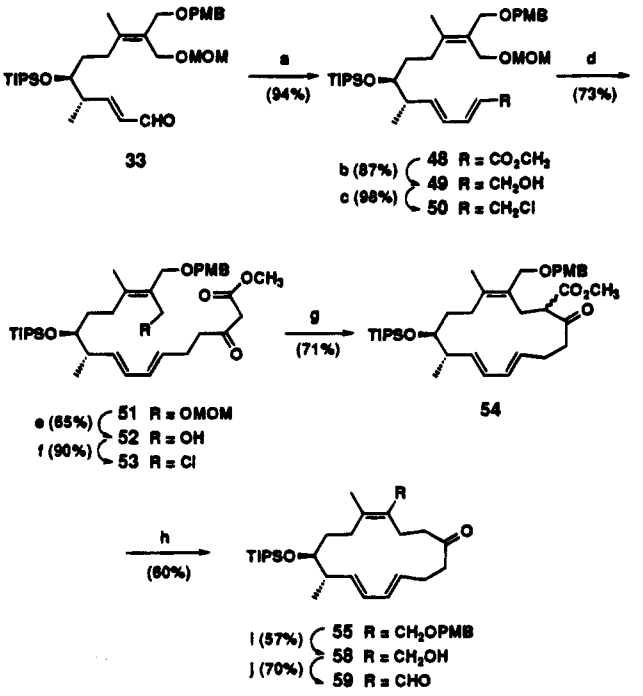
(47) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

reaction occurred.[48] Prolonged stirring under reflux led to extensive decomposition. Milder lanthanide acids such as Yb(fod)$_3$ were also ineffective at higher temperatures (150–250 °C).[49] Last chance attempts using microwave thermal activation[50] and ultrahigh pressures[38] (18 kbar, 24 h) were also vain. Thus, at the end, the combination of several difficulties normally associated with Diels–Alder reactions; namely a *trans,cis* open-chain diene, a tetrasubstituted dienophile, and concurrent formation of a 7-membered ring,[51] undermined our ambitious direct strategy to aphidicolin (**10**). Compared to **1**, the addition of a methyl group on the dienophile led to a significant raise in the energy of activation required for **46**. Obviously, this was highly detrimental to the TADA reaction of **46** leading to **47**. Therefore, on the basis of these results we decided to investigate the isomeric TTC cyclopentadecatrienes, which TADA reaction should prove feasible owing to the more favorable *cisoid* reactive conformation of the *trans,trans* diene.

Preparation and Thermolysis of TTC Macrocyclic Trienes 55 and 59. In principle, the TTC isomer of macrocycle **46** (i.e. **59** in Scheme 10) can lead to a TST (6.6.7) tricycle which constitutes a valuable intermediate for the construction of aphidicolin C8-epimer (**11**). All attempts in effecting the *E,Z* → *E,E* diene isomerization[52] on **42** (I_2 or PhSSPh, with or without a sunlamp) were not conclusive. Hence, *E* enal **33** acted as a common intermediate for synthesizing the desired TTC cyclopentadecatriene **59** (Scheme 10). A Wittig reaction between aldehyde **33** and methyl (triphenylphosphoranylidene)-acetate gave a 94% yield of pure *E,E* diene **48** after chromatographic separation of the crude mixture of isomers (^{1}H NMR ratio: **48**/**34** = 20:1). The next chemical steps leading to **59** were similar to those subjected to *E,Z* doubly unsaturated ester **34**. Thus, DIBALH reduction of **48** afforded allylic alcohol **49** in high yield (87%). Transformation of this intermediate to β-keto ester **51** via chloride **50** occurred in 72% overall yield. The laborious hydrolytic reaction leading to alcohol **52** was carried out in 65% yield upon two recycling operations. Then, allylic chlorination gave **53** in 90% yield, and macrocyclization of this *E,E,Z* pentadecatriene, now performed in acetonitrile,[53] yielded cyclic β-keto ester **54** in 71% yield (1:1 mixture of epimers at C14, only 4% of *O*-alkylation product). Finally, intermediate **54** was demethoxycarbonylated to give **55** (60–70% yield). According to ^{1}H NMR analysis, the *trans,trans* geometry of the diene was conserved along the sequence just described.

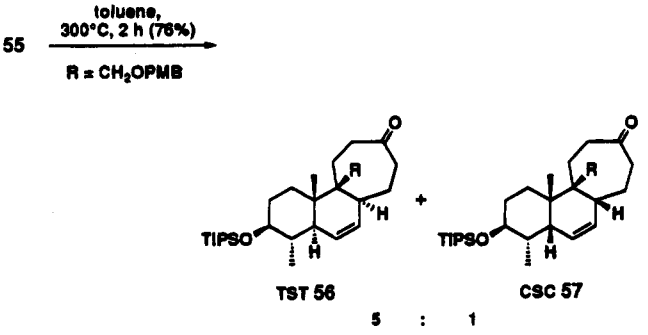
Upon heating at 300 °C (sealed tube, toluene, 2 h), unactivated TTC cyclopentadecatriene **55** gave a 5:1 ratio of tricyclic diastereomers **56** and **57**[54] (Scheme 11). The major one (**56**) was identified by chemical correlation with **60** (*vide infra*) through DDQ-promoted PMB cleavage and oxidation of the resulting mixture of alcohols. Energy

Scheme 10[a]



[a] (a)$Ph_3PCH_2CO_2CH_3$, CH_2Cl_2, rt, 90 h; (b) DIBALH, CH_2Cl_2, −78 °C, 1 h; (c) *s*-collidine, LiCl, MsCl, DMF, 0 °C, 7 h; (d) NaH, $CH_3COCH_2CO_2CH_3$, nBuLi, THF, 0 °C; and then **50**, 0 °C, 0.5 h; (e) $HCl_{(aq)}$, iPrOH, 55 °C, 6 h (3×); (f) PPh_3, $(Cl_3C)_2CO$, rt, 0.5 h; (g) Cs_2CO_3, CsI, CH_3CN, 65–70 °C; slow addition of **53** over 18 h (final conc = 0.001 M); (h) NaCN, H_2O, DMSO, 130 °C, 8 h; (i) DDQ, CH_2Cl_2/H_2O 18:1, rt, min; (j) Dess–Martin periodinane, CH_2Cl_2, rt, 1.5 h.

Scheme 11



minimization (AM1 program)[17] of *endo* and *exo* transition states (Figure 3), leading respectively to **56** and **57**, concurred with the experimental ratio. The higher energy of the disfavored *exo* transition state can be explained by the pseudo-axial position of C6 and C7 in the developing rings A and C. In the *endo* transition state, the same carbons occupy pseudo-equatorial positions. It is interesting to mention that the TADA reaction of **55** was only complete to the extent of ca. 50% at 250 °C for 13 h. Accordingly, when compared to **4**, this observation allows a rough estimation of the rather impressive cost for the activation temperature (ca. +100 °C) upon inclusion of the methyl group on the dienophile. Indeed, three new C–C gauche interactions are created as the TST (*endo*) chair–boat–twist chair (Figure 3)

(48) The cationic variant (TfOH, CH_2Cl_2, 0 °C) performed on the corresponding ethylene acetal failed as well: Gassman, P. G.; Singleton, D. A.; Wilwerding, J. J.; Chavan, S. P. *J. Am. Chem. Soc.* **1987**, *109*, 2182.

(49) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29.

(50) (a) Lei, B.; Fallis, A. G. *J. Org. Chem.* **1993**, *58*, 2186 and references therein. (b) Giguère, R. J. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; Jai Press: London, 1989; Vol. 2, p 162.

(51) In comparison, a successful uncatalyzed TADA transformation, at 150 °C, of a 13-membered analog was recently achieved in our group (P. Préville, unpublished results).

(52) Sonnet, P. E. *Tetrahedron* **1980**, *36*, 557.

(53) Acetonitrile was employed as a solvent to replace acetone which gives substantial amounts of the self-condensation aldol dimer.

(54) Compared to **4**, such a similar diastereomer ratio might indicate that the malonate moieties have a less important stereodirecting role than first envisaged.[4] Other factors such as the intrinsic preference of incipient ring junctions could be determinant at transition state level (*vide infra*).

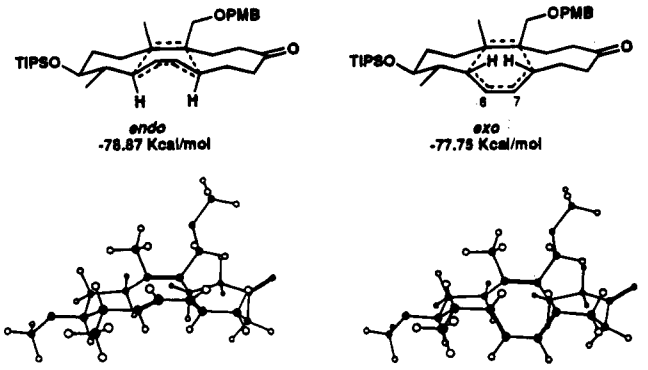
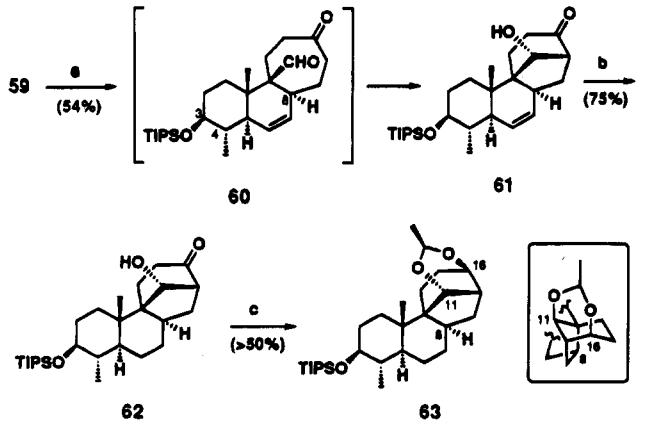


Figure 3. Diastereotopic *endo* and *exo* transition states for **55**. Transition structures were optimized (AM1) with the following simplifications: PMB and TIPS = Me.

Scheme 12[a]



[a] (a) 210 °C, toluene, sealed tube, 18 h; (b) NaOAc, NH_2NHTs, $EtOH/H_2O$, 80 °C, 5 h; (c) (i) ethyl vinyl ether, TsOH, CH_2Cl_2, rt, 1.5 h; (ii) L-Selectride, THF, 0 °C, 2 h; (iii) $HCl_{(aq)}$, THF, rt, 1.5 h; (iv) $CH_3CH(OEt)_2$, TsOH, CH_2Cl_2, rt, 2 h.

transition state develops to give two contiguous quaternary carbons. As discussed earlier, this significant temperature raise also accounts for the aforementioned problems encountered in going from model TCC cyclopentadecatriene **1** to **46**.

Formyl-substituted analogous macrocycle **59** was obtained, as for **46**, after PMB cleavage of **55** to alcohol **58** and oxidation of the latter in 70% yield (Scheme 10). Cyclopentadecatrienal **59** was thermolyzed (Scheme 12) at 210 °C (toluene, Et_3N as an acid scavenger, sealed tube, 18 h), resulting in a 54% yield of tetracyclic alcohol **61**, presumably formed via a tandem TADA/intramolecular aldol reaction. A minor fraction, ca. 2–3%, of a nonidentified adduct, possibly the CSC diastereomer, was also observed. Tricyclic aldehyde intermediate **60** could be isolated at lower temperatures for shorter reaction times. The tin tetrachloride-catalyzed version ($SnCl_4$, toluene, 60 °C, 3 h) gave even larger amounts of **60** although with more degradation and a lower combined yield with **61**. The intermediary role of **60** in the formation of **61** was clearly demonstrated by a control experiment in which a pure sample of **60** was transformed into aldol product **61** upon heating in a sealed tube (toluene, 200 °C, 12 h). On line with our model series,[4] the ^1H NMR resonance of the formyl proton of **60** appeared as a diagnostic doublet ($J = 1.0$ Hz) for *endo* stereochemistry; caused by a long range W coupling with C8 methine hydrogen in a *trans*-B.C[6.7] ring junction. Actually, the same steric effects encountered with the

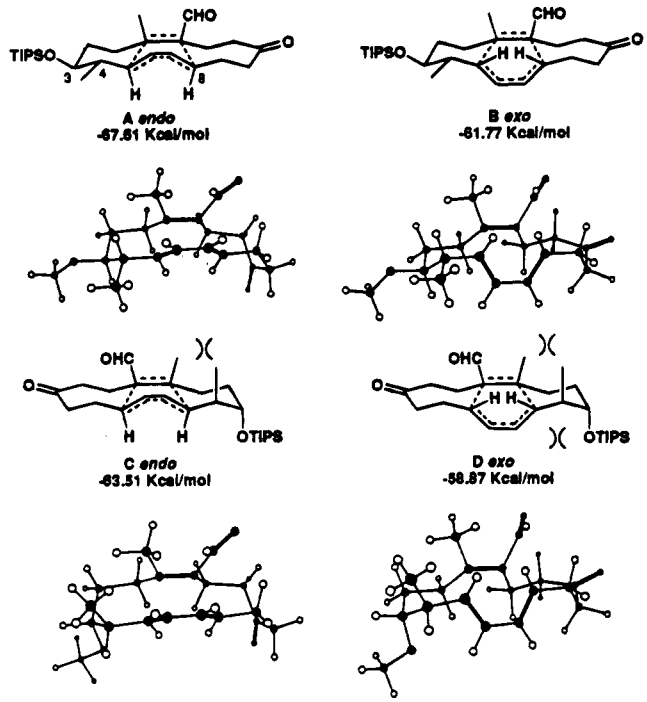


Figure 4. Diastereotopic *endo* and *exo* transition states for **59**. Transition structures were optimized (AM1) with the following simplification: TIPS = Me. Mirror images of C and D are shown.

cycloaddition of **55** account for the observed predominance of the adduct resulting from *endo* approach. Moreover, the "asynchronized transition state theory", which implies a transition structure with more advanced β-bonding (C10–C5), predicts high preference for a *trans* ring junction at this determinant incipient bond.[4] The four possible transition states A–D were calculated using AM1[17] (Figure 4). As expected, the *endo* transtion state A is free of any noticeable nonbonded interactions and was indeed found the lowest in energy compared to *exo* structure B by 5.8 kcal/mol. The corresponding diastereotopic transition states C and D seem unattainable as well since they are showing the development of a severe 1,3-diaxial steric interaction between the two methyl groups. Thus, the absolute stereochemistry of the tricyclic core of **60** originates from a highly efficient chirality induction process (see also Figure 2). In addition to these arguments, the diequatorial arrangement at C3–C4 resulting from the expected transition state A was also proven by ^1H NMR analysis.[55] The signal of the C3 methine proton was well resolved and showed two large coupling constants (9.5, 9.5 Hz), indicative of vicinal *trans*-diaxial relationships with the neighboring hydrogens at C2 and C4. Thereby, the syn stereochemistry of the earlier aldol adduct **27** was demonstrated as well. Owing to the conditions employed and the fact that triethylamine as an acidic buffer had no effect on the aldol step, we suggest that the latter reaction simply occurred thermally through keto–enol tautomery. Of the two possible enol forms, the one leading to bond formation at C15 is unlikely to be considered as a 4-membered ring would result upon attack to the aldehyde carbonyl. Therefore, the anticipated stereochemistry for the secondary alcohol is explained via a chairlike transition state

(55) Pretsch, E.; Clerc, T.; Seibl, J.; Simon, W. *Tables of Spectral Data for Structure Determination of Organic Compounds*, 2nd ed.; Springer-Verlag: Berlin, 1989; p H185.

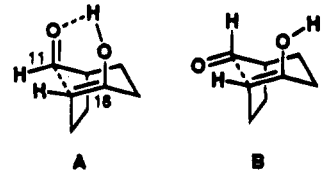


Figure 5. Transition states for aldol condensation (C/D rings).

A (Figure 5). The alternative transition state B cannot be involved in a similar hydrogen bonding situation and is further destabilized by the presence of nonbonded interactions with C7 sp^2 carbon and the methyl group at C10. The above hypothesis for C11 stereochemistry was confirmed by the following microscale chemical sequence (Scheme 12). Double-bond reduction with diimide[56] gave tetracycle **62**. The alcohol function was protected as a 1-ethoxyethyl ether[57] and ketone reduction with L-Selectride,[58] presumably from equatorial attack on the most accessible face,[59] gave the β-alcohol. The acetal was hydrolyzed[57] to give the *syn*-diaxial-1,3-diol unit. Then, upon treatment with excess acetaldehyde diethyl acetal and catalytic *p*-toluenesulfonic acid (TSOH),[60] a single ethylidene acetal **63** was formed as confirmed by ^{1}H NMR and mass spectral analysis. The newly introduced methyl substituent most likely exists in the indicated equatorial configuration (β). Due to obvious geometrical reasons, the formation of **63** accounts for the α-stereochemistry at C11 since only a 1,3-diaxial relationship for the two hydroxyl cyclohexyl substituents can lead to a cyclic derivative (see box, Scheme 12).

Thus, the synthesis of TTC cyclopentadecatrienal **59** containing two stereogenic centers allowed the highly selective construction of optically active tetracycle **61**, a valuable intermediate toward the synthesis of 8-epi-aphidicolin (**11**), and analogs thereof. Furthermore, six new asymmetric carbons were generated in a single operation. To our knowledge, this powerful process constitutes the first example of a Diels–Alder/aldol tandem reaction.

Further Transformations of 61 toward Aphidicolin and Its C8-Epimer: Functionalization at C16. In a desire to gain access to a larger variety of potential analogs of pharmaceutical interest, we choose to postpone the alkene reduction to the end of the synthesis. At this point, it was therefore appropriate to functionalize at C16. Although Smith's protocol could successfully realize this task in the aphidicolin series[15] and possibly apply here as well, we looked forward to take use of the C11-alcohol function of **61** as a stereodirecting group. The alcohol function was protected with the ethoxyethyl group[57] to give ketone **64** (Scheme 13), which is a ready substrate to react with alkoxymethylating agents from the α-face. The β-face of this cyclohexanone is indeed highly shielded by the axial ethoxyethoxy moiety (Figure 6). Unfortunately, as opposed to Corey,[11c] treatment of **64** with[(1-ethoxyethoxy)methyl]lithium[61] failed, probably as a result of ketone enolization. Radical variants of this

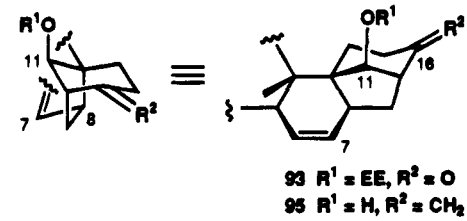
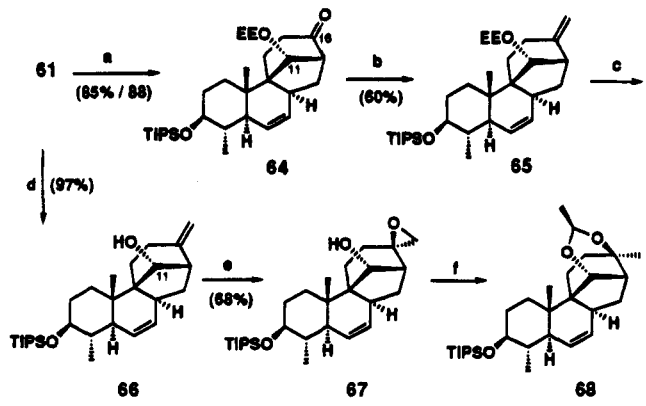


Figure 6. Steric environment around rings C/D.

Scheme 13[a]



[a] (a) Ethyl vinyl ether, TsOH, CH_2Cl_2, rt, 2 h; (b) $Cp_2Ti(CH_2)(Cl)AMe_2$, THF, rt, 0.5 h; (c) $HCl_{(aq)}$, THF, rt; (d) $Cp_2Ti(CH_2)(Cl)AlMe_2$, THF, 0 °C to rt, 20 min; (e) $VO(acac)_2$, tBuOOH, toluene, rt, 40 min; (f) (i) $LiAlH_4$, THF, 0 °C to rt, 1.5 h; (ii) $CH_3CH(OEt)_2$, TsOH, CH_2Cl_2, rt, 1 h.

reaction, the Samarium–Barbier reaction[62] (3 equiv of SmI_2, BOMCl), and epoxidation with trimethylsulfonium ylide,[5b] were not conclusive. However, the use of Tebbe reagent,[63] a nonbasic methylenation agent, gave alkene intermediate **65** which C11-alcohol was deprotected to give **66**. The latter could be directly obtained from **61** in 97% yield using 2 equiv of Tebbe reagent.

Thereafter, homoallylic alcohol **66** appeared as an ideal candidate for a hydroxyl-directed Sharpless epoxidation,[64] affording β-epoxide **67** (68% yield) with high chemio- and stereoselectivities.[65] The spatial orientation of the hydroxyl group and the resulting vanadium complex accounts for the observed selectivity. Thus, as shown on Figure 6, one can expect oxidation to occur on the proximal face (β) of the closest double bond of **66**, thus leaving intact the remote $\Delta_{6,7}$ unsaturation. These proposals were verified through synthesis of the cyclic acetal **68** (Scheme 13). More precisely, the epoxide ring of **67** was reductively opened at the less substituted carbon, giving the corresponding *syn*-diaxial 1,3-diol. The latter was then transformed into ethylidene acetal **68**. As for **63**, the relative stereochemistry of the diol moiety is the only one which can lead to a cyclic acetal and accounts for a β-epoxide in **67** as well. Thus, the correct stereochemistry at C16 was secured and could eventually

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(65) The selectivity of this epoxidation reaction is thus far more selective than the route employed by Hesp on 3α,18-(isopropylidenedioxy)-17-noraphidicolan-16-one.[4b]

lead to the required vicinal diol functionality of **10**–**11** by treatment with hydroxyde ion following a procedure previously employed by Hesp.[5b]

Conclusion

In summary, we have described in this article a convenient linear approach to the construction of optically active 15-membered macrocyclic trienes with the desired functionalities required for a stereocontrolled TADA approach to the synthesis of (+)-aphidicolin (**10**) and analogs. Modern methods of acyclic stereoselection such as organocopper-based conjugate addition, Evans' asymmetric aldol methodology, and Wittig–Horner–Wadsworth reactions have served this task with high selectivity.

With the fruitless TADA cycloaddition of TCC cyclopentadecatrienes **42** and **46**, this work has allowed a better understanding of the limiting factors influencing the feasability of TADA reactions. On the other hand, we have described for the first time an impressively powerful TADA/aldol tandem reaction. This way, optically active tetracyclic intermediate **61** was obtained from TTC cyclopentadecatrienal **59** in very high selectivity. The residual C11 hydroxyl group obtained thereof played a crucial stereodirecting function toward the obtention of epoxide **67**, thereby offering a new solution to the stereoselective functionalization at C16 of the aphidicolan framework. Following deoxygenation at C11, investigations aimed to invert the stereochemistry at C8 by making use of the residual double bond could be envisaged. The development of such a protocol would open a route to a fully enantio- and diastereocontrolled total synthesis of aphidicolin (**10**). Therefore, compound **67** constitutes a valuable "end game" intermediate toward the enantioselective synthesis of **10** and its unnatural C8-epimer (**11**), which we have revealed as a presumed isostere. Work in this direction is presently in progress.

Experimental Section

General. Reactions were performed under nitrogen atmosphere with oven-dried (150 °C) or flame-dried glassware. All solvents were dried and distilled shortly before use: acetone (calcium sulfate); diethyl ether and tetrahydrofuran (sodium/benzophenone ketyl); benzene, acetonitrile, dichloromethane, dimethyl sulfoxide, and toluene (calcium hydride); methanol (magnesium/iodine). Most amines were dried with calcium hydride and distilled; hexachloroacetone and methyl acetoacetate were distilled as such and methanesulfonyl chloride was dried with phosphorus pentoxide and distilled. Cesium carbonate, cesium iodide, and lithium chloride were flame-dried under reduced pressure before use. Triphenylphosphine was recrystallized from hexanes. The Tebbe reagent was purchased from Aldrich Chemical Co. All other starting materials and reactants were obtained commercially and used as such or purified by standard means. All solvents and reactants purified and dried were stored under nitrogen. Analytical (0.25 mm) and preparative thin-layer chromatographies (desorption solvent: ethyl acetate) 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 phosphomolybdic acid (10% in ethanol) followed by heating on a hot plate. For flash chromatography, Merck Kieselgel silica gel 60 (230–400 Mesh ASTM.) was used. All solvents used in chromatography were distilled. Concentration of organic solutions implies evaporation on a rotary evaporator followed by reduced pressure (< 0.5 mmHg).

Proton nuclear magnetic resonance (NMR) chemical shifts are reported in δ values relative to chloroform (7.26 ppm) or benzene (7.15 ppm) as internal standard. Proton-decoupled carbon NMR spectra used chloroform (77.00 ppm) or benzene (126.00 ppm) as internal standard and the following abbreviations were used: br, broad; s, singlet; d, doublet; dd, doublet of doublet; t, triplet; q, quartet; qn, quintet; and m, multiplet. Where necessary, decoupling experiments and two-dimensional techniques were performed. Melting points of crystalline materials are uncorrected.

1-(*tert*-Butyldiphenylsiloxy)-4-pentyne (20). To a stirred solution of 4-pentynol (**19**) (10.00 g, 0.120 mol) in tetrahydrofuran at room temperature were successively added imidazole (20.2 g, 0.300 mol) and *tert*-butyldiphenylchlorosilane (37.2 mL, 0.144 mol) over a 5 min period. The flask was stirred 1.5 h after which a saturated aqueous ammonium chloride solution (200 mL) was added. The resulting mixture was extracted with 1:1 diethyl ethyl/hexanes (1 × 500 mL, 3 × 200 mL) and the combined organic phases were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (10% ethyl acetate in hexanes) to give protected alcohol **20** (37.33 g, 97%, clear oil): IR (neat) 3300, 3065, 2935, 2860, 2370 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.69–7.63 (4H, m) and 7.46–7.33 (6H, m) (2 × –Ph), 3.75 (2H, t, J = 6.5 Hz, $-CH_2$-OTBDPS), 2.35 (2H, dt, J = 6.5, 2.5 Hz, $-CH_2C{\equiv}CH$), 1.92 (1H, t, J = 2.5 Hz, $-C{\equiv}CH$), 1.78 (2H, br, qn, J = 6.5 Hz, $-CH_2CH_2CH_2-$), 1.05 (9H, s, $-C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 135.54, 133.80, 129.57, 127.58, 84.22, 68.29, 62.25, 31.40, 26.80, 19.21, 14.98; MS m/e 265 (M^+ – t-Bu); HRMS calcd for $C_{17}H_{17}OSi$ = 265.1049; found = 265.1045 ± 0.0008.

Methyl 6-(*tert*-Butyldiphenylsiloxy)-2-hexynoate (21). A solution of *n*-butyllithium (75.5 mL, 0.121 mol, 1.6 M in hexanes) was added dropwise added over a 15 min period to a stirred solution of alkyne **20** (37.0 g, 0.115 mol) in tetrahydrofuran (600 mL) at −78 °C. The solution was stirred 30 min at −78 °C and brought to −25 °C (carbon tetrachloride/dry ice bath) for 1.5 h. Methyl chloroformate (26.8 mL, 0.345 mol) was added over a 5 min period, and the flask was stirred 0.5 h at −25 °C after which it was allowed to warm to room temperature over a 1.5 h period. Then, a saturated aqueous ammonium chloride solution (400 mL) was added to quench the mixture which was diluted with diethyl ether (500 mL). The phases were separated, and the aqueous one was extracted with diethyl ether (3 × 200 mL). The combined organic phases were washed with brine (100 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. Purification of the residue by flash chromatography (10% ethyl acetate in hexanes) afforded acetylenic ester **21** (41.43 g, 95%, yellowish oil): IR (neat) 3050, 2955, 2860, 1715 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.69–7.63 (4H, m) and 7.46–7.34 (6H, m) (2 × –Ph), 3.76 (3H, s, $-OCH_3$), 3.73 (2H, t, J = 6.0 Hz, $-CH_2$-OTBDPS), 2.51 (2H, t, J = 7.0 Hz, $-CH_2C{\equiv}C-$), 1.81 (2H, br, qn, J = 7.0 Hz, $-CH_2CH_2CH_2-$), 1.05 (9H, s, $-C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 154.06, 135.47, 133.49, 129.60, 127.64, 89.32, 76.60, 72.93, 61.82, 52.39, 30.37, 26.74, 19.13, 15.18; MS m/e 365 (M^+ – CH_3), 349 (M^+ – OCH_3), 323 (M^+ – $C(CH_3)_3$); HRMS calcd for $C_{22}H_{25}O_2Si$ = 349.1624; found = 349.1621 ± 0.0010.

Mixture of (*Z*)- and (*E*)-Methyl 6-(*tert*-Butyldiphenylsiloxy)-2-[[(*p*-methoxybenzyl)oxy]methyl]-3-methyl-2-hexenoate (22). A solution of methyllithium (106 mL, 0.148 mol, 1.40 M in diethyl ether) was dropwisely added over a 15 min period to a cooled (0 °C) stirred suspension of ultrapure copper(I) iodide (14.13 g, 74.4 mmol) in tetrahydrofuran (600 mL). The clear slightly yellowish solution was stirred a further 10 min after which it was cooled to −78 °C. A cooled solution (~−78 °C) of acetylenic ester **21** (28.12 g, 74.0 mmol) in tetrahydrofuran (100 mL) was cannulated dropwise for a period of 15 min, and the brownish solution was stirred 1.5 h at −78 °C. At this point, a control TLC revealed a homogeneous spot corresponding to the protonated *cis*-vinylcopper intermediate. Fresly prepared neat [(*p*-methoxybenzyl)oxy]-methyl chloride (~35 g, 0.19 mol) was then added dropwise over a short period (ca. 5 min) and the reaction flask was transferred to a ice/water bath and allowed to warm to 0 °C over 4 h. Excess reagents were quenched by the addition of a

saturated aqueous ammonium chloride solution (0.5 L), and the resulting mixture was extracted with diethyl ether (1 × 600 mL, 1 × 200 mL) and ethyl acetate (3 × 150 mL). The combined organic layers were washed with brine (100 mL), dried with anhydrous magnesium sulfate, filtered, and concentrated to give the crude reaction product (contains <10% of trisubstituted ethylenic ester, arising from incomplete alkylation, *Z*/*E* ^{1}H NMR ratio of tetrasubstituted ethylenic esters = 7:1). Purification by flash chromatography (5% to 15% ethyl acetate in hexanes) left a pure mixture of (*Z*)-**22** and (*E*)-**22** (30.3 g, 75%, yellowish oil, contaminated by a small proportion of PMBCl hydrolysis artifacts). The two geometric isomers thereof were difficult to separate on silica gel and were rather segregated at the alcohol stage.

Z/*E* mixture **22**: IR (neat) 3070, 2945, 2860, 1720, 1610 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.69–7.62 (4H, m) and 7.45–7.33 (6H, m) (–$SiPh_2$ *Z*/*E*), 7.31–7.18 (2H, m) and 6.92–6.79 (2H, m) (*p*-CH_3OAr– *Z*/*E*), 4.42 (2H, s, –OCH_2Ar *Z*), 4.40 (2H, s, –OCH_2Ar *E*), 4.19 (2H, s, =$C(CH_2OPMB)CO_2CH_3$ *E*), 4.18 (2H, s, =$C(CH_2OPMB)CO_2CH_3$ *Z*), 3.81 (3H, s, $-OCH_3$ *Z*), 3.76 (3H, s, $-OCH_3$ *E*), 3.68 (3H, s, CO_2CH_3 *Z*), 3.66 (3H, s, CO_2CH_3 *E*), 3.75–3.60 (2H, m, $-CH_2OTBDPS$ *Z*/*E*), 2.42 (2H, m, $-CH_2C(CH_3)=$ *Z*), 2.28 (2H, m, $-CH_2C(CH_3)=$ *Z*/*E*), 2.01 (3H, s, $-CH_3$ *E*), 1.82 (3H, s, $-CH_3$ *Z*), 1.79–1.65 (2H, m, $-CH_2CH_2CH_2OTBDPS$ *Z*/*E*), 1.05 (9H, s, $-C(CH_3)_3$ *E*), 1.04 (9H, s, $-C(CH_3)_3$ *Z*); MS *m*/*e* 489 (M^+ – $((CH_3)_3)$); HRMS calcd for $C_{29}H_{33}O_5Si$ = 489.7097; found = 489.2106 ± 0.0014.

(*Z*)- and (*E*)-6-(*tert*-Butyldiphenylsiloxy)-2-[[(*p*-methoxybenzyl)oxy]methyl]-3-methyl-2-hexenol (23). To a stirred solution of tetrasubstituted ethylenic esters (*Z*)-**22** and (*E*)-**22** (79.3 g, 0.145 mol, *Z*/*E* ratio ~7:1) in dichloromethane/hexanes (1:2, 1.5 L) cooled to –78 °C was dropwisely added diisobutylammonium hydride (435 mL, 0.435 mol, 1M in toluene) over a 45 min period. The solution was further stirred for 45 min at –78 °C, and excess hydride was quenched by the careful addition of methanol (150 mL). The mixture was then allowed to warm to room temperature with a water bath over a 30 min period. The resulting jelly was ground and diluted with diethyl ether (3 L) and transferred to an erlenmeyer flask. Brine (150 mL) was added and the mixture was stirred 15 min after which anhydrous magnesium sulfate (250 g) was added and the content stirred for a further 10 min. The mixture was filtered through a fritted glass funnel (medium porosity) and concentrated. The residue was purified by flash chromatography (15% to 30% ethyl acetate in hexanes), affording (*E*)-allylic alcohol **23** (53.4 g, 71%, clear oil) and its *Z* isomer (8.96 g, 12%, clear oil).

(*E*)-23 (less polar): IR (neat) 3445 (br), 3070, 2930, 1610 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.69–7.63 (4H, m) and 7.45–7.35 (6H, m) (–$SiPh_2$), 7.30–7.18 (2H, m) and 6.92–6.78 (2H, m) (*p*-CH_3OAr–), 4.45 (2H, s, –OCH_2Ar), 4.41 (2H, s, =$C(CH_2OPMB)$–), 4.22 (2H, d, *J* = 6.0 Hz, $-CH_2OH$), 3.81 (3H, s, $-OCH_3$), 3.65 (2H, t, *J* = 5.5 Hz, $-CH_2OTBDPS$), 2.32 (2H, t, *J* = 6.0 Hz, –OH), 2.26 (2H, m, $-CH_2C(CH_3)=$), 1.70 (3H, s, $-CH_3$), 1.61 (2H, m, $-CH_2CH_2CH_2OTBDPS$), 1.06 (9H, s, $-C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.11, 138.02, 135.47, 133.71, 130.19, 129.82, 129.52, 127.55, 113.73, 72.07, 69.02, 63.26, 61.28, 55.12, 31.19, 30.46, 26.78, 19.06, 18.27; MS *m*/*e* 500 ($M^+ - H_2O$), 461 ($M^+ - C(CH_3)_3$); HRMS calcd for $C_{28}H_{33}O_4Si$ = 461.2148; found = 461.2138 ± 0.0013.

(*Z*)-23 (more polar): IR (neat) 3440 (br), 3070, 2930, 1610 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.70–7.64 (4H, m) and 7.45–7.34 (6H, m) (–$SiPh_2$), 7.25–7.18 (2H, m) and 6.88–6.81 (2H, m) (*p*-CH_3OAr–), 4.40 (2H, s, –OCH_2Ar), 4.22 (2H, br s, $-CH_2OH$), 4.14 (2H, s, =$C(CH_2OPMB)$–), 3.78 (3H, s, $-OCH_3$), 3.63 (2H, t, *J* = 6.0 Hz, $-CH_2OTBDPS$), 2.22–2.12 (3H, m, $-CH_2C(CH_3)=$, –OH), 1.76 (3H, s, $-CH_3$), 1.60 (2H, m, $-CH_2CH_2CH_2OTBDPS$), 1.06 (9H, s, $-C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 138.15, 135.48, 133.79, 130.13, 129.51, 129.33, 127.58, 113.75, 72.27, 68.91, 63.38, 62.07, 55.14, 31.40, 30.77, 26.80, 19.14, 18.27; MS *m*/*e* 461 ($M^+ - C(CH_3)_3$); HRMS calcd for $C_{28}H_{33}O_4Si$ = 461.2148; found = 461.2156 ± 0.0013.

(*Z*)-6-(*tert*-Butyldiphenylsiloxy)-2-[[(p-methoxybenzyl)oxy]methyl]-1-[(methoxymethoxy)methyl]-3-methyl-2-hexene (24). To a stirred solution of (*E*)-allylic alcohol **23** (51.0 g, 99.0 mmol) in dichloromethane (1.0 L) at room temperature were successively added diisopropylethylamine (51.5 mL, 0.297 mol) and methoxymethyl chloride (15.0 mL, 0.198 mol) over a 10 min period. The solution was stirred 11 h at room temperature after which a saturated aqueous ammonium chloride solution (200 mL) was added. The aqueous phase was segregated, and the organic one was washed with water (100 mL), brine (100 mL), dried with anhydrous magnesium sulfate, filtered, and concentrated to give pure MOM ether **24** (55.3 g, 100%, slightly yellowish oil): IR (neat) 3070, 2930, 2860, 1510 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.68–7.63 (4H, m) and 7.45–7.32 (6H, m) (–$SiPh_2$); 7.29–7.23 (2H, m) and 6.91–6.84 (2H, m) (*p*-CH_3O–*Ar*–), 4.57 (2H, s, $-OCH_2O-$), 4.41 (2H, s, –OCH_2Ar), 4.13 (2H, s, =$C(CH_2OPMB)$–), 4.04 (2H, s, =$C(CH_2OMOM)$–), 3.81 (3H, s, $-ArOCH_3$), 3.66 (2H, t, *J* = 6.0 Hz, $-CH_2OTBDPS$), 3.31 (3H, s, $-CH_2OCH_3$), 2.26 (2H, m, $-CH_2C(CH_3)=$), 1.74 (3H, s, $-CH_3$), 1.65 (2H, m, $-CH_2CH_2CH_2OTBDPS$), 1.05 (9H, s, $-C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 141.32, 135.45, 133.84, 129.46, 129.28, 127.55, 127.01, 113.58, 95.68, 71.65, 67.46, 64.58, 63.56, 55.08, 31.52, 30.85, 26.78, 19.12, 18.39; MS *m*/*e* 505 ($M^+ - C(CH_3)_3$); HRMS calcd for $C_{30}H_{37}O_5Si$: 505.2410; found = 505.2414 ± 0.0015.

(*Z*)-2-[[(*p*-Methoxybenzyl)oxy]methyl]-1-[(methoxymethoxy)methyl]-3-methyl-2-hexen-6-ol (25). A stirred solution of silyl ether **24** (55.1 g, 98.0 mmol) in tetrahydrofuran (1.0 L) cooled to 0 °C was treated with tetra-*n*-butylammonium fluoride (108 mL, 108 mmol, 1.0 M in tetrahydrofuran). The mixture was stirred for 30 min at 0 °C and 2.0 h at room temperature. A saturated aqueous ammonium chloride solution (500 mL) was added, and the two phase mixture was extracted with diethyl ether (1 × 800 mL, 1 × 200 mL) and ethyl acetate (3 × 200 mL). The combined organic phases were dried with anhydrous magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography to get rid of the residual silanol (50% to 80% ethyl acetate in hexanes), affording alcohol **25** (30.18 g, 95%, clear oil): IR (neat) 3440 (br), 2933, 1615 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.30–7.24 (2H, m) and 6.92–6.84 (2H, m) (*p*-CH_3O–*Ar*–), 4.60 (2H, s, $-OCH_2O-$), 4.41 (2H, s, –OCH_2-Ar), 4.20 (2H, s, =$C(CH_2OPMB)$–), 4.05 (2H, s, $-CH_2OMOM$), 3.80 (3H, s, $-ArOCH_3$), 3.60 (2H, dt, *J* = 6.0, 6.0 Hz, $-CH_2$-OH), 3.35 (3H, s, $-CH_2OCH_3$), 2.54 (1H, t, *J* = 6.0 Hz, –OH), 2.32 (2H, t, *J* = 6.0 Hz, $-CH_2C(CH_3)=$), 1.76 (3H, s, $-CH_3$), 1.71 (2H, qn, *J* = 6.0 Hz, $-CH_2CH_2CH_2OH$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.05, 141.28, 130.44, 129.29, 127.39, 113.61, 95.74, 71.72, 67.72, 64.82, 61.13, 55.25, 55.13, 30.40, 30.09, 17.87; MS *m*/*e* 324 (M^+), 292 ($M^+ - CH_3OH$), 279 (M^+ – MOM); HRMS calcd for $C_{17}H_{24}O_4$ = 292.1674; found = 292.1672 ± 0.0008.

(*Z*)-2-[[(*p*-Methoxybenzyl)oxy]methyl]-1-[(methoxymethoxy)methyl]-3-methyl-2-hexen-6-al (26). To a stirred solution of oxalyl chloride (4.62 mL, 53.0 mmol) in dichloromethane (180 mL) at –78 °C was added a solution of dimethyl sulfoxide (7.87 mL, 0.110 mol) in dichloromethane (25 mL) dropwise over a 15 min period. The mixture was stirred for a further 10 min, and alcohol **25** (15.0 g, 46.0 mmol) in dichloromethane (25 mL) was added dropwise for a 15 min period. The mixture was stirred 1.0 h at –78 °C, and then triethylamine (31.3 mL, 0.225 mol) was added over 5 min. The resulting mixture was allowed to warm to room temperature for 1.0 h after which water (150 mL) and diethyl ether (1.0 L) were added. The phases were separated, and the organic one was washed with water (200 mL) and brine (100 mL), dried with anhydrous sodium sulfate, and filtered over a fritted glass funnel (medium porosity) filled with a 2 cm thick pad of silica gel. The filtrate was concentrated to give pure aldehyde **26** (14.60 g, 100%, yellowish oil): IR (neat) 2935, 2725, 1725, 1610 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.77 (1H, s, –CHO), 7.25 (2H, m) and 6.86 (2H, m) (*p*-CH_3O–*Ar*–), 4.59 (2H, s, $-OCH_2O-$), 4.41 (2H, s, –OCH_2Ar), 4.12 (2H, s, =$C(CH_2$-OPMB)–), 4.02 (2H, s, $-CH_2OMOM$), 3.79 (3H, s, –Ar–OCH_3), 3.33 (2H, s, $-CH_2OCH_3$), 2.60–2.42 (4H, m, $-CH_2CH_2CHO$), 1.75 (3H, s, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 201.54, 159.14, 139.37, 130.44, 129.36, 128.34, 113.67, 95.76, 71.92,

67.54, 64.65, 55.20 (2), 42.67, 26.74, 18.21; MS *m/e* 290 ($M^+ - CH_3OH$), 277 ($M^+ - CH_2CHO$); HRMS calcd for $C_{17}H_{22}O_4$ = 290.1518; found = 290.1514 ± 0.0008.

(*Z*)-[3(2*R*,3*S*)4*R*]-3[-3-Hydroxy-2,6-dimethyl-7-[[(*p*-methoxybenzyl)oxy]methyl]-8-(methoxymethoxy)-6-octenoyl]-4-benzyl-2-oxazolidinone (27). To a stirred solution of (*R*)-3-(1-oxopropyl)-4-benzyl-2-oxazolidinone (10.26 g, 44.0 mmol) in dichloromethane (135 mL) cooled to 0 °C was dropwisely added di-*n*-butylboron triflate (12.70 mL, 50.6 mmol) over a 20 min period at a rate allowing the internal temperature to stay below 7 °C (uncorrected temperature related to joint stem). To the pale yellowish solution was dropwisely added triethylamine (7.96 mL, 57.0 mmol) over a 25 min period while still keeping the internal temperature below 7 °C. The slightly yellowish solution was cooled down to −78 °C after which the above aldehyde **26** (14.89 g, 46.0 mmol) in dichloromethane (10 mL) was added over 10 min with a dropping funnel (5 mL rinse). The mixture was stirred 2.0 h at −78 °C and 4.0 h at −60 °C (chloroform/dry ice bath) and then quenched at this temperature with a pH 7 phosphate buffer solution (50 mL) and methanol (150 mL). The flask was immersed into an ice/water bath and the internal temperature was allowed to reach ~0 °C (15 min). A 2:1 methanol/30% hydrogen peroxide solution (127 mL) was added dropwise while keeping the internal temperature below 11 °C (~30 min). The mixture was stirred a further 30 min, and the flask was concentrated to near dryness by evaporating the volatiles. Water (150 mL) was added, and the aqueous phase was extracted with diethyl ether (5 × 200 mL). The combined ethereal layers were washed with a half-saturated aqueous sodium bicarbonate solution (50 mL) and brine (50 mL), dried with anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (30% to 70% ethyl acetate in hexanes), affording pure aldol condensation product **27** (21.33 g, 87%, clear visqueous oil): $[\alpha]^{25}_D$ −37.6° (*c* = 1.13, $CHCl_3$); IR (neat) 3455 (br), 2935, 1780, 1695, 1610 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.37−7.14 (7H, m, −Ph, two *of* −*Ar*−OCH_3), 6.86 (2H, m, two *of* −Ar−OCH_3), 4.64 (1H, m, −BnCHN−), 4.61 (2H, s, $-OCH_2O-$), 4.41 (2H, s, $-OCH_2Ar$), 4.23−4.07 (2H, m, $-BnCHCH_2O-$), 4.16 (2H, s, $=C(CH_2OPMB)-$), 4.04 (2H, AB m, $-CH_2OMOM$), 3.86 (1H, br m, −C*H*(OH)−), 3.78 (3H, s, Ar−OCH_3), 3.73 (1H, m, $-(CH_3)CHCO-$), 3.35 (3H, s, $-CH_2OCH_3$), 3.34 (1H, m, −OH), 3.23 (2H, dd, *J* = 13.5, 3.0 Hz, −*H*CHPh), 2.77 (1H, dd, *J* = 13.5, 9.5 Hz, −HC*H*Ph), 2.47−2.34 (1H, m, −*H*CHC(CH_3)=), 2.32−2.19 (1H, m, −HC*H*C(CH_3)=), 1.76 (3H, s, $-C(CH_3)=$), 1.68−1.53 (2H, m, $-(HO)CHCH_2-$), 1.25 (3H, d, *J* = 6.5 Hz, $-CH(CH_3)-$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 176.69, 159.02, 152.90, 141.22, 134.99, 130.49, 129.31, 128.82, 127.44, 127.26,113.61, 95.69, 71.68, 70.41, 67.66, 65.98, 64.78, 55.24, 55.12, 55.03, 42.67, 37.64, 32.31, 30.51, 18.05, 10.99; MS *m/e* 523 ($M^+ - CH_3OH$), 510 (M^+ − MOM); HRMS calcd for $C_{30}H_{37}O_7N$ = 523.2570; found = 523.2561 ± 0.0015.

(*Z*)-(2*R*,3*S*)-3-Hydroxy-*N*,2,6-trimethyl-*N*-methoxy-7-[[(*p*-methoxybenzyl)oxy]methyl]-8-(methoxymethoxy)-6-octenamide (28). To a stirred suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (2.64 g, 27.1 mmol) in dichloromethane (60 mL) cooled to 0 °C was dropwisely added trimethylalane (13.7 mL, 27.4 mmol) over a 35 min period (vigorous methane evolution occurs). The mixture was warmed to room temperature for 1.0 h and then cooled to −20 °C (tetrachloromethane/dry ice). Then, imide **27** (7.18 g, 12.94 mmol) in dichloromethane (15 mL) was added dropwise via cannula (5 mL rinse), and the mixture was allowed to warm to room temperature and stirred for 4.5 h. The content of the flask was then cannulated to a vigorously stirred, cooled (0 °C) 1.0 M aqueous tartaric acid solution. The resulting mixture was stirred 1.0 h at 0 °C, and the phases were separated. The aqueous one was extracted with dichloromethane (4 × 30 mL), and the combined halogenated layers were washed with brine (30 mL), dried with anhydrous sodium sulfate, filtered, and concentrated. The residue was crystallized into 30% ethyl acetate in hexanes (rt to 0 °C). The liquid phase was decanted, and the solids were rinsed with hexanes, giving recovered 4-benzyl 2-oxazolidinone (~1.5 g). The mother liquor were concentrated, yielding crude hydroxy amide **28** which was taken on directly to the next step. A small portion could however be purified by flash chromatography (40% to 100% ethyl acetate in hexanes), affording analytically pure **28**: $[\alpha]^{27}_D$ −16.9° (*c* = 1.00, $CHCl_3$); IR (neat) 3485 (br), 2940, 1655, 1515 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.25 (2H, m) and 6.86 (2H, m) (*p*-CH_3O−*Ar*−), 4.61 (2H, s, $-OCH_2O-$), 4.41 (2H, s, $-OCH_2Ar$), 4.19 (1H, d, *J* = 10.5 Hz, $=C(HCHOPMB)-$), 4.13 (1H, d, *J* = 10.5 Hz, $=C(HCHOPMB)-$), 4.06 (1H, d, *J* = 10.5 Hz, −*H*CHOMOM), 4.02 (1H, d, *J* = 10.5 Hz, −HC*H*OMOM), 3.93 (1H, br s, −OH), 3.79 (3H, s, −Ar−OCH_3), 3.74 (1H, m, −(HO)C*H*−), 3.67 (3H, s, −N−$(OCH_3)-$), 3.35 (3H, s, $-CH_2OCH_3$), 3.17 (3H, s, $-N(CH_3)-$), 2.86 (1H, m, $-(CH_3)CHCO-$), 2.43−2.32 (1H, m, $-HCHC(CH_3)=$), 2.24 (1H, ddd, *J* = 13.0, 9.0, 4.5 Hz, $-HCHC(CH_3)=$), 1.76 (3H, s, $-C(CH_3)=$), 1.67−1.42 (2H, m, $-(HO)CHCH_2-$), 1.17 (3H, d, *J* = 7.0 Hz, $-CH(CH_3)-$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 177.76, 159.08, 141.51, 130.56, 129.37, 127.32, 113.67, 95.81, 71.79, 70.96, 67.67, 64.84, 61.47, 55.22(2), 39.50, 32.67, 31.90, 30.64, 18.19, 11.29; MS *m/e* 408 ($M^+ - OCH_3$); HRMS calcd for $C_{22}H_{34}O_6N$ = 408.2386; found = 408.2381 ± 0.0012.

(*Z*)-(2*R*,3*S*)-3-(Triisopropylsiloxy)-*N*,2,6-trimethyl-*N*-methoxy-7-[[(*p*-methoxybenzyl)oxy]methyl]-8-(methoxymethoxy)-6-octenamide (29). To a stirred solution of the above crude hydroxyamide **28** in dichloromethane (53 mL) cooled to 0 °C were successively added 2,6-lutidine (6.20 mL, 53.3 mmol) and triisopropylsilyl triflate (7.90 mL, 29.5 mmol). The mixture was allowed to warm to room temperature (30 min). Then, excess triflate was consumed by addition of methanol (10 mL) and a saturated aqueous ammonium chloride solution (60 mL). The phases were separated and the aqueous layer was extracted with dichloromethane (4 × 50 mL). The combined organic phases were washed with a saturated aqueous sodium bicarbonate solution (100 mL), a 1 M aqueous sodium bisulfate solution (3 × 50 mL), and brine (50 mL), dried with anhydrous sodium sulfate, filtered, and concentrated. Purification by flash chromatography (10% ethyl acetate in hexanes) afforded silyl ether **29** (6.90 g, 89% (two steps from **27**), colorless oil): $[\alpha]^{27}_D$ +17.5° (*c* = 1.06, $CHCl_3$); IR (neat) 2945, 2870, 1665, 1615 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.25 (2H, m) and 6.86 (2H, m) (*p*-CH_3O−*Ar*−), 4.58 (2H, s, $-OCH_2O-$), 4.41 (2H, s, $-OCH_2Ar$), 4.18 (1H, dt, *J* = 6.0, 5.5 Hz, −(TIPSO)C*H*−), 4.10 (2H, s, $=C(CH_2OPMB)-$), 4.02 (2H, s, $-CH_2OMOM$), 3.79 (3H, s, −Ar−OCH_3), 3.68 (3H, s, −N$(OCH_3)-$), 3.32 (3H, s, $-CH_2OCH_3$), 3.16 (3H, s, −N$(CH_3)-$), 2.99 (1H, m, $-(CH_3)CHCO-$), 2.28−2.12 (2H, m, $-CH_2C(CH_3)=$), 1.73 (3H, s, $-C(CH_3)=$), 1.68−1.56 (2H, m, $-(TIPSO)CHCH_2-$), 1.20 (3H, d, *J* = 7.0 Hz, $-CH(CH_3)-$), 1.08 (21H, s, $-Si(CH(CH_3)_2)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 176.00, 159.08, 141.28, 130.57, 129.35, 126.96, 113.65, 95.69, 73.71, 71.79, 67.41, 64.59, 61.19, 55.18-(2), 40.39, 34.76, 32.07, 29.50, 18.40, 18.23, 13.56, 13.08; MS *m/e* 552 ($M^+ - C_3H_7$); HRMS calcd for $C_{29}H_{50}O_7N$ Si = 552.3356; found = 552.3348 ± 0.0016.

(*Z*)-(2*R*,3*S*)-3-(Triisopropylsiloxy)-2,6-dimethyl-7-[[(*p*-methoxybenzyl)oxy]methyl]-8-(methoxymethoxy)-6-octadienal (30). To a stirred solution of amide **29** (34.3 g, 57.6 mmol) in tetrahydrofuran (440 mL) cooled to −90 °C (hexanes$_{(s)}$/hexanes$_{(l)}$/N_2) was added dropwise diisobutylaluminum hydride (115 mL), 0.173 mol, 1.5 M in toluene) through a dropping funnel over a 35 min period. The mixture was stirred a further 45 min at −90 °C after which dry acetone (9 mL) was added. The contents of the flask was then cannulated into a stirred erlenmeyer flask containing a two-phase mixture of hexanes (400 mL) and a 1.0 M aqueous tartaric acid solution (600 mL). The flask was stirred 1.0 h and diethyl ether (900 mL) was added. The phases were then separated and the aqueous layer was extracted with diethyl ether (3 × 300 mL). The combined organic phases were washed with brine (100 mL), dried with anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography (10% to 30% ethyl acetate in hexanes), giving aldehyde **30** (29.40 g, 95%, clear oil): $[\alpha]^{27}_D$ −13.5° (*c* = 1.08, $CHCl_3$); IR (neat) 2945, 2870, 2720, 1730, 1610 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.85 (1H, s, −CHO), 7.26 (2H, m) and 6.87 (2H, m) (*p*-CH_3O−*Ar*−), 4.58 (2H, s, $-OCH_2O-$), 4.42

(2H, s, $-OCH_2Ar$), 4.32 (1H, m, $-$(TIPSO)CH$-$), 4.10 (2H, s, $=C(CH_2OPMB)-$), 4.02 (2H, s, $-CH_2OMOM$), 3.80 (3H, s, $-Ar-OCH_3$), 3.33 (3H, s, $-CH_2OCH_3$), 2.51 (1H, dq, J = 7.5, 3.0 Hz, $-(CH_3)CHCHO$), 2.13 (2H, m, $-CH_2C(CH_3)=$), 1.76 (3H, s, $-C(CH_3)=$), 1.67 (2H, m, $-$(TIPSO)CHCH_2-), 1.09 (3H, d, J = 7.5 Hz, $-(CH_3)CHCHO$), 1.05 (21H, s, $-Si(CH(CH_3)_2)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 205.19, 159.13, 140.65, 130.55, 129.41, 127.43, 113.71, 95.68, 72.92, 71.96, 67.57, 64.58, 55.23(2), 50.93, 33.37, 30.98, 18.52, 18.16, 12.77, 7.37; MS m/e 493 ($M^+ - C_3H_7$); HRMS calcd for $C_{27}H_{45}O_6Si$ = 493.2985; found = 493.2980 ± 0.0014.

(2*E*,8*Z*)-(4*S*,5*S*)-Methyl 5-(Triisopropylsiloxy)-4,8-dimethyl-9-[[(*p*-methoxybenzyl)oxy]methyl]-10-(methoxymethoxy)-2,8-decadienoate [(*E*)-31] and (2*Z*,8*Z*)-(4*S*,5*S*)-Methyl 5-(Triisopropylsiloxy)-4,8-dimethyl-9-[[(*p*-methoxybenzyl)oxy]methyl]-10-(methoxymethoxy)-2,8-decadienoate [(*Z*)-31]. To a cooled (0 °C) stirred suspension of sodium hydride (2.67 g, 69.0 mmol, 60% dispersion in mineral oil) in tetrahydrofuran (400 mL) was added dropwise a solution of methyl diethylphosphonoacetate (12.7 mL, 70.0 mmol) in toluene (15 mL) over a 30 min period. The mixture was brought to room temperature with a water bath (30 min) at which point anion formation completed, and the solution became clear yellowish. The solution was cooled back to 0 °C and cannulated within 20 min into a stirred solution of aldehyde **30** (29.4 g, 54.9 mmol) in tetrahydrofuran (400 mL). The resulting mixture was stirred 1.5 h (a white gummy precipitate interfered with stirring) at 0 °C after which a pH 7 phosphate buffer solution (100 mL) and diethyl ether (800 mL) were added. The mixture was allowed to warm to room temperature, and the phases were separated. The organic layer was washed with a saturated aqueous ammonium chloride solution (100 mL), and the combined aqueous phases were extracted with diethyl ether (3 × 200 mL). The combined organic phases were then washed with brine (100 mL), dried with anhydrous magnesium sulfate, filtered, and concentrated to give a oily crude product (~33 g, E/Z ratio by ^1H NMR = 16:1). Purification by flash chromatography (10% to 30% ethyl acetate in hexanes) afforded pure (*E*)-ethylenic ester **31** (30.29 g, 93%, >20:1 E/Z ratio by ^1H NMR, clear oil) and (*Z*)-ethylenic ester **31** (1.71 g, 5%, clear oil).

(*E*)-31 (more polar): $[\alpha]^{27}_D$ −9.5° (c = 1.00, $CHCl_3$); IR (neat) 2945, 2870, 1725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.25 (2H, m) and 6.86 (2H, m) (p-CH_3O-Ar-), 7.14 (1H, dd, J = 16.0, 7.0 Hz, $-HC=CHCO_2CH_3$), 5.83 (1H, dd, J = 16.0, 1.0 Hz, $-HC=CHCO_2CH_3$), 4.58 (2H, s, $-OCH_2O-$), 4.42 (2H, s, $-OCH_2Ar$), 4.09 (2H, s, $=C(CH_2OPMB)-$), 4.02 (2H, s, $-CH_2OMOM$), 3.84 (1H, br dt, J = 5.5, 5.5 Hz, $-$(TIPSO)CH$-$), 3.79 (3H, s, $-Ar-OCH_3$), 3.72 (3H, s, $-CO_2CH_3$), 3.33 (3H, s, $-CH_2OCH_3$), 2.57 (1H, m, $-(CH_3)CH-HC=$), 2.23 (1H, dt, J = 12.0, 5.5 Hz, $-HCHC(CH_3)=$), 2.11 (1H, dt, J = 12.0, 5.0 Hz, $-HCHC(CH_3)=$), 1.74 (3H, s, $-C(CH_3)=$), 1.52 (2H, m, $-$(TIPSO)CHCH_2-), 1.07 (21H, s, $-Si(CH(CH_3)_2)_3$), 1.05 (3H, d, J = 7.0 Hz, $-(CH_3)CH-HC=$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 166.98, 159.10, 151.83, 141.34, 130.56, 129.36, 127.03, 120.43, 113.67, 95.68, 75.93, 71.92, 67.49, 64.61, 55.17(2), 51.31, 41.55, 32.92, 31.00, 18.53, 18.18, 13.69, 12.86; MS m/e 560 ($M^+ - CH_3OH$), 549 ($M^+ - C_3H_7$); HRMS calcd for $C_{30}H_{49}O_7Si$ = 549.3247; found = 549.3236 ± 0.0016.

(*Z*)-31 (less polar): $[\alpha]^{27}_D$ +54.0° (c = 1.03, $CHCl_3$); IR (neat) 2945, 2865, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.25 (2H, m) and 6.86 (2H, m) (p-CH_3O-Ar-), 6.31 (1H, dd, J = 11.0 Hz, $-HC=CHCO_2CH_3$), 5.86 (1H, d, J = 11.0 Hz, $-HC=CHCO_2CH_3$), 4.58 (2H, s, $-OCH_2O-$), 4.42 (2H, s, $-OCH_2Ar$), 4.11 (2H, s, $=C(CH_2OPMB)-$), 4.02 (2H, s, $-CH_2$-OMOM), 3.86 (1H, m, $-$(TIPSO)CH$-$), 3.80 (3H, s, $-Ar-OCH_3$), 3.69 (3H, s, $-CO_2CH_3$), 3.33 (3H, s, $-CH_2OCH_3$), 2.25−2.05 (3H, m, $-CH_2C(CH_3)=$, $-(CH_3)CH-HC=$), 1.75 (3H, s, $-C(CH_3)=$), 1.52 (2H, m, $-$(TIPSO)CHCH_2-), 1.07 (21H, s, $-Si(CH(CH_3)_2)_3$), 1.05 (3H, d, J = 7.0 Hz, $-(CH_3)CH-HC=$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 166.45, 159.12, 154.14, 141.20, 130.68, 129.29, 127.01, 118.07, 113.64, 95.72, 75.87, 71.71, 67.48, 64.65, 55.05(2), 50.87, 36.62, 33.87, 30.59, 18.52, 18.17, 13.36, 12.98; MS m/e 561 ($M^+ - CH_3O$), 549 ($M^+ - C_3H_7$); HRMS calcd for $C_{32}H_{53}O_6Si$ = 561.3611; found = 561.3608 ± 0.0017.

(2*E*,8*Z*)-(4*S*,5*S*)-5-(Triisopropylsiloxy)-4,8-dimethyl-9-[[(*p*-methoxybenzyl)oxy]methyl]-10-(methoxymethoxy)-2,8-decadienol (32). To a stirred solution of (*E*)-ethylenic ester **31** (30.2 g, 51.1 mmol) in dichloromethane (500 mL) cooled to −78 °C was added dropwise diisobutylaluminum hydride (75.0 mL, 0.112 mol, 1.5 M in toluene) over a 20 min period. The solution was stirred for 1.0 h at 78 °C after which excess hydride was quenched by slow addition of methanol (60 mL). A saturated aqueous disodium tartrate solution (200 mL) was added, and the mixture was allowed to warm to room temperature over 1.0 h. Additional tartrate solution (400 mL) was then added, and the phases were separated. The aqueous layer was extracted with dichloromethane (5 × 200 mL) and the combined organic phases were dried with anhydrous sodium sulfate, filtered, and concentrated. The crude product obtained thereof was purified by flash chromatography (30% to 50% ethyl acetate in hexanes) over a short silica gel column, yielding pure allylic alcohol **32** (28.51 g, 99%, clear oil): $[\alpha]^{27}_D$ −7.4° (c = 0.98, $CHCl_3$); IR (neat) 3455 (br), 2940, 2865, 1610 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.26 (2H, m) and 6.86 (2H, m) (p-CH_3O-Ar-), 5.80 (1H, dd, J = 15.5, 5.5 Hz, $-HC=CHCH_2OH$), 5.63 (1H, dt, J = 15.5, 5.5 Hz, $-HC=CHCH_2OH$), 4.58 (2H, s, $-OCH_2O-$), 4.41 (2H, s, $-OCH_2Ar$), 4.11 (2H, s, $=C(CH_2OPMB)-$), 4.09 (2H, d, J = 5.5 Hz, $=CHCH_2OH$), 4.02 (2H, s, $-CH_2OMOM$), 3.79 (3H, s, $-Ar-OCH_3$), 3.76 (1H, dt, J = 5.5, 5.5 Hz, $-$(TIPSO)CH$-$), 3.34 (3H, s, $-CH_2OCH_3$), 2.42 (1H, m, $-(CH_3)CH-HC=$), 2.26 (1H, dt, J = 12.5, 5.5 Hz, $-HCHC(CH_3)=$), 2.09 (1H, dt, J = 12.5, 5.5 Hz, $-HCHC(CH_3)=$), 1.75 (3H, s, $-C(CH_3)=$), 1.62 (1H, t, J = 5.5 Hz, $-CH_2OH$), 1.52 (2H, m, $-$(TIPSO)-CHCH_2-), 1.07 (21H, s, $-Si(CH(CH_3)_2)_3$), 1.00 (3H, d, J = 7.0 Hz, $-(CH_3)CH-HC=$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.07, 141.76, 135.05, 130.59, 129.36, 128.65, 126.77, 113.66, 95.62, 76.41, 71.85, 67.40, 64.72, 63.85, 55.16, 41.28, 32.93, 30.58, 18.59, 18.23, 15.13, 12.95; MS m/e 564 (M^+), 521 ($M^+ - C_3H_7$); HRMS calcd for $C_{29}H_{49}O_6Si$ = 564.3846; found = 564.3859 ± 0.0016.

(2*E*,8*Z*)-(4*S*,5*S*)-5-(Triisopropylsiloxy)-4,8-dimethyl-9-[[(*p*-methoxybenzyl)oxy]methyl]-10-(methoxymethoxy)-2,8-decadienal (33). To a stirred solution of oxalyl chloride (2.14 mL, 24.5 mmol) in dichloromethane (110 mL) cooled to −78 °C was added a solution of dimethyl sulfoxide (3.62 mL, 51.1 mmol) in dichloromethane (5 mL) dropwise over a 5 min period. The mixture was stirred for a further 10 min, and alcohol **32** (12.0 g, 21.3 mmol) in dichloromethane (5 mL + 5 mL rinse) was added dropwise via syringe over a 5 min period. The solution was stirred 1.5 h at −78 °C after which diisopropylethylamine (18.1 mL, 0.103 mmol) was added over 5 min. The resulting mixture was allowed to warm to room temperature for 1.5 h after which water (100 mL) and diethyl ether (700 mL) were added. The phases were separated, and the organic one was successively washed with water (100 mL), a saturated aqueous sodium bisulfate solution (2 × 100 mL), and brine (50 mL) and dried with anhydrous sodium sulfate. The solvents were then filtered over a fritted glass funnel (medium porosity) filled with a 1 cm thick silica gel pad and concentrated, leaving pure enal **33** (12.0 g, 100%, yellowish oil). This material was immediately used for the second olefination sequence described below: $[\alpha]^{27}_D$ −17.9° (c = 1.12, $CHCl_3$); IR (neat) 2945, 2865, 2725, 1695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.52 (1H, d, J = 8.0 Hz, −CHO), 7.26 (2H, m) and 6.87 (2H, m) (p-CH_3O-Ar-), 7.06 (1H, dd, J = 16.0, 6.0 Hz, $-HC=CHCHO$), 6.13 (1H, dd, J = 16.0, 8.0 Hz, $-HC=CHCHO$), 4.57 (2H, s, $-OCH_2O-$), 4.42 (2H, s, $-OCH_2$-Ar), 4.10 (2H, s, $=C(CH_2OPMB)-$), 4.02 (2H, s, $-CH_2OMOM$), 3.91 (1H, br dt, J = 5.5, 5.5 Hz, $-$(TIPSO)CH$-$), 3.80 (3H, s, $-Ar-OCH_3$), 3.33 (3H, s, $-CH_2OCH_3$), 2.72 (1H, m, $-(CH_3)$-$CH-HC=$), 2.25 (1H, dt, J = 12.0, 5.0 Hz, $-HCHC(CH_3)=$), 2.12 (1H, dt, J = 12.0, 5.0 Hz, $-HCHC(CH_3)=$), 1.75 (3H, s, $-C(CH_3)=$), 1.52 (2H, m, $-$(TIPSO)CHCH_2-), 1.10 (3H, d, J = 7.0 Hz, $-(CH_3)CH-HC=$), 1.08 (21H, s, $-Si(CH(CH_3)_2)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 194.11, 161.10, 159.19, 141.09, 132.34, 130.55, 129.41, 127.25, 113.72, 95.68, 75.80, 72.02, 67.52, 64.63, 55.22(2), 42.13, 32.84, 31.22, 18.57, 18.22,

13.38, 12.89; MS *m/e* 530 ($M^+ - CH_3OH$), 519 ($M^+ - C_3H_7$); HRMS calcd for $C_{29}H_{47}O_6Si$ = 519.3142; found = 519.3136 ± 0.0015.

(2*Z*,4*E*,10*Z*)-(6*S*,7*S*)-Methyl 7-(Triisopropylsiloxy)-6,10-dimethyl-11-[[(*p*-methoxybenzyl)oxy]methyl]-12-(methoxymethoxy)-2,4,10-dodecatrienoate (34). To a stirred solution of methyl bis(trifluoroethoxy)phosphonoacetate (8.21 g, 0.103 mol) in tetrahydrofuran (380 mL) cooled to −78 °C was added dropwise potassium bis(trimethylsilyl)amide (49.5 mL, 24.8 mmol, 0.50 M in toluene) over a 20 min period. The cloudy orange mixture was warmed to −40 °C (acetonitrile/dry ice) and stirred for 1.0 h and then cooled back to −78 °C. Thereafter, aldehyde **33** (11.60 g, 20.6 mmol) in tetrahydrofuran (10 mL + 10 mL rinse) was added via cannula. The solution was stirred 3.0 h at −78 °C after which it was allowed to warm slowly to 0 °C (45 min). The reaction was found incomplete by TLC analysis but was nevertheless quenched by addition of a saturated aqueous ammonium chloride solution (100 mL) and diluted with diethyl ether (1 L). The aqueous layer was segregated and extracted with diethyl ether (5 × 100 mL). The combined organic phases were washed with brine (50 mL), dried with anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (10% to 30% ethyl acetate in hexanes), yielding recuperated aldehyde **33** (2.71 g, 23%) and (*E*,*Z*)-doubly unsaturated ester **34** (8.88 g, 70% (91% recuperated yield), slightly yellowish oil) with no observed traces of (*E*,*E*)-isomer **48** (as seen through ^{1}H NMR analysis of crude material): $[\alpha]^{27}_D$ −16.5° (*c* = 1.04, $CHCl_3$); IR (neat) 2945, 2865, 1715 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.37 (1H, dd, *J* = 15.5, 11.0 Hz, −HC=C*H*−HC=CHCO$_2$CH$_3$), 7.26 (2H, m) and 6.86 (2H, m) (*p*-CH$_3$O−*Ar*−), 6.56 (1H, dd, *J* = 11.0, 11.0 Hz, −*H*C=CHCO$_2$CH$_3$), 6.25 (1H, dd, *J* = 15.5, 7.0 Hz, −*H*C=CH−HC=CHCO$_2$CH$_3$), 5.58 (1H, d, *J* = 11.0 Hz, −HC=C*H*CO$_2$CH$_3$), 4.58 (2H, s, −OCH$_2$O−), 4.41 (2H, s, OC*H*$_2$Ar), 4.10 (2H, s, =C(C*H*$_2$OPMB)−), 4.02 (2H, s, −C*H*$_2$-OMOM), 3.83 (1H, m, −(TIPSO)CH−), 3.79 (3H, s, −Ar−OC*H*$_3$), 3.71 (3H, s, −CO$_2$CH$_3$), 3.33 (3H, s, −CH$_2$OC*H*$_3$), 2.58 (1H, m, −(CH$_3$)C*H*−HC=), 2.23 (1H, dt, *J* = 12.0, 5.0 Hz, −*H*CHC-(CH$_3$)=), 2.11 (1H, dt, *J* = 12.0, 5.0 Hz, −HC*H*C(CH$_3$)=), 1.74 (3H, s, −C(CH$_3$)=), 1.52 (2H, m, −(TIPSO)CHC*H*$_2$−), 1.07 (3H, d, *J* = 7.0 Hz, −(C*H*$_3$)CH−HC=), 1.06 (21H, s, −Si(CH-(CH$_3$)$_2$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 166.82, 159.07, 148.09, 145.61, 141.46, 130.61, 129.35, 126.90, 126.07, 115.23, 113.66, 95.69, 76.40, 71.85, 67.47, 64.64, 55.14(2), 50.95, 41.96, 33.00, 31.08, 18.53, 18.19, 14.02, 12.90; MS *m/e* 618 (M^+); HRMS calcd for $C_{35}H_{58}O_7Si$ = 618.3952; found = 618.3959 ± 0.0018.

(2*Z*,4*E*,10*Z*)-(6*S*,7*S*)-7-(Triisopropylsiloxy)-6,10-dimethyl-11-[[(*p*-methoxybenzyl)oxy]methyl]-12-(methoxymethoxy)-2,4,10-dodecatrienol (35). To a stirred solution of ester **34** (10.74 g, 17.38 mmol) in dichloromethane (190 mL) cooled to −78 °C was added dropwise diisobutylaluminum hydride (38.0 mL, 38.0 mmol, 1.0 M in dichloromethane) over a 15 min period. The solution was stirred for 45 min at −78 °C after which excess hydride was quenched by slow addition of methanol (30 mL). A saturated aqueous disodium tartrate solution (200 mL) was added, and the mixture was allowed to warm to room temperature over 1.5 h. The phases were then separated, and the aqueous one was extracted with dichloromethane (5 × 100 mL). The combined halogenated layers were dried with anhydrous sodium sulfate, filtered, and concentrated. Purification of the crude product by flash chromatography (20% to 40% ethyl acetate in hexanes) afforded allylic alcohol **35** (9.22 g, 90%, clear visqueous oil): $[\alpha]^{25}_D$ −6.0° (*c* = 1.04, $CHCl_3$); IR (neat) 3450 (br), 2945, 2865, 1615 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.26 (2H, m) and 6.86 (2H, m) (*p*-CH$_3$O−*Ar*−), 6.32 (1H, dd, *J* = 15.0, 11.0 Hz, −HC=C*H*−HC=CHCH$_2$OH), 6.05 (1H, dd, *J* = 11.0, 11.0 Hz, −*H*C=CHCH$_2$OH), 5.85 (1H, dd, *J* = 15.0, 7.0 Hz, −*H*C=CH−HC=CHCH$_2$OH), 5.50 (1H, dd, *J* = 11.0, 7.0 Hz, −HC=C*H*CH$_2$OH), 4.58 (2H, s, −OCH$_2$O−), 4.41 (2H, s, −OC*H*$_2$Ar), 4.27 (2H, br d, *J* = 7.0 Hz, =CHC*H*$_2$OH), 4.11 (1H, AB d, *J* = 11.0 Hz, =C(*H*CHOPMB)−), 4.07 (1H, AB d, *J* = 11.0 Hz, =C(HC*H*OPMB)−), 4.02 (2H, s, −C*H*$_2$OMOM), 3.79 (3H, s, −Ar−OC*H*$_3$), 3.77 (1H, m, −(TIPSO)C*H*−), 3.34 (3H, s, −CH$_2$OC*H*$_3$), 2.46 (1H, m, −(CH$_3$)C*H*−HC=), 2.25 (1H, dt, *J* = 12.0, 5.0 Hz, −*H*CHC(CH$_3$)=), 2.10 (1H, dt, *J* = 12.0, 5.0 Hz, −HC*H*C(CH$_3$)=), 1.86 (1H, br s, −OH), 1.74 (3H, s, −C-(CH$_3$)=), 1.63−1.42 (2H, m, −(TIPSO)CHC*H*$_2$−), 1.07 (21H, s, −Si(CH(CH$_3$)$_2$)$_3$), 1.02 (3H, d, *J* = 7.0 Hz, −(C*H*$_3$)CH−HC=); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.08, 141.64, 139.44, 131.06, 130.56, 129.36, 127.72, 126.84, 124.16, 113.66, 95.70, 76.46, 71.85, 67.40, 64.77, 58.66, 55.17(2), 41.89, 33.03, 30.63, 18.53, 18.23, 14.99, 12.95; MS *m/e* 590 (M^+), 572 ($M^+ - H_2O$), 547 ($M^+ - C_3H_7$); HRMS calcd for $C_{34}H_{58}O_6Si$ = 590.4002; found = 590.4015 ± 0.0017.

(6*Z*,8*E*,14*Z*)-(10*S*,11*S*)-Methyl-3-oxo-11-(triisopropylsiloxy)-10,14-dimethyl-15-[[(*p*-methoxybenzyl)oxy]methyl]-16-(methoxymethoxy)-6,8,14-hexadecatrienoate (37). To a stirred solution of allylic alcohol **35** (9.05 g, 15.4 mmol) in dry dimethylformamide (20 mL) cooled to 0 °C were successively added *s*-collidine (3.03 mL, 23.0 mmol) and dried lithium chloride (0.940 g, 22.0 mmol). Then, methanesulfonyl chloride (1.67 mL, 21.5 mmol) was dropwisely added over ~3 min. The mixture was stirred at 0 °C for 5.0 h (after 15 min, a white thick precipitate appeared and necessitated the addition of further solvent (10 mL) to facilitate stirring) after which it was poured into ice/water (100 mL) and extracted with 1:1 petroleum ether/diethyl ether (5 × 100 mL). The combined organic phases were washed with a saturated aqueous copper-(II) nitrate solution (2 × 75 mL), water (25 mL), and brine (25 mL), dried with anhydrous magnesium sulfate, filtered, and concentrated. A rapid purification of the crude product through flash chromatography (5% to 15% ethyl acetate in hexanes) over a short column yielded allylic chloride **36** (8.20 g, 88%, yellowish oil). This sensitive material was only characterized by ^{1}H NMR analysis and was immediately employed for the next alkylation step: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.32 (1H, dd, *J* = 15.0, 11.0 Hz, −HC=C*H*−HC=CHCH$_2$Cl), 6.13 (1H, dd, *J* = 11.0, 11.0 Hz, −*H*C=CHCH$_2$Cl), 5.96 (1H, dd, *J* = 15.0, 7.0 Hz, −*H*C=CH−HC=CHCH$_2$Cl), 5.51 (1H, br dt, *J* = 11.0, 8.0 Hz, −HC=C*H*CH$_2$Cl), 4.59 (2H, s, −OCH$_2$O−), 4.42 (2H, s, −OC*H*$_2$-Ar), 4.21 (2H, d, *J* = 8.0 Hz, =CHC*H*$_2$Cl), 4.10 (2H, s, =C-(C*H*$_2$OPMB)−), 4.03 (2H, s, −C*H*$_2$OMOM), 3.80 (3H, s, −Ar−OC*H*$_3$), 3.78 (1H, m, −(TIPSO)C*H*−), 3.34 (3H, s, −CH$_2$-OC*H*$_3$), 2.49 (1H, m, −C(CH$_3$)C*H*−HC=),=), 2.24 (1H, dt, *J* = 12.0, 5.5 Hz, −*H*CHC(CH$_3$)=), 2.12 (1H, dt, *J* = 12.0, 5.5 Hz, −HC*H*C(CH$_3$)=), 1.75 (3H, s, −C(CH$_3$)=), 1.52 (2H, m, −-(TIPSO)CHC*H*$_2$−), 1.06 (21H, s, −Si(CH(CH$_3$)$_2$)$_3$), 1.03 (3H, d, *J* = 6.0 Hz, −(C*H*$_3$)CH−HC=).

To a stirred suspension of sodium hydride (1.17 g, 29.4 mmol, 60% suspension in oil) in tetrahydrofuran (65 mL) cooled to 0 °C was added methyl acetoacetate (3.02 mL, 28.0 mmol) dropwise over a 10 min period. The clear homogeneous solution was further stirred for 15 min at 0 °C after which *n*-butyllithium (19.1 mL, 28.7 mmol, 1.50 M in hexanes) was dropwisely added over a 10 min period. The clear solution was stirred for 30 min (at that point the coloration was orange-like), and a cooled (0 °C) solution of the above chloride **36** (8.12 g, 13.30 mmol) in tetrahydrofuran (8 mL + 2 mL rinse) was added dropwise via cannula over ~5 min. The solution was stirred 30 min at 0 °C and excess alkylant was quenched by slow addition of a solution made from concentrated aqueous hydrochloric acid (5 mL) and water (15 mL). The resulting mixture was diluted with diethyl ether (100 mL) and the phases were separated (pH of aqueous layer ~2). The organic phase was washed with water (3−4 × 25 mL) until the aqueous layer showed a neutral pH. The combined aqueous phases were then neutralized and extracted with diethyl ether (5 × 75 mL). Finally, the combined organic phases were dried with anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (15% ethyl acetate in hexanes), yielding β-keto ester **37** (8.19 g, 88%, pale yellowish oil). A minor amount of easily separated alcohol **35**, arising from hydrolysis of the *O*-alkylation product formed from residual methyl acetoacetate mono-anion, was also observed: $[\alpha]^{27}_D$ −5.0° (*c* = 1.10, $CHCl_3$); IR (neat) 2945, 1750, 1720, 1615 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.25 (2H, m) and 6.85 (2H, m) (*p*-CH$_3$O−*Ar*−), 6.28 (1H, dd, *J* = 15.0, 11.0 Hz, −HC=C*H*−HC=CHCH$_2$−), 5.97 (1H, dd, *J* = 11.0,

11.0 Hz, $-HC{=}CHCH_2-$), 5.81 (1H, dd, J = 15.0, 7.0 Hz, $-HC{=}CH-HC{=}CHCH_2-$), 5.23 (1H, br dt, J = 11.0, 7.0 Hz, $-HC{=}CHCH_2-$), 4.58 (2H, s, $-OCH_2O-$), 4.41 (2H, s, $-OCH_2$-Ar), 4.10 (2H, s, $=C(CH_2OPMB)-$), 4.02 (2H, s, $-CH_2OMOM$), 3.78 (3H (3H, s, $-Ar-OCH_3$), 3.76–3.70 (1H, m, $-$(TIPSO)$CH-$), 3.71 (3H, s, $-CO_2CH_3$), 3.43 (2H, s, $-COCH_2CO_2$-CH_3), 3.32 (3H, s, $-CH_2OCH_3$), 2.60 (2H, br t, J = 7.0 Hz, $-HC{=}CHCH_2CH_2CO-$), 2.50–2.40 (1H, m, $-(CH_3)CH-HC{=}$), 2.44 (2H, br dt, J = 7.0, 7.0 Hz, $-HC{=}CHCH_2CH_2CO-$), 2.24 (1H, dt, J = 12.5, 5.5 Hz, $-HCHC(CH_3)-$), 2.11 (1H, dt, J = 12.5, 5.5 Hz, $-HCHC(CH_3){=}$), 1.74 (3H, s, $-C(CH_3){=}$), 1.62–1.42 (2H, m, $-$(TIPSO)$CHCH_2-$), 1.06 (21H, s, $-Si(CH(CH_3)_2)_3$), 1.01 (3H, d, J = 7.0 Hz, $-(CH_3)CH-HC{=}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 201.88, 167.47, 159.08, 141.72, 138.13, 130.58, 130.11, 129.34, 127.01, 126.73, 124.36, 113.64, 95.70, 76.67, 71.84, 67.49, 64.69, 55.15(2), 52.26, 48.97, 42.77, 41.74, 32.99, 31.01, 21.68, 18.52, 18.22, 14.64, 12.95; MS m/e 688 (M^+), 657 ($M^+ - CH_3O$), 645 ($M^+ - C_3H_7$); HRMS calcd for $C_{36}H_{57}O_8Si$ = 645.3822; found = 645.3815 ± 0.0019.

(6*Z*,8*E*,14*E*)-(10*S*,11*S*)-Methyl 3-Oxo-16-hydroxy-11-(triisopropylsiloxy)-10,14-dimethyl-15-[[(*p*-methoxybenzyl)oxy]methyl]-6,8,14-hexadecatrienoate (38). To a stirred solution of methoxymethyl ether **37** (1.00 g, 1.45 mmol) in dry isopropyl alcohol (10.0 mL) were added two drops (~0.06 mL) of concentrated aqueous hydrochloric acid. The solution was stirred at 55 °C for 10 h and although incomplete as indicated by TLC analysis, was allowed to cool to room temperature (prolonged reaction times tend to give substantial decomposition). A saturated aqueous sodium bicarbonate solution (20 mL) and diethyl ether (50 mL) were added to the mixture. The phases were separated and the aqueous layer was extracted with diethyl ether (5 × 50 mL). The combined organic phases were then washed with brine (10 mL), dried with anhydrous magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography (15% to 40% ethyl acetate in hexanes), yielding recuperated ether **37** (0.1 g, ~10%), which can be further recycled, and pure allylic alcohol **38** (0.63 g, 65% (74% recuperated yield), yellowish visqueous oil): $[\alpha]^{27}_D$ −2.2° (c = 1.04, $CHCl_3$); IR (neat) 3470 (br), 2945, 2865, 1750, 1720, 1615 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.26 (2H, m) and 6.87 (2H, m) (p-CH_3O-Ar-), 6.30 (1H, dd, J = 15.0, 11.0 Hz, $-HC{=}CH-HC{=}CHCH_2-$), 5.98 (1H, d, J = 11.0, 11.0 Hz, $-HC{=}CHCH_2-$), 5.80 (1H, dd, J = 15.0, 7.0 Hz, $-HC{=}CH-HC{=}CHCH_2-$), 5.25 (1H, dt, J = 11.0, 7.0 Hz, $-HC{=}CHCH_2-$), 4.46 (2H, s, $-OCH_2Ar$), 4.19 (2H, s, $-CH_2OH$), 4.13 (2H, s, $=C(CH_2OPMB)-$), 3.81 (3H, s, $-Ar-OCH_3$), 3.80–3.73 (1H, m, $-$(TIPSO)$CH-$), 3.73 (3H, s, $-CO_2CH_3$), 3.45 (2H, s, $-COCH_2CO_2CH_3$), 2.62 (2H, t, J = 7.0 Hz, $-HC{=}CHCH_2CH_2CO-$), 2.50–2.38 (1H, m, $-(CH_3)$-$CH-HC{=}$), 2.46 (2H, br dt, J = 7.0, 7.0 Hz, $-HC{=}CHCH_2$-CH_2CO-), 2.23 (1H, dt, J = 12.0, 5.5 Hz, $-HCHC(CH_3){=}$), 2.10 (1H, dt, J = 12.0, 5.5 Hz, $-HCHC(CH_3){=}$), 1.78–1.60 (1H, br s, $-OH$), 1.71 (3H, s, $-C(CH_3){=}$), 1.62–1.48 (2H, m, $-$(TIPSO)$CHCH_2-$), 1.06 (21H, s, $-Si(CH(CH_3)_2)_3$), 1.02 (3H, d, J = 7.0 Hz, $-(CH_3)CH-HC{=}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 202.00, 167.52, 159.23, 138.51, 138.14, 130.06, 129.35-(2), 128.8, 127.14, 124.36, 113.76, 76.50, 72.22, 69.13, 61.48, 55.19, 52.28, 48.98, 42.77, 41.80, 33.21, 30.50, 21.68, 18.49, 18.22, 14.94, 12.94; MS m/e 612 ($M^+ - CH_3OH$), 594 ($M^+ - CH_3OH - H_2O$); HRMS calcd for $C_{36}H_{56}O_6Si$ = 612.3846; found = 612.3838 ± 0.0018.

(14*S*)- and (14*R*)-(1*E*,7*E*,9*Z*)-(5*S*,6*S*)-14-(Methoxycarbonyl)-5-(triisopropylsiloxy)-2,6-dimethyl-1-[[(*p*-methoxybenzyl)oxy]methyl]-1,7,9-cyclopentadecatrien-13-one (40). To a stirred solution of allylic alcohol **38** (1.80 g, 2.80 mmol) in hexachloroacetone (5.0 mL) cooled to 0 °C was added powdered triphenylphosphine (1.10 g, 4.20 mmol). The heterogeneous mixture (triphenylphosphine dissolves slowly and the solution becomes progressively colored to end in a deep purple) was allowed to warm to room temperature and stirred for 2.5 h. The reaction mixture was rapidly passed through a silica gel column as a flash chromatography (primary, 100% hexanes (for removing hexachloroacetone); secondary, 30% to 50% ethyl acetate in hexanes), yielding sensitive allylic chloride **39** (1.85 g, quant, good purity state (~95%) through TLC and ^1H NMR analysis, yellowish oil) which was only characterized by ^1H NMR analysis and immediately treated via the following macrocyclization step: ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.27 (2H, m) and 6.88 (2H, m) (p-CH_3O-Ar-), 6.32 (1H, dd, J = 15.0, 11.0 Hz, $-HC{=}CH-HC{=}CHCH_2-$), 5.99 (1H, dd, J = 11.0, 11.0 Hz, $-HC{=}CHCH_2-$), 5.80 (1H, dd, J = 15.0, 7.0 Hz, $-HC{=}CH-HC{=}CHCH_2-$), 5.25 (1H, dt, J = 11.0, 7.0 Hz, $-HC{=}CHCH_2-$), 4.43 (2H, s, $-OCH_2Ar$), 4.19 (2H, br s, $-CH_2Cl$), 4.07 (2H, s, $=C(CH_2OPMB)-$), 3.81 (3H, s, $-Ar-OCH_3$), 3.82–3.74 (1H, m, $-$(TIPSO)$CH-$), 3.74 (3H, s, $-CO_2CH_3$), 3.45 (2H, s, $-COCH_2CO_2CH_3$), 2.63 (2H, t, J = 7.0 Hz, $-HC{=}CHCH_2CH_2CO-$), 2.52–2.42 (1H, m, $-(CH_3)CH-HC{=}$), 2.48 (2H, dt, J = 7.0, 7.0 Hz, $-HC{=}CHCH_2$-CH_2CO-), 2.29 (1H, dt, J = 12.5, 5.0 Hz, $-HCHC(CH_3){=}$), 2.11 (1H, dt, J = 12.5, 5.0 Hz, $-HCHC(CH_3){=}$), 1.74 (3H, s, $-C(CH_3){=}$), 1.68–1.42 (2H, m, $-$(TIPSO)$CHCH_2-$), 1.08 (21H, s, $-Si(CH(CH_3)_2)_3$), 1.04 (3H, d, J = 7.0 Hz, $=(CH_3)CH-HC{=}$).

To a vigorously stirred suspension of cesium iodide (3.63 g, 13.95 mmol) and cesium carbonate (4.55 g, 13.95 mmol) in dry acetone (2.6 L) at a near reflux temperature (~55 °C) was added a solution of the above allylic chloride **39** (1.85 g, 2.79 mmol) in acetone (25 mL) dropwise via gas-tight syringe through slow addition (over the vortex) with a syringe pump over a 15 h period. The mixture was allowed to cool to room temperature for 3 h and a saturated aqueous ammonium chloride solution (100 mL) was added. (NOTE: The small quantity of unadded **39** remaining in the syringe tip was shown homogeneous by TLC analysis, indicating that it survived the long standing time.) The acetone was evaporated and water (50 mL) was added to dissolve the solids. The aqueous residue was extracted with dichloromethane (1 × 200 mL, 5 × 75 mL) and the combined organic layers were washed with brine (25 mL), dried with anhydrous sodium sulfate, filtered, and concentrated. The crude product, which contains a substantial portion of acetone aldolization dimer, was purified by flash chromatography (10% ethyl acetate in hexanes), giving TCC macrocyclic β-keto ester **40** as a nonseparable 1:1 mixture of epimers at C14 (1.05 g, 60% from **38**, yellowish foamy oil, slightly less polar than starting material on TLC) and a small proportion of presumed O-alkylation isomeric macrocyclization product **41** (0.124 g, 7%, yellowish oil, unstable), obtained as a mixture of geometrical isomers.

TCC **40** (as a 1:1 mixture of epimers at C14): IR (neat) 2945, 2865, 1740, 1710, 1615 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) (NOTE: the stereochemistry at C14 was not assigned, differentiated signals are denoted by half-integrations; i.e. H/2) 7.30–7.20 (2H, m) and 6.86 (2H, m) (p-CH_3O-Ar-), 6.49 (H/2, dd, J = 15.0, 11.0 Hz, $-HC{=}CH-HC{=}CHCH_2-$), 6.20 (H/2, dd, J = 15.0, 11.0 Hz, $-HC{=}CH-HC{=}CHCH_2-$), 6.02 (H/2, dd, J = 11.0, 11.0 Hz, $-HC{=}CHCH_2-$), 5.98 (H/2, dd, J = 11.0, 11.0 Hz, $-HC{=}CHCH_2-$), 5.83 (H/2, dd, J = 7.0 Hz, $-HC{=}CH-HC{=}CHCH_2-$), 5.48 (H/2, dd, J = 15.0, 11.0 Hz, $-HC{=}CH-HC{=}CHCH_2-$), 5.45–5.30 (H/2 + H/2, m, $-HC{=}CH-HC{=}CHCH_2-$ and $-HC{=}CH-HC{=}CHCH_2-$), 4.48–4.22 (2H, m, $-OCH_2Ar$), 3.90–3.60 (3H, m, $-$(TIPSO)-$CH-$ and $=C(CH_2OPMB)-$), 3.79 (3H, s, $-Ar-OCH_3$), 3.65 (3H/2, s, $-CO_2CH_3$), 3.58 (3H/2, s, $-CO_2CH_3$), 3.49 (H/2, dd, J = 12.0, 3.5 Hz, $-CHCO_2CH_3$), 3.40 (H/2, dd, J = 9.0, 4.5 Hz, $-CHCO_2CH_3$), 2.92–1.85 (9H, m, $-$(TIPSO)$CHCH_2CH_2-$ and $-(CH_3)CH-HC{=}$ and $=CHCH_2CH_2CO-$ and $-CH_2CH-(CO_2CH_3)-$), 1.70–1.40 (2H, m, $-$(TIPSO)$CHCH_2-$), 1.15–1.00 (24H, m, $-Si(CH(CH_3)_2)_3$ and $-(CH_3)CH-HC{=}$), 1.67 (3H/2, s, $-C(CH_3){=}$), 1.63 (3H/2, s, $-C(CH_3){=}$); MS m/e 626 (M^+) 608 ($M^+ - H_2O$); HRMS calcd for $C_{37}H_{58}O_6Si$ = 626.4002; found = 626.3998 ± 0.0018.

(1*E*,7*E*,9*Z*)-(5*S*,6*S*)-5-(Triisopropylsiloxy)-2,6-dimethyl-1-[[(*p*-methoxybenzyl)oxy]methyl]-1,7,9-cyclopentadecatrien-13-one (42). To a stirred solution of β-keto ester **40** (1.62 g, 2.59 mmol) in dimethyl sulfoxide (26 mL) were added sodium cyanide (0.250 g, 5.10 mmol) and water (0.140 mL, 7.70 mmol). The mixture was stirred 6.0 h at 125 °C after which it was allowed to cool to room temperature and diluted with water (50 mL) and extracted with 1:1 diethyl ether/pentane (5 × 50 mL). The combined organic layers were dried with anhydrous magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography (15% to 60% ethyl acetate in hexanes), affording the desilylated alcohol

(0.13 g, 12%) which can be reprotected, and desired TCC macrocyclic triene **42** (0.99 g, 68% (80% including the alcohol), slightly yellowish foamy oil): $[\alpha]^{27}_D$ −3.6° (*c* = 1.05, $CHCl_3$); IR (neat) 3000−2800 (br), 1740, 1710, 1610 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.25 (2H, m) and 6.86 (2H, m) (*p*-CH_3O−*Ar*−), 6.27 (1H, dd, *J* = 15.0, 11.0 Hz, −HC=C*H*−HC=$CHCH_2$−), 6.01 (1H, dd, *J* = 11.0, 11.0 Hz, −*H*C=$CHCH_2$−), 5.68 (1H, dd, *J* = 15.0, 8.0 Hz, −*H*C=CH−HC=$CHCH_2$−), 5.33 (1H, dt, 11.0, 7.0 Hz, −HC=C*H*CH_2−), 4.39 (1H, AB d, *J* = 11.5 Hz, −O*H*CHAr), 4.35 (1H, AB d, *J* = 11.5 Hz, −OHC*H*Ar), 3.90 (1H, AB d, *J* = 11.0 Hz, =C(*H*CHOCH_2PMB)−), 3.86 (1H, AB d, *J* = 11.0 Hz, =C(HC*H*OCH_2OPMB)−), 3.79 (3H, s, −Ar−OCH_3), 3.79−3.73 (1H, m, −(TIPSO)C*H*−), 2.75−2.10 (10H, m) and 1.90 (1H, dt, *J* = 13.0, 3.5 Hz) (−CH_2C(CH_3)=, −(CH_3)C*H*−HC=, =CHCH_2CH_2COCH_2CH_2C=), 1.65 (3H, s, −C(CH_3)=), 1.65−1.43 (2H, m, −(TIPSO)CHCH_2−), 1.09 (21H, s, −Si(CH(CH_3)$_2$)$_3$), 1.08 (3H, d, *J* = 7.0 Hz, −(CH_3)CH−HC=); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 211.91, 159.04, 138.28, 136.40, 130.65, 130.26, 129.29, 128.84, 127.80, 123.84, 113.63, 75.45, 71.71, 69.19, 55.21, 43.24, 42.78, 41.88, 33.50, 27.64, 25.41, 24.06, 18.44, 18.26, 17.94, 12.91; MS *m*/*e* 568 (M^+), 550 (M^+ − H_2O); HRMS calcd for $C_{35}H_{56}O_4Si$ = 568.3948; found = 568.3953 ±.0.0016.

(1*E*,7*E*,9*Z*)-(5*S*,6*S*)-5-(Triisopropylsiloxy)-2,6-dimethyl-1-(bromomethyl)-1,7,9-cyclopentadecatrien-13-one (45). To a stirred solution of *p*-methoxybenzyl ether **42** (5.5 mg, 0.0096 mmol) in dichloromethane (0.5 mL, or alternatively chloroform) cooled to 0 °C was dropwisely added dimethylbromoborane (0.026 mL, 0.038 mmol, 1.5 M in 1,2-dichloroethane) over 30 s. The solution was stirred 5 min at 0 °C (only one homogeneous spot on TLC) and then quenched with a saturated aqueous sodium bicarbonate solution (1 mL) and diluted with diethyl ether (15 mL). The phases were separated and the organic layer was dried with anhydrous magnesium sulfate, filtered, and concentrated (without heating), affording very sensitive bromide **45** in good state of purity (5.7 mg, 95%, yellowish oil): (NOTE: This sample was isolated for analytical means but the compound often decomposes if concentrated to dryness. It is most likely better to keep it as a solution and use it in the next step without delay.) IR (neat) 2945, 2865, 1710, 1650 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.26 (1H, dd, *J* = 15.0, 11.0 Hz, −HC=C*H*−HC=$CHCH_2$−), 6.02 (1H, dd, *J* = 11.0, 11.0 Hz, −*H*C=$CHCH_2$−), 5.71 (1H, dd, *J* = 15.0, 8.0 Hz, −*H*C=CH−HC=$CHCH_2$−), 5.34 (1H, dt, *J* = 11.0, 7.0 Hz, −HC=C*H*CH_2−), 3.98 (2H, s, −CH_2Br), 3.80 (1H, m, −(TIPSO)C*H*−), 2.72−2.00 (10H, m) and 1.93 (1H, dt, *J* = 13.0, 3.5 Hz) (−CH_2C(CH_3)=, −(CH_3)C*H*−HC=, =CHCH_2CH_2COCH_2CH_2C=), 1.73 (3H, s, −C(CH_3)=), 1.68−1.40 (2H, m, −(TIPSO)CHCH_2−), 1.09 (21H, s, −Si(CH(CH_3)$_2$)$_3$), 1.08 (3H, d, *J* = 7.0 Hz, −(CH_3)CH−HC=); MS *m*/*e* 510 (M^+), 431 (M^+ − Br); HRMS calcd for $C_{27}H_{47}O_2SiBr$ = 510.2528; found = 510.2517 ± 0.0015.

(1*E*,7*E*,9*Z*)-(5*S*,6*S*)-5-(Triisopropylsiloxy)-1-(hydroxymethyl)-2,6-dimethyl-1,7,9-cyclopentadecatrien-13-one (44). To a stirred solution of PMB ether **42** (0.063 g, 0.111 mmol) in dichloromethane/water (1.0 mL/0.050 mL) at room temperature was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.028 g, 0.122 mmol) over a 30 s period. The solution was stirred 50 min, and three drops of a saturated aqueous sodium bicarbonate solution were added. The mixture was then concentrated to near dryness with a nitrogen stream, and the residue was purified by flash chromatography (20% ethyl acetate in hexanes), yielding TCC cyclopentadecatrienol **44** (0.031 g, 63%, slightly yellowish oil): $[\alpha]^{30}_D$ −9.1° (*c* = 1.52, $CHCl_3$); IR (neat) 3410, 2945, 2860, 1705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.28 (1H, dd, *J* = 15.0, 11.0 Hz, −HC=C*H*−HC=$CHCH_2$−), 6.01 (1H, dd, *J* = 11.0, 11.0 Hz, −*H*C=$CHCH_2$−), 5.67 (1H, dd, *J* = 15.0, 8.0 Hz, −*H*C=CH−HC=$CHCH_2$−), 5.32 (1H, dt, *J* = 11.0, 7.0 Hz, −HC=C*H*CH_2−), 4.07 (2H, s, −CH_2OH), 3.80−3.74 (1H, m, −(TIPSO)C*H*−), 2.75−2.10 (11H, m) and 1.90 (1H, dt, *J* = 13.0, 2.5 Hz) (−C*H*(CH_3)HC=, −CH_2C(CH_3)=, =CCH_2CH_2COCH_2CH_2CH=, −OH), 1.71 (3H, s, −C(CH_3)=), 1.61 (1H, tdd, *J* = 14.0, 4.0, 4.0 Hz, −(TIPSO)CH−*H*CH−), 1.48 (1H, tm, −(TIPSO)CH−HC*H*−), 1.09 (21H, s, −OSi(CH(CH_3)$_2$)$_3$), 1.08 (3H, d, *J* = 7.0 Hz, −CH(C*H*$_3$)HC=); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 212.00, 138.33, 135.59, 131.43, 130.25, 127.89, 123.91, 75.50, 62.32, 43.35, 42.91, 41.76, 33.58, 27.54, 25.11, 24.10, 18.30, 18.05, 12.98; MS *m*/*e* 430 (M^+ − H_2O), 387 (M^+ − H_2O − C_3H_7); HRMS calcd for $C_{27}H_{46}O_2Si$ = 430.3267; found = 430.3264 ± 0.0012.

(1*E*,7*E*,9*Z*)-(5*S*,6*S*)-5-(Triisopropylsiloxy)-1-formyl-2,6-dimethyl-1,7,9-cyclopentadecatrien-13-one (46). To a stirred solution of allylic alcohol **44** (0.090 g, 0.20 mmol) in dichloromethane (2.0 mL) at room temperature was added the Dess−Martin periodinane (0.102 g, 0.24 mmol). The solution was stirred 1.0 h after which it was diluted with diethyl ether (50 mL). A saturated aqueous sodium bicarbonate solution (5 mL) and solid pentahydrated sodium thiosulfate (0.45 g) were added and the resulting mixture was stirred until the cloudy organic layer became clear (~15 min). The phases were separated, and the organic layer was successively washed with saturated aqueous sodium bicarbonate solution (5 mL) and water (3 mL), and then dried with anhydrous magnesium sulfate and concentrated. The crude product was purified by flash chromatography (15% ethyl acetate in hexanes), yielding pure TCC aldehyde **46** (0.075 g, 83%, oil): $[\alpha]^{30}_D$ +9.8° (*c* = 0.78, $CHCl_3$); IR (neat) 2945, 2865, 1710, 1665 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 10.03 (1H, s, −CHO), 6.20 (1H, dd, *J* = 15.0, 11.0 Hz, −HC=C*H*−HC=$CHCH_2$−), 6.02 (1H, dd, *J* = 11.0, 11.0 Hz, −HC=CH−*H*C=$CHCH_2$−), 5.78 (1H, dd, *J* = 15.0, 7.0 Hz, −CH(CH_3)*H*C=CH−), 5.36 (1H, dt, *J* = 11.0, 7.0 Hz, −HC=C*H*CH_2−), 3.87 (1H, ddd, *J* = 7.5, 4.0, 2.0 Hz, −(TIPSO)CH−), 2.65−2.25 (9H, m) and 2.15-2.00 (2H, m) (−C*H*(CH_3)HC=, −CH_2C(CH_3)=, =CCH_2CH_2COCH_2CH_2CH=), 2.12 (3H, s, −C(CH_3)=), 1.73−1.50 (2H, m, −(TIPSO)-CHCH_2−), 1.09 (21H, s, −OSi(CH(CH_3)$_2$)$_3$), 1.09 (3H, d, *J* = 6.0 Hz, −CH(C*H*$_3$)HC=); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 211.33, 190.91, 160.17, 137.98, 135.90, 130.52, 128.07, 123.74, 74.96, 42.86, 42.67, 42.02, 32.32, 30.32, 24.49, 19.70, 18.23, 17.50, 17.31, 12.83; MS *m*/*e* 446 (M^+), 417 (M^+ − CHO), 403 (M^+ − C_3H_7); HRMS calcd for $C_{27}H_{46}O_3Si$ = 446.3216; found = 446.3213 ± 0.0013.

(2*E*,4*E*,10*Z*)-(6*S*,7*S*)-Methyl 7-(Triisopropylsiloxy)-6,10-dimethyl-11-[[(*p*-methoxybenzyl)oxy]methyl]-12-(methoxymethoxy)-2,4,10-dodecatrienoate (48). To a stirred solution of aldehyde **33** (12.50 g, 222.0 mmol) in dichloromethane (220 mL) was added methyl (triphenylphosphoranylidene)acetate (37.0 g, 0.111 mol). The mixture was stirred 90 h at room temperature after which it was concentrated to near dryness. The crude product (*E*/*Z* isomer ratio by ^1H NMR: **48**/**34** = 20:1) was purified by flash chromatography (10% to 30% ethyl acetate in hexanes), affording *E*,*E* doubly unsaturated ester **48** (12.92 g, 94%, >20:1 (*E*,*E*)-**48**/(*E*,*Z*)-**34**, clear oil): $[\alpha]^{27}_D$ −10.0° (*c* = 1.04, $CHCl_3$); IR (neat) 2945, 2865, 1720, 1645 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.27 (1H, dd, *J* = 15.5, 10.5 Hz, −*H*C=C*H*CO_2CH_3), 7.25 (2H, m) and 6.86 (2H, m) (*p*-CH_3O−*Ar*−), 6.29 (1H, dd, *J* = 15.5, 6.0 Hz, −*H*C=CH−HC=C*H*CO_2CH_3), 6.17 (1H, dd, *J* = 15.5, 10.5 Hz, −HC=C*H*−HC=C*H*CO_2CH_3), 5.80 (1H, d, *J* = 15.5 Hz, −HC=C*H*CO_2CH_3), 4.57 (2H, s, −OCH_2O−), 4.41 (2H, s, −OCH_2Ar), 4.09 (2H, s, =C(CH_2OPMB)−), 4.02 (2H, s, −CH_2-OMOM), 3.81 (1H, br dt *J* = 6.0, 6.0 Hz, −(TIPSO)C*H*−), 3.79 (3H, s, −Ar−OCH_3), 3.73 (3H, s, −CO_2CH_3), 3.33 (3H, s, −CH_2-OCH_3), 2.53 (1H, m, −(CH_3)C*H*−HC=), 2.23 (1H, dt, *J* = 12.0, 5.5 Hz, −*H*CHC(CH_3)=), 2.11 (1H, dt, *J* = 12.0, 5.5 Hz, −HC*H*C(CH_3)=), 1.73 (3H, s, −C(CH_3)=), 1.50 (2H, br m, −(TIPSO)CHCH_2−), 1.06 (21H, s, −Si(CH(CH_3)$_2$)$_3$), 1.04 (3H, d, *J* = 7.0 Hz, −(CH_3)CH−HC=); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 167.64, 159.07, 146.92, 145.35, 141.44, 130.56, 129.35, 127.63, 126.96, 119.00, 113.66, 95.69, 76.27, 71.89, 67.47, 64.62, 55.15(2), 51.36, 42.03, 32.85, 31.00, 18.52, 18.18, 14.10, 12.90; MS *m*/*e* 618 (M^+), 586 (M^+ − CH_3OH), 575 (M^+ − C_3H_7); HRMS calcd for $C_{35}H_{58}O_7Si$ = 618.3952; found = 618.3947 ± 0.0018.

(2*E*,4*E*,10*Z*)-(6*S*,7*S*)-7-(Triisopropylsiloxy)-6,10-dimethyl-11-p-methoxybenzyloxymethyl-12-(methoxymethoxy)-2,4,10-dodecatrienol (49). Following the procedure described for the preparation of (*E*,*Z*)-dienol **35**, *E*,*E* unsaturated ester **48** (12.90 g, 20.9 mmol) was reduced with diisobutylaluminum hydride. In the work-up procedure, the dried

organic phases were filtered over a fritted glass funnel (medium porosity) filled with a 2 cm thick silica gel pad (rinsed with dichloromethane). The filtrate was concentrated, yielding pure (*E,E*)-dienol **49** (10.69 g, 87%, slightly yellowish oil): $[\alpha]^{27}_D$ −5.4° (*c* = 1.06, $CHCl_3$); IR (neat) 3445 (br), 2940, 2865, 1615 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.26 (2H, m) and 6.87 (2H, m) (*p*-CH_3O−*Ar*−), 6.22 (1H, dd, *J* = 15.0, 10.0 Hz, −HC=CH−*H*C=CHCH$_2$OH), 6.05 (1H, dd, *J* = 15.0, 10.0 Hz, −HC=C*H*−HC=CHCH$_2$OH), 5.82 (1H, dd, *J* = 15.0, 7.0 Hz, −*H*C=CH−HC=CHCH$_2$OH), 5.76 (1H, dt, *J* = 15.0, 5.5 Hz, −HC=C*H*CH$_2$OH), 4.59 (2H, s, −OCH$_2$O−), 4.42 (2H, s, −OC*H*$_2$Ar), 4.16 (2H, d, *J* = 5.5 Hz, −C*H*$_2$OH), 4.08 (2H, s, =C(C*H*$_2$OPMB)−), 4.02 (2H, s, −C*H*$_2$OMOM), 3.80 (3H, s, −Ar−OC*H*$_3$), 3.76 (1H, dt, *J* = 5.0, 5.0 Hz, −(TIPSO)C*H*−), 3.34 (3H, s, −CH$_2$OC*H*$_3$), 2.44 (1H, m, −(CH$_3$)C*H*−HC=), 2.25 (1H, dt, *J* = 12.0, 6.0 Hz, −*H*CHC(CH$_3$)=), 2.11 (1H, dt, *J* = 12.0, 5.0 Hz, −HC*H*C(CH$_3$)=), 1.74 (3H, s, −C(CH$_3$)=), 1.62−1.40 (3H, m, −(TIPSO)CHC*H*$_2$− and −OH), 1.07 (21H, s, −Si(CH(CH$_3$)$_2$)$_3$), 1.01 (3H, d, *J* = 7.0 Hz, −(C*H*$_3$)CH−HC=); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.05, 141.62, 137.52, 131.95, 130.58, 129.97, 129.34, 128.80, 126.77, 113.64, 95.67, 76.51, 71.83, 67.36, 64.70, 63.31, 55.15, 55.07, 41.76, 33.05, 30.61, 18.57, 18.21, 15.15, 12.94; MS *m/e* 590 (M^+), 572 ($M^+ - H_2O$); HRMS calcd for $C_{34}H_{58}O_6Si$ = 590.4002; found = 590.3993 ± 0.0017.

(6*E*,8*E*,14*Z*)-(10*S*,11*S*)-Methyl 3-Oxo-11-(triisopropylsiloxy)-10,14-dimethyl-15-[[(*p*-methoxybenzyl)oxy]methyl]-6,8,14-hexadecatrienoate (51). Following the procedure described for the preparation of chloride **36**, allylic alcohol **49** (10.65 g, 18.0 mmol) was transformed (total reaction time = 7.0 h, half of the initial amounts of reagents were further added after 2.0 h and 5.0 h; instead of the usual chromatographic purification, the dried organic phases were filtered over a fritted glass funnel filled with a 1.5 cm thick silica gel pad) into allylic chloride **50** (10.77 g, 98%, yellowish oil). This sensitive material was only characterized by ^1H NMR analysis and was immediately employed for the next alkylation step: ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.26 (2H, m) and 6.87 (2H, m) (*p*-CH_3O−*Ar*−), 6.27 (1H, dd, *J* = 15.5, 10.0 Hz, −HC=CH−*H*C=CHCH$_2$Cl), 6.04 (1H, dd, *J* = 15.5, 10.0 Hz, −HC=C*H*−HC=CHCH$_2$Cl), 5.90 (1H, dd, *J* = 15.5, 6.5 Hz, −*H*C=CH−HC=CHCH$_2$Cl), 5.69 (1H, dt, *J* = 7.5 Hz, −HC=C*H*CH$_2$Cl), 4.59 (2H, s, −OCH$_2$O−), 4.42 (2H, s, −OC*H*$_2$-Ar), 4.11 (2H, d, *J* = 7.5 Hz, −CH$_2$Cl), 4.10 (2H, s, =C(C*H*$_2$-OPMB)−), 4.03 (2H, s, −C*H*$_2$OMOM), 3.80 (3H, s, −Ar−OC*H*$_3$), 3.77 (1H, dt, *J* = 5.0, 5.0 Hz, −(TIPSO)C*H*−), 3.34 (3H, s, −CH$_2$OC*H*$_3$), 2.46 (1H, m, −(CH$_3$)C*H*−HC=), 2.24 (1H, dt, *J* = 12.0, 6.0 Hz, −*H*CHC(CH$_3$)=), 2.11 (1H, dt, *J* = 12.0, 5.5 Hz, −HC*H*C(CH$_3$)=), 1.74 (3H, s, −C(CH$_3$)=), 1.60−1.40 (2H, m, −(TIPSO)CHC*H*$_2$−), 1.07 (21H, s, −Si(CH(CH$_3$)$_2$)$_3$), 1.01 (3H, d, *J* = 7.0 Hz, −(C*H*$_3$)CH−HC=).

Following the procedure described for the preparation of β-keto ester **37**, allylic chloride **50** (10.70 g, 17.6 mmol) was reacted with methylacetoacetate dianion to give purified β-keto ester **51** (8.67 g, 73%, yellowish oil). Again, some quantity of easily separated alcohol **49** was observed: $[\alpha]^{27}_D$ −5.8° (*c* = 1.04, $CHCl_3$); IR (neat) 2945, 1750, 1720, 1615 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.25 (2H, m) and 6.86 (2H, m) (*p*-CH_3O−*Ar*−), 6.09−5.91 (2H, m, −HC=C*H*−*H*C=CHCH$_2$−), 5.71 (1H, dd, *J* = 15.0, 7.0 Hz, −*H*C=CH−HC=CHCH$_2$−), 5.52 (1H, dt, *J* = 15.0, 7.0 Hz, −HC=C*H*CH$_2$−), 4.57 (2H, s, −OCH$_2$O−), 4.41 (2H, s, −OC*H*$_2$Ar), 4.09 (2H, s, =C(C*H*$_2$-OPMB)−), 4.02 (2H, s, −C*H*$_2$OMOM), 3.78 (3H, s, −Ar−OC*H*$_3$), 3.75 (1H, dt, *J* = 4.5, 4.5 Hz, −(TIPSO)C*H*−), 3.71 (3H, s, −CO$_2$CH$_3$), 3.43 (2H, s, −COC*H*$_2$CO$_2$CH$_3$), 3.32 (3H, s, −CH$_2$-OC*H*$_3$), 2.62 (2H, t, *J* = 7.0 Hz, =CHCH$_2$C*H*$_2$CO−), 2.48−2.35 (1H, m, −(CH$_3$)C*H*−HC=), 2.34 (1H, dt, *J* = 7.0, 7.0 Hz, =CHC*H*$_2$CH$_2$CO−), 2.24 (1H, dt, *J* = 12.0, 6.0 Hz, −*H*CHC-(CH$_3$)=), 2.10 (1H, dt, *J* = 12.0, 6.0 Hz, −HC*H*C(CH$_3$)=), 1.74 (3H, s, −C(CH$_3$)=), 1.60−1.40 (2H, m, −(TIPSO)CHC*H*$_2$−), 1.06 (21H, s, −Si(CH(CH$_3$)$_2$)$_3$), 0.99 (3H, d, *J* = 7.0 Hz, −(C*H*$_3$)-CH−HC=); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 201.67, 167.42, 159.11, 141.57, 135.63, 131.74, 130.67, 129.74, 129.66, 129.28, 126.82, 113.64, 95.72, 76.72, 71.83, 67.49, 64.68, 55.15(2), 52.17, 48.94, 42.53, 41.53, 32.98, 30.88, 26.34, 18.47, 18.21, 14.84, 12.92; MS *m/e* 688 (M^+), 657 ($M^+ - OCH_3$), 645 ($M^+ - C_3H_7$); HRMS calcd for $C_{38}H_{61}O_7Si$ = 657.4186; found = 657.4182 ± 0.0020.

(6*E*,8*E*,14*E*)-(10*S*,11*S*)-Methyl 3-Oxo-16-hydroxy-11-(triisopropylsiloxy)-10,14-dimethyl-15-[[(*p*-methoxybenzyl)oxy]methyl]-6,8,14-hexadecatrienoate (52). Following the procedure described for the preparation of alcohol **38**, methoxymethyl ether **51** (8.65 g, 12.6 mmol) was hydrolyzed (reaction time: 5.5 h (TLC analysis indicated ca. 50−60% completion); the aqueous work-up phase was further extracted with ethyl acetate (3 × 75 mL) to give recuperated **51** (3.59 g, 42%) and allylic alcohol **52** (3.81 g, 47% (80% yield based on recuperated **51**), yellowish visqueous oil). Recuperated starting material **51** was further recycled twice under the same conditions, affording a combined quantity of pure product **52** (5.24 g, 65%): $[\alpha]^{27}_D$ −5.0° (*c* = 1.14, $CHCl_3$); IR (neat) 3460 (br), 2945, 2865, 1745, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.26 (2H, m) and 6.87 (2H, m) (*p*-CH_3O−*Ar*−), 6.00 (2H, m, −HC=C*H*−*H*C=CHCH$_2$−), 5.70 (1H, dd, *J* = 15.0, 7.0 Hz, −*H*C=CH−HC=CHCH$_2$−), 5.53 (1H, dt, *J* = 15.0, 7.0 Hz, −HC=CH−HC=C*H*CH$_2$−), 4.45 (2H, s, −OC*H*$_2$Ar), 4.18 (2H, s, −C*H*$_2$OH), 4.12 (2H, s, =C(C*H*$_2$OPMB)−), 3.80 (3H, s, −Ar−OC*H*$_3$), 3.78−3.70 (1H, m, −(TIPSO)C*H*−), 3.73 (3H, s, −CO$_2$CH$_3$), 3.45 (2H, s, −COC*H*$_2$CO$_2$CH$_3$), 2.63 (2H, t, *J* = 7.0 Hz, =CHCH$_2$C*H*$_2$CO−), 2.45−2.35 (1H, m, −(CH$_3$)-C*H*−HC=), 2.36 (2H, dt, *J* = 7.0, 7.0 Hz, =CHC*H*$_2$CH$_2$CO−), 2.22 (1H, dt, *J* = 12.0, 5.5 Hz, −*H*CHC(CH$_3$)=), 2.09 (1H, dt, *J* = 12.0, 5.0 Hz, −HC*H*C(CH$_3$)=), 1.80 (1H, br s, −OH), 1.70 (3H, s, −C(CH$_3$)=), 1.48 (2H, m, −(TIPSO)CHC*H*$_2$−), 1.06 (21H, s, −Si(CH(CH$_3$)$_2$)$_3$), 0.99 (3H, d, *J* = 7.0 Hz, −(C*H*$_3$)-CH−HC=); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 201.75, 167.47, 159.26, 138.47, 135.65, 131.74, 130.21, 130.08, 129.83, 129.60, 129.33, 113.78, 76.58, 72.22, 69.17, 61.50, 55.18, 52.25, 49.01, 42.55, 41.60, 33.21, 30.60, 26.36, 18.47, 18.22, 15.00, 12.94; MS *m/e* 613 ($M^+ - CH_3O$), 595 ($M^+ - H_2O - CH_3O$); HRMS calcd for $C_{36}H_{57}O_6Si$ = 613.3924; found = 613.3917 ± 0.0018.

(14*S*)- and (14*R*)-(1*E*,7*E*,9*E*)-(5*S*,6*S*)-14-(Methoxycarbonyl)-5-(triisopropylsiloxy)-2,6-dimethyl-1-[[(*p*-methoxybenzyl)oxy]methyl]-1,7,9-cyclopentadecatrien-13-one (54). Following the procedure described for the preparation of chloride **39**, allylic alcohol **52** (1.29 g, 2.00 mmol) was transformed (reaction time: 30 min) into allylic chloride **53** (1.20 g, 90%, homogeneous through TLC and ^1H NMR analysis, slightly yellowish oil): ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.27 (2H, m) and 6.88 (2H, m) (*p*-CH_3O−Ar−), 6.10−5.95 (2H, m, −HC=C*H*−*H*C=CHCH$_2$−), 5.70 (1H, dd, *J* = 14.5, 7.0 Hz, −*H*C=CH−HC=CHCH$_2$−), 5.55 (1H, dt, *J* = 14.5, 7.0 Hz, −HC=C*H*CH$_2$−), 4.43 (2H, s, −OC*H*$_2$Ar), 4.18 (1H, AB m, −CH$_2$Cl), 4.07 (2H, s, =C(C*H*$_2$OPMB)−), 3.81 (3H, s, −Ar−OC*H*$_3$), 3.80−3.70 (1H, m, −(TIPSO)C*H*−), 3.74 (3H, s, −CO$_2$CH$_3$), 3.45 (2H, s, −COC*H*$_2$CO$_2$CH$_3$), 2.64 (2H, t, *J* = 7.5 Hz, =CHCH$_2$C*H*$_2$CO−), 2.50−2.37 (1H, m, −(CH$_3$)-C*H*−HC=), 2.36 (2H, dt, *J* = 7.0, 7.0 Hz, =CHC*H*$_2$CH$_2$CO−), 2.29 (1H, dt, *J* = 12.5, 5.5 Hz, −*H*CHC(CH$_3$)=), 2.10 (1H, dt, *J* = 12.5, 4.5 Hz, −HC*H*C(CH$_3$)=), 1.73 (3H, s, −C(CH$_3$)=), 1.65−1.42 (2H, m, −(TIPSO)CHC*H*$_2$−), 1.08 (21H, s, −Si(CH-(CH$_3$)$_2$)$_3$), 1.01 (3H, d, *J* = 7.0 Hz, −(C*H*$_3$)CH−HC=).

To a vigorously stirred suspension of cesium iodide (2.34 g, 9.00 mmol) and cesium carbonate (5.91 g, 18.1 mmol) in dry acetonitrile (1.8 L) at a near reflux temperature (65−70 °C) was added a solution of the above allylic chloride **53** (1.20 g, 1.80 mmol) in acetonitrile (25 mL) dropwise via a gas-tight syringe through slow addition (over the vortex) with a syringe pump over an 18 h period. The mixture was allowed to cool to room temperature for 2 h and half-saturated aqueous ammonium chloride solution (100 mL) was added. (NOTE: The small quantity of remaining **53** in the syringe tip was found homogeneous by TLC analysis, indicating that it survived the long standing time.) The acetonitrile was evaporated, and the residue was extracted with dichloromethane (2 × 75 mL, tends to form emulsions) and diethyl ether (3 × 75 mL). The combined organic layers were dried with anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography (5% to 10% ethyl acetate in hexanes), yielding TTC macrocyclic β-keto ester **54** as a nonseparated 1:1 mixture of epimers at C14 (0.79

g, 71%, yellowish foamy oil, the two epimers can be slightly differentiated on silica gel ($\Delta R_f \sim 0.03$) and are less polar than starting material (**53**). A small proportion of presumed *O*-alkylation isomeric macrocyclization product (0.047 g, 4%, yellowish oil, unstable) was also isolated.

TTC **54**, as a 1:1 mixture of epimers at C14: IR (neat) 2945, 2865, 1740, 1710, 1610 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): (NOTE: the stereochemistry at C14 was not assigned, differentiated signals are denoted by half-integrations; i.e. H/2) 7.30–7.20 (2H, m) and 6.90–6.82 (2H, m) (*p*-CH_3O–*Ar*–), 6.08–5.88 (2H, m, –HC=C*H*–*H*C=CHCH$_2$–), 5.63–5.41 (2H, m, –*H*C=CH–HC=C*H*CH$_2$–), 4.34 (2H/2, s, –OC*H*$_2$Ar), 4.32 (2H/2, s, –OCH$_2$Ar), 3.96–3.42 (4H, m, –(TIPSO)C*H*- and =C-(C*H*$_2$OPMB)- and –C*H*CO$_2$CH$_3$), 3.80 (3H, AB m, –Ar–OC*H*$_3$), 3.61 (3H/2, s, –CO$_2$CH$_3$), 3.59 (3H/2, s, –CO$_2$CH$_3$), 2.63–1.90 (9H, m, –(TIPSO)CHCH$_2$C*H*$_2$- and –(CH$_3$)C*H*–HC= and =CHC*H*$_2$C*H*$_2$CO– and –C*H*$_2$CH(CO$_2$CH$_3$)–), 1.70–1.40 (2H, m, –(TIPSO)CHC*H*$_2$–), 1.65 (3H, br s, –C(CH$_3$)=), 1.12–1.03 (24H, m, –Si(CH(CH$_3$)$_2$)$_3$) and –(C*H*$_3$)CH–HC=); MS *m/e* 626 (M^+), 608 ($M^+ - H_2O$); HRMS calcd for $C_{37}H_{58}O_6Si$ = 626.4002; found = 626.3998 ± 0.0018.

(1*E*,7*E*,9*E*)-(5*S*,6*S*)-5-(Triisopropylsiloxy)-2,6-dimethyl-1-[[(*p*-methoxybenzyl)oxy]methyl]-1,7,9-cyclopentadecatrien-13-one (55). Following the procedure described for the preparation of TCC macrocycle **42**, β-keto ester **54** (1.40 g, 2.23 mmol) was demethoxycarbonylated (reaction time, 8 h at 130–135 °C) to give TTC macrocyclic triene **55** (0.58 g, 46% (60% combined yield), yellowish foamy oil) and the desilylated alcohol (0.200 g, 17%). This compound was then reprotected (imidazole, TIPSOTf, CH_2Cl_2, 0 °C, 1.5 h) to give the desired product **55** (0.180 g, 68%): $[\alpha]^{27}_D$ +1.8° (*c* = 1.00, $CHCl_3$); IR (neat) 2945, 2865, 1710, 1610 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.25 (2H, m) and 6.86 (2H, m) (*p*-CH_3O–*Ar*–), 5.96 (2H, m, –HC=C*H*–*H*C=CHCH$_2$–), 5.57 (1H, dt, *J* = 14.5, 7.5 Hz, –HC=C*H*CH$_2$–), 5.53 (1H, dd, *J* = 14.5, 9.0 Hz, –*H*C=CH–HC=CHCH$_2$–), 4.39 (1H, AB d, *J* = 12.0 Hz, –O*H*CHAr), 4.36 (1H, AB d, *J* = 12.0 Hz, –OHC*H*Ar), 3.86 (1H, AB d, *J* = 12.0 Hz, =C(*H*CHOPMB)–), 3.82 (1H, AB d, *J* = 12.0 Hz, =C(HC*H*OPMB)–), 3.80 (3H, s, –Ar–OC*H*$_3$), 3.62 (1H, m, –(TIPSO)C*H*), 2.49–2.12 (9H, m) and 2.04 (2H, m) (–C*H*$_2$C(CH$_3$)=, –(CH$_3$)C*H*–HC=, =CHC*H*$_2$C*H*$_2$-COC*H*$_2$C*H*$_2$C=), 1.64 (3H, s, –C(CH$_3$)=), 1.59–1.48 (2H, m, –(TIPSO)CHC*H*$_2$), 1.08 (21H, s, –Si(CH(CH$_3$)$_2$)$_3$), 1.05 (3H, d, *J* = 7.0 Hz, –(C*H*$_3$)CH–HC=); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 213.43, 159.18, 136.04, 135.04, 132.62, 130.62, 130.01, 129.44, 129.33, 128.51, 113.76, 76.63, 71.90, 68.91, 55.22(2), 45.03, 41.73, 34.26, 30.03, 29.16, 24.87, 18.29, 17.91, 12.98; MS *m/e* 568 (M^+), 550 ($M^+ - H_2O$); HRMS calcd for $C_{35}H_{56}O_4Si$ = 568.3948; found = 568.3941 ± 0.0017.

Thermolysis of 55: Mixture of Tricyclic Products TST 56 and CSC 57. A solution of macrocyclic triene **55** (3.0 mg, 0.005 mmol) in toluene (1.0 mL) was sealed in a dry, clean quartz tube. The tube was heated at 300 °C for 2.0 h in a temperature-controlled oven after which it was allowed to cool to room temperature. The tube was opened and its content tranferred in a round bottom flask (rinsed with diethyl ether) and concentrated. The residue was purified by preparative thin layer chromatography (10 × 20 cm plate, 0.05 cm thickness, 20% ethyl acetate in hexanes), affording a pure mixture of tricyclic products TST **56** and CSC **57** (2.3 mg, 75%, ^1H NMR ratio **56**/**57** = 5:1, oil). **56**/**57**: IR (neat) 2940, 2865, 1705, 1610, 1095 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): (NOTE: unassigned signals originate from both diastereomers) 7.21 (2H, m) and 6.87 (2H, m) (*p*-CH_3O–*Ar*–), 5.72 (1H, dm, *J* = 9.0 Hz, –*H*C=CH- **56**), 5.60 (2H, AB narrow m, –HC=CH- **57**), 5.54 (1H, br d, *J* = 9.0 Hz, –HC=C*H*- **56**), 4.37 (2H, AB narrow m, –OCH$_2$Ar **57**), 4.36 (1H, d, *J* = 11.5 Hz, –O*H*CHAr **56**), 4.26 (1H, d, *J* = 11.5 Hz, –OHC*H*Ar **56**), 3.81 (3H, s, –Ar–OCH$_3$ **56**), 3.80 (3H, s, –Ar–OCH$_3$ **57**), 3.61 (1H, d, *J* = 10.0 Hz, –*H*CHOPMB **57**), 3.50 (1H, d, *J* = 10.0 Hz, –*H*CHOPMB **56**), 3.38 (1H, d, *J* = 10.0 Hz, –HC*H*OPMB **57**), 3.30 (1H, d, *J* = 10.0 Hz, –HC*H*OPMB **56**), 3.30–3.22 (1H, m, –(TIPSO)C*H*–), 2.60–1.00 (15H, m, –other–CH$_2$– and –CH–), 1.12–0.95 (27H, m, –Si(CH(CH$_3$)$_2$)$_3$, –(C*H*$_3$)CH–HC=, –C-(CH$_3$)–); MS *m/e* 525 ($M^+ - C_3H_7$); HRMS calcd for $C_{32}H_{49}O_4Si$ = 525.3400; found = 525.3405 ± 0.0015.

(1*E*,7*E*,9*E*)-(5*S*,6*S*)-5-(Triisopropylsiloxy)-1-(hydroxymethyl)-2,6-dimethyl-1,7,9-cyclopentadecatrien-3-one (58). Following the procedure described for the preparation of alcohol **44**, PMB ether **55** (0.340 g, 0.60 mmol) was treated (dichloromethane/water 5.6 mL/0.4 mL; reaction time, 45 min) with DDQ (0.150 g, 0.66 mmol) to give TTC cyclopentadecatrienol **58** (0.150 g, 57%, yellowish oil) after flash chromatography purification (10% to 50% ethyl acetate in hexanes): $[\alpha]^{25}_D$ –7.1° (*c* = 0.75, $CHCl_3$); IR (neat) 3440, 2945, 2865, 1705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.03 (1H, dd, *J* = 14.5, 10.5 Hz, –HC=C*H*–HC=CH–), 5.94 (1H, dd, *J* = 14.5, 10.5 Hz, –HC=CH–*H*C=CH–), 5.61 (1H, m, =C*H*-CH$_2$–), 5.55 (1H, dd, *J* = 14.5, 8.5 Hz, –*H*C=CH–HC=CHCH$_2$–), 4.09 (1H, AB d, *J* = 13.0 Hz, –*H*CHOH), 4.04 (1H, AB d, *J* = 13.0 Hz, –HC*H*OH), 3.64 (1H, dt, *J* = 7.5, 4.0 Hz, –(TIPSO)CH–), 2.53–2.10 (9H, m) and 2.03 (2H, m) (–C*H*$_2$C(CH$_3$)=, –(CH$_3$)C*H*–HC=, =CHC*H*$_2$C*H*$_2$COC*H*$_2$C*H*$_2$C=), 1.72 (3H, s, –C(CH$_3$)=), 1.58–1.50 (2H, m, –(TIPSO)CHC*H*$_2$–), 1.09 (21H, s, –Si(CH(CH$_3$)$_2$)$_3$), 1.06 (3H, d, *J* = 7.0 Hz, –(C*H*$_3$)CH–HC=); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 213.50, 135.19, 135.00, 132.58, 131.08, 129.92, 129.28, 76.53, 61.89, 45.02(2), 41.75, 34.16, 29.98, 28.93, 24.40, 18.23, 12.91; MS *m/e* 448 (M^+), 430 ($M^+ - H_2O$), 387 ($M^+ - H_2O - C_3H_7$); HRMS calcd for $C_{27}H_{46}O_2Si$ = 430.3267; found = 430.3277 ± 0.0013.

(1*E*,7*E*,9*E*)-(5*S*,6*S*)-5-(Triisopropylsiloxy)-1-formyl-2,6-dimethyl-1,7,9-cyclopentadecatrien-13-one (59). Following the procedure described for the preparation of aldehyde **46**, allylic alcohol **58** (0.135 g, 0.30 mmol) was oxidized (reaction time, 1.5 h) to give pure TTC cyclopentadecatrienal **59** (0.094 g, 70%, mossy visqueous oil): $[\alpha]^{30}_D$ –3.0° (*c* = 0.88, $CHCl_3$); IR (neat) 2940, 2865, 1710, 1665 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 10.05 (1H, s, –CHO), 6.03 (1H, dd, *J* = 14.5, 10.5 Hz, –HC=C*H*–HC=CH–), 5.93 (1H, dd, *J* = 14.5, 10.5 Hz, –HC=CH–*H*C=CH–), 5.59 (1H, dd, *J* = 14.5, 8.0 Hz, –CH(CH$_3$)*H*C=CH–), 5.64–5.52 (1H, m, –HC=C*H*CH$_2$–), 3.75 (1H, dt, *J* = 7.5, 4.0 Hz, –CHOTIPS), 2.55–2.05 (11H, m, –C*H*(CH$_3$)HC=, –C*H*$_2$C(CH$_3$)=, =CC*H*$_2$C*H*$_2$COC*H*$_2$CH$_2$-HC=), 2.14 (3H, s, –C(CH$_3$)=), 1.68–1.56 (2H, m, –(TIPSO)-CHC*H*$_2$–), 1.09 (21H, s, –OSi(CH(CH$_3$)$_2$)$_3$), 1.07 (3H, d, *J* = 7.5 Hz, –CH(CH$_3$)HC=); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 212.25, 191.27, 159.30, 135.78, 134.60, 132.49, 130.13, 129.63, 75.94, 45.08, 44.52, 41.23, 32.71, 30.96, 30.03, 19.77, 18.27, 18.09, 17.40, 12.92; MS *m/e* 446 (M^+), 417 (M^+ – CHO), 403 ($M^+ - C_3H_7$); HRMS calcd for $C_{27}H_{46}O_3Si$ = 446.3216; found = 446.3213 ± 0.0012.

Lewis Acid-Catalyzed TADA Reaction of 59: Isolation of TST Tricyclic Product 60. To a stirred solution of cyclopentadecatrienal **59** (4 mg, 0.009 mmol) in toluene (0.5 mL) was added tin tetrachloride (0.027 mL, 0.027 mmol, 1.0 M in dichloromethane). The yellowish solution was stirred for 1.0 h at room temperature, at which point TLC analysis showed very slow conversion to products. Then, the solution was warmed to 60 °C for 3.0 h and allowed to cool to room temperature. A saturated aqueous sodium bicarbonate solution (3 drops) was added under stirring, and the mixture was directly purified through flash chromatography on a small column (20% ethyl acetate in hexanes), giving tetracycle **61** (~1 mg, ~25%) and quite pure TST tricyclic aldehyde intermediate **60** (2 mg, 50%, oil): IR (neat) 2940, 2865, 1710, 1665 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.45 (1H, d, *J* = 1.5 Hz, –CHO), 5.91 (2H, AB m, –HC=CH–), 3.28 (1H, ddd, *J* = 10.0, 10.0, 5.0 Hz, –CH(OTIPS)), 2.60–0.80 (15H, m, other –CH$_2$– and –CH–), 1.07 (3H, d, *J* = 8.0 Hz, –CH(C*H*$_3$)–), 1.06 (21H, s, –Si(CH(CH$_3$)$_2$)$_3$), 0.86 (3H, s, –CH$_3$); MS *m/e* 446 (M^+), 403 ($M^+ - C_3H_7$); HRMS calcd for $C_{27}H_{46}O_3Si$ = 446.3216; found = 446.3213 ± 0.0013.

3β-(Triisopropylsiloxy)-11α-hydroxy-3,4,8-epi-17,18-dinoraphidicol-6-en-16-one (61). A solution of TTC cyclopentadecatrienal **59** (0.080 g, 0.179 mmol) in toluene (1.0 mL + 2 × 0.5 mL rinse) was taken in a dry and clean pyrex tube (successively washed with acetone, water, saturated ammonium hydroxyde solution, and many times with distilled water then dried in the oven at 150 °C for 12 h). A small quantity of triethylamine (0.005 mL) was added as an acid scavenger and the tube was sealed under vacuum. The tube was then heated at 210 °C for 18.0 h in a temperature-

controlled oven. Upon cooling down to room temperature, it was opened and the contents was tranferred (rinsed with diethyl ether) in a round bottom flask and concentrated. The crude product contained only a minor proportion (ca. <5%) of byproducts and was purified by preparative thin layer chromatography (three 20 × 20 cm plates, 0.05 cm thickness, 25% ethyl acetate in hexanes, two elutions), yielding tetracyclic intermediate **61** (0.043 g, 54%, yellowish oil): $[\alpha]^{30}_D$ −66.8° (*c* = 0.65, $CHCl_3$); IR (neat) 3440 (br), 2940, 2865, 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.69 (1H, AB d, *J* = 9.5 Hz, −*H*C=CH−), 5.64 (1H, AB dm, *J* = 9.5 Hz, −HC=C*H*−), 4.35 (1H, br d, *J* = 4.5 Hz, −C*H*(OH)−), 3.30 (1H, ddd, *J* = 9.5, 9.5, 5.0 Hz, −CH(OTIPS)−), 2.69 (1H, dd, *J* = 5.5, 5.5 Hz, −COC*H*−), 2.55 (1H, br t, *J* = 9.5 Hz) and 2.49−2.26 (3H, m) and 2.06 (1H, dd, *J* = 14.0, 10.0 Hz) and 1.81−1.72 (2H, m) and 1.71−0.80 (7H, m) (other $-CH_2-$ and −CH−, −OH), 1.08 (21H, s, $-Si(CH(CH_3)_2)_3$), 1.07 (3H, d, *J* = 8.5 Hz, −CH(C*H*$_3$)−), 0.93 (3H, s, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 214.43, 132.93, 78.93, 77.56, 57.09, 49.44, 46.78, 41.17, 40.17, 38.31, 35.32, 31.17, 30.71, 27.11, 18.32, 17.59, 12.92; MS *m*/*e* 403 (M^+ − C_3H_7); HRMS calcd for $C_{24}H_{39}O_3Si$ = 403.2668; found = 403.2665 ± 0.0012.

3β-(Triisopropylsiloxy)-11α-hydroxy-3,4,8-epi-17,18-dinoraphidicolan-16-one (62). To a stirred solution of alkene **61** (~2 mg, 0.0045 mmol) and tosylhydrazine (~10 mg, 0.053 mmol) in low refluxing (80 °C) ethanol (1.0 mL) was added a solution of sodium acetate (~7 mg, 0.088 mmol) in water (0.5 mL) dropwise via a syringe pump over a 5.0 h period. The solution was allowed to cool to room temperature, and a saturated aqueous ammonium chloride solution (3 mL) was added. The mixture was then extracted with dichloromethane (3 × 5 mL), and the combined organic layers were dried with anhydrous magnesium sulfate, filtered, and concentrated. The crude product contains a small amount of the corresponding isomeric tosylhydrazones which could be removed by preparative thin layer chromatography (8 × 10 cm plate, 0.05 cm thickness, 20% ethyl acetate in hexanes) giving pure tetracyclic keto alcohol **62** (~1.5 mg, ~75%, oil): IR (neat) 3450 (br), 2940, 2865, 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 4.60 (1H, br dd, *J* = 6.0, 3.0 Hz, −C*H*(OH)−), 3.20 (1H, ddd, *J* = 10.0, 10.0, 5.0 Hz, −C*H*(OTIPS)), 2.63 (1H, dd, *J* = 6.0, 6.0 Hz, −COCH−), 2.55−2.40 (1H, m) and 2.33−2.21 (2H, m) and 2.11−1.98 (1H, m) and 1.92 (1H, dd, *J* = 11.5, 9.0 Hz) and 1.93−1.82 (1H, m) and 1.80−1.15 (12H, m) (other $-CH_2-$ and −CH−, OH), 1.18 (3H, s, $-CH_3$), 0.07 (21H, s, −OSi(CH(CH$_3$)$_2$)$_3$), 1.00 (3H, d, *J* = 6.0 Hz, −CH(C*H*$_3$)−); MS *m*/*e* 405 (M^+ − C_3H_7); HRMS calcd for $C_{24}H_{41}O_3Si$ = 405.2825; found = 405.2835 ± 0.0012.

3β-(Triisopropylsiloxy)-11α,16β-(β)-(ethylidenedioxy)-3,4,8-epi-17,18-dinoraphidicolan (63). To a stirred solution of tetracyclic alcohol **62** (1.8 mg, 0.004 mmol) in dichloromethane (0.5 mL) were added ethyl vinyl ether (~0.001 mL, 0.012 mmol) and a pinch of monohydrated *p*-toluenesulfonic acid. The solution was stirred 1.5 h at room temperature after which it was quenched with a saturated aqueous ammonium chloride solution (3 mL) and extracted with dichloromethane (4 × 5 mL). The combined organic layers were dried with anhydrous magnesium sulfate, filtered, and concentrated to give a dark-colored crude product. This material was purified by preparative thin layer chromatography (8 × 10 cm plate, 0.05 cm thickness, 30% ethyl acetate in hexanes), yielding a diastereomeric mixture of C11 1-ethoxyethoxy ethers.

To a stirred solution of the above ketone in tetrahydrofuran (0.5 mL) cooled to −78 °C was added L-Selectride (~0.004 mL, ~0.003 mol, 1.0 M in tetrahydrofuran). The solution was then stirred 2.0 h in an ice/water bath (0 °C). A 0.1 N aqueous sodium hydroxide solution (1 mL) and two drops of 30% aqueous hydrogen peroxide solution were successively added. The mixture was diluted with diethyl ether (~5 mL) and stirred 15 min. The phases were separated, and the aqueous one was extracted with diethyl ether (4 × 5 mL). The combined organic layers were then washed with brine (~5 mL), dried with anhydrous magnesium sulfate, filtered, and concentrated to give the corresponding crude monoprotected diol.

To a stirred solution of the above alcohol in tetrahydrofuran (0.5 mL) at room temperature was added a 0.1 N aqueous hydrochloric acid solution (3 drops). The solution was stirred ~1.5 h after which it was quenched by addition of a saturated aqueous sodium bicarbonate solution (2 mL). The mixture was then extracted with diethyl ether (3 × 5 mL) and ethyl acetate (2 × 5 mL). The combined organic layers were washed with brine (~3 mL), dried with anhydrous magnesium sulfate, filtered, and concentrated to give the crude diol, apparently diastereomerically pure by ^1H NMR analysis, and a minor percentage of cyclized acetal **63**.

To a stirred solution of the above diol in dichloromethane (0.5 mL) were successively added acetaldehyde diethyl acetal (~0.002 mL, ~0.005 mmol) and a few crystals of monohydrated *p*-toluenesulfonic acid. The solution was stirred 2.0 h at room temperature after which it was quenched by addition of a saturated aqueous sodium bicarbonate solution (3 mL). The resulting mixture was extracted with dichloromethane (3 × 5 mL), and the combined organic layers were dried with anhydrous magnesium sulfate, filtered, and concentrated. The crude nonpolar product (exclusive homogeneous compound by TLC analysis) was purified by preparative thin layer chromatography (10 × 20 cm plate, 0.05 cm thickness, 10% ethyl acetate in hexanes), yielding pure ethylidene acetal **63** (1.2 mg, ≥50% from **62**, oil): IR (neat) 2935, 2865, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.27 (1H, q, *J* = 4.5 Hz, −OC*H*(CH$_3$)O−), 4.48 (1H, d, *J* = 6.0 Hz, −CH−O−), 4.08 (1H, br d, *J* = 6 Hz, $-CH_2CH-O-$), 3.18 (1H, ddd, *J* = 10.0, 10.0, 4.5 Hz, −CHOTIPS), 2.79 (1H, ddd, *J* = 6.0, 6.0, 6.0 Hz, −O−CHC*H*CH−O−), 2.29 (1H, dd, *J* = 15.5, 7.5 Hz) and 2.21 (1H, dd, *J* = 13.0, 7.5 Hz) and 1.85−0.80 (15H, m) (other$-CH_2-$ and −CH−), 1.22 (3H, d, *J* = 4.5 Hz, −OCH(C*H*$_3$)O−), 1.07 (3H, s, $-CH_3$), 1.06 (21H, s, −OSi(CH(CH$_3$)$_2$)$_3$), 0.96 (3H, d, *J* = 6.5 Hz, −CH(C*H*$_3$)CH−); MS *m*/*e* 433 (M^+ − C_3H_7); HRMS calcd for $C_{26}H_{45}O_3Si$ = 433.3138; found = 433.3148 ± 0.0013.

3β-(Triisopropylsiloxy)-11α-((*R*/*S*)-1-ethoxyethoxy)-3,4,8-epi-17,18-dinoraphidicol-6-en-16-one (64). To a stirred solution of keto alcohol **61** (0.025 g, 0.056 mmol) in dichloromethane (1.0 mL) at room temperature were successively added ethyl vinyl ether (0.011 mL, 0.112 mmol) and a few grains of monohydrated *p*-toluenesulfonic acid (catalytic). The solution was stirred 2.0 h after which a saturated aqueous ammonium chloride solution (5 mL) was added. The resulting mixture was extracted with dichloromethane (4 × 10 mL) and the combined organic layers were dried with anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (5% to 30% ethyl acetate in hexanes), giving recuperated alcohol **61** (0.0105 g, 42%) and C11 1-ethoxyethoxy ether **64** (0.0160 g, 55%, yellowish oil) as a 1:1 mixture of epimers: IR (neat) 2945, 2870, 1715, 1095 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.73−5.59 (2H, m, −HC=CH−), 4.76 (H/2, q, *J* = 5.0 Hz, EtOC*H*(CH$_3$)O−), 4.74 (H/2, q, *J* = 5.0 Hz, EtOC*H*(CH$_3$)O−, other epimer), 4.29 (H/2, br d, *J* = 5.0 Hz, EEOC*H*−), 3.98 (H/2, br d, *J* = 4.5 Hz, EEOC*H*−, other epimer), 3.57−3.37 (2H, m, CH_3CH_2O-), 3.30 (1H, m, TIPSOCH−), 2.92 (1H, m, −COCH−), 2.58−0.80 (13H, m, other$-CH_2-$ and −CH−), 1.27 (3H/2, d, *J* = 5.5 Hz, EtOCH(C*H*$_3$)O−), 1.21 (3H/2, d, *J* = 5.5 Hz, EtOCH(C*H*$_3$)O−, other epimer), 1.23−1.00 (6H, m, CH_3CH_2O-, −CH(C*H*$_3$)−), 1.08 (21H, s, −Si(CH(CH$_3$)$_2$)$_3$), 0.91 (3H/2, s, $-CH_3$), 0.85 (3H/2, s, $-CH_3$, other epimer); MS *m*/*e* 489 (M^+ − C_2H_5), 475 (M^+ − C_3H_7); HRMS calcd for $C_{28}H_{47}O_4Si$ = 475.3243; found = 475.3238 ± 0.0014.

3β-(Triisopropylsiloxy)-11α-((*R*/*S*)-1-ethoxyethoxy)-3,4,8-epi-18-noraphidicol-6,16-diene (65). To a stirred solution of ketone **64** (2.0 mg, 0.004 mmol) in tetrahydrofuran (0.5 mL) at room temperature was added the Tebbe reagent (0.009 mL, 0.0045 mmol, 0.5 M in toluene) dropwise over 1 min. The deep maroon solution was stirred 30 min after which one drop of a 0.1 N aqueous sodium hydroxide solution was added. The mixture was diluted with diethyl ether (10 mL) and stirred for 15 min. Anhydrous sodium sulfate was then added, and the flask was stirred for a further 15 min. The content was filtered over a fritted glass funnel (medium porosity) covered with a thin celite pad. The filtrate was concentrated and

purified through preparative thin layer chromatography (10 × 20 cm, 0.05 cm thickness, 10% ethyl acetate in hexanes), affording alkene **65** (1.2 mg, ~60%, oil) as a mixture of epimers at C11: IR (neat) 2935, 2865, 1095 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.64 (1H, br d, J = 9.0 Hz, $-HC{=}CH-$), 5.55 (1H br dt, J = 9.0, 3.0, 3.0 Hz, $-HC{=}CH-$), 4.78 (H/2, q, J = 5.5 Hz, $EtOCH(CH_3)O-$), 4.75 (H/2, q, J = 5.0 Hz, $EtOCH(CH_3)O-$, other epimer), 4.68 and 4.64 and 4.60 and 4.52 (2H, 4 × br s, $C{=}CH_2$ of both epimers), 3.98 (H/2, d, J = 5.0 Hz, $EEOCH-$), 3.66 (H/2, d, J = 5.0 Hz, $EEOCH-$, other epimer), 3.63–3.48 (2H, m, CH_3CH_2O-), 3.27 (1H, ddd, J = 9.0, 9.0, 4.5 Hz, TIPSOCH–), 2.89 (H/2, dd, J = 5.0, 5.0 Hz, $H_2C{=}CCH-$), 2.81 (H/2, dd, J = 5.0, 5.0 Hz, $H_2C{=}CCH-$, other epimer), 2.45–0.80 (13H, m, other–CH_2– and –CH–), 1.25–1.00 (9H, m, $-CH(CH_3)$, CH_3CH_2O-, $-OCH(CH_3)O-$), 1.07 (21H, s, $-Si(CH(CH_3)_2)_3$), 0.87 (3H/2, s, $-CH_3$), 0.81 (3H/2, s, $-CH_3$, other epimer); MS m/e 473 ($M^+ - C_3H_7$); HRMS calcd for $C_{29}H_{49}O_3Si$ = 473.3451; found = 473.3448 ± 0.0014.

3β-(Triisopropylsiloxy)-11α-hydroxy-3,4,8-epi-18-noraphidicol-6,16-diene (66). To a stirred solution of tetracyclic keto alcohol **61** (0.0185 g, 0.042 mmol) in tetrahydrofuran (1.0 mL) at 0 °C was added the Tebbe reagent (0.174 mL, 0.087 mmol, 0.5 M in toluene) dropwise over 1 min. The maroon solution was allowed to warm to room temperature over a 20 min period after which excess reagent were quenched by slow addition of 0.1 N aqueous sodium hydroxyde solution (3 drops). The mixture was diluted with diethyl ether, dried with anhydrous sodium sulfate, and filtered over a fritted glass funnel (medium porosity) containing a thin celite pad. The filtrate was concentrated, and the residue was purified by flash chromatography (5% ethyl acetate in hexanes), yielding pure homoallylic alcohol **66** (0.0180 g, 97%, clear oil): $[\alpha]^{30}_D$ −59.1° (c = 0.87, $CHCl_3$); IR (neat) 3450, 2935, 2865, 1460 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.65 (1H, AB br dd, J = 9.5, 2.0 Hz, $-HC{=}CH-$), 5.57 (1H, AB ddd, J = 9.5, 3.0, 3.0 Hz, $-HC{=}CH-$), 4.82 (1H, d, J = 2.0 Hz, $-C{=}HCH$), 4.71 (1H, dd, J = 2.0, 2.0 Hz, $-C{=}HCH$), 3.97 (1H, br dd, J = 6.5, 5.5 Hz, $-CH(OH)-$), 3.28 (1H, ddd, J = 9.5, 9.5, 5.0 Hz, $-CH(OTIPS)-$), 2.62 (1H, dd, J = 5.5, 5.5 Hz, $-C(=CH_2)-CH-$), 2.41–2.27 (2H, m) and 2.24 (1H, ddd, J = 14.5, 14.5, 6.0 Hz) and 1.98 (1H, dd, J = 13.0, 10.0 Hz) and 1.81 (1H, ddd, J = 12.5, 12.5, 6.0 Hz) and 1.77–1.65 (1H, m) and 1.65–0.80 (8H, m) (other–CH_2– and –CH–, –OH), 1.07 (21H, s, $-Si(CH(CH_3)_2)_3$), 1.06 (3H, d, J = 7.0 Hz, $-CH(CH_3)-$), 0.91 (3H, s, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 148.68, 133.63, 132.61, 110.12, 77.72, 76.58, 49.86, 49.41, 46.88, 40.75, 40.08, 38.53, 32.87, 32.59, 31.22, 28.47, 28.31, 18.36, 18.29, 17.98, 17.64, 12.94; MS m/e 401 ($M^+ - C_3H_7$); HRMS calcd for $C_{25}H_{41}O_2Si$ = 401.2876; found = 401.2871 ± 0.0012.

Note: Compound **95** was also synthesized through hydrolytic treatment of **94** on a milligram scale (~1.2 mg, 0.002 mmol) in tetrahydrofuran (0.5 mL) with a drop of 1 N aqueous hydrochloric acid. The solution was stirred 15 h at room temperature after which a saturated aqueous sodium bicarbonate solution (3 mL) was added. The resulting mixture was extracted with diethyl ether (4 × 5 mL), dried with anhydrous magnesium sulfate, filtered, and concentrated. A preparative thin layer chromatography purification (8 × 20 cm plate, 0.05 cm thickness, 15% ethyl acetate in hexanes) furnished homoallylic alcohol **66** (~1.0 mg, 90–100%).

3β-(Triisopropylsiloxy)-11α-hydroxy-16β,17-epoxy-3,4,8-epi-18-noraphidicol-6-ene (67). To a stirred solution of homoallylic alcohol **66** (0.0173 g, 0.039 mmol) in toluene (1.0 mL) at room temperature was added a pinch of vanadyl acetyl acetonate (~0.1 mg, ~0.0004 mmol, catalytic). Thereafter, a solution of *tert*-butyl hydroperoxide (0.285 mL, 0.049 mmol, 0.17 M solution in toluene (made from a ~2.3 M solution in benzene with ca. 5% of water)) was added dropwise over a 3 min period. The solution was stirred 40 min (TLC analysis indicated completion after 15 min) and then diluted with diethyl ether (25 mL). A solution of aqueous sodium bisulfite (5 mL) was added, and the mixture was stirred 15 min. The phases were then separated, and the aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried with anhydrous magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography (10% to 20% ethyl acetate in hexanes), affording syn epoxy alcohol **67** (0.0120 g, 68%, clear oil): $[\alpha]^{30}_D$ −51.8° (c = 0.57, $CHCl_3$); IR (neat) 3580, 3490(br), 2940, 2865, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.65 (1H, AB ddd, J = 9.0, 2.0, 2.0 Hz, $-HC{=}CH-$), 5.59 (1H, AB ddd, J = 9.0, 3.0, 3.0 Hz, $-HC{=}CH-$), 4.06 (1H, br dd, J = 6.0, 5.0 Hz, $-CH(OH)-$), 3.29 (1H, ddd, J = 9.5, 9.5, 4.5 Hz, $-CH(OTIPS)-$), 2.64 (1H, d, J = 6.0 Hz, $-CH(OH)-$), 2.55 (1H, d, J = 4.5 Hz, $HCHO-$), 2.49 (1H, d, J = 4.5 Hz, $HCHO-$), 2.33 (1H, br t, J = 7 Hz, $-(HO)CHCH-$) and 2.29–2.10 (2H, m) and 1.96 (1H, dd, J = 13.5, 10.5 Hz) and 1.80–0.80 (10H, m) (other–CH_2– and –CH–), 1.07 (21H, s, $-Si(CH(CH_3)_2)_3$), 1.06 (3H, d, J = 6 Hz, $-CH(CH_3)-$), 0.92 (3H, s, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 133.11,132.94, 77.75, 77.62, 60.51, 49.93, 49.01, 46.88, 45.52, 40.05, 39.85, 32.28, 31.15, 30.53, 29.71,27.33, 24.93, 18.29, 17.83, 17.65, 12.92; MS m/e 417 ($M^+ - C_3H_7$); HRMS calcd for $C_{24}H_{41}O_3Si$ = 417.2825; found = 417.2820 ± 0.0012.

3β-(Triisopropylsiloxy)-11α,16β-(β)-(ethylidenedioxy)-16α-methyl-3,4,8-epi-18-noraphidicol-6-ene (68). To a stirred solution of a submilligram quantity of epoxy alcohol **67** (~0.5 mg, ~0.001 mol) in diethyl ether (0.5 mL) cooled to 0 °C was added an excess (~0.5 mg) of lithium aluminum hydride. The solution was stirred 1.5 h at room temperature after which a saturated aqueous ammonium chloride solution (3 mL) was slowly added, and the resulting mixture was extracted with diethyl ether (3 × 5 mL). The combined organic phases were washed with brine (3 mL), dried with anhydrous magnesium sulfate, filtered, and concentrated to give the corresponding crude diol, homogenous upon TLC analysis.

The above crude diol was dissolved in dichloromethane (0.5 mL). Acetaldehyde diethyl acetal (~0.002 mL, excess) and a few grains of monohydrated *p*-toluenesulfonic acid were successively added and the solution was stirred 1.0 h at room temperature. A saturated aqueous sodium bicarbonate solution (3 mL) was added, and the mixture was extracted with dichloromethane (3 × 5 mL). The combined halogenated layers were dried with anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by preparative thin layer chromatography (10 × 20 cm plate, 0.05 cm thickness, 10% ethyl acetate in hexanes), yielding cyclic diaxial acetal **68** (~0.5 mg, oil): IR (neat) 2930, 2865, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.58 (2H, AB m, $-HC{=}CH-$), 5.22 (1H, q, J = 5.0 Hz, $-OCH(CH_3)O-$), 4.16 (1H, d, J = 6.0 Hz, $-CHOCH(CH_3)-$), 3.29 (1H, ddd, J = 9.5, 9.5, 5.0 Hz, $-CH(OTIPS)-$), 2.51 (1H, br dd, J = 6.0, 6.0 Hz, $-OC(CH_3)-CH-$), 2.40–2.00 (4H, m) and 1.92 (1H, dd, J = 14.0, 10.0 Hz) and 1.80–0.80 (8H, m) (other–CH_2– and –CH–), 1.22 (3H, d, J = 5.0 Hz, $-OCH(CH_3)O-$), 1.17 (3H, s, $-O-C(CH_3)-$), 1.08 (21H, s, $-Si(CH(CH_3)_2)_3$), 1.07 (3H, d, J = 7.0 Hz, $-CH(CH_3)-$), 0.85 (3H, s, $-CH_3$); MS m/e 461 ($M^+ - C_2H_3$), 445 ($M^+ - C_3H_7$); HRMS calcd for $C_{27}H_{45}O_3Si$ = 445.3138; found = 445.3131 ± 0.0013.

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Supporting Information Available: ^1H and selected ^{13}C NMR spectra for all significant new compounds (51 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm edition of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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