Stereocontrolled construction of 1,7-dimethyl A.B.C.[6.6.6] tricycles. Part II. Transannular Diels–Alder reaction of 14-membered macrocycles containing *cis*-dienophiles

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The synthesis and transannular Diels–Alder reactions of 14-membered macrocyclic trienes containing a methyl-substituted diene and a methyl-substituted *cis*-dienophile moiety are described. As a result of the dienophile *cis* geometry the 1,7-dimethyl A.B.C.[6.6.6] tricycles obtained from the Diels–Alder reaction have a different stereochemistry at the four chiral centers than similar tricycles that were the subject of the preceding paper in this series. Thus *trans-syn-cis* (TSC) tricycle **30** was the sole product obtained from the *trans-cis-cis* (TCC) macrocycle **1***b*. In a similar fashion TCC macrocycle **1***d* afforded only *trans-syn-cis* (TSC) tricycle **31**. On the contrary, the transannular Diels–Alder reaction in *cis-trans-cis* (CTC) macrocycle **1***a* and *trans-trans-cis* (TTC) macrocycle **1***c* led to a mixture of the same four tricyclics (**30**, **32–34**) but in different ratio. The above experimental results are rationalized by taking into consideration the interconversion of macrocyclic trienes **1***a*, **1***b*, and **1***c*. Pathways for these interconversions are also proposed.

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La synthèse ainsi que la réaction de Diels–Alder transannulaire, des triènes macrocycliques à 14 chaînons dont l'unité diène et l'unité *cis*-diénophile portent un substituant méthyle, seront décrites. La cycloaddition transannulaire génère des tricycles A.B.C.[6.6.6]-1,7-diméthyle. Cependant, dû à la géométrie *cis* du diénophile, la stéréochimie observée pour les quatre centres chiraux est différente de celle obtenue pour des composés similaires qui ont été examinés dans l'article précédent de cette série. Ainsi le tricycle **30**, de stéréochimie *trans-syn-cis* (TSC), a été le seul produit obtenu à partir du macrocycle **1***b*, de stéréochimie *trans-cis-cis* (TCC). De la même manière le macrocycle TCC **1***d* a fournit uniquement le tricycle TSC **31**. Contrairement à ces résultats, les macrocycles *cis-trans-cis* (CTC) **1***a* et *trans-trans-cis* (TTC) **1***c* ont fourni, dans des proportions différentes, un mélange des mêmes quatre produits (**30**, **32–34**). Ces résultats expérimentaux ont été rationalisés prenant en considération l'interconversion des triènes macrocycliques **1***a*, **1***b* et **1***c*. On a proposé aussi des mécanismes pour ces interconversions.

Introduction

In the preceding article (1), we reported the syntheses and transannular Diels–Alder reactions of 14-membered macrocyclic trienes containing *E* dienophiles. As indicated in Scheme 1, the A.B.C.[6.6.6] tricyclic compound **2**, which may be derived from macrocycle **1**, contains two methyl groups at the quaternary C1 and C7 positions and could be constructed in a stereoselective manner by changing the geometry of the diene double bonds. This new methodology, which is complementary to other methods such as aldol condensations (2), biomimetic cyclization (3), intramolecular Diels–Alder reaction (4), and intramolecular Michael addition (5), provides a powerful tool for the synthesis of polycyclic natural products such as steroids and terpenes (6).

In this article, we would like to report our continued investigation (7) of this new methodology specifically applied to the macrocyclic system **1**, which contains a *cis* dienophile.

Preparation of dienophiles and dienes

In the preceding publication, a stereoselective synthesis of an *E* dienophile was reported, and this basic building block was used in the syntheses of three macrocycles (1). In this series, a *Z* dienophile was used as a basic building block in constructing four other macrocyclic trienes. Since both *Z* and *E* dienophiles are required for our systematic studies, a method for the simultaneous synthesis of both isomers was desirable.

Scheme 2 illustrates the synthetic route to both dienophiles via a Wittig reaction as the key step. The coupling reaction of commercially available (ethyl)triphenylphosphonium bromide with tetrahydropyranyl bromide ether **3**, which was prepared from 2-bromoethanol and 3,4-dihydro-2*H*-pyran (8), gave rise in the presence of potassium bis(trimethylsilyl)amide as a base to phosphonium salt **4**, in good yield (9). Swern oxidation (10) of alcohol **5**, which was obtained by mono-protection of commercially available 1,3-propanediol (11), furnished aldehyde **6** in 86% yield, thus setting the stage for the olefination reaction.

The Wittig olefination reaction was carried out in tetrahydrofuran at 0°C by adding aldehyde **6** to a solution of the phosphonium ylide, generated from **4** and butyllithium, to provide an isomeric mixture of *Z* and *E* dienophiles **7** with both hydroxyl groups protected. The ratio of *Z* and *E* isomers is roughly 43:57 as determined by integration of the proton nmr signals.

Attempts to separate the isomeric mixture **7** by chromatography met with little success. It was finally found, however, that after selective removal of the tetrahydropyranyl protecting group with pyridinium *p*-toluenesulfonate in isopropanol at 75°C[2] the resulting alcohols of the isomeric mixture **8** could be separated by the use of medium-pres-

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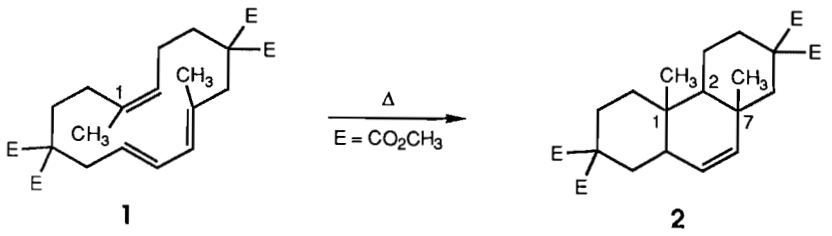
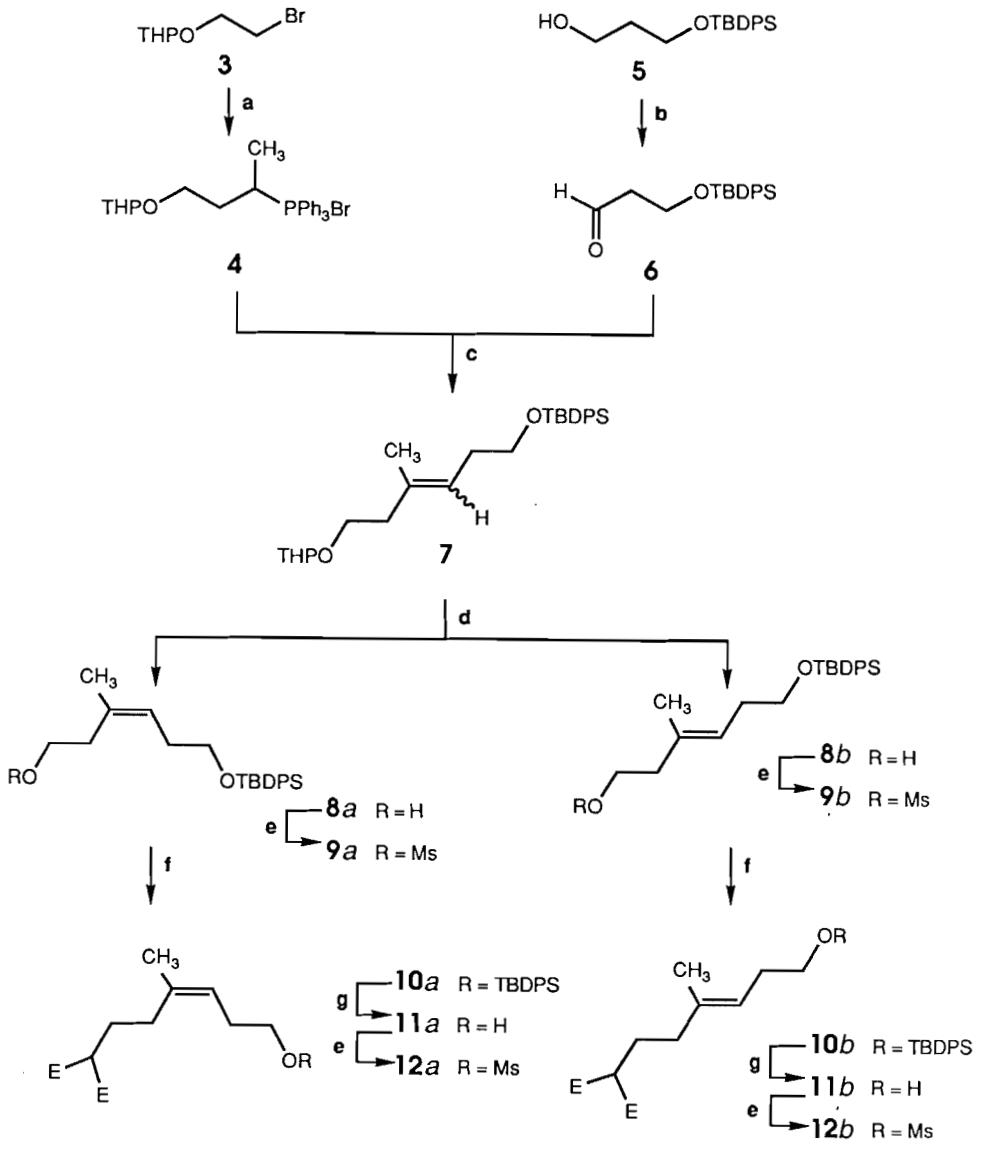
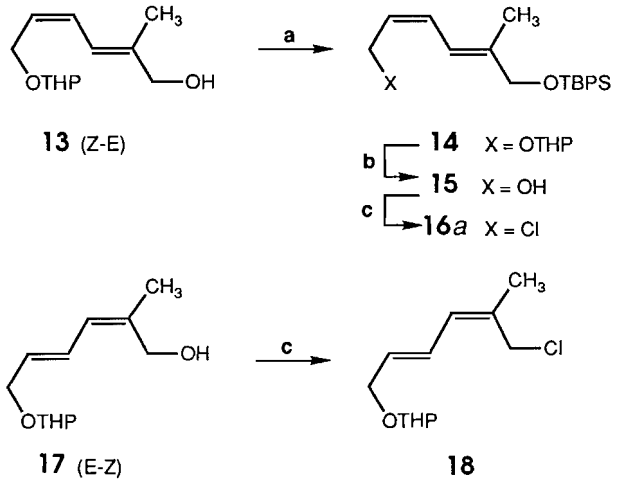


SCHEME 1



(a) $EtPPh_3Br$, $KN(TMS)_2$, THF, 0°C to r.t., 88%;
(b) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, -78°C to r.t., 86%;
(c) nBuLi, THF, 0°C, 61%;
(d) PPTS, iPrOH, 80°C, 98%;
(e) MsCl, Et_3N, CH_2Cl_2, 0°C, 93-97%;
(f) NaH, CH_2E_2, KI, DMF, THF, 0° to 70°C, 87-88%;
(g) nBu_4NF, THF, 0°C to r.t., 74-91%.

SCHEME 2



(a) *t*-BuPh$_2$SiCl, imidazole, THF, 0°C, 99%;

(b) PPTS, iPrOH, 80°C, 86%;

(c) LiCl, MsCl, *s*-collidine, DMF, 0°C to r.t., 99%.

SCHEME 3

sure chromatography. It is interesting to note that the isomeric mixture of alcohols resulting from desilylation of **7** was practically inseparable.

After separation, both alcohols **8***a* and **8***b* were subjected, in separate experiments, to the same transformations as indicated in Scheme 2, in order to produce the proper functionality necessary for the coupling reaction with dienes. Thus, **8***a* and **8***b* were converted in good yields to their respective methanesulfonate esters **9***a* and **9***b*. Potassium-iodide-catalyzed alkylation of methanesulfonate esters **9***a* and **9***b* with the sodium-hydride-generated enolate of dimethyl malonate in a mixture of DMF and THF (1:1) at 85°C afforded methyl octenoates **10***a* and **10***b*, respectively. Desilylation of **10***a* and **10***b* by tetrabutylammonium fluoride (12) in THF then gave alcohols **11***a* and **11***b*, which were similarly converted, as described above, to their methanesulfonate esters **12***a* and **12***b* as the desired dienophiles. A stereoselective synthesis of *Z* dienophile **12***a* was also developed in our laboratory; the details will be reported in near future (13).

In the studies of transannular Diels–Alder reactions for this series, four different diene moieties were required. Syntheses of dienes **16***b* (*E-Z*) and **16***c* (*E-E*) used as depicted in Scheme 4 were reported in the preceding article (1). The other two dienes **16***a* (*Z-E*) and **18** (*E-Z*) were derived from dienes **13** and **17** (1), respectively, by functional group manipulations. As presented in Scheme 3, hydroxyl group protection in **13** with *tert*-butylchlorodiphenylsilane gave diene diether **14** (11). Selective deprotection of the tetrahydropyranyl ether (THP) with pyridinium *p*-toluenesulfonate (PPTS) ether was performed with isopropanol[2] to give allylic alcohol **15**, which could be transformed into allylic chloride **16***a* by use of Meyers' method (14). Similarly, allylic alcohol **17** could be converted to allylic chloride **18** (14).

Preparation of macrocycles

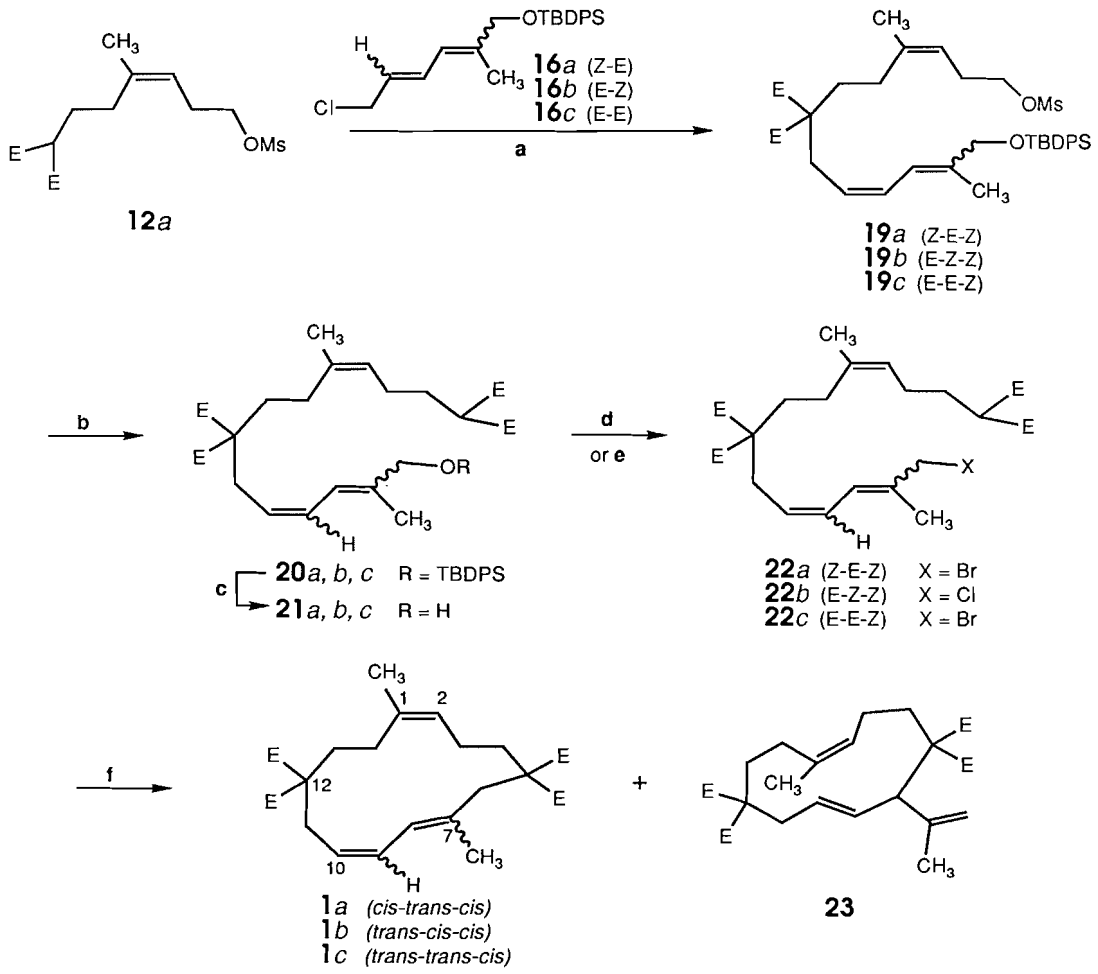
Our basic strategy for the synthesis of acyclic trienes, which are the immediate precursors of macrocycles, is based on the coupling reaction of dienes and dienophiles, which has been used extensively in our laboratory (7). As presented in Scheme 4, the coupling reactions were conducted by alkylation of the sodium-hydride-generated enolate of dimethyl malonate **12***a* with allylic chlorides **16***a*, **16***b*, or **16***c* in a mixture of THF and DMF (15), which provided three acyclic trienes **19***a* (*Z-E-Z*), **19***b* (*E-Z-Z*), and **19***c* (*E-E-Z*), respectively, in good yields. Introduction of the malonate connector was accomplished by substitution of the methanesulfonate ester groups of **19***a*, **19***b*, and **19***c* with the sodium salt of dimethyl malonate in the presence of a catalytic amount of potassium iodide to produce **20***a*, **20***b*, and **20***c*, respectively. Deprotection of the silyl ether groups was carried out by treatment of **20***a*, **20***b*, and **20***c* with tetrabutylammonium fluoride in THF (12) to give **21***a*, **21***b*, and **21***c*. The allylic alcohol **21***b* was converted to allylic chloride **22***b* by Meyers' method (LiCl, CH_3SO_2Cl, and *s*-collidine in DMF (14)). The allylic chloride has been used very often for the preparation of macrocycles in our laboratory (7). However, it was recently found that the corresponding allylic bromide is superior to the allylic chloride for the macrocyclization process (1). Therefore, allylic alcohols **21***a* and **21***c* were transformed into allylic bromides **22***a* and **22***c*, respectively, using PPh_3 and CBr_4 in CH_2Cl_2 (16). Allylic halides **22***a*, **22***b*, and **22***c* decomposed slowly when they were purified by flash chromatography; however, this problem could be avoided if the newly prepared allylic halides were filtered through a short-path silica gel column and then used immediately for the next cyclization reaction.

Having synthesized the requisite carbon chain and appropriate functional groups at each end, the acyclic trienes **22***a–c* were ready for the construction of macrocycles. All macrocyclizations were performed in the same way by slowly adding a solution of allylic halides **22***a*, **22***b*, **22***c* in THF to a stirred suspension of cesium carbonate in a mixture of DMF and THF (1:1) at about 80°C under dilute conditions to avoid dimerization (7). Macrocyclic products **1***a* (*cis-trans-cis*, CTC), **1***b* (TCC), and **1***c* (TTC) were formed as white solids in very good yields (66–93%) via an intramolecular displacement of allylic halides by the base-generated dimethyl malonate anion. In all cases, no detectable amount of dimerization product was observed by ^{1}H nmr spectra. However, a side-product **23**, which was derived from an S_N2'-like mechanism, was obtained from **22***c* but in less than 5% yield.

The structures of macrocycles **1***a*, **1***b*, and **1***c* were rigorously established by spectroscopic data including ^{13}C and ^{1}H nmr, ir, and high- and low-resolution ms. The conservation of the double bond geometries in the macrocyclic products has been confirmed by comparing the ^{1}H nmr data with those of their triene precursors such as **22** or **21**. Further confirmation of the structures by X-ray crystallography was also obtained for macrocycles **1***a*[3] and **1***b* (17).

Macrocycle **1***d*, which has methyl substituents at the C2 and C7 positions and which possesses the same olefin geometries (*trans-cis-cis*) as macrocycle **1***b*, was synthesized via a slightly different procedure than that used for the preparation of other macrocycles. As presented in Scheme 5, the *Z* dienophile **24**, previously prepared in our laboratory (1), was first converted to its enolate anion with sodium hydride in tetrahydrofuran. The coupling reaction (15)

[3]A.G. Michel, Y.C. Xu, and P. Deslongchamps. Unpublished results.



(a) NaH, THF, DMF, 0°C to r.t., 59-77%;

(b) NaH, CH_2E_2, KI, DMF, THF, 0°C to r.t., 76-91%;

(c) nBu_4NF, THF, 0°C to r.t., 60-90%;

(d) CBr_4, PPh_3, CH_2Cl_2, 0°C to r.t., 74-87%;

(e) LiCl, MsCl, *s*-collidine, DMF, 0°C to r.t.;

(f) Cs_2CO_3, DMF, THF, 70°C, 63-90%.

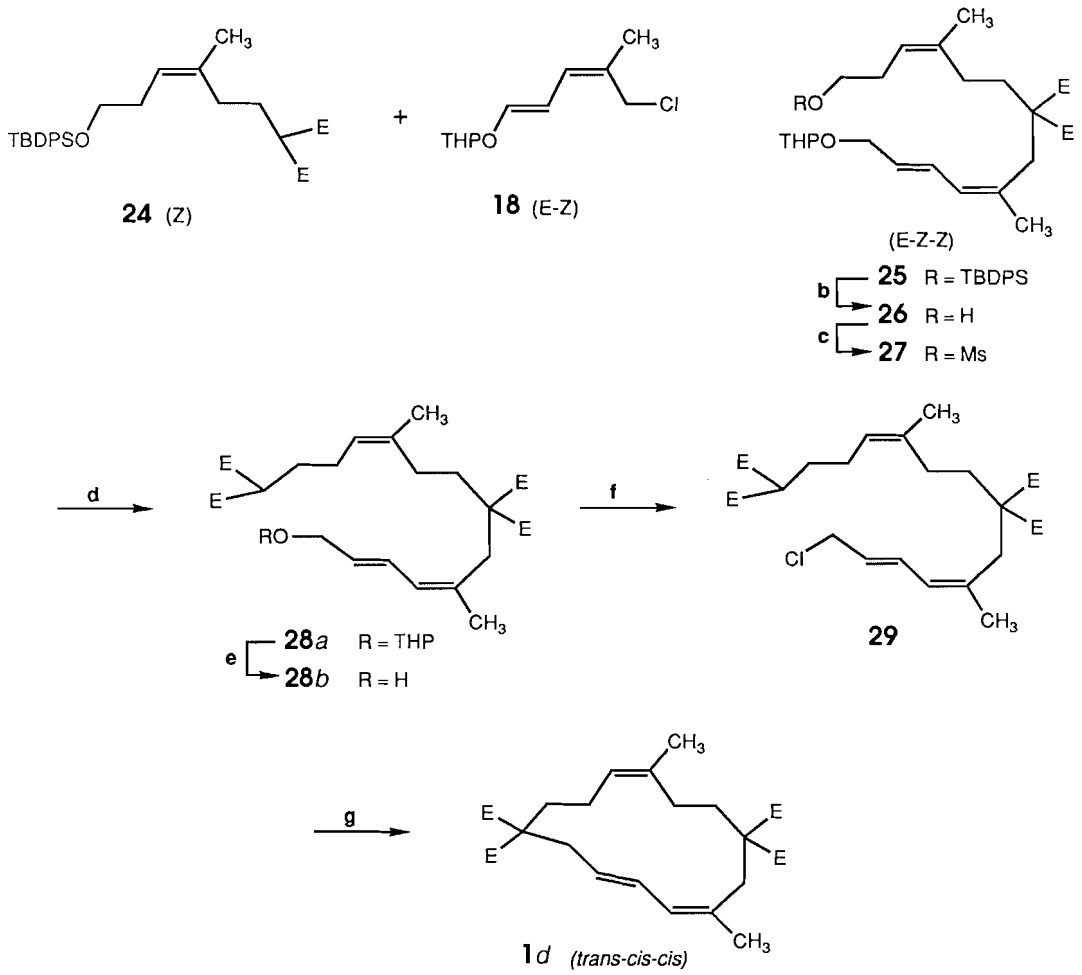
SCHEME 4

of this enolate with allylic chloride **18** took place at room temperature (DMF–THF) to give *E-Z-Z* triene **25**. After treatment of **25** with tetrabutylammonium fluoride in THF (12), the resulting alcohol **26** was converted to its methanesulfonate ester **27** with methanesulfonyl chloride and triethylamine. Introduction of the malonate connector to give **28***a* was accomplished according to the previously described procedures. Treatment of compound **28***a* with pyridium *p*-toluenesulfonate in methanol at 55°C (8) resulted in the formation of alcohol **28***b*, which was subsequently transformed into allylic chloride **29** by Meyers' procedure (14). Without further purification, triene allylic chloride **29** was immediately subjected to the previously described cyclization conditions. TCC macrocycle **1***d* was thus obtained as a crystalline solid in 69% overall yield from alcohol **28**. Again, the structure of macrocycle **1***d* was rigorously established by spectroscopic analysis including nmr, ir, and ms as well as X-ray crystallography (17).

*Diels–Alder reaction of TCC macrocycles 1*b *and 1*d

In the case of TCC macrocycle **1***b*, the cycloaddition reaction was carried out at 320°C in a sealed tube for 90 min, providing the crystalline *trans-syn-cis* (TSC) tricycle **30** (Scheme 6) in 87% isolated yield. The structure of **30** was rigorously established by X-ray crystallographic analysis (18).

In principle, a macrocyclic triene can yield two different diastereoisomeric products. However, and as previously discussed (7*a*), there are cases where a particular diastereoisomer cannot be formed because of conformational restrictions due to the fact that the Diels–Alder reaction must take place via a boat transition state. Such a situation occurs in the case of a TCC macrocycle, which is predicted to give exclusively a TSC tricycle since a CST tricycle cannot be



(a) NaH, THF, DMF, 0°C to r.t., 35%;

(b) nBu_4NF, THF, 0°C to r.t., 99%;

(c) MsCl, Et_3N, CH_2Cl_2, 0°C;

(d) NaH, CH_2E_2, KI, DMF, THF, 0°C to 85°C, 73% from **26**;

(e) PPTS, iPrOH, 55°C, 95%;

(f) LiCl, MsCl, *s*-collidine, DMF, 0°C to r.t.;

(g) Cs_2CO_3, DMF, THF, 70°C, 69% from **28B**.

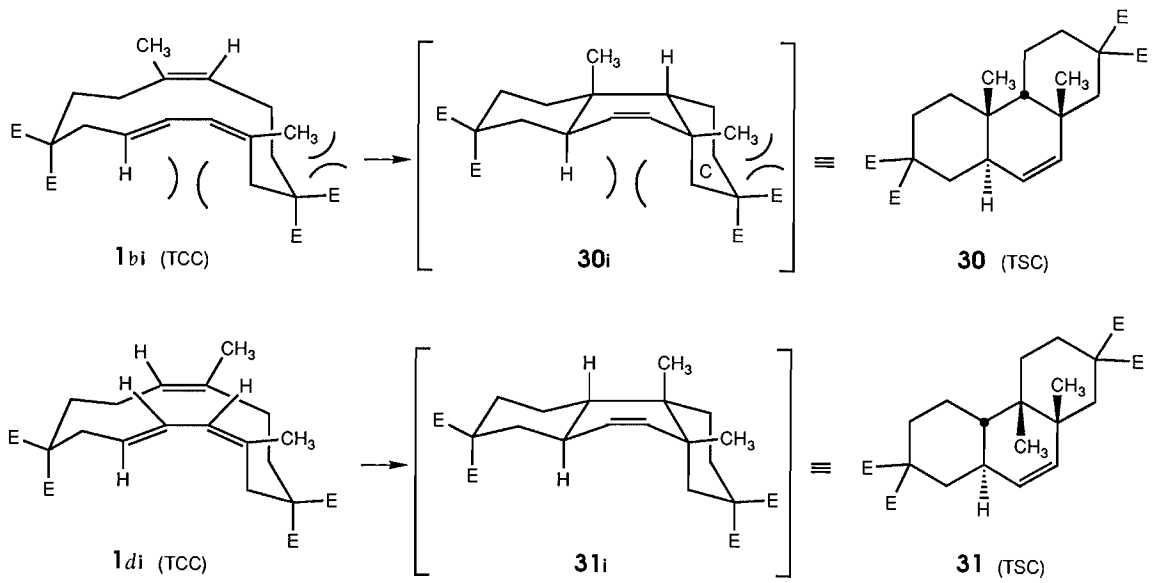
SCHEME 5

formed. The above experimental result is thus readily explained. Indeed, macrocycle **1***b* must react via conformation **1***bi* to produce the TSC tricycle **30** in the chair–boat–chair conformation **30***i*. The high temperature (320°C) required is primarily due to a steric repulsion that occurs when the *trans-cis* diene takes the *cisoid* conformation necessary for the cycloaddition as shown in **1***bi*. There is also a steric interaction between the methyl group of the diene and one of the ester functions. This is best visualized in conformation **30***i* of the Diels–Alder product where the methyl group at C7 is in a 1,3 diaxial disposition relative to the axial ester of ring C. The above result is also in complete agreement with the previously reported (7*b*) cycloaddition of a TCC macrocyclic triene having only one methyl group on the dienophile. In this case, a TSC macrocycle is again exclusively formed but a slightly lower temperature (300°C) appears to be required because there is less steric hindrance due to the absence of the methyl group on the diene moiety.

In a similar fashion, TCC macrocycle **1***d* was transformed into TSC tricycle **31** in 90% yield (Scheme 6). The stereochemistry of **31** was confirmed by X-ray diffraction analysis (19). Thus, as expected, the macrocyclic triene reacted via the *cisoid* conformation **1***di*, which gave **31** in conformation **31***i*, having steric interactions similar to those taking place during the conversion of TCC macrocycle **1***b* into TSC tricycle **30**.

Diels–Alder reaction of CTC macrocycle **1***a and TTC macrocycle* **1***c*

Upon heating at 325°C in toluene in a sealed quartz tube for 18 h, CTC macrocycle **1***a* was converted into a mixture



SCHEME 6

of four tricyclic isomers **30** and **32–34** in a 7:20.6:5.9:1 ratio as determined by ^{1}H nmr spectroscopy. The first isomer **30** was shown to have the TSC tricyclic geometry by comparison with an authentic sample obtained from the Diels–Alder reaction of macrocycle **1***b*. Isomers **33** and **34** could be obtained pure by chromatography and characterized by the usual spectroscopic techniques. Isomer **33** was shown to have the CSC stereochemistry by X-ray diffraction analysis.[4] Assignment of the basic skeleton of isomer **32** could be made by ^{1}H nmr spectroscopic analysis of the mixture. Isomers **32** and **34** have been tentatively assigned the CST and TST relative stereochemistry.

We have found that when TTC macrocycle **1***c* is heated at 200°C for 4 h, it is quantitatively isomerized into CTC macrocyclic triene **1***a*, indicating that the triene having a second *cis* olefin is more stable. It was also found that upon heating at 310°C, TTC macrocycle **1***c* gave the same mixture of tricyclic isomers as that observed with **1***a*, but in a different ratio, namely, 2.3:1:29.9:5.3.

It is thus very likely that **1***a* and **1***c* are interconverted prior to the Diels–Alder reactions. Also, **1***a* and (or) **1***c* must probably undergo an isomerization into macrocycle **1***b* since we previously observed that **1***b* yields exclusively the TSC isomer **30**, which is one of the four isomers observed from **1***a* and **1***c*.

It is possible to understand why such a complex mixture was obtained and to propose pathways for the interconversion of macrocyclic trienes **1***a*, **1***b*, and **1***c*. The facile conversion of macrocyclic triene **1***a* into **1***c* can be explained by two consecutive hydrogen migrations via the intermediate formation of macrocycle **35** as shown in Scheme 7. The isomerization of macrocycle **1***a* into macrocycle **1***b* is a more complex process that can take place via four consecutive 1,5 hydrogen migrations. Macrocycle **1***a* would first be converted to TCC macrocycle **36**, which can then give CCC macrocycle **37**. Finally, CTC macrocycle **38** would be obtained from **37**, and converted into TCC macrocycle **1***b*. The isomerization of a CC diene into a CT or TC diene has previously been observed in our laboratory (*7b*).

Assuming that macrocycles **35**, **36**, and **38** do not undergo a cycloaddition because they would produce tricycles containing a seven-membered ring, the formation of the mixtures of stereoisomers **30** and **32–34** having respectively the TSC, CST, CSC, and TST stereochemistry would be the result of cycloaddition of macrocycles CTC (**1***a*), TCC (**1***b*), TTC (**1***c*), and CCC (**37**), which would be thermally interconvertible prior to the Diels–Alder reaction. These interconversions are summarized in Fig. 1.

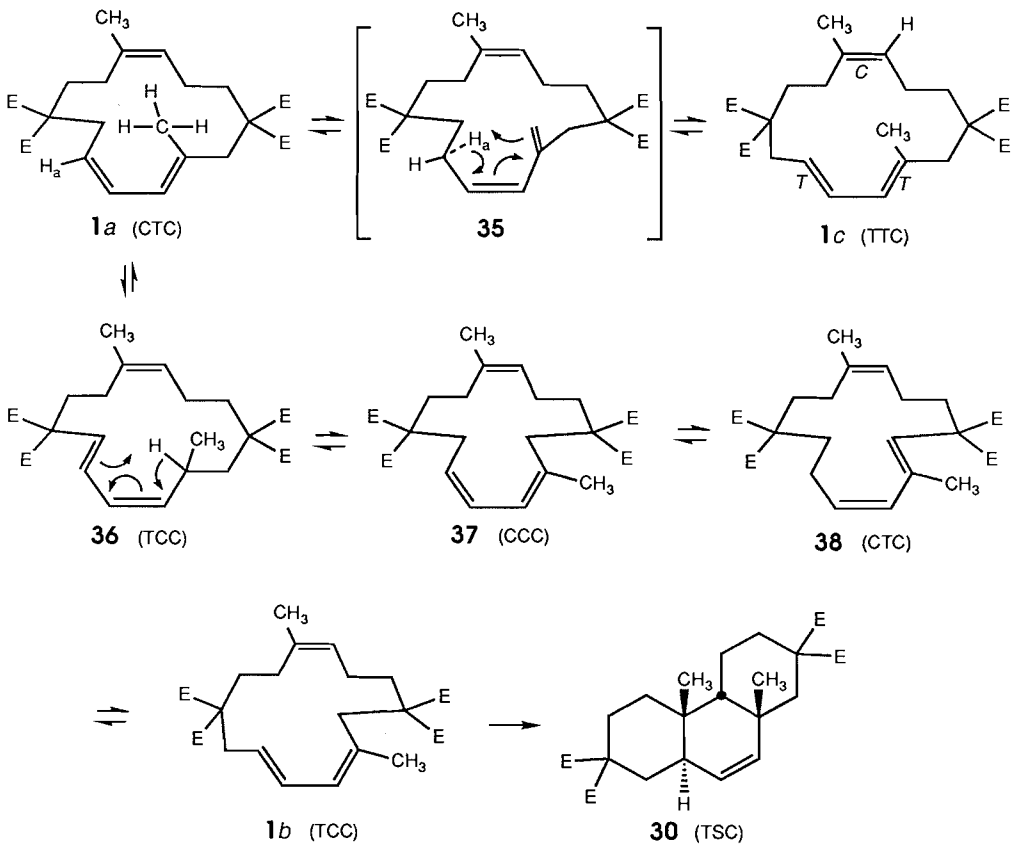
First, CTC macrocyclic trienes are predicted (*7a*) to give only one tricyclic isomer having the *cis-syn-trans* (CST) stereochemistry. In the case of CTC macrocycle **1***a*, this means that it should react via conformation **1***ai*, which would undergo a cycloaddition to produce CST tricycle **32** in conformation **32***i* as illustrated in Scheme 8. The required *cisoid* conformation of the diene moiety is highly hindered (cf. **1***ai*), and the resulting product will have ring B in a boat form that is very severely encumbered by the presence of the methyl group at C7. In addition, this methyl group also experiences a 1,3 diaxial steric interaction with the axial ester of ring C. The energy barrier for this cycloaddition must be quite high and it is therefore not surprising that other processes can compete with the formation of this CST tricycle.

We have previously shown that TCC macrocycle **1***b* gives TSC tricycle **30** exclusively and this result has been already rationalized (Scheme 6).

TTC macrocyclic trienes are predicted (*7a*) to give the TST and the CSC tricycles. Indeed, TTC macrocycle **1***c* can either take conformation **1***ci* (Scheme 9) to produce the TST tricycle **34** (via **34***i*) or conformation **1***cii* to yield the CSC tricycle **33** (via **33***i*). Both processes are somewhat hindered, but the formation of the TST isomer should be favored since it appears to be less sterically crowded.

Finally, the cycloaddition of CCC macrocycle **37** is predicted to give the CSC tricycle **33**. This cycloaddition involves rather severe steric interactions at the transition state, resulting from a diene having a *cis-cis* configuration. In-

[4]A.G. Michel, M. Drouin, and P. Soucy. Unpublished results.



SCHEME 7

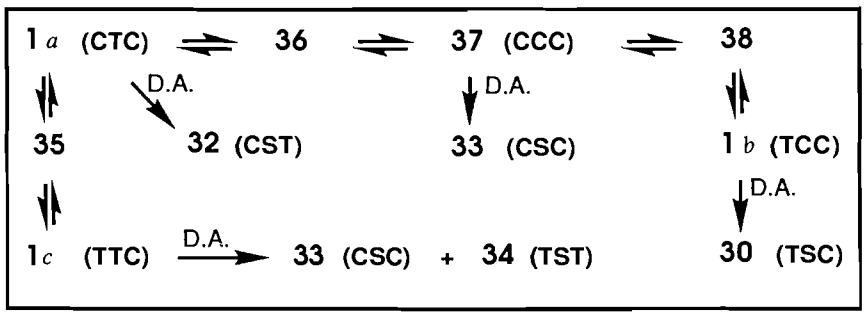
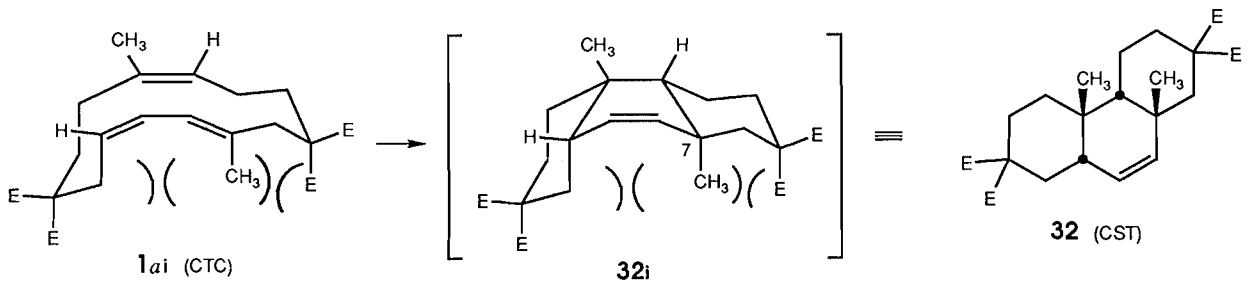


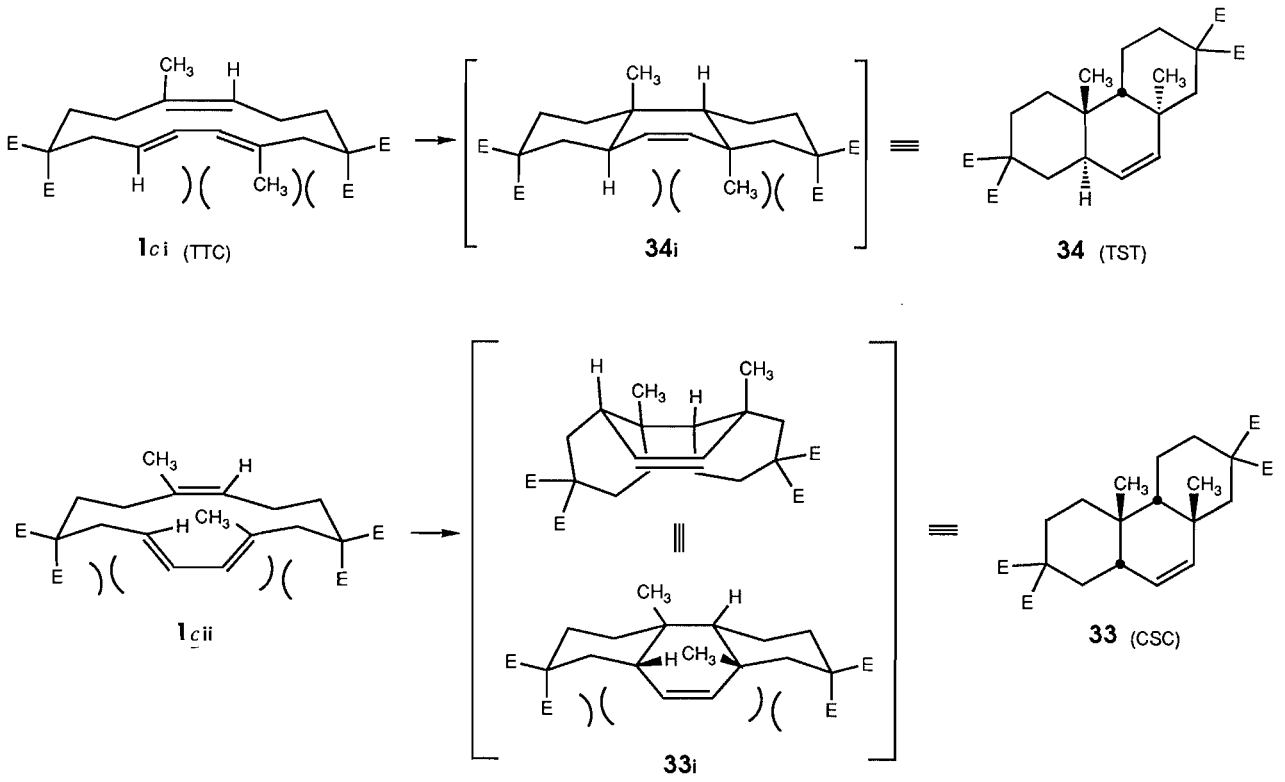
FIG. 1. Summary of possible interconversion.



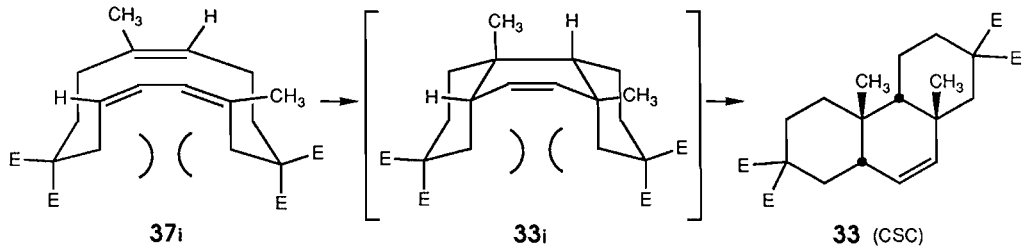
SCHEME 8

deed, CCC macrocycle **37** must react via the very crowded *cisoid* conformation **37***i* (Scheme 10) to yield tricycle **33** in the high-energy conformation **33***i*.

All the cycloadditions must take place via transition states that experience severe steric repulsions. It is therefore not surprising that the macrocycles are thermally interconverted



SCHEME 9



SCHEME 10

prior to the cycloaddition reaction. The exclusive formation of TSC tricycle **30** from TCC macrocycle **1***b* shows that its thermal isomerization to the other macrocycles is, however, higher is energy than the cycloaddition reaction to give TSC tricycle **30**. The different ratios of stereoisomers obtained from macrocycles **1***a* and **1***c* indicate that the Diels–Alder reaction can compete to some extent with the isomerization process of the macrocycles, although this process is known to take place at lower temperature. This may be because the Diels–Alder reaction is probably more favorable from an entropy point of view than the sigmatropic 1,5 hydrogen migration. Finally, an unexplained result is the large percentage of CSC tricycle **33** obtained from **1***c*. On the basis of steric effect arguments, it can be predicted that TST tricycle **34** and CSC tricycle **33** should have been the major and the minor isomer, respectively (Scheme 9). Of course, CSC tricycle **33** can also be obtained from CCC macrocycle **37**. However, on that basis CSC tricycle **33** should have been produced in large amount from CTC macrocycle **1***a*, as **1***a* is an intermediate in the interconversion of macrocycles **1***c* (TTC) and **37** (CCC).

In conclusion, four macrocyclic trienes (two TCC, one CTC, and one TTC) were successfully synthesized in good yield. The TCC macrocycles **1***b* and **1***d* gave, respectively, the TSC tricycles **30** and **31** via a transannular Diels–Alder reaction. On the other hand, the transannular Diels–Alder reaction of CTC macrocycle **1***a* and TTC macrocycle **1***c* led to a mixture of the same four tricycles (**30** (TSC), **32** (CST), **33** (CSC), and **34** (TST)) but in a different ratio. These results are explained by taking into consideration the interconversion of macrocyclic trienes **1***a* (CTC), **1***b* (TCC), **1***c* (TTC), and **37** (CCC) prior to the Diels–Alder reaction. A useful summary of the results obtained with the various dimethyl-substituted macrocyclic trienes reported in this paper and the preceding one (1) is shown in Fig. 2. This information is presently being used for the elaboration of new routes for the synthesis of various polycyclic natural products of the diterpene and triterpene family.

Experimental

2-(2-Bromoethyloxy)tetrahydropyran 3

To a stirred solution of 2-bromoethanol (19.2 g, 154 mmol) in 200 mL of CH_2Cl_2 were added at 0°C under argon pyridinium *p*-toluenesulfonate (PPTS) (387 mg, 1.5 mmol) and 3,4-dihydro-

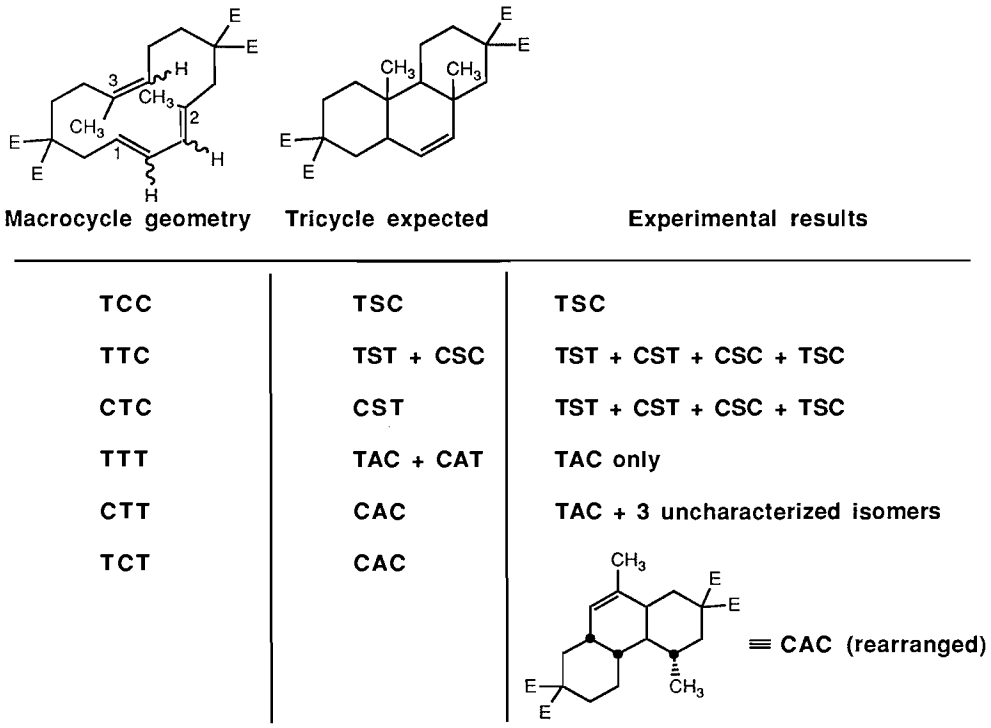


FIG. 2. Summary of transannular Diels–Alder reactions of disubstituted macrocyclic trienes.

2*H*-pyran (21.0 mL, 230 mmol). The resulting mixture was stirred at room temperature for 2.3 h and then poured into a saturated $NaHCO_3$ solution (120 mL). The organic phase was washed with water, dried, and concentrated to a crude residue that was purified by distillation (1.4 Torr (1 Torr = 133.3 Pa), 63–64°C) to give colorless oil **3** (25.7 g, 81%); ir (neat): 2945, 2850, 1125, 1030 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.50–1.86 (m, 6H, -OCHOCH$_2$(CH_2)$_3$-), 3.48–3.54 (m, 2H, BrCH_2-), 3.48–3.57 and 3.85–3.94 (2m, 2H, -OCHOCH_2-), 3.72–3.82 and 3.97–4.06 (2dt, 2H, J = 11.2 Hz, 6.2 Hz, -CH_2OTHP), 4.68 (t, 1H, J = 3.3 Hz, -OC*H*O).

2-Triphenylphosphonium bromide ***4***

To a stirred solution of (ethyl)triphenylphosphonium bromide (32.3 g, 87 mmol) in 200 mL of THF was added dropwise, at 0°C under argon, potassium hexamethyldisilazane (0.5 M in toluene, 174 mL, 87 mmol). The resulting suspension was stirred at 0°C for 0.5 h and then a solution of compound **3** (25.8 g, 125 mmol) in 70 mL of THF was introduced dropwise over 20 min. The orange mixture was warmed to room temperature and then stirred for 50 h. The resulting thick, pink mixture was filtered through a Buchner funnel and the solid was washed several times with THF. The filtrate collection flask was changed and the solid was washed with CH_2Cl_2 until only solid, grey, KBr remained in the funnel. The CH_2Cl_2 filtrate was concentrated to an off-white crude salt (40.8 g) that was recrystallized from CH_2Cl_2 and hexane to give pure compound **4** (38.0 g, 88%) as clear crystals; ir ($CHCl_3$): 3060–3010, 2950–2860, 1442, 1115, 1038 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.44 (dd, 3H, J = 19.8 Hz, 7.1 Hz, -CH(CH_3)-), 1.32–1.64 (m, 6H, -OCH$_2$(CH_2)$_3$-), 1.70–1.87 and 2.20–2.30 (2m, 2H, -CHCH_2-CH$_2$OTHP), 3.45–3.54 and 3.79–3.85 (2m, 2H, -CHOCH_2-), 3.88–4.17 (m, 2H, -CH_2OTHP), 4.57–4.59 and 4.62–4.64 (2m, 1H, -OC*H*O-), 4.87–5.08 and 5.13–5.28 (2m, 1H, -C*H*PCH$_2$-), 7.62–8.01 (m, 15H, PPh_3).

*3-*tert*-Butyldiphenylsilyloxy 1-propanol* ***5***

To a stirred solution of 1,3-propanediol (20.0 g, 263 mmol) and imidazole (3.58 g, 52.6 mmol) in 180 mL of THF was added at room temperature under argon *tert*-butylchlorodiphenylsilane (13.7 mL, 52.6 mmol). After the mixture was stirred for 25 h, 100 mL of water was introduced. The aqueous layer was extracted with hexane (5 × 100 mL) and the combined organic layers were washed with H_2O, dried over $MgSO_4$, filtered, and concentrated to a crude brown residue that was purified by flash chromatography (hexane – ethyl acetate, 9:1) to afford **5** (15.86 g, 96%) as a colorless oil; ir ($CHCl_3$): 3620–3510, 3080–3020, 2960–2860, 1430, 1115, 1068 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.05 (9H, s, -(CH_3)$_3$CSi-), 1.52–1.98 (m, 2H, -CH_2CH$_2$OH), 2.35 (t, 1H, J = 5.4 Hz, -CH$_2$O*H*), 3.86 (q, 2H, J = 5.7 Hz, -CH_2OH), 3.88 (t, 2H, J = 5.7 Hz, -CH_2OSi-), 7.46–7.66 (m, 10H, Ph_2Si-).

Aldehyde ***6***

To a stirred solution of oxalyl chloride (4.8 mL, 55.3 mmol) in 115 mL of CH_2Cl_2 was added dropwise, at −78°C under argon over a period of 20 min, a solution of DMSO (7.9 mL, 110.6 mmol) in 25 mL of CH_2Cl_2. The stirring was continued for 20 min before adding a solution of alcohol **5** (15.8 g, 50.3 mmol) in 50 mL of CH_2Cl_2 over 25 min. After the mixture was stirred at −78°C for 45 min, triethylamine (35 mL) was introduced. The reaction mixture was warmed to room temperature for 1 h, followed by addition of 100 mL of water. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic phases were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to a yellow residue that was purified by flash chromatography (hexane – ethyl acetate, 9:1) to give aldehyde **6** (13.6 g, 86%); ir ($CHCl_3$): 3080–3010, 2960–2860, 2740, 1728, 1430, 1115 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.05 (s, 9H, -(CH_3)$_3$CSi-), 2.61 (dt, 2H, J = 5.6 Hz, 2.8 Hz, -CH_2CHO), 4.03 (t, 2H, J = 6.1 Hz, -CH_2OSi-), 7.35–7.81 (m, 10H, Ph_2Si-), 9.83 (t, 1H, J = 2.4 Hz, -C*H*O); ms m/e: 255 ($M^+ - C_4H_9$).

3-Hexene diether ***7***

To a stirred solution of phosphonium bromide **4** (25.9 g, 51.9 mmol) in 200 mL of THF, butyllithium (1.6 M in hexane, 29.7 mL, 47.6 mmol) was added dropwise at 0°C under argon. After the mixture was stirred for 40 min, a solution of aldehyde **6** (13.5 g, 43.3 mmol) in 70 mL of THF was introduced dropwise over 35 min. The stirring was continued at 0°C for 3 h, followed

by addition of a mixture (petroleum ether – hexane, 1:1). After the mixture was filtered through a Celite plug on a fritted-disk funnel, the filtrate was concentrated to a crude yellow oil (15.2 g). The solid remaining in the funnel was dissolved in H_2O, which was then extracted with ether (5 × 100 mL). The combined organic phases were dried, filtered, and concentrated to a crude residue (5.0 g) that was combined with the original crude material. Purification by flash chromatography (hexane – ethyl acetate, 96:4) gave pure product **7** (12.0 g, 61%) as a colorless oil. The following spectral data were obtained from a mixture of *Z*- and *E*-**7**; ir (neat): 3075, 2940, 2860, 1430, 1115, 1036 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.04 (s, 9H, -(CH_3)$_3$C), 1.59 (s, 3H, -CH=C(CH_3)-, *E*), 1.71 (d, 3H, *J* = 1.3 Hz, -CH=C(CH_3)-, *Z*), 1.30–1.89 (m, 6H, -OCH$_2$(CH_2)$_3$-), 2.20–2.35 (m, 4H, CH_2CH=C(CH_3)CH_2-), 3.62 and 3.63 (2t, 2H, *J* = 7.1 Hz, -CH_2OSi-), 3.32–3.52 and 3.71–3.88 (2m, 4H, -OCH_2-CH$_2$-, -CH_2OTHP), 4.54–4.58 (m, 1H, -OC*H*O-), 5.12–5.24 (m, 1H, -C*H*=C(CH_3)-), 7.33–7.49 and 7.62–7.70 (2m, 10H, Ph_2Si-). The ratio for *Z* and *E* isomers is approximately 43:57 as determined by ^1H nmr.

Alcohols ***8***a *and* ***8***b

General procedure A

To a stirred solution of *Z*- and *E*-**7** (8.0 g, 17.7 mmol) in 370 mL of isopropanol was added under argon pyridinium *p*-toluenesulfonate (0.89 g, 3.2 mmol) and the resulting mixture was heated to 80°C for 4 h. The reaction was stopped by addition of H_2O (200 mL) and ether (300 mL). The aqueous phase was extracted with ether (2 × 100 mL). The combined organic phases were dried, filtered, and concentrated to a crude oil (6.7 g). Initial attempts to separate the isomers by flash chromatography met with only limited success. Considerably better separation was obtained by the use of medium-pressure chromatography under a pressure of 30 psi (1 psi = 6.9 kPa) with a 85:15 mixture of hexane and ethyl acetate as eluant. Purification of 1 g crude oil gave rise to *Z* isomer **8***a* (355 mg) and *E* isomer **8***b* (522 mg) along with a mixture of **8***a* and **8***b* (80 mg). Based on this set of data, the yield for this reaction is 98%.

Spectral data for ***8***a: ir ($CHCl_3$): 3618, 3460, 3075–3055, 2960–2860, 1430, 1385, 1110, 1055 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.04 (s, 9H, -(CH_3)$_3$C), 1.72 (d, 3H, *J* = 1.3 Hz, -CH=C(CH_3)-), 2.26 (t, 2H, *J* = 6.4 Hz, -CH=C(CH_3)CH_2-), 2.32 (qd, 2H, *J* = 6.8 Hz, 0.7 Hz, SiOCH$_2$CH_2-), 3.62 (t, 2H, *J* = 6.4 Hz, -CH_2OH), 3.64 (t, 2H, *J* = 6.7 Hz, -SiOCH_2-), 5.31 (t, 1H, *J* = 7.0 Hz, -C*H*=C(CH_3)-), 7.34–7.47 and 7.64–7.73 (2m, 10H, Ph_2Si-).

Spectral data for ***8***b: ir (neat): 3360, 3070–3045, 2925–2858, 1430, 1385, 1110, 1050 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.04 (s, 9H, -(CH_3)$_3$C), 1.45 (s, 1H, -CH_2O*H*), 1.59 (m, 3H, -CH=C(CH_3)-), 2.24 (t, 2H, *J* = 6.6 Hz, -CH=C(CH_3)CH_2-), 2.29 (q, 2H, *J* = 6.9 Hz, -SiOCH$_2$CH_2-), 3.64 (t, 2H, *J* = 6.2 Hz, -CH_2OH), 3.65 (t, 2H, *J* = 6.8 Hz, -SiOCH_2-), 5.25 (td, 1H, *J* = 7.3 Hz, 1.3 Hz, -C*H*=C(CH_3)-), 7.27–7.46 and 7.63–7.70 (2m, 10H, Ph_2Si-); ms *m/e*: 311 ($M^+ - C_4H_9$).

Mesylates ***9***a *and* ***9***b

General procedure B

To a stirred solution of alcohol **8***a* (130 mg, 0.35 mmol) and triethylamine (180 g, 1.75 mmol) in 8 mL of CH_2Cl_2, methanesulfonyl chloride (50 mg, 0.42 mmol) was added dropwise at 0°C under argon. The stirring was continued at 0°C for 1 h before the mixture was poured into H_2O (40 mL). The aqueous phase was extracted with CH_2Cl_2 (4 × 10 mL) and the combined organic phases were washed with H_2O, dried over $MgSO_4$, filtered, and concentrated to a crude residue that was purified by flash chromatography (hexane – ethyl acetate, 9:1) to furnish mesylate **9***a* (145 mg, 93%) as a clear oil; ^1H nmr ($CDCl_3$) δ: 1.04 (s, 9H, -(CH_3)$_3$C), 1.73 (m, 3H, -CH=C(CH_3)-), 2.26 (m, 2H, -CH_2CH=), 2.42 (t, 2H, *J* = 7.2 Hz, =C(CH_3)CH_2-), 2.91 (s, 3H, -SO_2CH_3), 3.64 (t, 2H, *J* = 6.8 Hz, -SiOCH_2-), 4.18 (t, 2H, *J* = 7.0 Hz, -CH_2OSO$_2$-), 5.32 (m, 1H, -C*H*=C-), 7.34–7.44 and 7.65–7.68 (m, 10H, Ph_2Si-).

The mesylation for alcohol **8***b* was carried out exactly as described above. Thus, treatment of alcohol **8***b* (580 mg, 1.6 mmol) with triethylamine (0.33 mL, 1.9 mmol) and methanesulfonyl chloride (0.15 mL, 1.9 mmol) in 20 mL of CH_2Cl_2 yielded *Z*-mesylate **9***b* (685 mg, 97%); ir (neat); 3070–3018, 2930, 2860, 1430, 1380, 1358, 1175, 1110 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.06 (s, 9H, -(CH_3)$_3$C), 1.63 (m, 3H, -CH=C(CH_3)-), 2.25–2.51 (m, 4H, -CH_2CH=C(CH_3)CH_2-), 2.95 (s, 3H, -SO_2CH_3), 3.67 (t, 2H, *J* = 6.7 Hz, -SiOCH_2-), 4.26 (t, 2H, *J* = 7.1 Hz, -CH_2OSO$_2$-), 5.28 (m, 1H, -C*H*=C(CH_3)-), 7.28–7.85 (m, 10H, Ph_2Si-); ms *m/e*: 389 ($M^+ - C_4H_9$).

Dimethyl malonates ***10***a *and* ***10***b

General procedure C

To a stirred suspension of NaH (130 mg, 5.4 mmol) in a mixture of DMF and THF (1:1, 40 mL) was added dropwise, over 20 mins at 0°C under argon, dimethyl malonate (800 mg, 6.0 mmol). The stirring was continued at 0°C for 1 h before adding a solution of mesylate **9***a* (540 mg, 1.2 mmol) in 2 mL of THF and KI (20 mg, 0.12 mmol). The resulting mixture was heated at 70°C for 36 h, then poured into 200 mL of water. The aqueous phase was extracted with hexane–ether (1:1, 3 × 200 mL), and the combined organic phases were washed with H_2O, dried over $MgSO_4$, filtered, and concentrated to a crude residue that was purified by flash chromatography (hexane – ethyl acetate, 9:1) to give **10***b* (509 mg, 88%) as a colorless oil; ^1H nmr ($CDCl_3$) δ: 1.04 (s, 9H, -(CH_3)$_3$C), 1.67 (m, 3H, -CH=C(CH_3)-), 1.92–2.04 (m, 4H, -CH=(CH_3)CH_2CH_2-), 2.18–2.28 (m, 2H, -SiOCH$_2$CH_2-), 3.32 (t, 1H, *J* = 7.0 Hz, -C*H*(CO_2CH_3)$_2$), 3.62 (t, 2H, *J* = 6.9 Hz, -SiOCH_2-), 3.73 (s, 6H, 2 × -OCH_3), 5.19 (m, 1H, -C*H*=C-), 7.34–7.43 and 7.65–7.69 (2m, 10H, Ph_2Si-).

The preparation of **10***b* was carried out in the same way as described above. Thus, treatment of dimethyl malonate (0.865 mL, 7.6 mmol) with NaH (272 mg, 60%, 6.8 mmol) in THF–DMF mixture (1:1), followed by addition of mesylate **9***b* (675 mg, 1.5 mmol) in 2 mL of THF, afforded product **10***b* (631 mg, 87%) as a colorless oil; ir (neat): 3070–3000, 2950, 2860, 1738, 1430, 1385, 1230, 1155, 1115 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.05 (s, 9H, -(CH_3)$_3$C), 1.57 (s, 3H, -CH=C(CH_3)-), 1.99–2.03 (m, 4H, -CH=C(CH_3)CH_2CH_2-), 2.27 (q, 2H, *J* = 6.8 Hz, -SiOCH$_2$CH_2-), 3.36 (m, 1H, -C*H*(CO_2CH_3)$_2$), 3.64 (t, 2H, *J* = 6.6 Hz, -SiOCH_2-), 3.72 and 3.73 (2s, 6H, 2× -OCH_3), 5.17 (m, 1H, -C*H*=C-), 7.35–7.78 (2m, 10H, Ph_2Si-); ms *m/e*: 425 ($M^+ - C_4H_9$).

Alcohols ***11***a *and* ***11***b

General procedure D

To a stirred solution of silyl ether **10***a* (316 mg, 0.655 mmol) in 6 mL of THF, tetrabutylammonium fluoride (1.0 M in THF, 1.2 mL, 1.2 mmol) was added at 0°C under argon. The mixture was warmed to room temperature and stirred for 2.5 h. The solvent was removed by evaporation and the oily residue was purified by flash chromatography (hexane – ethyl acetate, 7:3) to give alcohol **11***a* (119 mg, 74%) as a viscous oil; ir (neat): 3420, 2955, 2870, 1738, 1438, 1230, 1155, 1050 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.71 (d, 3H, -CH=C(CH_3)-), 1.95–2.12 (m, 4H, =C(CH_3)CH_2CH_2-), 2.22 (qd, 2H, *J* = 6.7 Hz, 1.0 Hz, HOCH$_2$CH_2-), 3.35 (t, 1H, *J* = 7.0 Hz, -C*H*(CO_2CH_3)$_2$), 2.61 (t, 2H, *J* = 6.4 Hz, HOCH_2-), 3.74 (s, 6H, 2× -OCH_3), 5.20 (td, 1H, *J* = 6.8 Hz, 1.1 Hz, -C*H*=C-); ms *m/e*: 244 ($M^+ - H_2O$).

The desilylation of **10***b* was carried out in the same way as described above. Thus, treatment of silyl ether **10***b* (603 mg, 1.3 mmol) with tetrabutylammonium fluoride (1.0 M in THF, 1.4 mL, 1.4 mmol) in THF yielded alcohol **11***b* (277 mg, 91%) as a colorless oil that has spectral data identical with the same compound reported in the preceding article.

Mesylates ***12***a *and* ***12***b

The mesylation of **12***a* was carried out in the same way as described in the general procedure B. Thus, treatment of alcohol **11***a*

(100 mg, 0.41 mmol) with triethylamine (86.1 μL, 0.45 mmol) and methanesulfonyl chloride (35 μL, 0.45 mmol) at 0°C in CH_2Cl_2 yielded mesylate **12***a* (110 mg, 83%) as a colorless oil; ir (neat): 2960, 2866, 1732, 1435, 1355, 1225, 1172 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.72 (d, 3H, J = 1.2 Hz, -CH=C(CH_3)-), 1.93–2.11 (m, 4H, -CH=C(CH_3)CH_2CH_2-), 2.42 (q, 2H, J = 7.0 Hz, $MsOCH_2$-CH_2-), 3.01 (s, 3H, $-SO_2CH_3$), 3.33 (t, 1H, -$CH(CO_2CH_3)_2$), 3.74 (s, 6H, 2× -OCH_3), 4.17 (t, 2H, J = 6.9 Hz, -CH_2OMs), 5.17 (t, 1H, J = 7.5 Hz, -CH=C-); ms m/e: 322 (M^+), 290 (M^+ – CH_3OH).

The preparation of **12***b* from **11***b* was reported in the preceding article: the same reaction procedure as described in the general procedure B was used.

(Z,E)-Diene diether ***14***

To a solution of alcohol **13** (619.2 mg, 2.9 mmol) and imidazole (453.0 mg, 6.7 mmol) in 18 mL of THF, *tert*-butylchlorodiphenylsilane (0.89 mL, 3.4 mmol) was added at 0°C under argon. The mixture was stirred for 1 h before a saturated ammonium chloride solution (25 mL) was added. The aqueous layer was extracted with a mixture of hexane and ether (2:1, 3 × 25 mL). The combined organic layers were washed with water, dried over $MgSO_4$, filtered, and concentrated to a crude residue that was purified by flash chromatography (hexane – ethyl acetate, 98:2) to give **14** (1298.7 mg, 2.88 mmol, 99%). The clear oil was used immediately for the next reaction without characterization.

Diene alcohol ***15***

The hydrolysis of the THP ether was carried out in a similar fashion as described in the general procedure A. Thus, treatment of THP ether **14** (1298.7 mg, 2.88 mmol) with pyridinium *p*-toluenesulfonate (131.0 mg) in 35 mL of isopropanol afforded alcohol **15** (911.6 mg, 2.49 mmol, 86%) as a colorless oil; ir (neat): 3340, 3040, 2950, 2860, 1450, 1375, 1110 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.08 (s, 9H, -(CH_3)$_3$C), 1.26 (t, 1H, J = 5.7 Hz, -CH_2OH), 1.70 (s, 3H, -CH_3), 4.13 (s, 2H, -CH_2OSi-), 4.34 (t, 2H, J = 6.2 Hz, -CH_2OH), 5.62 (dt, 1H, J = 10.3 Hz, 6.9 Hz, $HOCH_2CH$=CH-), 6.30–6.51 (m, 2H, $HOCH_2CH$=CHCH=C-), 7.35–7.48 and 7.65–7.73 (2m, 10H, Ph_2Si-).

Allylic chloride ***16***a

General procedure E

To a round-bottom flask containing flame-dried LiCl (69.6 mg, 1.64 mmol) was introduced, under argon, a solution of alcohol **15** (150.2 mg, 0.41 mmol) in 2.5 mL of DMF and *s*-collidine (0.11 mL, 99.9 mg, 0.82 mmol). The solution was then cooled to 0°C before methanesulfonyl chloride (63μL, 93.2 mg, 0.81 mmol) was added dropwise over 10 min. The resulting mixture was stirred at 0°C for 1 h and at 25°C for an additional hour. The reaction was stopped by adding 15 mL of ice water. The aqueous phase was extracted with ether (5 × 10 mL) and the combined organic phases were washed with cold, saturated, copper nitrate solution, and then with water. After drying over $MgSO_4$, the mixture was filtered through a short-path column containing silica gel and Celite. The filtrate was evaporated to a crude oil, **16***a* (155.7 mg, 0.40 mmol, 99%), which was used immediately for the next coupling reaction without further purification and characterization.

Allylic chloride ***18***

The preparation of allylic chloride **18** was accomplished in a similar fashion as described in the general procedure E. Thus, treatment of allylic alcohol **17** (2.2 g, 10.4 mmol) with LiCl (1.32 g, 31.2 mmol), *s*-collidine (2.1 mL, 15.6 mmol), and methanesulfonyl chloride (1.2 mL, 15.6 mmol) in DMF (37 mL) at 0°C yielded **18** (2.4 g) as a crude oil that was used immediately in the coupling reaction without further purification and characterization.

Mesylate triene ***19***a

General procedure F

To a stirred suspension of NaH (12.3 mg, 60%, 0.31 mmol) in 2 mL of THF was added at 0°C under argon a solution of dimethyl malonate **12***a* (90.1 mg, 0.28 mmol) in 2 mL of THF. The mixture was stirred at 0°C for 45 min, at room temperature for 30 min, and then cooled to 0°C. A solution of the crude allylic chloride **16***a* (155.7 mg, 1.40 mmol) in 4 mL of DMF was introduced dropwise by syringe. The stirring was continued at 0°C for 2 h and then at room temperature for 15 h. The mixture was poured into a saturated ammonium chloride solution (15 mL). The aqueous layer was extracted with ether–hexane (2:1, 4 × 10 mL). The combined organic phases were washed with H_2O, $NaHCO_3$ solution (5%), and brine and dried over $MgSO_4$. After removal of the solvents, the residue was purified by flash chromatography (hexane – ethyl acetate, 85:15) to give triene **19***a* (127.1 mg, 0.19 mmol, 68%) along with recovered starting material (12.6 mg, 14%); ir (neat): 3060–3020, 2950, 2855, 1732, 1430, 1360, 1175, 1110 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.08 (s, 9H, -(CH_3)$_3$C), 1.68 (s, 3H, -CH_2C(CH_3)=$CHCH_2$-), 1.65–1.75 (m, 4H, -CH_2CH_2C-(CH_3)=CH-), 1.90 (s, 3H, -CH-CHCH=C(CH_3)-), 2.36 (q, 2H, J = 7.2 Hz, -$CH_2CH_2OSO_2$-), 2.85 (d, 2H, J = 8.1 Hz, -CH_2CH=CHCH=C-), 2.97 (s, 3H, $-SO_2CH_3$), 3.71 (s, 6H, 2× -OCH_3), 4.13 (s, 2H, -CH_2OSi-), 4.14 (t, 2H, J = 7.0 Hz, -CH_2SO_2-), 5.10 (t, 1H, J = 7.0 Hz, -CH_2C(CH_3)=$CHCH_2$-), 5.24 (dt, 1H, J = 11.0 Hz, 6.0 Hz, -CH=CHCH=C-), 6.38 (t, 1H, J = 11.2 Hz, -CH=CHCH=C-), 6.52 (d, 1H, J = 11.3 Hz, -CH=CHCH=C-), 7.35–7.45 and 7.65–7.71 (2m, 10H, Ph_2Si-); ms m/e: 670 (M^+), 613 (M^+ – C_4H_9).

Mesylate triene ***19***b

A similar procedure as that described above was employed. Thus, treatment of **12***a* (110 mg, 0.34 mmol) with NaH (15 mg, 60%, 0.63 mmol), followed by allylic chloride **16***b* (162 mg, 0.42 mmol) in a mixture of THF and DMF, afforded triene **19***b* (175 mg, 77%) as a colorless oil; ir (neat): 3070–3020, 2950, 2860, 1730, 1428, 1357, 1174, 1110 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.04 (s, 9H, -(CH_3)$_3$C), 1.64 (d, 3H, J = 1.2 Hz, -CH_2CH_2C(CH_3)=), 1.84–1.86 (m, 7H, -CH_2CH_2- and -CH=CHCH=C(CH_3)-), 2.35 (q, 2H, J = 6.3 Hz, -CH_2CH_2OMs), 2.60 (d, 2H, J = 7.6 Hz, -CH_2CH=CHCH=C-), 2.97 (s, 3H, $-SO_2CH_3$), 3.68 (s, 6H, 2 × -OCH_3), 4.12 (t, 2H, J = 6.8 Hz, -CH_2OMs), 4.25 (s, 2H, -CH_2OSi-), 5.08 (t, 1H, J = 7.4 Hz, -CH_2CH_2CH=), 5.32 (dt, 1H, J = 14.8 Hz, 7.4 Hz, -CH=CHCH=C-), 5.80 (d, 1H, J = 11.0 Hz, -CH=CHCH=C-), 6.08 (dd, 1H, J = 14.8 Hz, 11.0 Hz, -CH=CHCH=C-), 7.35–7.44 and 7.65–7.70 (m, 10H, Ph_2Si-); ms m/e: 670 (M^+), 613 (M^+ – C_4H_9).

Mesylate triene ***19***c

The general procedure F described above was employed. Thus, treatment of **12***a* (380.1 mg, 1.18 mmol) with NaH (52.4 mg, 60%, 1.31 mmol), followed by crude allylic chloride **16***c* (589.9 mg, 1.53 mmol) in a mixture of THF and DMF, furnished triene **19***c* (461.9 mg, 0.69 mmol, 59%) along with recovered starting material (121.3 mg, 32%); ir (neat): 3070–3020, 2950, 2858, 1735, 1440, 1360, 1265, 1170, 1110 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.06 (s, 9H, -(CH_3)$_3$C), 1.70, (s, 3H, -CH_2CH=C(CH_3)CH_2-), 1.71 (s, 3H, -CH=CHCH=C(CH_3)-), 1.90–1.94 (m, 4H, =C(CH_3)CH_2CH_2-), 2.40 (q, 2H, J = 7.0 Hz, -CH_2CH_2OMs), 2.75 (d, 2H, J = 7.5 Hz, -CH_2CH=CHCH=C), 2.98 (s, 3H, $-SO_2CH_3$), 3.74 (s, 6H, 2× -OCH_3), 4.07 (s, 2H, -CH_2OSi-), 4.16 (t, 2H, J = 6.8 Hz, -CH_2OMs), 5.12 (t, 1H, J = 6.7 Hz, -CH_2CH_2CH=), 5.43 (dt, 1H, J = 14.9 Hz, 7.4 Hz, -CH=CHCH=C-), 6.08 (d, 1H, J = 10.0 Hz, -CH=CHCH=C-), 6.36 (dd, 1H, J = 15.0 Hz, 11.0 Hz, -CH=CHCH=C-), 7.35–7.44 and 7.65–7.70 (m, 10H, Ph_2Si-); ms m/e: 670 (M^+), 639 (M^+ – OCH_3), 613 (M^+ – C_4H_9).

Dimethyl malonate triene ***20***a

The general procedure C described before was employed. Thus, treatment of dimethyl malonate (0.11 mL, 127.1 mg, 0.96 mmol) with NaH (33.6 mg, 60%, 0.84 mmol), followed by mesylate triene **19***a* (125.2 mg, 0.19 mmol) and KI (3.1 mg, 19 μmol) in a mixture of THF and DMF (1:1, 8 mL), at 80°C for 20 h yielded dimethyl malonate triene **20***a* (121.0 mg, 0.17 mmol, 90%) as a

viscous oil, which was used for the following reaction without characterization.

Dimethyl malonate triene ***20***b

The general procedure C described before was employed. Thus, treatment of dimethyl malonate (0.145 mL, 1.3 mmol) with NaH (45 mg, 60%, 1.1 mmol), followed by mesylate triene **19***b* (170 mg, 0.253 mmol) and KI (4.2 mg, 25 μmol) in a mixture of THF and DMF (8 mL), at 85°C for 16 h yielded **20***b* (136 mg, 76%) as a viscous oil; ir (neat): 3070–3000, 2950, 2855, 1735, 1435, 1200, 1110 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.04 (s, 9H, -(CH_3)$_3$C), 1.60 (s, 3H, -$CH_2CH_2C(CH_3)$=), 1.80 (s, 4H, -CH_2CH_2-CR(CO_2CH_3)$_2$), 1.85 (s, 3H, =CHCH=C(CH_3)-), 1.92 (m, 4H, -CH_2CH_2CH-(CO_2CH_3)$_2$), 2.58 (d, 2H, J = 7.5 Hz, =CHCH_2CR(CO_2CH_3)$_2$), 3.33 (t, 1H, J = 7.1 Hz, -CH(CO_2CH_3)$_2$), 3.67, 3.71 (2s, 12H, 4 × -OCH_3), 4.25 (s, 2H, -CH_2OSi-), 5.04 (t, 1H, J = 7.0 Hz, -CH_2CH_2CH=), 5.33 (dt, 1H, J = 14.9 Hz, 7.6 Hz, -CH_2CH=CH-), 5.80 (d, 1H, J = 11.2 Hz, =CHCH=C(CH_3)-), 6.07 (dd, 1H, J = 14.7 Hz, 11.0 Hz, -CH_2CH=CH-), 7.34–7.47 and 7.64–7.70 (2m, 10H, *Ph*Si-); ms *m/e*: 706 (M^+), 675 ($M^+ - OCH_3$), 649 ($M^+ - C_4H_9$).

Dimethyl malonate triene ***20***c

The general procedure **20***c* described before was employed. Thus, treatment of dimethyl malonate (0.231 mL, 2.02 mmol) with NaH (71.8 mg, 60%, 1.80 mmol), followed by mesylate triene **19***c* (267.3 mg, 0.40 mmol) and KI (6.6 mg, 0.04 mmol) in a mixture of THF and DMF (1:1, 18 mL), at 85°C for 15 h yielded **20***c* (256.2 mg, 0.36 mmol, 91%) as a viscous oil; ir (neat): 3070–3000, 2950, 2855, 1740, 1435, 1340, 1200, 1110 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.06 (s, 9H, -(CH_3)$_3$C), 1.68 (br, s, 7H, -CH_2CH=C(CH_3)-CH_2CH_2-), 1.87 (s, 3H, =CHCH=C(CH_3)-), 1.88–2.01 (m, 4H, -CH_2CH_2CH=), 2.73 (d, 2H, J = 7.5 Hz, -CH=CHCH_2-), 3.35 (t, 1H, J = 7.2 Hz, -CH(CO_2CH_3)$_2$), 3.72 and 3.74 (2s, 12H, 4 × -OCH_3), 4.07 (s, 2H, -CH_2OSi-), 5.07 (t, 1H, J = 6.8 Hz, -CH_2C(CH_3)=C$H$$CH_2$-), 5.43 (dt, 1H, J = 14.7 Hz, 7.1 Hz, -CH=CHCH=C-), 6.07 (d, 1H, J = 11.0 Hz, -CH=CHCH=C-), 6.35 (dd, 1H, J = 14.6 Hz, 10.8 Hz, -CH=CHCH=C-), 7.34–7.47 and 7.64–7.70 (2m, 10H, Ph_2Si-); ms *m/e*: 706 (M^+), 675 ($M^+ - OCH_3$), 649 ($M^+ - C_4H_9$).

Allylic alcohol ***21***a

The general procedure D described before was employed. Thus, treatment of silyl ether **20***a* (121.0 mg, 0.17 mmol) with nBu$_4$NF (1 M in THF, 0.37 mL, 0.37 mmol) in 3 mL of THF at room temperature for 5 h yielded allylic alcohol **21***a* (70.6 mg, 0.15 mmol, 88%) as a viscous oil; ir (neat): 3530, 3020, 1950, 1860, 1735, 1438, 1200, 1100 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.65 (s, 3H, -(CH_3)C=CH-), 1.76 (s, 3H, -CH=CHCH=C(CH_3)-), 1.78–2.02 (m, 9H, -CH_2CH_2C(CH_3)=CHCH_2CH_2- and -CH_2OH), 2.84 (d, 2H, J = 7.5 Hz, -CH_2CH=CHCH=), 3.34 (t, 1H, J = 7.2 Hz, -CH(CO_2CH_3)$_2$), 3.72 and 3.73 (2s, 12H, 4 × -OCH_3), 4.10 (d, 2H, J = 5.6 Hz, -CH_2OH), 5.06 (t, 1H, J = 6.0 Hz, -CH_2C(CH_3)=C$H$$CH_2$-), 5.21–5.34 (m, 1H, -$CH$=CHCH=), 6.28–6.39 (m, 2H, -CH=CHCH=); ms *m/e*: 468 (M^+), 466 ($M^+ - H_2$), 450 ($M^+ - H_2O$). Exact Mass ($M^+ - H_2$) calcd.: 466.2203; found: 466.2195.

Allylic alcohol ***21***b

The general procedure D described before was employed. Thus, treatment of silyl ether **20***b* (112 mg, 0.159 mmol) with nBu$_4$NF (1.0 M in THF, 0.286 mL, 0.286 mmol) in 2 mL of THF at room temperature for 2.5 h yielded allylic alcohol **21***b* (45 mg, 60%) as a colorless oil; ir (neat): 3500, 2950, 2860, 1735, 1435, 1200 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.65 (d, 3H, J = 1.0 Hz, -CH_2C(CH_3)=CHCH_2-), 1.85 (br s, 7H, -CH_2CH_2CR(CO_2CH_3)$_2$ and =CHCH=C(CH_3)-), 1.89–2.00 (m, 4H, -CH_2CH_2CH-(CO_2CH_3)$_2$), 2.70 (d, 2H, J = 7.5 Hz, =CHCH_2CR(CO_2CH_3)$_2$), 3.35 (t, 1H, J = 7.2 Hz, -CH(CO_2CH_3)$_2$), 3.73 (s, 12H, 4 × -OCH_3), 4.22 (s, 2H, -CH_2OH), 5.06 (t, 1H, J = 6.0 Hz, -CH_2CH_2CH=), 5.41 (dt, 1H, J = 14.9 Hz, 7.5 Hz, -CH_2-CH=CH-), 5.89 (d, 1H, J = 10.9 Hz, -CH=CHCH=C-), 6.40 (dd, 1H, J = 14.9 Hz, 11.1 Hz, -CH=CHCH=C-); ms *m/e*: 450 ($M^+ - H_2O$).

Allylic alcohol ***21***c

The general procedure D described before was employed. Thus, treatment of silyl ether **20***c* (406.1 mg, 0.57 mmol) with nBu$_4$NF (1.0 M in THF, 1.15 mL, 1.15 mmol) in 8 mL of THF at room temperature for 2 h yielded allylic alcohol **21***c* (241.1 mg, 0.515 mmol, 90%) as a viscous oil; ir (neat): 3530, 3020, 2960, 2855, 1435, 1440, 1220, 1170 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.66 (s, 3H, -CH_2CH=C(CH_3)CH_2-), 1.76 (s, 3H, -CH=CHCH=C(CH_3)-), 1.83–2.02 (m, 9H, -CH_2CH_2CH=C(CH_3)CH_2CH_2- and -CH_2OH), 2.74 (d, 2H, J = 7.6 Hz, -CH_2CH=CHCH=), 3.34 (t, 1H, J = 7.1 Hz -CH(CO_2CH_3)$_2$), 3.73 (s, 12H, 4 × -OCH_3), 4.05 (d, 2H, J = 6.2 Hz, -CH_2OH), 5.09 (t, 1H, J = 6.2 Hz, -CH_2CH=C(CH_3)CH_2-), 5.49 (dt, 1H, J = 15.0 Hz, 7.5 Hz, -CH=CHCH=), 6.03 (d, 1H, J = 10.7 Hz, -CH=CHCH=C(CH_3)-), 6.35 (dd, 1H, J = 15.0 Hz, 10.8 Hz, -CH=CHCH=C-); ms *m/e*: 468 (M^+), 450 ($M^+ - H_2O$).

Allylic bromide ***22***a

General procedure G

To a stirred solution of allylic alcohol **21***a* (52.5 mg, 0.11 mmol) and CBr_4 (42.0 mg, 0.127 mmol) in 1.2 mL of CH_2Cl_2 was added dropwise at 0°C under argon over a period of 15 min a solution of PPh_3 (37.6 mg, 0.143 mmol) in 0.7 mL of CH_2Cl_2. The resulting mixture was allowed to warm to room temperature and then stirred for 2 h. The volatile was evaporated to dryness and the residue was purified by flash chromatography (hexane – ethyl acetate) using a short-path column to afford allylic bromide **22***a* (43.2 mg, 0.081 mmol, 74%) and recovered starting material **21***a* (8.8 mg, 17%). Compound **22***a* was used immediately for the next macrocyclization without characterization.

Allylic chloride ***22***b

The general procedure E described before was employed. Thus, treatment of allylic alcohol **21***b* (45 mg, 96 μL) with LiCl (12.7 mg, 288 μmol), *s*-collidine (38 μL, 288 mmol), and methanesulfonyl chloride (22 μL, 288 mmol) in DMF (0.5 mL) at 0°C for 6 h yielded allylic chloride **22***b* as a crude oil (45 mg), which was used immediately in the cyclization step without further purification and characterization.

Allylic bromide ***22***c

The general procedure G described before was employed. Thus, treatment of alcohol **21***c* (46.4 mg, 99 μmol) with CBr_4 (37.8 mg, 114 μmol) and PPh_3 (33.8 mg, 129 μmol) in 1.6 mL of CH_2Cl_2 at room temperature for 2 h yielded allylic bromide **22***c* (46.0 mg, 87 μmol, 87%) as an oil; ir (neat): 3030, 2950, 2860, 1740, 1440, 1250, 1200 cm^{-1}; ^1H nmr (C_6D_6) δ: 1.59 (s, 3H, -CH_2CH=C(CH_3)CH_2-), 1.64 (s, 3H, -CH=CHCH=C(CH_3)-), 1.94–2.21 (m, 8H, -CH_2CH_2CH=C(CH_3)CH_2CH_2-), 2.91 (d, 2H, J = 7.5 Hz), 3.34 and 3.38 (2s, 12H, 4 × -OCH_3), 3.41 (t, 1H, J = 7.0 Hz, -CH(CO_2CH_3)$_2$), 3.59 (s, 2H, -CH_2Br), 5.01 (t, 1H, J = 6.0 Hz, -CH_2CH=C(CH_3)CH_2-), 5.65 (dt, 1H, J = 15.0 Hz, 7.6 Hz, -CH=CHCH=), 5.78 (d, 1H, J = 10.9 Hz, -CH=CHCH=C(CH_3)-), 6.20 (dd, 1H, J = 15.0 Hz, 10.9 Hz, -CH=CH=); ms *m/e*: 532 (M^+), 530 (M^+), 501 ($M^+ - OCH_3$), 499 ($M^+ - OCH_3$), 451 ($M^+ - Br$).

CTC macrocycle ***1***a

General procedure H

To a stirred suspension of Cs_2CO_3 (152.0 mg, 0.467 mmol) in THF–DMF (1:1, 40 mL) at 74°C was added slowly, by automatic syringe pump over a period of 5.5 h under argon, a solution of allylic bromide **22***a* (43.2 mg, 81 μL) in THF–DMF (1:1, 15 mL). After completion of the addition, the stirring was continued for 17 h at 74°C. The solid was removed by filtration and the filtrate was evaporated to dryness, in vacuo. The crude residue thus obtained was purified by flash chromatography (hexane – ethyl ace-

tate, 5:1) to give cyclized product **1***a* (32.9 mg, 73 μmol, 90%) as a solid; mp 185–187°C; ir (neat): 3025, 2950, 2850, 1735, 1448, 1275, 1220, 1170, 1070 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.56 (s, 3H, $-CH_2CH{=}C(CH_3)CH_2-$), 1.66 (s, 3H, $=CHCH{=}C(CH_3)-$), 1.70–1.98 (m, 8H, $-CH_2CH_2CH{=}C(CH_3)CH_2CH_2-$), 2.85 (d, 2H, J = 7.8 Hz, $-CH_2CH{=}CH-$), 2.86 (s, 2H, $-CH_2C(CH_3){=}$), 3.72–3.74 (2s, 12H, 4 × $-OCH_3$), 5.00 (q, 1H, J = 8.8 Hz, $-CH{=}CHCH{=}$), 5.11 (t, 1H, J = 6.0 Hz, $-CH_2CH{=}C(CH_3)CH_2-$), 6.27–6.45 (m, 2H, $-CH{=}CHCH{=}$), ms *m/e*: 450 (M^+), 435 ($M^+ - CH_3$), 432 ($M^+ - H_2O$), 418 ($M^+ - CH_3OH$). Exact Mass (M^+) calcd.: 450.2253; found: 450.2250. The structure of compound **1***a* was further confirmed by X-ray crystallography.

TCC macrocycle ***1***b

The general procedure H described above was employed. Thus, a solution of crude allylic chloride **22***b* (45 mg) in THF–DMF (1:1, 6 mL) was added slowly at 70°C over a period of 1.5 h to a Cs_2CO_3 (150 mg, 0.46 mmol) suspension in THF–DMF (1:1, 50 mL). The stirring was continued for an additional 2.5 h after addition. Work-up of the reaction mixture followed by flash chromatography and crystallization (CH_2Cl_2–hexane) furnished a crystalline compound **1***b* (27 mg, 63% for two steps from alcohol **21***b*); mp 178–181°C; ir ($CHCl_3$): 3035–3000, 2950, 2860, 1730, 1435, 1220 cm^{-1}; ^1H nmr (C_6D_6): δ: 1.52 (s, 3H, $-CH_2CH_2C(CH_3){=}$), 1.57 (s, 3H, $=CHCH{=}C(CH_3)-$), 1.76–2.32 (m, 8H, $-CH_2CH_2CH{=}C(CH_3)CH_2CH_2-$), 2.88–3.30 (m, 4H, $-H_2CH{=}CHCH{=}C(CH_3)CH_2-$), 3.32 and 3.34 (2s, 12H, 4 × $-OCH_3$), 4.98 (t, 1H, J = 6.6 Hz, $-CH_2CH_2CH{=}$), 5.38 (dt, 1H, J = 15.0 Hz, 7.7 Hz, $-CH_2CH{=}CH-$), 5.80 (d, 1H, J = 11.0 Hz, $-CH{=}CHCH{=}C-$), 6.32 (dd, 1H, J = 14.7 Hz, 11.1 Hz, $-CH{=}CHCH{=}C-$); ms *m/e*: 450 (M^+). Exact Mass (M^+) calcd.: 450.2253; found: 450.2250. The structure of this compound was further confirmed by X-ray crystallography.

TTC macrocycle ***1***c

The general procedure H described above was employed. Thus, a solution of allylic bromide **22***c* (42.8 mg, 80.6 μmol) in THF–DMF (1:1, 10 mL) was added slowly at 72°C over a period of 13.5 h to a Cs_2CO_3 (131.0 mg, 402.0 μmol) suspension in THF–DMF (1:1, 34 mL). The stirring was continued for an additional 36 h after completion of the addition. Work-up of the reaction mixture followed by flash chromatography (hexane – ethyl acetate; 5:1) furnished macrocycle **1***c* (28.0 mg, 62.2 μmol, 77%) and by-product **23** (1.0 mg, 2.2 mmol, 3%).

Compound ***1***c: mp 115–117°C; ir (neat): 3025, 2950, 1740, 1440, 1240 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.64 (s, 3H, $-CH_2CH{=}C(CH_3)-CH_2-$), 1.67 (s, 3H, $-CH{=}CHCH{=}C(CH_3)-$), 1.68–2.50 (br m, 8H, $-CH_2CH_2CH{=}C(CH_3)CH_2CH_2-$), 2.60–3.22 (br m, 4H, $-CH_2CH{=}CHCH{=}C(CH_3)CH_2-$), 3.72 and 3.74 (2s, 12H, 4 × $-OCH_3$), 5.01 (t, 1H, J = 6.0 Hz, $-CH_2CH{=}C(CH_3)CH_2-$), 5.80 (dt, 1H, J = 15.1 Hz, 7.6 Hz, $-CH{=}CHCH{=}$), 6.10 (d, 1H, J = 10.9 Hz, $-CH{=}CHCH{=}$), 6.29 (dd, 1H, J = 14.6 Hz, 10.8 Hz, $-CH{=}CHCH{=}$); ms *m/e*: 450 (M^+), 445 ($M^+ - CH_3$), 442 ($M^+ - H_2O$), 418 ($M^+ - CH_3OH$). Exact Mass (M^+) calcd.: 450.2253; found: 450.2250.

Compound ***23***: mp 140–142°C; ir (neat): 3090–3000, 2960, 2860, 1740, 1450, 1200 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.40–1.85 and 1.95–2.27 (2m, 8H, $-CH_2CH_2CH{=}C(CH_3)CH_2CH_2-$), 1.67 and 1.72 (2s, 6H, $=C(CH_3)-$ and $CH_2{=}C(CH_3)-$), 2.58–2.70 and 2.88–3.00 (2m, 2H, $-CH_2CH{=}CH-$), 3.61–3.67 (m, 1H, $-CHRC(CH_3){=}CH_2$), 3.71, 3.73, 3.74 (3s, 12H, 4 × $-OCH_3$), 4.74 and 4.86 (2s, 2H, $-C(CH_3){=}CH_2$), 5.18 (t, 1H, J = 7.2 Hz, $-CH{=}C(CH_3)-$), 5.49 (dt, 1H, J = 15.4 Hz, 7.8 Hz, $-CH_2CH{=}CH-$), 6.10 (dd, 1H, J = 15.4 Hz, 7.7 Hz, $-CH_2CH{=}CH-$); ms *m/e*: 450 (M^+). Exact Mass (M^+) calcd. 450.2253; found: 450.2258.

Triene diether ***25***

The general procedure F previously described was employed. Thus, treatment of dimethyl malonate **24** (2.89, 7.8 mmol) with NaH (344 mg, 60% in oil, 14.3 mmol), followed by crude allylic chloride **18** (2.2 g, 9.4 mmol) in a mixture of THF and DMF (1:1, 180 mL) at room temperature for 16.5 h, yielded acyclic triene **25** (1.5 g, 35%) as a colorless oil; ir (neat): 2950, 2860, 1738, 1450, 1200, 1110 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 0.04 (s, 6H, $(CH_3)_2Si-$), 0.88 (s, 9H, $-(CH_3)_3C$), 1.64 (d, 3H, J = 1.3 Hz, $-CH_2CH{=}C(CH_3)CH_2-$), 1.89 (d, 3H, J = 1.6 Hz, $=CHCH{=}C(CH_3)-$), 1.45–1.99 (m, 10H, $=C(CH_3)CH_2CH_2-$ and $-OCHOCH_2(CH_2)_3-$), 2.13 (qd, 2H, J = 7.1 Hz, 1.1 Hz, $-CH_2CH_2OSi-$), 2.90 (s, 2H, $=CHCH{=}C(CH_3)CH_2-$), 3.54 (t, 2H, J = 7.0 Hz, $-CH_2OSi-$), 3.71 (s, 6H, 2 × $-OCH_3$), 3.40–3.53 and 3.80–3.92 (2m, 2H, $-OCHOCH_2-$), 4.01 (dd, 1H, J = 12.3 Hz, 6.9 Hz, $-CHHOTHP$), 4.26 (dd, 1H, J = 12.9 Hz, 5.6 Hz, $-CHHOTHP$), 4.63 (t, 1H, J = 3.0 Hz, $-OCHO-$), 5.12 (td, 1H, J = 7.2 Hz, 1.4 Hz, $-CH_2CH_2CH{=}$), 5.70 (dt, 1H, J = 14.9 Hz, 6.5 Hz, $-CH_2CH{=}CH-$), 5.98 (d, 1H, J = 11.0 Hz, $=CHCH{=}C(CH_3)-$), 6.48 (dd, 1H, J = 15.0 Hz, 11.1 Hz, $-CH_2CH{=}CH-$); ms *m/e*: 552 (M^+), 537 ($M^+ - CH_3$), 495 ($M^+ - C_4H_9$).

Triene alcohol ***26***

The general procedure D previously described was employed. Thus, treatment of silyl ether **25** (504 mg, 0.91 mmol) with nBu$_4$NF (1 M in THF, 1.6 mL, 1.6 mmol) in 8 mL of THF at room temperature for 2 h yielded triene alcohol **26** (397 mg, 0.90 mmol, 99%) as a colorless oil, which was used in the following mesylation without further characterization.

Triene mesylate ***27***

The general procedure B previously described was employed. Thus, treatment of alcohol **26** (397 mg, 0.91 mmol) with triethylamine (0.19 mL, 1.4 mmol) and methanesulfonyl chloride (77 μL, 1.0 mmol) in CH_2Cl_2) (12 mL) at 0°C for 1 h gave mesylate **27** (480 mg) as a crude oil, which was used immediately for the following alkylation without further purification and characterization.

Dimethyl malonate triene ***28***a

The general procedure C previously described was employed. Thus, treatment of dimethyl malonate (0.52 mL, 4.6 mmol) with NaH (164 mg, 60%, 4.1 mmol), followed by mesylate **27** (480 mg, obtained as a crude oil from the above reaction) and KI (15 mg, 91 μmol) in THF–DMF (1:1, 24 mL) at 85°C for 17 h, yielded **28***a* (366 mg, 73% for two steps from alcohol **26**) as a colorless oil; ir (neat): 2950, 2860, 1734, 1437, 1210 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.64 (s, 3H, $-CH_2CH_2CH{=}C(CH_3)-$), 1.71 (s, 3H, $=CHCH{=}C(CH_3)-$), 1.45–1.80 (m, 6H, $-OCHOCH_2(CH_2)_3-$), 1.80–2.04 (m, 8H, $-CH_2CH_2CH{=}C(CH_3)CH_2CH_2-$), 2.89 (s, 2H, $=CHCH{=}C(CH_3)CH_2-$), 3.34 (t, 1H, J = 7.0 Hz, $-CH(CO_2CH_3)_2$), 3.71 and 3.73 (2s, 12H, 4 × $-OCH_3$), 3.45–3.90 (m, 2H, $-OCHOCH_2-$), 4.00 (dd, 1H, J = 12.0 Hz, 7.0 Hz, $-CHHOTHP$), 4.26 (dd, 1H, J = 13.1 Hz, 5.6 Hz, $-CHHOTHP$), 4.63 (t, 1H, J = 3.0 Hz, $-OCHO-$), 5.05 (t, 1H, J = 6.0 Hz, $-CH_2CH_2CH{=}$), 5.70 (dt, 1H, J = 15.1 Hz, 6.1 Hz, $-CH_2CH{=}CH-$), 5.97 (d, 1H, J = 11.3 Hz, $=CHCH{=}C(CH_3)-$), 6.47 (dd, 1H, J = 15.0 Hz, 11.1 Hz, $-CH_2CH{=}CH-$); ms *m/e*: 552 (M^+), 534 ($M^+ - H_2O$), 520 ($M^+ - CH_3OH$), 467 ($M^+ - THP$).

Triene allylic alcohol ***28***b

The general procedure A previously described was employed. Thus, treatment of THP ether **28***a* (366 mg, 0.663 mmol) with pyridinium *p*-toluenesulfonate (20 mg, 80 μmol) in methanol (7 mL) at 55°C for 75 min yielded allylic alcohol **28***b* (295 mg, 95%) as a viscous oil; ir (neat): 3500, 2955, 2860, 1735, 1435, 1210 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.25 (m, 1H, $-CH_2OH$), 1.64 (s, 3H, $-CH_2CH_2CH{=}C(CH_3)-$), 1.70 (s, 3H, $=CHCH{=}C(CH_3)-$), 1.78–2.04 (m, 8H, $-CH_2CH_2CH{=}C(CH_3)CH_2CH_2-$), 2.91 (s, 2H, $=CHCH{=}C(CH_3)CH_2-$), 3.43 (t, 1H, J = 7.0 Hz, $-CH(CO_2CH_3)_2$), 3.72, 3.73 (2s, 12H, 4 × $-OCH_3$), 4.19 (t, 2H, J = 5.8 Hz, $-CH_2OH$), 5.05 (t, 1H, J = 6.0 Hz, $-CH_2CH_2CH{=}$), 5.76 (dt, 1H, J = 15.0 Hz, 5.8 Hz, $-CH_2CH{=}CH-$), 5.97 (d, 1H, J = 11.1 Hz, $=CHCH{=}C(CH_3)-$), 6.49 (dd, 1H, J = 15.0 Hz, 11.1 Hz, $-CH_2CH{=}CH-$).

Allylic chloride ***29***

The general procedure E previously described was employed. Thus, treatment of allylic alcohol **28***b* (150 mg, 0.32 mmol) with LiCl (41 mg, 0.96 mmol), *s*-collidine (63 μL, 0.48 mmol), and methanesulfonyl chloride (37 μL, 0.48 mmol) in DMF (1.2 mL) at 0°C for 3 h yielded allylic chloride **29** as a crude oil (140 mg), which was used immediately in the next cyclization without purification and characterization.

TTC macrocycle ***1***d

The general procedure H previously described was employed. Thus, a solution of allylic chloride **29** (140 mg, obtained as a crude oil from the above reaction) in THF–DMF (1:1, 18 mL) was added slowly by syringe pump at 70°C over 1 h to a Cs_2CO_3 (469 mg, 1.4 mmol) suspension in THF–DMF (1:1, 50 mL). The stirring was continued for an additional 2 h after completion of the addition. Work-up of the reaction mixture followed by flash chromatography (hexane – ethyl acetate – CH_2Cl_2; 75:9:16) and crystallization (CH_3OH) provided macrocycle **1***d* (100 mg, 69% for two steps from alcohol **28***b*) as a crystalline solid; mp 167–170°C; ir ($CHCl_3$): 3030, 2960, 2860, 1730, 1450, 1215 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.57 (s, 3H, -$CH_2CH_2C(CH_3)$=), 1.66 (d, 3H, J = 1.0 Hz, =CHCH=C(CH_3)-), 1.15–1.70 (br m, 8H, -CH_2CH_2-CH=C(CH_3)CH_2CH_2-), 2.77 (d, 2H, J = 7.9 Hz, =CHCH_2CR-(CO_2CH_3)$_2$), 2.80–3.10 (m, 2H, =C(CH_3)CH_2CR(CO_2CH_3)$_2$), 3.73 (s, 12H, 4 × -OCH_3), 5.14 (m, 1H, -CH_2CH_2CH=), 5.31 (dt, 1H, J = 14.9 Hz, 7.9 Hz, -CH_2CH=CH-), 6.00 (d, 1H, J = 10.9 Hz, =CHCH=C(CH_3)-), 6.48 (dd, 1H, J = 14.8 Hz, 11.1 Hz, -CH_2CH=CH-); ms *m/e*: 450 (M^+). Exact Mass (M^+) calcd.: 450.2253; found: 450.2246. The structure of this macrocycle was further characterized by X-ray crystallography.

Diels–Alder reaction of ***1***a

A solution of macrocycle **1***a* (10.4 mg, 23.1 μmol) in 0.8 mL of toluene was sealed in a quartz tube (20 cm long, 8 mm diameter) under vacuum and then heated at 320°C for 18 h. After the tube was opened, the mixture was transferred into a flask and then evaporated to dryness. The residue thus obtained was eluted through a silica gel column (hexane – ethyl acetate, 7:3) to give a mixture (8.8 mg, 19.6 μmol, 85%), containing four tricyclic compounds **30**, **32**, **33**, and **34**. The characteristic spectral data for the mixture were obtained; ir (neat): 2960, 2870, 1735, 1440, 1250, 1170 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 0.78–1.12 (8s, -CH_3), 1.13–2.90 (m, all other CH and CH_2), 3.60–3.80 (14s, -OCH_3), 5.13–6.00 (m, -CH=CH-). The ratio for compounds **30**, **32**, **33**, and **34** was found to be 7.0:20.6:5.9:1.0 as determined by the ^1H nmr integration of their methyl peaks and olefin proton peaks. The assignment is the following:

Compound ***30***: 0.95 (s, 3H, -CH_3), 1.12 (s, 3H, -CH_3), 5.16 (d, 1H, J = 10.5 Hz, -CHRCH=CH-), 5.31 (dd, 1H, J = 10.5 Hz, 3.0 Hz, -CHRCH=CH-).

Compound ***32***: 0.78 (s, 3H, -CH_3), 1.07 (s, 3H, -CH_3), 1.12–2.68 (br m, 14H, all other CH and CH_2), 3.74, 3.72, 3.69, 3.68 (4s, 12H, 4 × -OCH_3), 5.45 (dd, 1H, J = 10.5 Hz, 1.8 Hz, -CHRCH=CH-), 5.97 (dt, 1H, J = 10.5 Hz, 1.8 Hz, -CHRCH=CH-).

Compound ***33***: 0.87 (s, 3H, -CH_3), 1.10 (s, 3H, -CH_3), 5.22 (dd, 1H, J = 10.5 Hz, 1.8 Hz, -CHRCH=CH-), 5.35 (dd, 1H, J = 10.5 Hz, 3.0 Hz, -CHRCH=CH-). The structure of this compound was further characterized by X-ray crystallography and shown to have the CSC stereochemistry.

Compound ***34***: 0.83 (s, 3H, -CH_3), 0.85 (s, 3H, -CH_3), 5.50 (dd, 1H, J = 10.5 Hz, 2.8 Hz, -CHRCH=CH-), 5.72 (dd, 1H, J = 10.5 Hz, 1.6 Hz, -CHRCH=CH-).

Separation of the four isomers from the mixture was attempted by flash chromatography with different solvent systems. A mixture of hexane and ethyl acetate (9:1) was found to be the best system, the use of which in flash chromatography of the mixture provided two fractions. Fraction 1, which contained tricycles **32** and **34**, was then purified by plate chromatography with silica gel (toluene–acetone, 9:1) to give pure tricycle **34**. Fraction 2, which contained tricycles **30** and **33**, was purified by plate chromatography with silica gel (toluene–acetone, 98:2) to give pure tricycle **33**.

Thermolysis of TTC macrocycle ***1***c

Neat macrocycle **1***c* (4.0 mg, 8.9 μmol) was sealed in a quartz tube under vacuum and then heated in an oven at 200°C for 4 h. After the tube was opened, the product was transferred into a flask with CH_2Cl_2 and then evaporated to dryness. Purification of the residue by flash chromatography (hexane – ethyl acetate; 7:3) furnished CTC macrocycle **1***a* (4.0 mg, 100%), which had spectral properties identical with the compound obtained from the cyclization of acyclic triene **22***a*.

Diels–Alder reaction of ***1***c

A solution of **1***c* (20.1 mg, 44.7 μmol) in 1.5 mL of toluene was sealed in a quartz tube under vacuum and then heated in an oven at 310°C for 18 h. After the tube was opened, the mixture was transferred into a flask and then evaporated to dryness. The ^1H nmr of the crude residue indicated the presence of the same four tricyclic compounds **30**, **32**, **33**, and **34**. The crude residue was then purified by flash chromatography (hexane – ethyl acetate, 9:1) to give two fractions (fraction 1: 3.2 mg, 7.1 μmol, 16%; fraction 2: 16.3 mg, 36.2 mmol, 81%). Fraction 1 contained tricycles **32** and **34** in a ratio of 1:5 by ^1H nmr and 1:5.6 by gc. Fraction 2 contained tricycles **30** and **33** in a ratio of 1:14 by ^1H nmr and 1:12 by gc. The overall ratio of **30**, **32**, **33**, and **34** was found to be 2.3:1.0:29.9:5.3.

Spectral data for fraction 1: ir (neat): 1960, 1860, 1740, 1440, 1250 cm^{-1}; ms *m/e*: 450 (M^+). The ^1H nmr data for fraction 1 are identical with those of tricycles **32** and **34** obtained from the Diels–Alder reaction of **1***a*.

The ir spectral data for fraction 2: (neat): 2960, 2860, 1735, 1450, 1200 cm^{-1}; ^1H nmr data for fraction 2 are identical with those of tricycles **33** and **30** obtained from the Diels–Alder reaction of **1***c*.

Diels–Alder reaction of ***1***b

The crystalline macrocycle **1***b* (11.5 mg, 26 μmol) was sealed in a quartz tube under vacuum and then heated in an oven at 320°C for 1.5 h. After the tube was opened, the mixture was transferred into a flask with CH_2Cl_2 and then evaporated to dryness. The residue thus obtained was purified by flash chromatography (hexane – ethyl acetate, 9:1) to give tricycle **30** (10 mg, 87%) as a crystalline compound: mp 68–71°C; ir ($CHCl_3$): 3022, 2950, 2870, 1730, 1435, 1250 cm^{-1}; ^1H nmr (C_6D_6) δ: 0.88 (s, 3H, -CH_3), 1.06 (s, 3H, =CHCR(CH_3)-), 1.43–2.60 (m, 14H, all CH and CH_2), 3.27, 3.28, 3.31, 3.32 (4s, 12H, 4 × -OCH_3), 5.17 (dd, 1H, J = 10.0 Hz, 1.4 Hz, -CHRCH=CH-), 5.25 (dd, 1H, J = 10.0 Hz, 2.7 Hz, -CHRCH=CH-); ms *m/e*: 450 (M^+). Exact Mass (M^+) calcd.: 450.2253; found: 450.2246. The structure of this tricycle was further characterized by X-ray crystallography.

Diels–Alder reaction of ***1***d

The crystalline macrocycle **1***d* (25.0 mg, 56 μmol) was sealed in a quartz tube under vacuum and then heated in an oven at 360°C for 1 h. After the tube was opened, the mixture was transferred into a flask with CH_2Cl_2 and then evaporated to dryness. The residue thus obtained was purified by flash chromatography (hexane – ethyl acetate, 4:1) to give tricycle **31** (22.6 mg, 90%) as a crystalline solid; mp 138–140°C; ir ($CHCl_3$): 3020, 2955, 2870, 1730, 1435, 1245 cm^{-1}; ^1H nmr (C_6D_6) δ: 0.69 (s, 3H, -CH_3), 0.78 (s, 3H, =CHCR(CH_3)-), 1.20–2.78 (m, 14H, all CH and CH_2), 3.26, 3.27, 3.30, and 3.34 (4s, 12H, 4 × -OCH_3), 5.26 and 5.31 (2d, 2H, J = 11.0 Hz, -CH=CH-); ms *m/e*: 450 (M^+). Exact Mass (M^+) calcd.: 450.2253; found: 450.2246. The structure of this compound was further characterized by X-ray crystallography.

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