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

YAO-CHANG XU, ANDREW L. ROUGHTON, RAYMOND PLANTE, SOLO GOLDSTEIN, AND PIERRE DESLONGCHAMPS[1]

Laboratoire de synthèse organique, Département de chimie, Faculté des sciences, Université de Sherbrooke, Sherbrooke (Québec), Canada J1K 2R1

Received February 18, 1992

YAO-CHANG XU, ANDREW L. ROUGHTON, RAYMOND PLANTE, SOLO GOLDSTEIN, and PIERRE DESLONGCHAMPS. Can. J. Chem. **71**, 1152 (1993).

Transannular Diels–Alder reactions of 14-membered macrocyclic trienes possessing a methyl substituent on both the diene and dienophile moiety have been investigated. Macrocyclic structures **1***a*, **1***b*, and **1***c* having *cis-trans-trans* (CTT), *trans-cis-trans* (TCT), and *trans-trans-trans* (TTT) geometries could be stereoselectively constructed by coupling appropriately functionalized dienes **5** and dienophile **4** following an intramolecular displacement of an allylic halide by the anion of an appropriately located dimethyl malonate unit. The transannular Diels–Alder reaction performed on **1***a* led to a mixture of four major tricyclic products, including **34** possessing the unexpected *trans-anti-cis* (TAC) stereochemistry. When heated at 300°C, macrocycle **1***b* underwent an unique conversion via an ene–retroene, Diels–Alder process, producing the unexpected tricycle **41** (racemic form) containing five contiguous chiral centers. A rationale for the above experimental facts is presented. In contrast to the previous results, the transannular Diels–Alder reaction of macrocycle **1***c* was straightforward, producing a 95% isolated yield of *trans-anti-cis* (TAC) tricycle **34**. This investigation demonstrates a general methodology for the stereocontrolled synthesis of 1,2-dimethyl A.B.C[6.6.6] tricyclic compounds, which are potential precursors to polycyclic natural products such as steroids and terpenes.

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La réaction de Diels–Alder transannulaire macrocycles à 14 chaînons contenant un diène et un diénophile substitués par un radical méthyl est décrite. Les macrocycles **1***a*, **1***b* et **1***c* de géométrie *cis-trans-trans* (CTT), *trans-cis-trans* (TCT), et *trans-trans-trans* (TTT) ont été préparés de manière stéréosélective par le couplage des diènes **5** et du diénophile **4** suivi par un déplacement intramoléculaire d'un halogénure allylique par l'anion d'une unité malonate. Le macrocycle **1***a* fournit par une réaction de Diels–Alder transannulaire un mélange de quatre produits tricycliques dont **34**, produit inattendu, de stéréochimie *trans-anti-cis* (TAC). Par chauffage à 300°C le macrocycle **1***b* subit une transformation unique par une suite de réactions ène–rétroène, Diels–Alder conduisant au tricycle inattendu **41** (forme racémique) qui possède cinq centres chiraux contigus. Une rationalisation de ces faits expérimentaux est proposée. Contrairement aux résultats précédents, la réaction Diels–Alder transannulaire effectuée sur le macrocycle **1***c* donna comme attendu le tricycle *trans-anti-cis* (TAC) **34** avec un rendement de 95% en produit isolé. Dès lors cette étude démontre une méthodologie générale permettant de synthétiser de manière stéréocontrôlée des structures tricycliques 1,2-diméthyl A.B.C.[6.6.6], précurseurs potentiels de produits naturels tels les stéroïdes et les terpènes.

Introduction

Recent research in our laboratories has centered on the development of general methodologies that can be used to prepare polycyclic compounds in a stereocontrolled manner (1, 2). Our approach, illustrated in Scheme 1, makes use of the transannular Diels–Alder reaction on macrocyclic trienes like **1** to give A.B.C.[6.6.6] tricyclic compounds such as **2**. The [4+2] cycloaddition adducts **2**, which possess four newly created chiral centers as well as different substituents and functional groups on the three fused six-membered rings, are potential precursors to polycyclic natural products such as steroids and terpenes (3).

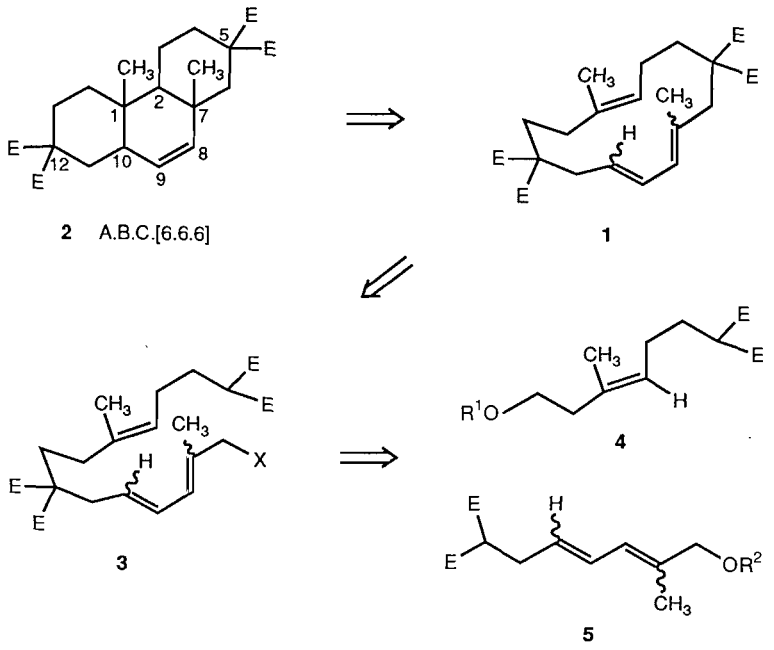
Our earlier studies (4) involving the syntheses of carbon macrocycles having various ring size (10–14 carbons) by base-assisted intramolecular displacement reaction laid the foundation for the development of this new methodology. Having successfully constructed the necessary macrocyclic triene, the first transannular Diels–Alder reaction of 13-membered macrocycles was found to produce B.C.D.[6.6.5] tricyclic compounds (2*f–j*). Further investigations of the transannular Diels–Alder cycloaddition in 14-membered macrocycles such as **1** with no methyl (2*d*, *e*) or with one methyl substituent (2*a*, *b*) showed them to be very promising for the construction of A.B.C.[6.6.6] tricyclic compounds. In both cases, racemic tricyclic products could be obtained in good yields and excellent stereoselectivities of the four contiguous asymmetric centers. In the course of our study, a total synthesis of a steroid derivative using the transannular Diels–Alder approach was reported by Takahashi et al. (5).

In this article, we would like to report further investigations (1) of the transannular Diels–Alder reaction in a 14-membered macrocycle system containing a methyl substituent on both the diene and dienophile moiety. As indicated in Scheme 1, the cycloaddition in macrocycle **1** would lead to the formation of 1,7-dimethyl tricyclic product **2**. The skeleton of such a tricyclic system having two methyl groups, on C(1) and C(7), is a common constituent of many natural diterpene and triterpene products. This study can therefore lead to the development of new strategies for the synthesis of some of these polycyclic natural products.

Methods and discussion

Our general approach towards the tricyclic compounds bearing two methyl groups at C(1) and C(7) positions is

[1]Author to whom correspondence may be addressed.



(E = $COOCH_3$)

SCHEME 1

outlined in Scheme 1. The target product **2** could be obtained by the transannular [4+2] cycloaddition in 14-membered macrocycle **1**, which, in turn, could be easily prepared from acyclic triene **3** via an intramolecular displacement of the allylic halide by base-generated dimethyl malonate anion. Triene **3** having different olefin geometries could be derived from the coupling reaction of appropriately functionalized dienes **5** and *E*-dienophile **4**.

Synthesis of E-*dienophile 4*

The basic strategy for the preparation of this trisubstituted olefin is based on the palladium-catalyzed coupling reaction of 2-carbomethoxypropyl zinc iodide **10** (6) and vinyl iodide **11** (7) as depicted in Scheme 2.

The preparation of zinc iodide **10** was readily achieved starting from commercially available γ-butyrolactone **6**. Methanolysis (methanol–pyridine) of acyl chloride **7**, which was obtained from **6** by reaction with thionyl chloride in the presence of zinc chloride (8), provided methyl 4-chlorobutyrate **8**. A halide exchange reaction on **8** (potassium iodide in acetone) gave the corresponding alkyl iodide **9**, which was treated with metal zinc at 60°C to give the desired product **10**.

The preparation of vinyl iodide **11** was realized stereoselectively starting from 4-butynol using Negishi's procedures (7) followed by silylation (9) of the primary alcohol. The coupling reaction of **11** and **10** provided *E*-dienophile **12**, no *Z* isomer being observed by nmr spectroscopy. The desired malonate **4** was obtained by treatment of **12** with lithium diisopropylamide followed by the addition off methyl chloroformate (10).

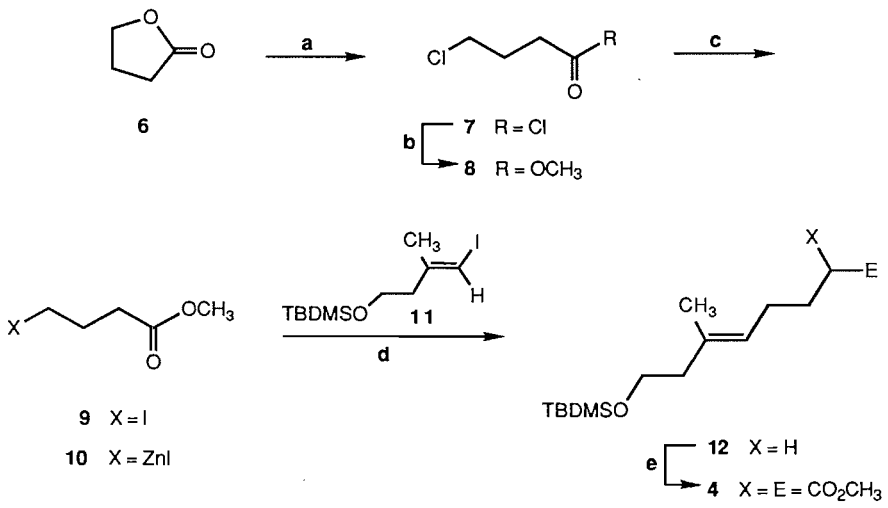
Syntheses of dienes 5

The syntheses of 2-methyl-substituted 2,4-diene **5***a* (*Z-E*), **5***b* (*E-Z*), and **5***c* (*E-E*) are outlined in Scheme 3 starting from the commercially available *Z*-2-butene-1,4-diol **13**. Swern oxidation of the monoprotected diol **14** (11) led to the α,β-unsaturated aldehyde **15***a* with the *Z*-olefin geometry retained (12). The selective *E* olefination of the aldehyde was performed via a Wittig–Horner–Emmons reaction with ethyldiisopropyl-2-phosphonopropionate and sodium hydride to provide the *Z-E* diene **16***a* (13), which was subsequently converted to the allylic alcohol **17***a* by diisobutylaluminium hydride (DIBAL-H) reduction. The desired allylic chloride **5***a* was finally obtained from **17***a* via Meyers' procedures (lithium chloride, methanesulfonyl chloride, and *s*-collidine in dimethylformamide (DMF) (14)).

Oxidation of mono-protected diol **14** with pyridinium chlorochromate at room temperature yielded the thermodynamically stable *E*-unsaturated aldehyde **15***b* (15), isomer of **15***a*. Condensation of **15***b* with ethyl bis(trifluoroethyl)-2-phosphonopropinate following Still's procedure (16) gave stereoselectively *E-Z* diene ester **16***b*, which was then reduced to alcohol **17***b* by diisobutylaluminium hydride. Protection of the allylic alcohol with *tert*-butyldiphenylchlorosilane in the presence of triethylamine (17) resulted in the formation of silyl ether **18***b*. Treatment of **18***b* with pyridinium *p*-toluenesulfonate in isopropanol selectively removed the tetrahydropyranyl ether to produce allylic alcohol **19***b*,[2] which was converted to allylic chloride **5***b* by the use of the previously mentioned Meyers' method (14).

Similarly, treatment of **15***b* with Wittig reagent derived from ethydiisopropyl-2-phosphonopropionate afforded the *E-E* diene ester **16***c* (13). This stereoselective *E*-olefination reaction from **15***b* to **16***c* could also be realized in good yield by commercially available triethyl-2-phosphonopropionate and sodium hydride. Diisobutylaluminium hydride reduc-

[2]L. Ruest, S. Lamothe, and P. Deslongchamps. Unpublished results.



(a) $SOCl_2$, $ZnCl_2$, 55°C, 22 h, 65%;

(b) CH_3OH, Pyridine, 0°C to r.t., 18 h, 77%;

(c) NaI, acetone, reflux, 42 h, 78%;

(d) Zn-Cu, **9**, benzene/DMF, 25°C, 1 h, 60°C, 3 h; then $Pd(PPh_3)_4$, **13**, 60°C, 1 h, 65%;

(e) LDA, -78°C, 0.5 h; then $ClCO_2CH_3$, 67%.

SCHEME 2

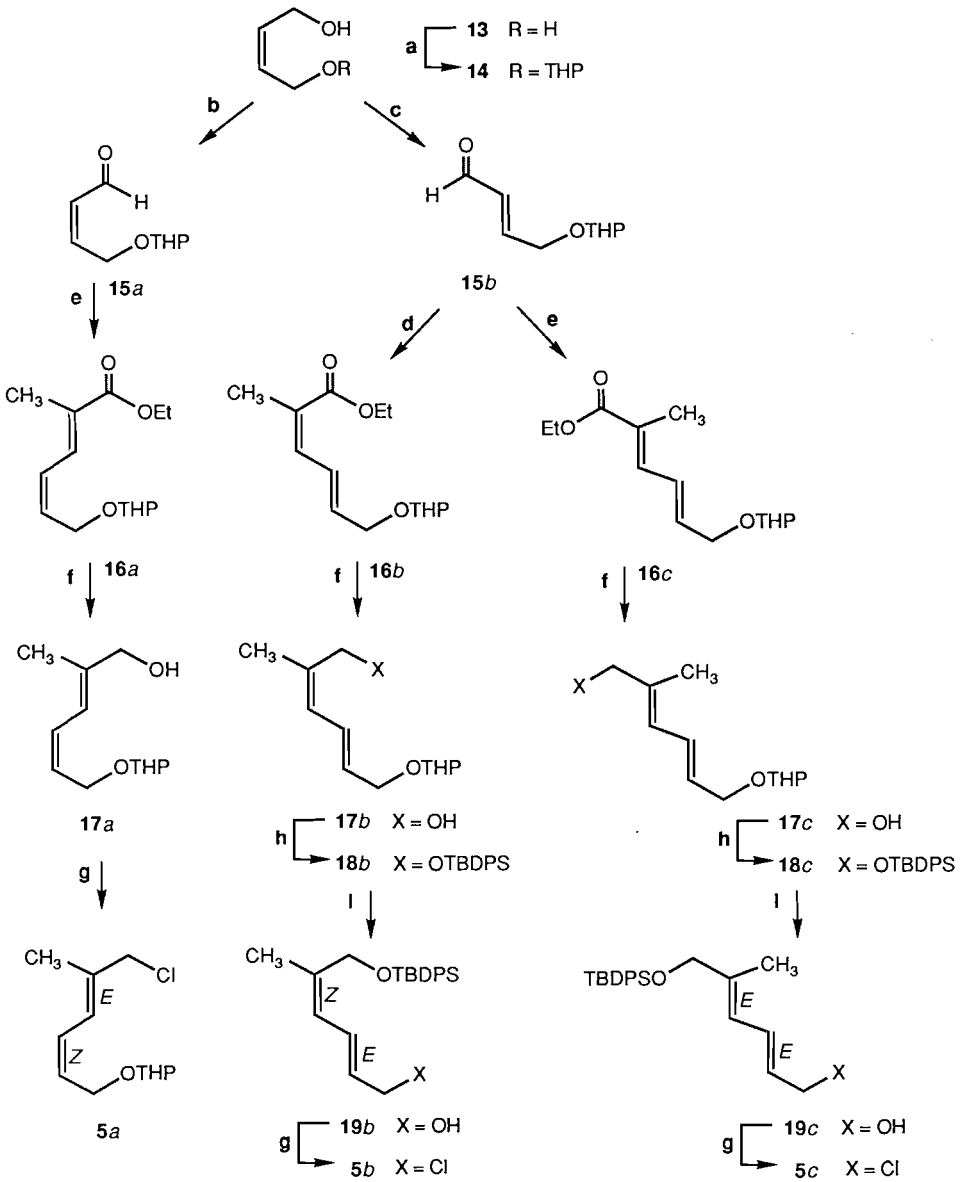
tion of **16***c* followed by protection of the resulting allylic alcohol with *tert*-butyldiphenylchlorosilane (17) yielded diene diether **18***c*. Selective removal of the tetrahydropyranyl ether was realized by the previously mentioned method[2] to afford allylic alcohol **19***c*, which was then converted to allylic chloride **5***c* having the *E-E* diene geometry (14).

Preparations of macrocycles 1

The precursors of macrocycles **1***b* (*trans-cis-trans*, TCT) and **1***c* (*trans-trans-trans*, TTT), namely acyclic trienes **22***b* and **22***c*, are readily synthesized by coupling the appropriately functionalized basic building blocks, dienes **5***b* and **5***c*, with dienophile **4**. Thus, deprotection of *E*-dienophile **4** with tetrabutylammonium fluoride (18) provided alcohol **20**, which was subsequently transformed into the methanesulfonate ester **21** with methanesulfonyl chloride and triethylamine (Scheme 4). The coupling reactions were performed by treatment of dienophile **21** with sodium hydride to form the sodium enolate, followed by addition of dienes **5***b* and **5***c* to produce alkylated products **22***b* and **22***c*, respectively, in good yields (19). Introduction of the second malonate connector into the acyclic trienes was accomplished by displacement of the methanesulfonate ester group of trienes **22***b* and **22***c* with the sodium salt of dimethyl malonate in the presence of potassium iodide. The cleavage of the silyl ether protecting group of trienes **23***b* and **23***c* was effected with *n*-Bu_4NF in good yields (18). The resulting allylic alcohol **24***b* was then transformed into the corresponding allylic chloride **25***b* by Meyers' procedure (14), while the allylic alcohol **24***c* was converted to the allylic bromide **25***c* using carbon tetrabromide and triphenylphosphine in dichloromethane (20). A slight decomposition was observed when allylic halides **25***b* and **25***c* were submitted to purification by flash chromatography. This problem, however, could be avoided if the crude allylic halides were filtered through a short-path silica gel column and used for the next reaction immediately without purification by chromatography.

Having built the requisite carbon chain and appropriate functional groups at each end, acyclic trienes **25***b* and **25***c* were ready for the construction of 14-membered macrocycles. The macrocyclizations were performed by slow addition of a solution of allylic chloride **25***b* or allylic bromide **25***c* in tetrahydrofuran to a stirred suspension of cesium carbonate in a mixture of DMF and THF at about 80°C under dilution conditions so as to avoid dimerization (2). Macrocyclic products **1***b* (TCT) and **1***c* (TTT) were respectively obtained in good yields, as white solids, via an intramolecular displacement of allylic halides by base-generated dimethyl malonate anion. Small quantities (≤10%) of the corresponding macrocyclic dimers **26***b* and **26***c* were also isolated. The structures of macrocycles **1***b* and **1***c* were established by spectroscopic characterization including carbon-13 and proton nmr, infrared, and mass spectra. The conservation of the double bond geometries in the cyclization has been clearly established by comparing the proton nmr data of the cyclic products with those of their acyclic triene precursor. Furthermore, the structure of macrocycle **1***b* was confirmed by X-ray analysis (21).

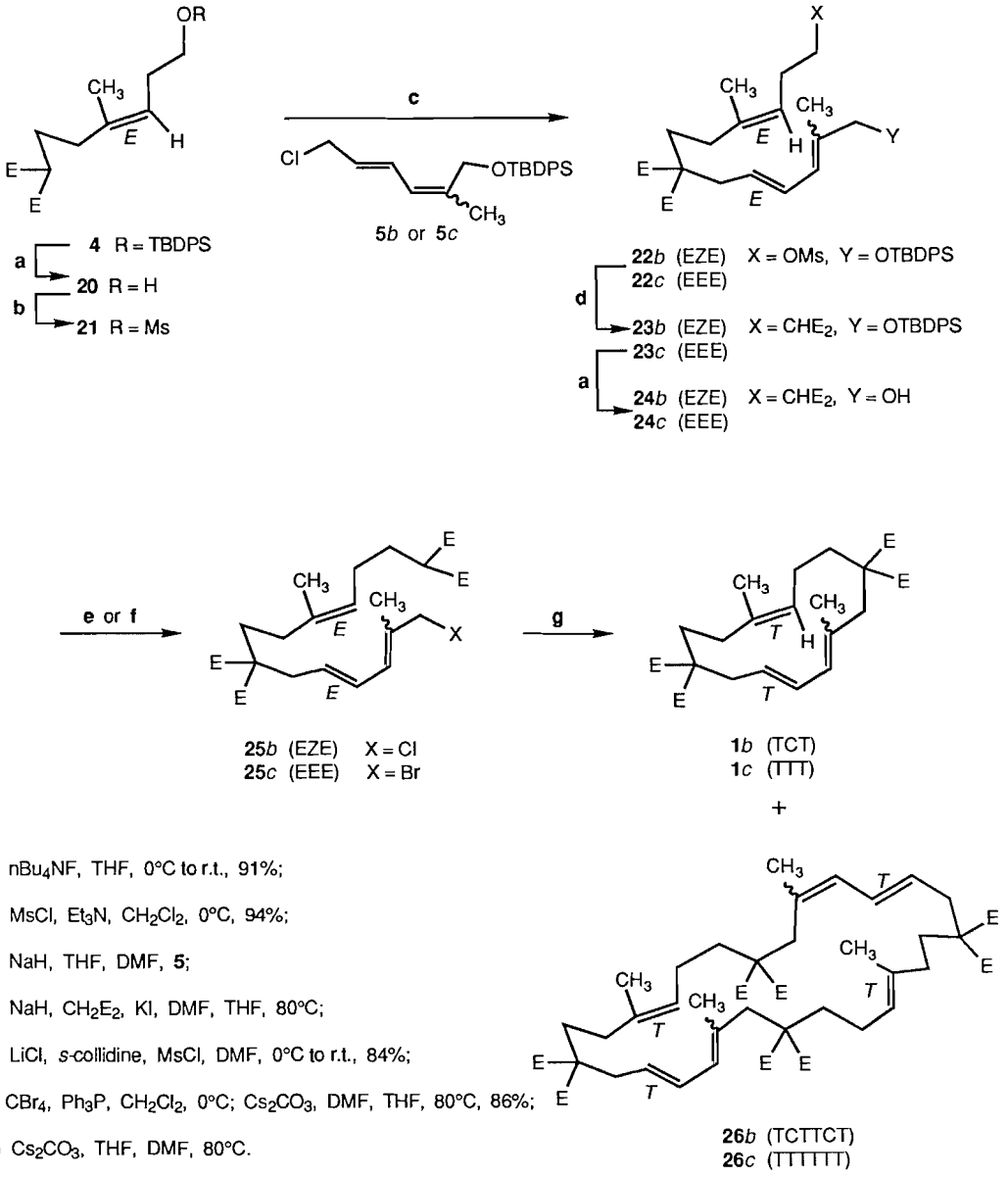
The isolation of the stable 14-membered macrocycle **1***c* having *trans-trans-trans* (TTT) olefin geometries should be noted because previous attempts to isolate such macrocycles had failed due to the facile transannular Diels–Alder reaction under the cyclization conditions (2*b*, 2*e*). The introduction of a methyl substituent on the diene as in **1***c* considerably lowers its reactivity in the transannular Diels–Alder reaction. This is indeed true since the Diels–Alder reaction of **1***c* requires temperatures as high as 250°C (vide infra).



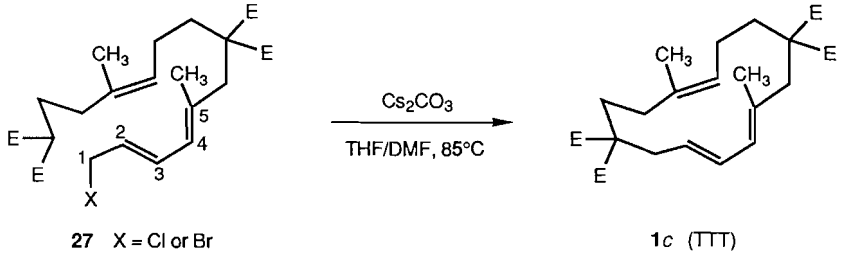
(a) 3,4-Dihydro-2H-pyran, PTSA, CH_2Cl_2, THF, 0°C;
(b) $(COCl)_2$, DMSO, iPr_2NEt, CH_2Cl_2, -60°C;
(c) PCC, NaOAc, Molecular sieves, CH_2Cl_2, 0°C to r.t.;
(d) $(CF_3CH_2O)_2POCH(CH_3)CO_2Et$, 18-crown-6-ether, $KN(TMS)_2$, tol., THF, -78°C;
(e) $iPrO_2POCH(CH_3)CO_2Et$, NaH, THF, -78°C;
(f) DIBAL, CH_2Cl_2, -78°C;
(g) LiCl, *s*-collidine, MsCl, DMF, 0°C to r.t.;
(h) *t*-$BuPh_2SiCl$, imidazole, THF, r.t.;
(i) PPTS, iPrOH, 75°C.

SCHEME 3

It should be also noted that in the case of TTT acyclic triene **25***c*, the allylic bromide was employed for macrocyclization instead of the allylic chloride, which was used extensively in our previous studies (2). As presented in Scheme 5, our original plan to synthesize *trans-trans-trans* macrocycle **1***c* was based on the cyclization of allylic chloride triene **27** (X = Cl). Such an approach was expected to be advantageous due to the reduced steric interactions (methyl group remote from the reaction site) for the cyclization process. However, no macrocyclic product **1***c* could be obtained after several attempts employing the usual cyclization conditions; only decomposition of starting material **27** was observed under various conditions of temperature and reaction time. This failure in transforming acyclic triene **27** to **1***c* prompted us to use the corresponding acyclic triene bromide **27** (X = Br), which is expected to be more reactive than the chloride. Macrocyclization of **27** (X = Br) under the same conditions provided a 24% yield of macrocycle **1***c*. Attempts to increase the yield failed, and we found that allylic bromide **27** decomposed quickly under the cyclization conditions. The instability of such a compound could be rationalized by the fact that **27** (X = Br) can easily form a stable



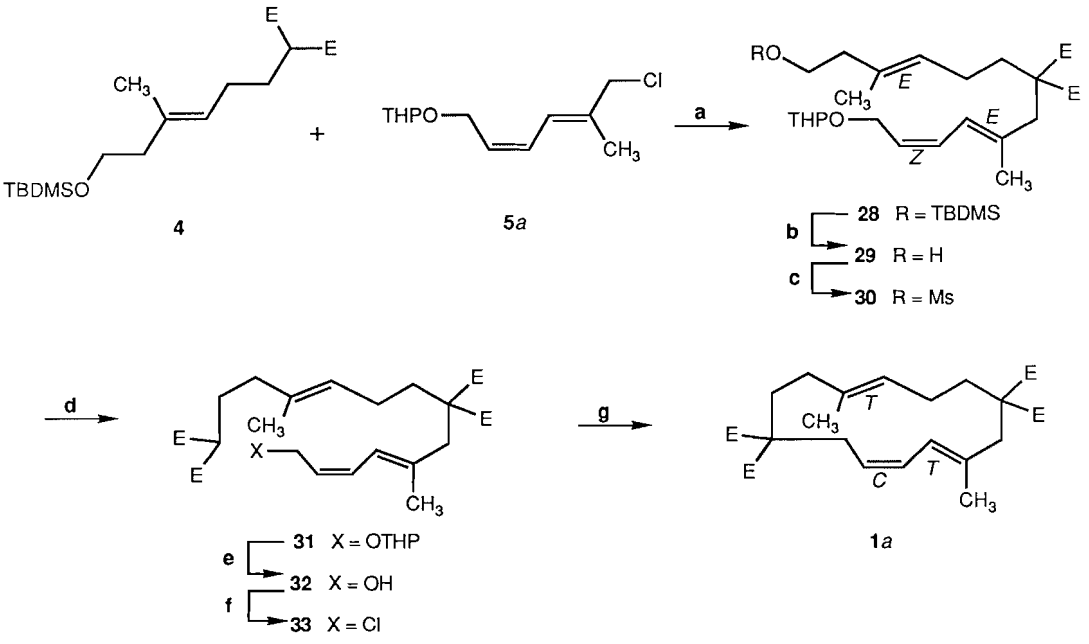
SCHEME 4



SCHEME 5

allylic carbocation, which is further stabilized by the presence of the methyl group. To circumvent this problem, our original plan was modified so that the cyclization would take place on the side of the diene bearing the methyl group as indicated by structure **25***c*, since we anticipated that **25***c* would be more stable than **27**. Indeed, the allylic bromide **25***c* was found to be stable even under flash chromatographic conditions and it cyclized efficiently to give **1***c* in 73% yield along with 5% of the dimer **26***c*.

The preparation of macrocycle **1***a* having the *cis-trans-*



(a) NaH, THF, DMF, 61%;

(b) nBu_4NF, THF, 0°C to r.t., 81%;

(c) MsCl, Et_3N, CH_2Cl_2, 0°C, 98%;

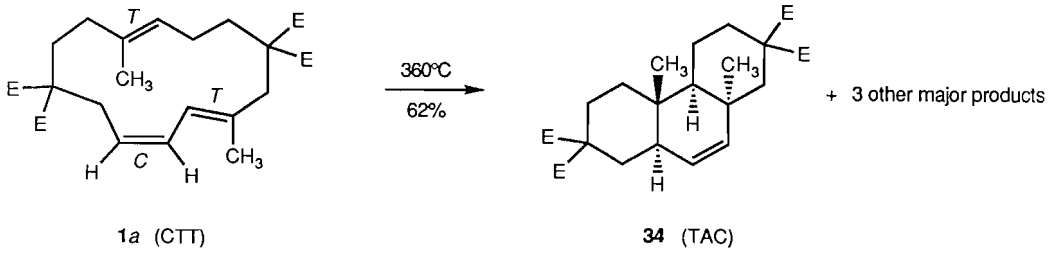
(d) NaH, CH_2E_2, KI, DMF, THF, 80°C, 72%;

(e) PPTS, CH_3OH, 70°C, 97%;

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

(g) Cs_2CO_3, DMF, THF, 70°C.

SCHEME 6



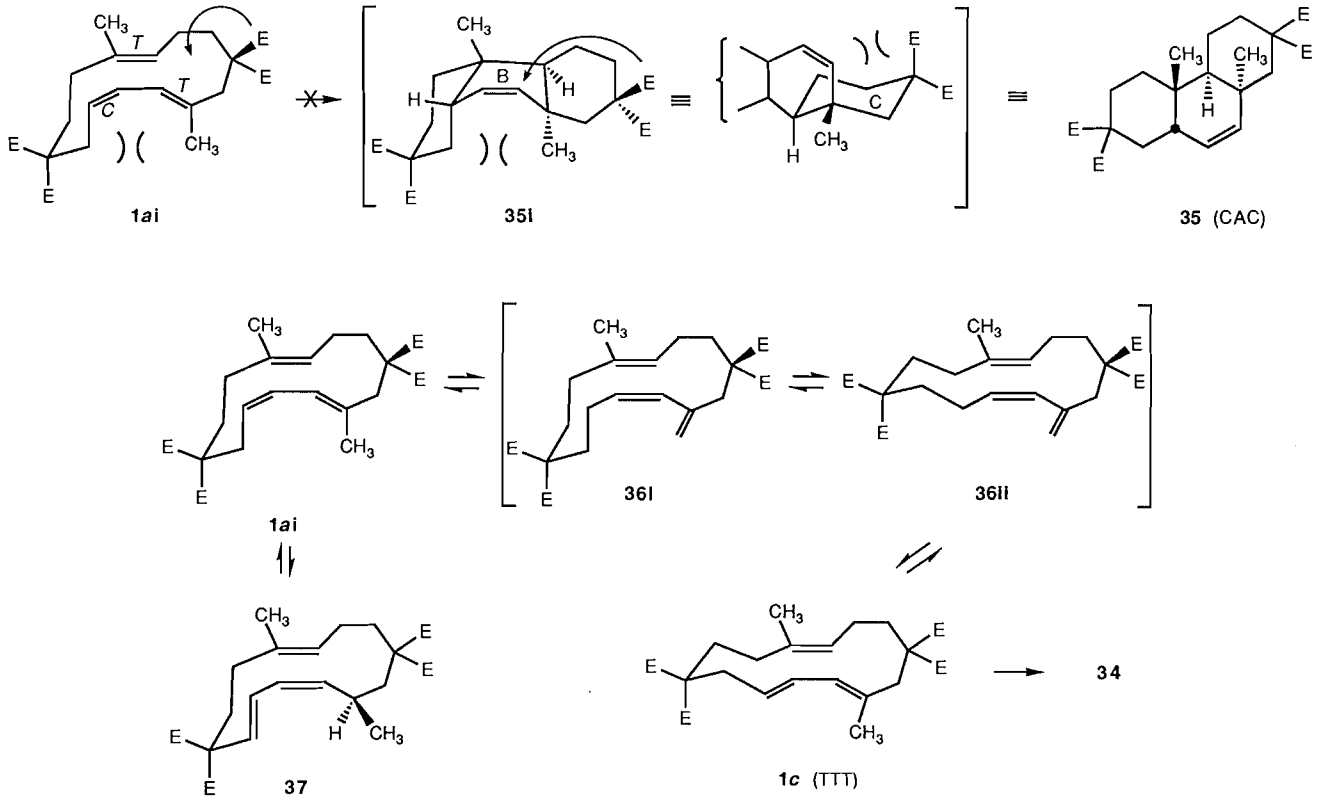
SCHEME 7

trans (CTT) geometry was accomplished following the procedures described in Scheme 6. The coupling reaction of diene **5***a* with dienophile **4** was conducted in the presence of sodium hydride to provide *Z-E-E* acyclic triene **28** (19), which was then converted to the methanesulfonate ester **30** by desilylation (n-Bu_4NF (18)) following mesylation of the resulting alcohol **29** (MsCl and Et_3N). After replacement of the mesylate group by dimethylmalonate, the resulting triene **31** was hydrolyzed to the allylic alcohol **32** (11), which was subsequently converted to the allylic chloride **33** (14). The cyclization step was then conducted in a similar fashion as described before to provide macrocycle **1***a* (CTT) as a crystalline solid. Again, the structure of **1***a* was established by spectroscopic data (nmr, ir, ms).

Synthesis of tricycles, Transannular Diels–Alder reaction

1. From CTT macrocycle ***1****a*

The transannular Diels–Alder reaction of CTT **1***a* was carried out by thermolysis in a sealed quartz tube at 360°C for 80 min to yield a mixture of four major products (Scheme 7). Each compound contributed between 10 and 19% to the total crude reaction mixture as determined by vapour phase chromatography (vpc). Thin-layer chromatography of the crude reaction mixture also revealed the presence of several other minor products. The identification and characterization of the major products was attempted, but failed due to the difficulty in isolating each compound in a pure state. The presence of tricycle **34** having the *trans-anti-cis* (TAC) stereochemistry was, however, demonstrated by comparing



SCHEME 8

the products of the reaction mixture with an authentic sample of **34** prepared by the Diels–Alder reaction of TTT macrocycle **1***c* (vide infra, cf. Scheme 10).

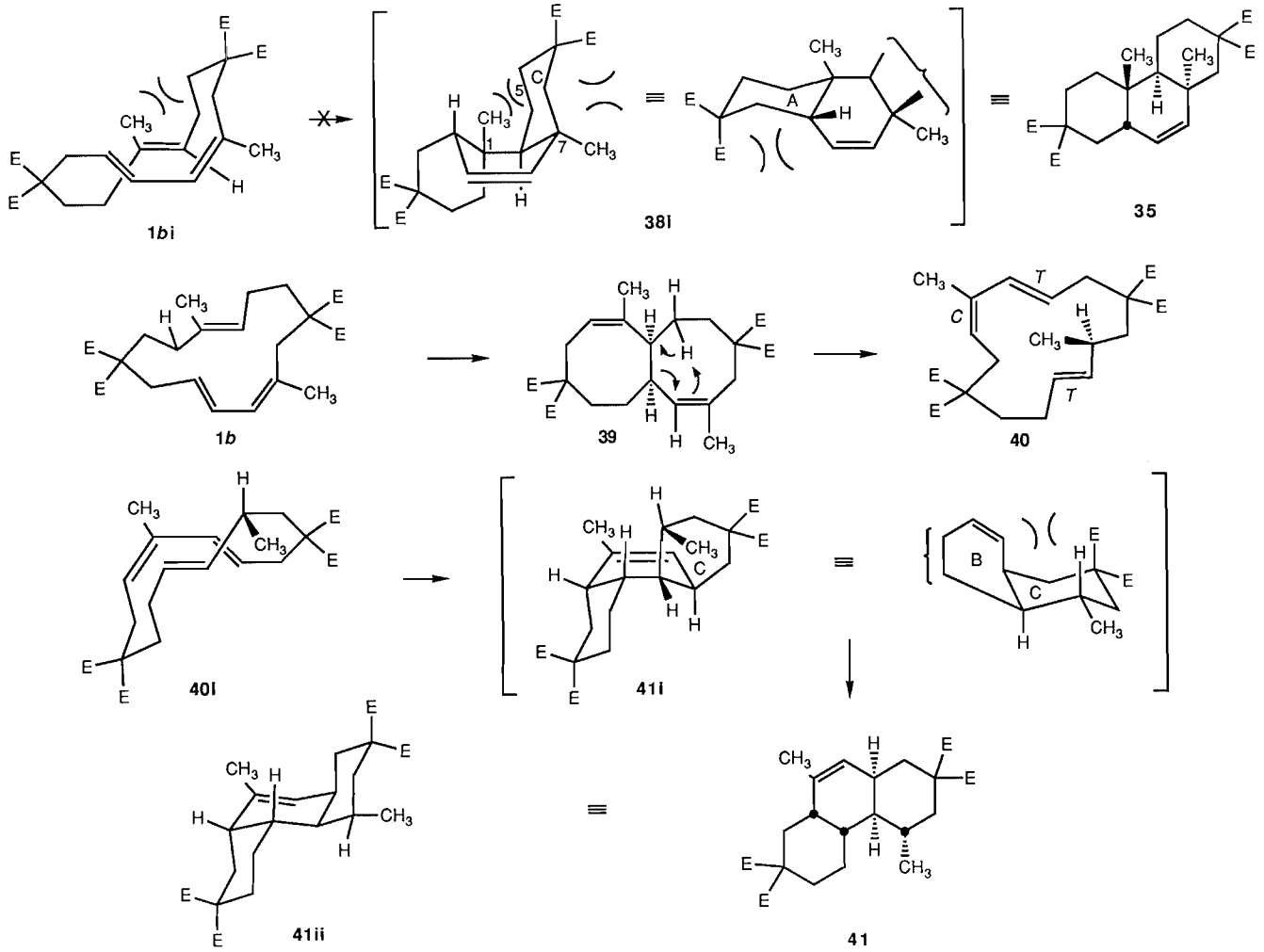
The formation of this complex mixture of tricyclic products can be explained in the following way. In principle, a macrocyclic triene can yield two different diastereoisomers. However, and as previously discussed (2*a*), there are cases where one of the expected diastereoisomers cannot be formed because of a conformational restriction imposed by the fact that the Diels–Alder reaction must take place via a boat transition state. As shown in Scheme 8, the CTT macrocyclic triene **1***a* is expected to produce only the CAC tricycle **35** via the chair–boat–chair conformation **35***i*. Examination of molecular models reveals however that this process is, sterically, extremely crowded: the *cisoid* conformation **1***ai* of the diene that is required for the Diels–Alder reaction is severely hindered sterically due to the presence of the methyl group on the diene, and also due to steric repulsion between one of the ester functions and the diene moiety (Scheme 8); these effects are best seen in the conformation **35***i* of the Diels–Alder product **35** from which the CAC tricycle should be produced: one methyl group in the boat ring B is very severely hindered, and the β-ester function in ring C is in a 1,3 diaxial disposition relative to the olefin of ring B. These severe steric interactions will raise considerably the energy of this process and will allow competing processes to take place.

The unexpected formation of the TAC tricycle **34** as well as the formation of the other major products may be explained in the following way. CTT tricycle **1***a* in conformation **1***ai* can undergo a 1,5 sigmatropic hydrogen migration to give **36** in conformation **36***i*. This new macrocyclic triene can then undergo another 1,5 sigmatropic hydrogen migration via conformation **36***ii* to give TTT macrocyclic triene **1***c*, which can then give the TAC tricycle **34** (vide infra). The other tricyclic products may come from the [4+2] cycloaddition of **36** or via other unknown side reactions. For instance, CTT macrocycle **1***ai* could undergo another 1,5 sigmatropic hydrogen migration to give the isomeric macrocycle **37**, which can also produce tricycles via the transannular Diels–Alder reaction. It should be pointed out that the 1,5 sigmatropic hydrogen migration in a macrocyclic triene followed by a [4+2] cycloaddition process has already been previously observed in our laboratory (2*f*).

2. From TCT macrocycle **1**b

The transannular Diels–Alder reaction of TCT macrocycle **1***b* was carried out at 300°C in a fashion similar to that described for **1***a*, and the interpretation of the results is presented in Scheme 9. To our surprise, a totally unexpected tricyclic product **41** having a methyl-substituted olefin was isolated in 66% yield. The presence of the methyl group on the double bond in ring B and of the secondary methyl group in ring C was shown by proton nmr, the former one being a singlet at 1.62 ppm and the latter a doublet at 0.92 ppm. The presence of only one rather than two vinyl protons further indicated that the tricycle did not have an expected structure. The overall structure and relative stereochemistry of tricycle **41** was established unambiguously by X-ray analysis (21). It is interesting to note that this compound exists in the solid state in conformation **41***ii* in which the secondary methyl group in ring C is axially oriented.

We previously predicted (2*a*) that 14-membered macrocyclic trienes having a *trans-cis-trans* geometry should give only one tricycle having the *cis-anti-cis* (CAC) stereochem-



SCHEME 9

istry. It was therefore expected that the TCT macrocycle **1***b* would give the CAC tricycle **35** via conformation **1***bi*. Examination of this process in more detail reveals, however, that it must have a relatively high activation energy due to severe steric interactions caused by the presence of the methyl groups and the ester functions. This can best be seen in conformation **38***i*: the methyl group at C1 is sterically hindered by ring C while the other one at C7 is experiencing a 1,3 diaxial steric interaction with one of the esters of ring C. There is also a 1,3 diaxial steric interaction between the axial ester function in ring A and the olefin of ring B. It is therefore not surprising that macrocycle **1***b* underwent other reactions having a lower activation energy.

The formation of the CAC tricycle **41** having a methyl-substituted olefin can be rationalized by a transannular ene, a retroene, and finally a transannular Diels–Alder reaction as presented in Scheme 9. Thus, the transannular ene reaction would transform macrocycle **1***b* into the *cis*-bicyclic intermediate **39** having two eight-membered rings. This would then be followed by a retroene reaction from **39** to produce the macrocyclic triene **40**. This overall transformation is the equivalent of an oxidation–reduction process whereby the diene and dienophile have been interchanged. The new CTT macrocycle **40** can now easily undergo a transannular Diels–Alder reaction because both methyl groups are no longer located on carbon atoms directly involved in bond formation and therefore are almost completely devoid of severe steric repulsion during this process. Indeed, compound **40** would react via conformation **40***i*, which will produce tricycle **41** in conformation **41***i* having ring B in a boat form and an equatorially oriented secondary methyl group in ring C. In **41***i*, there is only one 1,3 diaxial interaction between an ester function in ring C and the olefin of ring B. Conformation **41***i*, once produced, would then revert to the more stable chair–half-chair–chair conformation **41***ii* having the secondary methyl group axially oriented as shown by X-ray crystallography.

The above interpretation is also in accord with previous studies on less substituted TCT macrocyclic trienes. Indeed, we found (2*e*) that when the TCT macrocyclic trienes bear no methyl groups on the diene and the dienophile, only the theoretically expected CAC tricycle corresponding to **35** (CH_3 = H) was obtained. This is of course not surprising as all the undesired steric effects that unduly raised the transition state energy in **38***i* have now been removed. On the other hand, we also observed (2*b*, 23) that when there is no substituent on the diene and only one methyl group on the dienophile, an intermediate situation occurs. In these cases two processes occur: one equivalent to **1***b* → **35** (40%) and the second equivalent to **1***b* → **41** (60%). In the dimethyl case, the process **1***b* → **35** does not take place because there is

TABLE 1. Chemical shifts of the methyl and olefin protons change on heating macrocycle **1***b* at 300°C

Entry[a]	Time (h)	Distinguishing ^{1}H nmr characteristics
1	0	5.92–6.11 (2H, m, olefin) 5.17 (1H, dt, olefin) 5.09 (1H, br t, olefin) 1.62 (3H, s, methyl) 1.57 (3H, s, methyl)
2	0.5	5.48 (1H, t, olefin) 4.93 (1H, d, olefin) 1.77 (3H, s, methyl) 1.47 (3H, s, methyl)
3	2	5.19 (1H, s, olefin) 1.62 (3H, d, methyl) 0.92 (3H, d, methyl)

[a]Entries 1 and 3 correspond to the NMR chemical shifts of **1***b* and **41**.

additional steric hindrance that further increases its energy barrier.

Our overall interpretation was further confirmed by detecting the presence of bicyclic intermediate **39** at shorter reaction time in a proton nmr monitored experiment. The intermediate **39** could not, however, be obtained pure by chromatography. Table 1 lists the chemical shifts for the characteristic olefin and methyl protons, which changed with time upon heating the macrocycle **1***b* at 300°C. The proton nmr data in entry 2 of Table 1 were obtained by subtracting the ^{1}H nmr data of both starting material **1***b* (entry 1) and product **41** (entry 3) from that of the reaction mixture after 0.5 h at 300°C. This set of ^{1}H nmr data in entry 2 is in full agreement with the proposed bicyclic structure **39**. The failure to isolate or even detect the TCT macrocyclic intermediate **40** can be explained by its higher reactivity in leading to tricycle **41** at 300°C via the transannular Diels–Alder reaction. In fact a macrocyclic TCT system similar to intermediate **40** was found to undergo a transannular Diels–Alder reaction at 250°C (*2e*).

The observation of this unique conversion, namely, **1***b* → **39** → **40** → **41** is mechanistically very interesting, since it is the first example of larger ring transformations through a transannular ene–retroene, Diels–Alder process, leading stereoselectively to a racemic tricyclic product **41** containing five contiguous chiral centers.

3. From TTT macrocycle **1***c*

In contrast to the previous results of CTT and TCT macrocycles, the transannular Diels–Alder reaction of TTT macrocycle **1***c* turned out to be straightforward. As illustrated in Scheme 10, thermolysis of **1***c* in toluene at 200°C for 18 h provided a 95% isolated yield of tricyclic compound **34** having the *trans-anti-cis* (TAC) stereochemistry, which was firmly established by X-ray analysis (22).

Theoretically, it is expected that the transannular Diels–Alder reaction of a 14-membered TTT macrocycle triene will produce a mixture of two tricycles having the TAC and CAT stereochemistry (*2a*). This was indeed observed in the case of a TTT macrocycle having a methyl group on the dienophile, which gave a 2:1 mixture of TAC and CAT tricycles (*2b*). In the present case, the TAC tricycle is formed exclusively and this result can be easily understood by examining the steric effects involved at the transition level of the two competing processes.

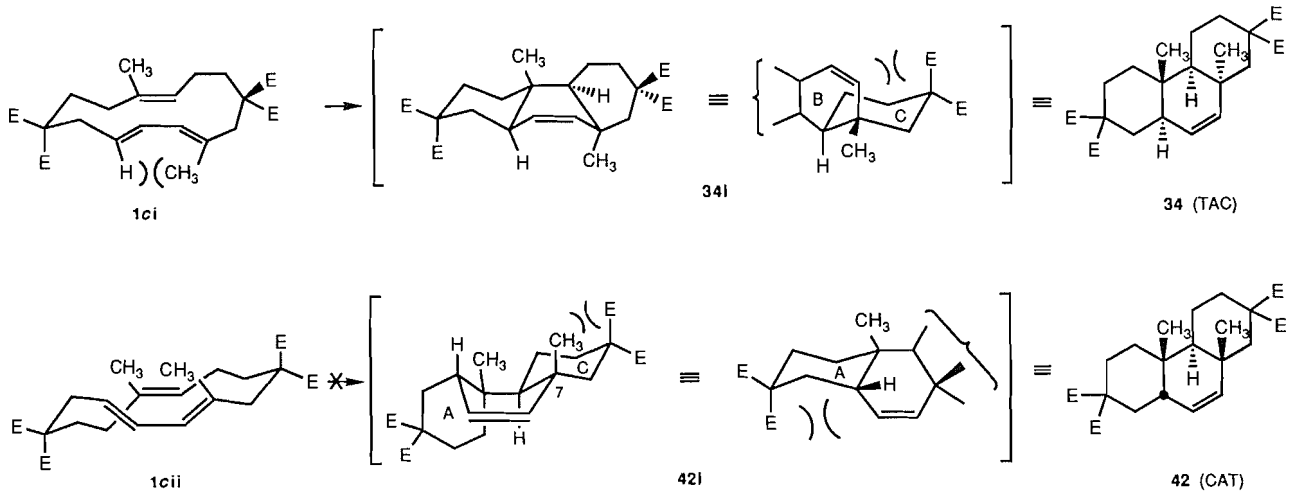
Tricycle TAC **34** and CAT **42** will be formed in conformations **34***i* and **42***i*, respectively, via the Diels–Alder reaction of macrocyclic triene **1***c* reacting in conformations **1***ci* and **1***cii*. Again, steric effects are best analyzed in the conformation in which the reaction products are formed. In stereoisomer **34***i*, there is a 1,3 diaxial steric interaction between the β-ester of ring C and the olefin of ring B. In stereoisomer **42***i*, there are two major steric interactions. The first one is essentially identical to that found in **34***i* (a 1,3 diaxial interaction between the α-ester of ring A and the olefin of ring B). The second one is the result of a 1,3 diaxial interaction between the methyl group at C7 and the β-ester in ring C, expected to be at least 2.5 kcal/mol. On that basis, one should anticipate the exclusive formation of TAC tricycle **34**, in agreement with the experimental result.

We also used molecular modeling to examine these assumptions. We recently (23) described a study of a 14-membered TTT macrocyclic triene, like **1***c* but lacking the methyl substituent of the diene moiety, using the Sybyl software.[3] The transition states of the chair–boat–chair (CBC) and chair–boat–boat (CBB) leading to the corresponding TAC and CAT macrocycles were mimicked and a Boltzman distribution based on their steric energies gave a calculated TAC:CAT ratio in complete agreement with the experimental results. As mentioned above, since the only difference between the two cases is a methyl substituent on the diene moiety, we reasoned that appropriate modifications might produce a fair description of transition structures for the present case as well. Thus the previously obtained transition state mimics (24) were modified by addition of a methyl substituent on the diene (a model of **1***c*), followed by a systematic conformational analysis (10° step) using the Search algorithm within Sybyl. The torsion angle between the forming bonds and the torsion angle in the butadiene moiety were kept at 0° as found by ad initio calculations for the transition state of butadiene and ethylene (24). Distances between the termini of the dienophile and the diene were left at 3 Å as in our previous study and the lowest energy conformers obtained in each case were minimized using the above-mentioned constraints. The four structures thus obtained and their respective steric energies are shown in Fig. 1. The lowest energy structures **A** (chair–boat–chair) and **B** (chair–boat–boat) would produce TAC tricycle **34** while the structures **C** and **D**, which are quite a bit higher in energy, would produce CAT tricycle **42**. A Boltzman distribution at 473 K of these four transition-state-like structures could lead to a product ratio TAC:CAT of 99:1, in excellent agreement with the experimental result.

Finally, as mentioned above, the Diels–Alder reaction of TTT macrocycle **1***c* requires a temperature of 250°C whereas that of the corresponding TTT macrocycle having no substituents on the diene takes place at ≤80°C (*2b*, *2d*). This is readily explained by the fact that when the methyl-substituted *trans-trans* diene takes the required *cisoid* conformation to undergo the cycloaddition, there is an additional severe steric repulsion between the methyl group and the diene moiety (cf. **1***ci*).

In résumé, CTT and TCT macrocycles **1***a* and **1***b* failed

[3]Sybyl 5.5 Tripos Associates, 1699 S. Hanley Road, Suite 303, St. Louis, MO 63144, U.S.A.



SCHEME 10

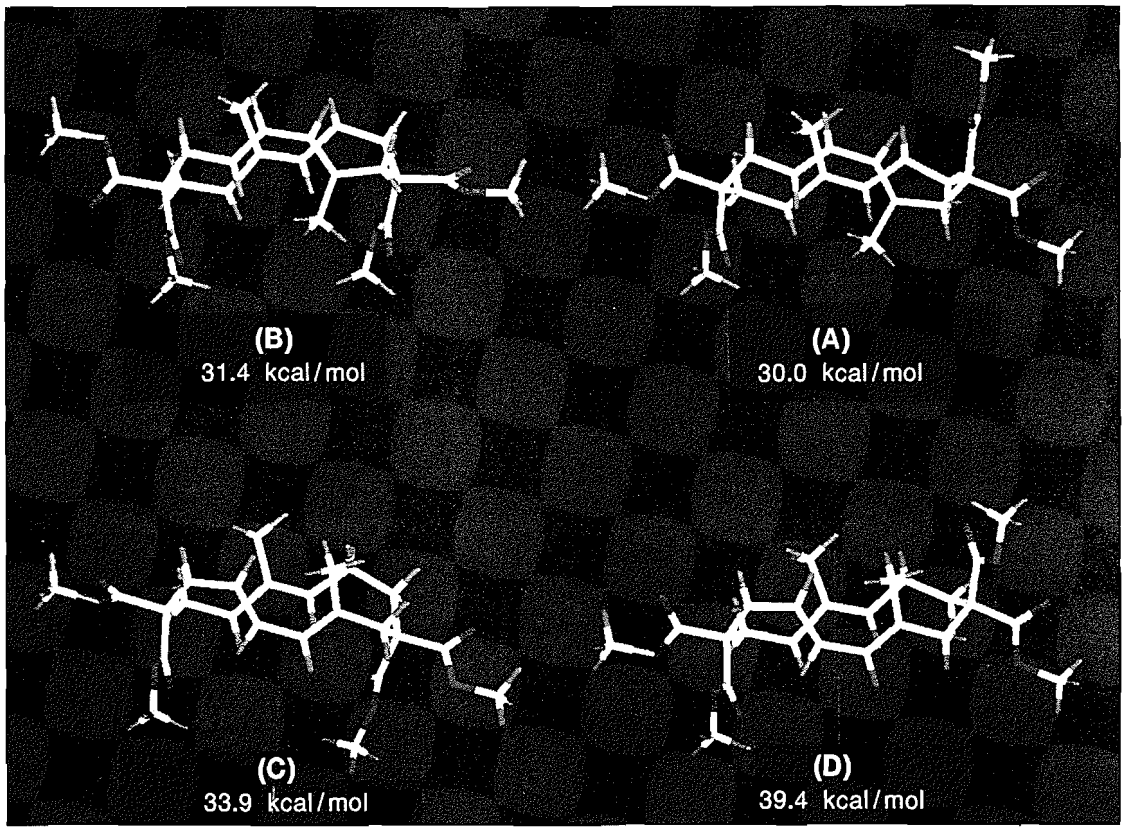


FIG. 1. Geometries and energies of transition state mimics.

to give the predicted CAC tricycle **35** because of severe steric hindrance at the transition level of the transannular Diels–Alder reaction. Macrocycle **1***a* gave a mixture of TAC tricycle **34** plus three unidentified isomers. The formation of **34** from macrocycle **1***a* can be explained by the isomerization of **1***a* into TTT macrocycle **1***c* via two consecutive 1,5 sigmatropic hydrogen migrations. The specific formation of tricycle **41** from macrocycle **1***b* took place via the intermediate formation of bicycle **39** via an ene–retroene process. Finally, TTT macrocycle **1***c* gave only TAC tricycle **34**; none of the other predicted CAT tricycle **42** was observed, a result which is explained on the basis of relative steric hindrance at the Diels–Alder transition state level.

In conclusion, this investigation has demonstrated a general methodology for the stereocontrolled synthesis of 1,7-dimethyl A.B.C.[6.6.6] tricyclic compounds. The macrocyclic trienes were constructed in good yields using an intramolecular displacement of allylic halides by a malonate anion in the acyclic triene precursors, which were assembled by coupling the diene and dienophile moieties. The

formation of unexpected tricycles from the CTT and TCT macrocycles has provided interesting information on competing transannular processes. The transannular Diels–Alder reaction of the TTT macrocycle stereoselectively produced a TAC tricyclic compound in excellent yield. This synthetic route could prove useful for the synthesis of suvanine (25), and kaurane and atisane diterpenes (26), which have the TAC stereochemistry with substituents at positions 8 and 10. The synthesis of these polycyclic natural products is currently under investigation.

Experimental

General

The ir spectra were taken on a Perkin–Elmer 681 spectrophotometer. Proton nmr spectra were recorded on a Bruker WP-80 or Bruker WM-250 instrument. The following abbreviations were used: s, singlet; d, doublet; dd, doublet of doublets; dt, doublet of triplets; ddd, doublet of doublets of doublets; ddt, doublet of doublets of triplets; t, triplets; q, quartet, and m, multiplet. Chemical shifts are reported in δ values relative to tetramethylsilane or chloroform as internal standard. Carbon nuclear magnetic resonance spectra were recorded on a Bruker WP-80 or Bruker WM-250 instrument (chloroform as internal standard). Mass spectra were obtained on a Micromass ZAB-2F instrument. Melting points were determined on a Büchi M-50 or on a Reichert apparatus and are uncorrected.

Thin-layer chromatography was performed using silica gel 60 F-250. For flash chromatography, Merck Kieselgel 60 (230–400 mesh A.S.T.M.) was used. All solvents used in chromatography were distilled. Unless otherwise noted, starting materials and reactants were obtained commercially and were used as such or purified by standard means. All solvents and reactants purified and dried were stored under argon.

Anhydrous reactions were performed under an inert atmosphere of argon. Organic solutions were dried over magnesium sulfate, and were evaporated on a rotatory evaporator and under reduced pressure.

4-Chlorobutyryl chloride 7

To a stirred mixture containing thionyl chloride (32.8 g, 19.9 mL, 0.28 mmol) and anhydrous zinc chloride (1.5 g, 11 mmol) at room temperature was rapidly added γ-butyrolactone **6** (21.6 g, 0.25 mol). The resulting mixture was then heated at 55°C for 22 h. The crude mixture was purified by distillation under reduced pressure to give **7** as a colorless oil (23.0 g, 65%). Boiling point: 51–59°C (5.0 Torr; 1 Torr = 133.3 Pa) (lit. (8) bp 69–74°C (14 Torr).

Methyl 4-chlorobutyrate 8

To a solution of pyridine (12.9 g, 13.2 mL, 0.136 mol) in methanol (6.53 g, 8.3 mL, 0.200 mol) was added, in dropwise fashion at 0°C, 4-chlorobutyryl chloride **7** (23.0 g, 0.163 mol). The mixture was then stirred at 25°C for 18 h following addition of precooled sulfuric acid (11.0 N, 55%, 75 mL). The mixture was extracted with diethyl ether (3 × 50 mL). The combined organic phases were washed with water and dried over Na_2SO_4. After filtration, the solvents were removed under reduced pressure and the residue was purified by vacuum distillation to provide methyl 4-chlorobutyrate **8** (17.1 g, 77%) as a colorless oil. Boiling point: 27–29°C (0.7 Torr) (lit. (8) bp 50–52°C (2–3 Torr); ir (neat): 2950, 1730, 1440, 1368, 1215 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 2.10 (tt, 2H, J = 7.2 Hz, 6.3 Hz, $-CH_2CH_2CH_2-$), 2.51 (t, 2H, J = 7.2 Hz, $-CH_2COOCH_3$), 3.60 (t, 2H, J = 6.3 Hz, $-CH_2Cl$), 3.69 (s, 3H, $-COOCH_3$).

Methyl 4-iodobutyrate 9

Methyl 4-chlorobutyrate **8** (8.96 g, 65.5 mmol) in 65 mL of acetone was then heated to reflux for 42 h in the presence of sodium iodide (11.7 g, 78.6 mmol). The solution was cooled and filtered and the solvent was then evaporated. The residue was dissolved in 100 mL of diethyl ether, washed with aqueous sodium thiosulfate solution (5%), and then with saturated sodium chloride solution. The organic phase was dried over $MgSO_4$, filtered, and evaporated. The oily residue was purified by distillation under reduced pressure to give **9** (11.6 g, 77.5%) as a colorless oil. Compound **9** decomposes slowly even at −20°C under argon atmosphere. Boiling point 53–54°C (0.7 Torr), 50–52°C (0.35 Torr); ir (neat): 2940, 1735, 1435, 1365, 1200, 1120, 1018 cm^{-1}.

Methyl (E)-3-methyl-1-tert-butyldimethylsilyloxy-3-octenoate 12

To a flask containing the Zn–Cu couple (4.17 g, 63.9 mmol) under an argon atmosphere was added a solution of methyl 4-iodobutyrate **9** (9.51 g, 41.7 mmol) in a mixture of benzene and DMF (32 mL/5.6 mL). The resulting mixture was stirred at 25°C for 1 h and at 60°C for 3 h. A suspension of tetrakis(triphenylphosphine)palladium(0) (4.06 g, 3.53 mmol) in 28 mL of benzene was introduced by cannula and the mixture was stirred at 60°C for 5 min. Vinyl iodide **11** (9.06 g, 27.8 mmol) in 11 mL of benzene was added and the resulting mixture was stirred at 60°C for another hour. The reaction was stopped by addition of 150 mL ethyl acetate followed by filtration to remove the Zn–Cu. The orange filtrate was kept in a refrigerator overnight and the volatiles were then removed by evaporation. After addition of 50 mL ethyl acetate, the mixture was filtered again. The red solid was washed with 100 mL ethyl acetate and the filtrate was concentrated under reduced pressure to give a crude oily residue, which was passed through a short-path silica gel using hexane – ethyl acetate (10:1) as eluant. The oil obtained after evaporation was purified by flash chromatography with a mixture of hexane and ethyl acetate (20:1) as eluant to give compound **12** (5.38 g, 64.5%); ir (neat): 2950, 2920, 2860, 1740, 1435, 1252, 1100, 835 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 0.04 (s, 6H, t-Bu-$(CH_3)_2Si$-), 0.89 (s, 9H, $(CH_3)_3CSi(CH_3)_2$)), 1.60 (d, 3H, J = 1.0 Hz, CH_3-C=C-), 1.66 (tt, 2H, J = 7.5 Hz, 7.6 Hz, $-CH_2CH_2CH_2COOCH_3$), 2.01 (dt, 2H, J = 6.2 Hz, 7.5 Hz, $-CH_2CH_2CH_2COOCH_3$), 2.19 (t, 2H, J = 7.1 Hz, $-OCH_2CH_2C$=C-), 2.30 (t, 2H, J = 7.6 Hz, $-CH_2COOCH_3$), 3.65 (t, 2H, J = 7.1 Hz, $-OCH_2CH_2$-), 3.66 (s, 3H, $-COOCH_3$), 5.14 (m, 1H, -C=CH-); ^{13}C nmr ($CDCl_3$) δ: 16.2, 18.1, 24.8, 25.8, 27.1, 33.3, 43.0, 51.1, 62.2, 125.1, 133.2, 173.9; ms m/e: 243 ($M^+ - C_4H_9$). Exact Mass ($M - C_4H_9$) calcd.: 243.1416; found: 243.1416.

Methyl (E)-3-octenoate 4

To a solution of the methyl ester **12** (1.00 g, 3.3 mmol) in 20 mL of THF was added, at −78°C under an argon atmosphere, a solution of lithium diisopropylamide (3.3 mmol) in THF. After stirring the mixture at −78°C for 30 min, methyl chloroformate (256 μL, 312 mg, 3.3 mmol) was introduced dropwise by syringe. The reaction was quenched with 50 mL of saturated ammonium chloride solution and extracted with a solvent mixture of hexane and ether (1:2). The organic phase was washed with water, dried over $MgSO_4$, filtered, and then concentrated under reduced pressure. The crude residue was purified by flash chromatography with a 20:1 mixture of hexane and ethyl acetate as eluant to give product **4** (792 mg, 67%) as a clear oil; ir (neat): 1740, 1435, 1255, 1150, 1100, 840 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 0.04 (s, 6H, t-Bu-$CH_3)_2Si$-), 0.88 (s, 9H, $(CH_3)_3CSi(CH_3)_2$), 1.59 (s, 3H, CH_3-C=C-), 1.92–2.04 (m, 4H, $-CH_2CH_2CH(COOCH_3)_2$), 2.19 (t, 2H, J = 7.1 Hz, $-OCH_2CH_2C$=CH-), 3.38 (t, 1H, J = 7.2 Hz, $-CH(COOCH_3)_2$), 3.65 (t, 2H, J = 7.1 Hz, $-OCH_2CH_2$-), 3.73 (s, 6H, $-CH(COOCH_3)_2$), 5.11 (t, 1H, J = 6.2 Hz, CH_3C=CH-); ms m/e: 301 ($M^+ - C_4H_9$). Exact Mass ($M - C_4H_9$) calcd.: 301.1471; found: 301.1460.

2-Butene-1-ol 14

(Z)-2-Butene-1,4-diol **13** (49.5 mL, 52.9 g, 0.60 mol) and 3,4-dihydro-2H-pyran (54.7 mL, 50.5 g, 0.60 mol) were dissolved in 200 mL of CH_2Cl_2 and 500 mL of THF at 0°C. To this solution was then added p-toluenesulfonic acid monohydrate (2.65 g, 14 mmol) and the resulting mixture was stirred at 0°C for 2 h and at 20°C for

20 min. Solid sodium bicarbonate (2.35 g, 28 mmol) was added and the solution was stirred for 5 min. After filtration, the solvents were removed and the crude oil obtained was purified by flash chromatography with a 9:1 mixture of CH_2Cl_2 and acetone as eluant to provide monoprotected alcohol **14** (50.7 g, 49.1%) as an oil; ir (CH_2Cl_2): 3600, 3620–3300, 2940, 1200, 1120, 1024 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.43–1.88 (m, 6H, -(CH_2)$_3$$CH_2$O-), 2.04 (t, 1H, J = 2.5 Hz, -CH_2O*H*), 3.49–3.58 and 3.81–3.90 (2m, 2H, -CH_2CH_2O-), 4.10–4.32 (m, 4H, -CH_2CH=CH-CH_2-), 4.69 (t, 1H, J = 3.0 Hz, -OC*H*O-), 5.66–5.77 and 5.81–5.92 (2m, 2H, -C*H*=C*H*-); ^{13}C nmr ($CDCl_3$) δ: 18.9, 25.1, 30.2, 57.8, 61.8, 62.2, 97.4, 127.3, 132.2; ms *m/e*: 155 (M^+ − OH). Exact Mass (M^+ − OH) calcd.: 155.1072; found: 155.1075.

(Z,E)-Diene ester ***16***a

To a stirred solution of oxalyl chloride (5.0 mL, 55 mmol) in 125 mL of CH_2Cl_2 was added, at between −50 and −60°C, a solution of DMSO (8.5 mL, 110 mmol) in 25 mL of CH_2Cl_2. After stirring the mixture for 2 min, alcohol **14** (8.61 g, 50 mmol) in 50 mL of CH_2Cl_2 was introduced over a 5 min period. The stirring was continued for an additional 45 min following addition of diisopropylethylamine (43.5 mL, 250 mmol). After 5 min, the reaction mixture was allowed to warm to −10°C. The oxidation was stopped by addition of water (125 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 180 mL) and the combined organic phases were washed with saturated NaCl solution (200 mL), dried over $MgSO_4$, filtered, and evaporated. The oil, which contained *cis*-α,β-unsaturated aldehyde ***15a***, was used for the next reaction without further purification.

To a stirred suspension of NaH (2.47 g, 60% in oil, 62 mmol) in 100 mL of THF was rapidly added, at 0°C under an argon atmosphere, a solution of ethyldiisopropyl-2-phosphonopropinate (16.5 g, 62 mmol) in 60 mL of THF. Once the evolution of hydrogen gas ended, the solution was cooled to −78°C. Crude aldehyde ***15a*** in 15 mL of THF was introduced and the resulting mixture was stirred at −78°C for 30 min and at 0°C for 15 min. The reaction was stopped by addition of saturated ammonium chloride (100 mL) and diethyl ether (150 mL). The aqueous phase was extracted with diethyl ether. The combined organic phases were washed with brine, dried over $MgSO_4$, and then filtered. After removal of volatiles, the oily residue was purified by flash chromatography using a 7:2 mixture of hexane and ethyl acetate to provide ***16a*** (6.63 g, 52% for two steps) as an oil; ir (neat): 2940, 2870, 1710, 1633, 1600, 1245, 1201, 1025, 905, 870 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.29 (t, 3H, J = 7.5 Hz, CH_3CH_2O-), 1.49–1.88 (m, 6H, -(CH_2)$_3$$CH_2$O-), 1.94 (d, 3H, J = 1.0 Hz, CH_3C=CH-), 3.49–3.58 and 3.84–3.94 (2m, 2H, -CH_2CH_2O-), 4.22 (q, 2H, J = 7.5 Hz, CH_3CH_2O-), 4.31 and 4.49 (2ddd, 2H, J = 14 Hz, 1.0 Hz, 6.2 Hz, -CH_2OTHP), 4.66 (t, 1H, J = 2.5 Hz, -OC*H*O-), 5.93 (dt, 1H, J = 11.2 Hz, 6.2 Hz, -OCH$_2$C*H*=CH-), 6.43 (ddt, 1H, J = 11.2 Hz, 11.0 Hz, 1.0 Hz, -OCH$_2$CH=C*H*CH-), 6.48 (dq, 1H, J = 11.0 Hz, 1.0 Hz, -OCH$_2$CH=C*H*=C-CH$_3$); ^{13}C nmr ($CDCl_3$) δ: 12.1, 14.1, 19.1, 25.2, 30.4, 60.3, 61.9, 63.0, 98.0, 125.4, 128.7, 131.9, 134.1.

Allylic alcohol ***17***a

General procedure A

To a stirred solution of ester ***16a*** (6.44 g, 25 mmol) in 450 mL of CH_2Cl_2 was added, over a period of 15 min at −78°C under an argon atmosphere, a solution of diisobutylaluminum hydride (1 M, 55 mL, 55 mmol). After 30 min, 16 g of solid $Na_2SO_4 \cdot 10$ H_2O was added. The reaction mixture was allowed to warm to room temperature following addition of 200 mL acetone. The reaction mixture was stirred for an additional hour, the solids were removed by filtration, and the filtrate was evaporated to dryness. The crude residue was purified by flash chromatography using a 7:3 mixture of hexane and ethyl acetate to provide alcohol ***17a*** (3.48 g, 66%) as an oil; ir (neat): 3600–3100, 2940, 2860, 1655, 1200, 1020, 902, 868 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.49–1.77 (m, 7H, -(CH_3)$_3$$CH_2$O- and -$CH_2$O*H*), 1.79 (s, 3H, CH_3C=CH-), 3.49–3.58 and 3.86–3.95 (2m, 2H, -OCH$_2$C*H*$_2$O-), 4.11 (s, 2H, -CH_2OH), 4.21–4.46 (m, 2H, -CH_2OTHP), 4.67 (t, 1H, J = 2.5 Hz, -OC*H*O-), 5.59–5.69 (m, 1H, -CH$_2$C*H*=CH(CH=C-)), 6.32–6.47 (m, 2H, -C*H*$_2$CH=C*HCH*=C-); ^{13}C nmr ($CDCl_3$) δ: 13.6, 19.1, 25.2, 30.4, 61.9, 62.6, 67.7, 97.5, 118.6, 126.3, 126.6, 139.3.

Allylic chloride ***5***a

General procedure B

To a solution containing alcohol ***17a*** (467 mg, 2.2 mmol) vacuum dried (heat-gun), lithium chloride (374 mg, 8.8 mmol), and *s*-collidine (0.58 mL, 532 mg, 4.4 mmol) in 12 mL of DMF was added, dropwise at 0°C under an argon atmosphere, methanesulfonyl chloride (0.34 mL, 504 mg, 4.4 mmol). The resulting mixture was stirred at 0°C for 1 h and then at 25°C for an additional hour. The reaction mixture was poured into 10 mL of ice water, and extracted with a 2:1 mixture of diethyl ether and hexane (3 × 25 mL). The combined organic phases were washed successively with precooled, saturated $Cu(NO_3)_2$ solution and water. After drying over $MgSO_4$, the mixture was filtered through a short-path column containing silica gel and Celite on top. After removal of the solvents, allylic chloride ***5a*** was obtained (504 mg, 99%) as an oil that was used for the next reaction without further purification and characterization.

(E)-α,β-Unsaturated aldehyde ***15***b

To a solution of alcohol **14** (10.0 g, 58 mmol) and sodium acetate (14.4 g, 170 mmol) in 250 mL of CH_2Cl_2 over type 4Å molecular sieves (20 g) was added, portionwise at 0°C under an argon atmosphere, pyridinium chlorochromate (18.9 g, 87 mmol). The reaction mixture was then stirred at room temperature until disappearance of starting material, monitored by tlc. A solution of hexane and diethyl ether (500 mL, 1:1) was added, and the resulting mixture was filtered until colorless (three filtrations) using a Büchner funnel containing Celite, silica gel, and sodium sulfate (after the second filtration, the filtrate was treated with activated carbon for a few minutes). The solvents were removed by evaporation, and the crude residue was purified by flash chromatography using a 1:1 mixture of hexane and diethyl ether to afford aldehyde ***15b*** (5.44 g, 55%) as a clear oil; ir (CH_2Cl_2): 2943, 1690, 1120, 1040 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.51–1.82 (m, 6H, -(CH_2)$_3$$CH_2$O), 3.50–3.56 and 3.77–3.88 (2m, 2H, -CH_2CH_2O-), 4.20–4.57 (m, 2H, -OCH_2CH=CH-), 4.68 (t, 1H, J = 2.5 Hz, -OC*H*O-), 6.38 (ddt, 1H, J = 16.0 Hz, 8.7 Hz, 2.5 Hz, -CH$_2$CH=C*H*CHO), 6.87 (dt, 1H, J = 16.0 Hz, 3.0 Hz, -CH$_2$C*H*=CHCHO), 9.58 (d, 1H, J = 8.7 Hz, CH=CHC*H*O); ^{13}C nmr ($CDCl_3$) δ: 18.9, 25.1, 30.1, 61.9, 65.3, 98.2, 131.3, 153.2, 193.1; ms *m/e*: 169 (M^+ − H). Exact Mass (M − H) calcd.: 169.0865; found: 169.0865.

(E,Z)-Diene ester ***16***b

To a stirred solution of ethyl bis(trifluoroethyl)-2-phosphonopropionate (10.0 g, 29.0 mmol) and 18-crown-6 ether (38.0 g, 144.0 mmol) in 450 mL of THF was added at −78°C under argon a solution of potassium bis(trimethylsilyl)amide (0.657 M, 44 mL, 28.9 mmol) in toluene. The mixture was stirred for 5 min at −78°C before the *trans*-aldehyde ***15b*** (4.9 g, 29.0 mmol) dissolved in 50 mL of THF was introduced by cannula over a period of 30 min. The cloudy mixture was stirred at −78°C for 1 h and then slowly allowed to warm to room temperature. A saturated ammonium chloride solution (300 mL) was added and the products were extracted with ether (3 × 150 mL). The combined organic phases were dried, filtered, and concentrated to a yellow oil that was purified by flash chromatography using a 9:1 mixture of hexane and ethyl acetate to furnish ester ***18b*** (6.5 g, 88%) as a colorless oil; ir ($CHCl_3$): 3000–2850, 1700, 1640, 1605, 1452, 1375, 1218, 1167, 1118, 1022 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 7.29 (ddt, 1H, J = 15.4 Hz, 11.2 Hz, 1.6 Hz, THPOCH$_2$-CH=C*H*-), 6.42 (d, 1H, J = 11.2 Hz, -CH=CH-C*H*=C-), 5.95 (dt, 1H, J = 15.4 Hz, 6.0 Hz, THPO-CH$_2$-C*H*=CH-), 4.65 (t, 1H, J = 3.4 Hz, -OC*H*O-), 4.34 and 4.08 (2dd, 2H, J = 13.6 Hz, 5.8 Hz,

THPOCH_2CH=), 4.22 (q, 2H, J = 7.1 Hz, OCH_2CH$_3$), 3.92–3.82 and 3.56–3.47 (2m, 2H, OCHOCH_2), 1.96 (s, 3H, -CH=C(CH_3), 1.88–1.49 (m, 6H, -OCH$_2$(CH_2)$_3$-), 1.32 (t, 3H, J = 7.1 Hz, -CH$_2$CH_3); ms m/e: 254 (M^+), 153 (M^+ − OTHP).

Allylic alcohol ***17***b

The reaction was carried out according to the previously described general procedure A. Thus, the reaction of ethyl ester **16***b* (6.5 g, 25.6 mmol) with diisobutylaluminum hydride (1.0 M, 56.4 mL, 56.4 mmol) and $Na_2SO_4 \cdot 10\ H_2O$ (16.2 g, 50.3 mmol) furnished alcohol **17***b* (5.3 g, 98%) as a colorless oil; ir (neat): 3410, 2940–2865, 1450, 1125, 1025 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 6.55 (dd, 1H, J = 15.0 Hz, 11.0 Hz, THPOCH$_2$CH=C*H*-), 5.96 (d, 1H, J = 11.2 Hz, -C*H*=C(CH$_3$)-), 5.74 (dt, 1H, J = 15.0 Hz, 6.2 Hz, THPOCH$_2$-C*H*=CH-), 4.65 (t, 1H, J = 3.5 Hz, -O-C*H*-O-), 4.32–4.24 and 4.06–3.98 (2dd, 2H, J = 13.0 Hz, 6.9 Hz, THPO-CH_2CH=), 4.25 (d, 2H, J = 5.8 Hz, =C(CH$_3$)CH_2OH), 3.92–3.83 and 3.55–3.47 (2m, 2H, -OCHOCH_2-), 1.88 (s, 3H, =C(CH_3)-), 1.86–1.49 (m, 6H, -OCH$_2$(CH_2)$_3$-), 1.35 (t, 1H, J = 5.9 Hz, -CH$_2$O*H*).

Diene diether ***18***b

General procedure C

To a stirred solution of alcohol **17***b* (1.9 g, 9.0 mmol) and imidazole (1.4 g, 20.5 mmol) in 80 mL of THF was added dropwise over 5 min under argon, and at room temperature, *tert*-butylchlorodiphenylsilane (2.8 mL, 10.7 mmol). After stirring the cloudy white suspension for 1 h, a saturated ammonium chloride solution (50 mL) was added. The reaction mixture was extracted with a 2:1 mixture of hexane and ether (3 × 50 mL). The combined organic phases were washed with water, dried over $MgSO_4$, filtered, and concentrated to a crude residue that was purified by flash chromatography using a 98:2 mixture of hexane and ethyl acetate as eluant to afford **18***b* (4.0 g, 98%) as a colorless oil; ir ($CHCl_3$): 3075–3010, 2940, 2860, 1430, 1365, 1115, 1078, 1025 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 7.72–7.62 and 7.44–7.36 (2m, 10H, *Ph*$_2$Si-), 6.26 (dd, 1H, J = 14.8 Hz, 10.2 Hz, THPOCH$_2$CH=C*H*-), 5.87 (d, 1H, J = 11.8 Hz, -C*H*=C(CH$_3$)-), 5.64 (dt, 1H, J = 14.7 Hz, 6.4 Hz, THPOCH$_2$-C*H*=), 4.60 (t, 1H, J = 3.6 Hz, -OC*H*O-), 4.29 (s, 2H, =C(CH$_3$)CH_2OSi-), 4.18 and 3.91 (2dd, 2H, J = 12.5 Hz, 6.6 Hz, THPOCH_2-), 3.88–3.80 and 3.53–3.44 (2m, 2H, -O-CH_2-), 1.89 (s, 3H, -CH=C(CH_3)-), 1.88–1.43 (m, 6H, -O-CH$_2$(CH_2)$_3$-), 1.05 (s, 9H, -(CH_3)$_3$C).

Diene alcohol ***19***b

General procedure D

To a stirred solution of diene diether **18***b* (4.0 g, 8.9 mmol) in 180 mL of isopropanol was added, under argon at room temperature, pyridinium *p*-toluenesulfonate (400 mg). The resulting mixture was heated at 75°C for 3 h. After adding 100 mL of a saturated $NaHCO_3$ solution, the mixture was extracted with ether (4 × 100 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated to a crude oil that was purified by flash chromatography using a 4:1 mixture of hexane and ethyl acetate as eluant to afford **19***b* (2.8 g, 85%) as a colorless oil; ir (neat): 3340, 3070–3000, 2930, 2858, 1470, 1430, 1112, 1070, 1000 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 7.71–7.67 and 7.44–7.35 (2m, 10H, Ph_2Si=), 6.16 (dd, 1H, J = 14.9 Hz, 11.0 Hz, -CH=C*H*-), 5.84 (d, 1H, J = 11.8 Hz, =CH-C*H*=C(CH$_3$)-), 5.66 (dt, 1H, J = 15.0 Hz, 5.9 Hz, HOCH$_2$C*H*=), 4.30 (s, 2H, -CH_2OSi-), 4.05 (t, 2H, J = 6.0 Hz, HOCH_2-CH=), 1.90 (s, 3H, =C(CH_3)-), 1.13 (t, 1H, J = 6.0 Hz, *H*OCH$_2$-), 1.05 (s, 9H, -(CH_3)$_3$C); ms m/e: 366 (M^+), 335 (M^+ − OCH$_3$), 309 (M^+ − C_4H_9).

Allylic chloride ***5***b

The reaction was carried out according to the general procedure B described before. Thus, the reaction of alcohol **19***b* (180 mg, 0.49 mmol), lithium chloride (63 mg, 1.5 mmol), *s*-collidine (97 μL, 0.74 mmol), and methanesulfonyl chloride (57 μL, 0.74 mmol) in 2 mL of DMF afforded the allylic chloride **5***b* (188 mg, 99%) as an oil, which was used immediately in the coupling reaction without further purification and characterization.

(E,E)-Diene ester ***16***c

To a stirred suspension of NaH (1.48 g, 60% in oil, 37 mmol) in 60 mL of THF was rapidly added at 0°C under argon a solution of ethyl diisopropyl-2-phosphonopropionate (9.86 g, 37 mmol) in 35 mL of THF. Once the evolution of hydrogen gas ended, the solution was cooled to −78°C. Aldehyde **15***b* (5.2 g, 30 mmol) in 10 mL of THF was introduced and the resulting mixture was stirred at −78°C for 1.5 h and then at 0°C for 30 min. The reaction was stopped by addition of saturated ammonium chloride solution (75 mL) and ether (125 mL). The aqueous phase was extracted with ether (3 × 100 mL). The combined organic phases were washed with brine, dried, filtered, and evaporated to a crude residue that was purified by flash chromatography using a 7:3 mixture of hexane and ethyl acetate to furnish ester **16***c* (6.28 g, 82%) as a colorless oil; ir (CH_2Cl_2): 2940, 1700, 1644, 1610, 1230, 1038, 1025, 922 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 1.30 (t, 3H, J = 7.5 Hz, CH_3CH$_2$O-), 1.51–1.84 (m, 6H, (CH_2)$_3$CH_2O-), 1.94 (d, 3H, J = 1.0 Hz, CH_3C=CH-), 3.48–3.57 and 3.83–3.92 (2m, 2H, -OCH_2CH$_2$-), 4.21 (q, 2H, J = 7.5 Hz, -OCH_2CH$_3$), 4.37–4.41 (m, 2H, -OCH_2CH=CH), 4.66 (t, 1H, J = 2.5 Hz, -OC*H*O-), 6.13 (dt, 1H, J = 15.3 Hz, 5.6 Hz, -OCH$_2$C*H*=CH-), 6.59 (ddt, 1H, J = 15.3 Hz, 1.6 Hz, 11.5 Hz, -OCH$_2$CH=C*H*CH=), 7.18 (d, 1H, J = 11.5 Hz, =CHC*H*=CCH$_3$); ^{13}C nmr ($CDCl_3$) δ: 12.4, 14.1, 19.2, 25.2, 30.4, 60.3, 61.9, 66.7, 97.8, 126.7, 127.3, 136.9, 137.1, 168.1; ms m/e: 254 (M^+). Exact Mass (M^+) calcd.: 254.1518; found: 254.1513.

Allylic alcohol ***17***c

The reduction was carried out according to the general procedure A described before. Thus, the reaction of ester **16***c* (6.08 g, 24 mmol) with diisobutylaluminum hydride (1 M in dichloromethane, 53 mL, 53 mmol) and $Na_2SO_4 \cdot 10\ H_2O$ (15 g, 46.6 mmol) in 450 mL of CH_2Cl_2 afforded alcohol **17***c* (4.43 g, 87%) as a colorless oil; ir (CH_2Cl_2): 3620, 1200, 1075, 1035, 1020 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 1.35 (t, 1H, J = 5.0 Hz, -CH$_2$O*H*), 1.47–1.90 (m, 6H, (CH_2)$_3$CH$_2$O-), 1.79 (s, 3H, CH_3-), 3.48–3.57 and 3.84–3.94 (2m, 2H, -CH$_2$CH_2O-), 4.01–4.34 (m, 4H, -CH_2OH and CH_2OTHP), 4.66 (t, 1H, J = 2.5 Hz, -OC*H*O-), 5.80 (dt, 1H, J = 15.0 Hz, 5.0 Hz, -CH$_2$C*H*=CHCH=C), 6.09 (d, 1H, J = 11.0 Hz, -CH$_2$CH=CHC*H*=C), 6.51 (ddt, 1H, J = 15.0 Hz, 11.0 Hz, 1.0 Hz, -CH$_2$CH=C*H*CH=C); ^{13}C nmr ($CDCl_3$) δ: 13.8, 19.1, 25.2, 30.4, 61.9, 67.4, 67.6, 97.5, 123.5, 128.4, 128.7, 137.9; ms m/e: 212 (M^+). Exact Mass (M^+) calcd. 212.1412; found: 212.1410.

Diene diether ***18***c

The reaction was carried out according to the previously described general procedure C. Thus, the reaction of alcohol **17***c* (1.137 g, 5.36 mmol), imidazole (0.833 g, 12.24 mmol), and *tert*-butylchlorodiphenylsilane (1.64 mL, 1.73 g, 6.31 mmol) in 32 mL of THF afforded diene diether **18***c* (2.29 g, 95%) as a colorless oil; ir (neat): 3080–3010, 2945, 2860, 1450, 1360, 1120–1000 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 1.06 (s, 9H, -(CH_3)$_3$C), 1.47–1.95 (m, 6H, -(CH_2)$_3$CH$_2$O-), 1.71 (s, 3H, -CH_3), 3.48–3.57 and 3.84–3.94 (2m, 2H, -CH$_2$CH_2O-), 4.00–4.10 and 4.30–4.39 (2m, 2H, -CH_2OTHP), 4.10 (s, 2H, -CH_2OSi-), 4.68 (t, 1H, J = 2.8 Hz, -OC*H*O-), 5.77 (dt, 1H, J = 15.0 Hz, 6.4 Hz, OCH$_2$C*H*=CHCH=C), 6.21 (d, 1H, J = 11.2 Hz, -CH=CHC*H*=C), 6.54 (dd, 1H, J = 15.1 Hz, 11.2 Hz, -CH$_2$CH=C*H*CH=C), 7.35–7.48 and 7.65–7.72 (2m, 10H, Ph_2Si-).

Diene alcohol ***19***c

The reaction was carried out according to the previously described general procedure D. Thus, the reaction of diene diether **18***c* (734.4 mg, 1.63 mmol) with pyridinium *p*-toluenesulfonate (73.4 mg) in 20 mL of isopropanol provided allylic alcohol **19***c* (484.9 mg, 81%) as a colorless oil; ir (neat): 3340, 3050, 2940, 2860, 1470, 1430, 1370, 1110, 1070 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ:

1.07 (s, 9H, -(CH_3)$_3$C), 1.32 (t, 1H, J = 5.9 Hz, -CH_2OH), 1.72 (s, 3H, -CH_3), 4.20 (s, 2H, -CH_2OSi-), 4.23 (t, 2H, J = 5.7 Hz, HOCH_2CH=), 5.83 (dt, 1H, J = 15.0 Hz, 6.1 Hz, HOCH_2CH=CH-), 6.20 (d, 1H, J = 11.2 Hz, -CH=CHCH=C), 6.53 (dd, 1H, J = 15.1 Hz, 11.1 Hz, -CH=CHCH=C), 7.30–7.48 and 7.65–7.71 (2m, 10H, Ph_2Si-).

Allylic chloride **5**c

The reaction was carried out according to the general procedure B as described before. Thus, alcohol **19***c* (1.096 g, 2.99 mmol) reacted with lithium chloride (0.507 g, 11.97 mmol), *s*-collidine (0.79 mL, 0.724 g, 5.98 mmol), and methanesulfonyl chloride (0.46 mL, 0.681 g, 5.98 mmol) in 19 mL of DMF to give **5***c* (1.109 g, 96%) as a yellowish oil; ^{1}H nmr ($CDCl_3$) δ: 1.26 (s, 9H, -(CH_3)$_3$C), 1.71 (s, 3H, -CH_3), 4.11 (s, 2H, -CH_2OSi-), 4.18 (d, 2H, J = 6.9 Hz, ClCH_2CH=), 5.78 (dt, 1H, J = 14.8 Hz, 7.3 Hz, -CH_2CH=CH-), 6.21 (d, 1H, J = 10.0 Hz, -CH=CHCH=C-), 6.57 (dd, 1H, J = 14.8 Hz, 11.2 Hz, -CH=CHCH=C), 7.35–7.48 and 7.65–7.75 (2m, 10H, Ph_2Si-).

Alcohol **20**

General procedure E

To a stirred solution of silyl ether **4** (490.5 mg, 1.37 mmol) in 12 mL of THF was added dropwise over 12 min at 0°C under argon a solution of tetrabutylammonium fluoride (1.5 mL, 1 M, 1.5 mmol) in THF. The resulting mixture was stirred at 0°C for 10 min and then at room temperature for 2.5 h. The solvent was removed by evaporation and the resulting yellow residue was purified by flash chromatography using a 7:3 mixture of hexane and ethyl acetate as eluant to afford colorless oil **20** (305.4 mg, 91%); ir (neat): 3420, 2955, 2880, 1740, 1437, 1380, 1240, 1155, 1050 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 1.64 (s, 3H, =C-CH_3), 2.10–2.00 (m, 4H, =C(CH_3)-CH_2CH_2-), 2.28 (q, 2H, J = 7.0 Hz, HOCH_2CH_2=CH), 3.34 (t, 1H, J = 7.0 Hz, -CH_2CH(CO_2CH_3)$_2$), 3.63 (m, 2H, HOCH_2CH_2-), 3.73 (s, 6H, CH(CO_2CH_3)$_2$), 5.16 (t, 1H, J = 7.0 Hz, -CH=C(CH_3)-); ms m/e: 244 (M^+), 213 (M^+ − OCH_3).

Methanesulfonate ester **21**

General procedure F

To a stirred solution of the alcohol **20** (277 mg, 1.1 mmol) and triethylamine (0.24 mL, 1.7 mmol) in 16 mL of CH_2Cl_2 was added, dropwise over 5 min at 0°C under argon, methanesulfonyl chloride (0.10 mL, 1.3 mmol). The mixture was stirred at 0°C for 1 h and then poured into 80 mL of H_2O. The aqueous layer was extracted with CH_2Cl_2 (4 × 50 mL) and the combined organic phases were washed with water, dried over $MgSO_4$, filtered, and concentrated to a crude residue that was purified by flash chromatography using a 3:1 mixture of hexane and ethyl acetate to provide **21** (346 mg, 94%) as a colorless oil; ir (neat): 2950, 2850, 1730, 1440, 1358, 1230, 1172 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 1.64 (d, 3H, J = 1.1 Hz, =C(CH_3)-), 2.03–2.00 (m, 4H, -C(CH_3)CH_2CH_2-), 2.46 (q, 2H, J = 7.0 Hz, MsOCH_2CH_2-), 3.00 (s, 3H, -SO_2CH_3), 3.33 (m, 1H, -CH(CO_2CH_3)$_2$), 3.74 (s, 6H, -(CO_2CH_3)$_2$), 4.18 (t, 2H, J = 6.9 Hz, MsOCH_2CH_2-), 5.13 (t, 1H, J = 6.0 Hz, -CH=C(CH_3)-); ms m/e: 322 (M^+), 290 (M^+ − CH_3OH).

Triene **22**b

General procedure G

To a stirred suspension of NaH (46 mg, 60%, 1.2 mmol) in 6 mL of THF was added dropwise at 0°C under argon a solution of the mesylate **21** (340 mg, 1.1 mmol) in 6 mL of THF. The mixture was slowly warmed to room temperature and stirred for 45 min. After cooling again to 0°C, a solution of the crude allylic chloride **5***b* (540 mg, 1.4 mmol) in 6 mL of DMF was added dropwise over 15 min. The resulting mixture was stirred at room temperature for 36 h before it was poured into 60 mL of saturated ammonium chloride solution. The aqueous phase was extracted with a 2:1 mixture of ether and hexane (5 × 40 mL). The combined organic phases were washed with water, 5% $NaHCO_3$ solution, and brine, then dried, filtered, and concentrated. The thick yellow residue was purified by flash chromatography using a 5:1 mixture of hexane and ethyl acetate to give triene **22***b* (355 mg, 50%) along with both starting materials **21** and **5***b* in about 10% each. Compound **22***b*: ir (neat); 3070–3000, 2950, 2860, 1740, 1430, 1360, 1178, 1112 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 1.05 (s, 9H, -(CH_3)$_3$C), 1.58 (d, 3H, J = 0.9 Hz, -CH_2CH_2C(CH_3)=), 1.80–1.95 (m, 7H, (CO_2CH_3)$_2$CRCH_2CH_2- and =CH-CH=C(CH_3)-), 2.41 (q, 2H, J = 7.0 Hz, -CH_2CH_2OMs), 2.59 (d, 2H, J = 7.5 Hz, (CO_2CH_3)$_2$CRCH_2-CH=), 2.98 (s, 3H, -SO_2CH_3), 3.67 (s, 6H, (CO_2CH_3)$_2$), 4.14 (t, 2H, J = 7.0 Hz, -CH_2OMs), 4.25 (s, 2H, -CH_2OSi-), 5.08 (t, 1H, J = 7.3 Hz, -C(CH_3)=CHCH_2-), 5.32 (dt, 1H, J = 14.8 Hz, 7.4 Hz, -CH_2CH=CH-), 5.80 (d, 1H, J = 11.0 Hz, =CHCH=C(CH_3)-), 6.08 (dd, 1H, J = 14.8 Hz, 11.0 Hz, -CH_2CH=CH-), 7.35–7.48 and 7.65–7.71 (2m, 10H, Ph_2Si-); ms m/e: 670 (M^+), 631 (M^+ − C_4H_9).

Triene **22**c

The reaction was carried in a similar fashion as described in the general procedure G. Thus, the reaction of dienophile **21** (201.1 mg, 0.62 mmol) with NaH (29.0 mg, 60%, 0.73 mmol) and diene **5***c* (310.0 mg, 0.81 mmol) in a mixture of DMF and THF (1:1, 6 mL) afforded triene **22***c* (289.6 mg, 70%) and recovered starting material **21** (35.4 mg, 18%). Compound **22***c*: ir (neat): 3020, 2940, 2850, 1740, 1430, 1350, 1170, 1110 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 1.06 (s, 9H, -(CH_3)$_3$C), 1.64 (s, 3H, =CCH_3),1.68 (s, 3H, =CCH_3), 1.84–2.00 (m, 4H, C(CO_2CH_3)$_2$CH_2CH_2-), 2.45 (q, 2H, J = 7.2 Hz, -CH_2CH_2OMs), 2.72 (d, 2H, J = 7.5 Hz, -CH_2CH=CH-), 2.99 (s, 3H, -SO_2CH_3), 3.73 (s, 6H, C(CO_2CH_3)$_2$), 4.07 (s, 2H, -CH_2OSi-), 4.17 (t, 2H, J = 7.0 Hz, -CH_2OMs), 5.13 (t, 1H, J = 7.4 Hz, -(CH_3)C=CHCH_2-), 5.42 (dt, 1H, J = 14.8 Hz, 7.4 Hz, -CH_2CH=CHCH=C), 6.07 (d, 1H, J = 11.5 Hz, -CH=CHCH=C), 6.33 (dd, 1H, J = 14.7 Hz, 10.8 Hz, -CH=CHCH=C), 7.34–7.47 and 7.64–7.71 (2m, 10H, Ph_2Si-).

Tetraester **23**b

General procedure H

To a stirred suspension of NaH (84 mg, 60% in oil, 2.1 mmol) in a mixture of DMF and THF (1:1, 6 mL), dimethyl malonate (0.27 mL, 2.3 mmol) was added dropwise at 0°C under argon. After stirring the mixture at 0°C for 45 min, a solution of triene **22***b* (311 mg, 0.46 mmol) in a mixture of DMF and THF (1:1, 6 mL) was introduced by syringe, followed by addition of potassium iodide (7.6 mg, 46 mmol). The resulting mixture was heated at 80°C for 18 h before it was poured into 60 mL of H_2O. The mixture was extracted with CH_2Cl_2 (3 × 40 mL) and ether (3 × 40 mL). 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 using a mixture of hexane and ethyl acetate (85:15) to afford **23***b* (235 mg, 72%) as a colorless oil; ir (neat): 3070–3000, 2955, 2860, 1735, 1435, 1200, 1110 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 1.05 (s, 9H, -(CH_3)$_3$C), 1.52 (d, 3H, =C(CH_3)-CH_2CH_2), 1.85–2.00 (m, 11H, -CH_2CH_2CH=C(CH_3)CH_2CH_2-, and SiOCH_2-C(CH_3)=), 2.58 (d, 2H, J = 7.3 Hz, =CHCH_2CR(CO_2CH_3)$_2$), 3.24–3.40 (m, 1H, -CH-(CO_2CH_3)$_2$), 3.66–3.75 (3s, 12H, 4 × -OCH_3), 4.25 (s, 2H, -CH_2OSi-), 4.95–5.50 (m, 2H, -CH_2CH= and MsOCH_2CH_2-CH=), 5.70–6.25 (m, 2H, -C(CH_3)=CHCH=), 7.38–7.75 (m, 10H, Ph_2Si-).

Tetraester **23**c

The reaction was prepared as described in the general procedure H. Thus, the reaction of dimethyl malonate (0.25 mL, 2.15 mmol) with NaH (77.4 mg, 60%, 1.94 mmol) and triene **22***c* (289.6 mg, 0.43 mmol) in the presence of KI (7.1 mg, 43 mmol) yielded the tetraester **23***c* (273.3 mg, 90%); ^{1}H nmr ($CDCl_3$) δ: 1.05 (s, 9H, -(CH_3)$_3$C), 1.56 (s, 3H, =CCH_3), 1.67 (s, 3H, =CCH_3), 1.80–2.05 (m, 8H, -CH_2CH_2CH=C(CH_3)CH_2CH_2-), 2.71 (d, 2H, J = 7.5 Hz, -CH_2CH=CH-), 3.35 (m, 1H, -CH(CO_2CH_3)$_2$), 3.72

and 3.75 (2s, 12H, 4 × -OCH_3), 4.06 (s, 2H, -CH_2OSi-), 5.11 (t, 1H, J = 7.0 Hz, -(CH$_3$)C=CHCH$_2$-), 5.43 (dt, 1H, J = 15.0 Hz, 7.0 Hz, -CH=CHCH=CH-), 6.07 (d, 1H, J = 11.0 Hz, -CH=CHCH=C), 6.33 (dd, 1H, J = 15.0 Hz, 11.0 Hz, -CH=CHCH=C-), 7.30–7.47 and 7.63–7.70 (2m, 10H, Ph_2Si-).

Allylic alcohol ***24****b*

The reaction was performed in a similar fashion as described in the general procedure E. Thus, the silyl ether **23***b* (231 mg, 0.33 mmol) was treated with tetrabutylammonium fluoride (1.0 M in THF, 0.49 mL, 0.49 mmol) in 3 mL of THF to give the alcohol **24***b* (110 mg, 72%) as a colorless oil; ir (neat): 3500, 2950, 2860, 1735, 1438, 1200 cm^{-1}; ^{1}H nmr (CDCl$_3$) δ: 1.38 (t, 1H, J = 5.0 Hz, -CH$_2$OH), 1.56 (s, 3H, -CH$_2$CCCH_3)=), 1.85 (s, 3H, =CHCH=C(CH_3)-), 1.87–2.04 (m, 8H, -CH_2CH_2CH=C(CH$_3$)-CH_2CH_2-), 2.69 (d, 2H, J = 7.6 Hz, -CH_2CR(CO$_2$CH$_3$)$_2$), 3.35 (t, 1H, J = 7.1 Hz, -CH(CO$_2$CH$_3$)$_2$), 3.72 and 3.73 (2s, 12H, 4 × -OCH_3), 4.22 (d, 2H, J = 4.8 Hz, HOCH_2-), 5.09 (t, 1H, J = 7.0 Hz, -CH$_2$CH=), 5.42 (dt, 1H, J = 14.9 Hz, 7.5 Hz, -CH=CHCH=C-), 5.89 (d, 1H, J = 11.4 Hz, -CH=CHCH=C-), 6.36 (dd, 1H, J = 14.9 Hz, 11.1 Hz, CH=CHCH=C-); ms m/e: 468 (M$^+$), 450 (M$^+$ − H$_2$O).

Allylic alcohol ***24****c*

The reaction was carried out as described in the general procedure E. Thus, the silyl ether **23***c* (273.3 mg, 0.39 mmol) was treated with tetrabutylammonium fluoride (1.0 M in THF, 0.7 mL, 0.70 mmol) in 6 mL of THF to furnish the alcohol **24***c* (174.0 mg, 95%) as a colorless oil; ir (neat): 3520, 2950, 2850, 1735, 1435, 1200 cm^{-1}; ^{1}H nmr (CDCl$_3$) δ: 1.42 (t, 1H, J = 5.8 Hz, -CH$_2$OH), 1.56 (s, 3H, =CCH_3), 1.76 (s, 3H, =CCH_3), 1.80–2.08 (m, 8H, -CH_2CH_2CH=C(CH$_3$)CH_2CH_2-), 2.72 (d, 2H, J = 7.6 Hz, -CH_2CH=CHCH=C), 3.35 (t, 1H, J = 7.1 Hz, -CH(CO$_2$CH$_3$)), 3.72 and 3.73 (2s, 12H, 4 × -OCH_3), 4.05 (d, 2H, J = 5.9 Hz, -CH_2OH), 5.09 (t, 1H, J = 7.0 Hz, CH$_2$CH=CCCH$_3$-), 5.48 (dt, 1H, J = 14.9 Hz, 7.6 Hz, -CH=CHCH=C-), 6.01 (d, 1H, J = 10.4 Hz, -CH=CHCH=C-), 6.32 (dd, 1H, J = 14.9 Hz, 10.8 Hz, -CH=CHCH=C-).

Allylic chloride ***25****b*

The reaction was carried out as described in the general procedure B. Thus, treatment of allylic alcohol **24***b* (58.8 mg, 0.13 mmol) with lithium chloride (21.2 mg, 0.50 mmol), *s*-collidine (66.3 μL), and methanesulfonyl chloride (39 μL, 0.50 mmol) in DMF provided the allylic chloride **25***b* (51.0 mg, 84%) as a colorless oil that was used immediately in the next cyclization step without further purification and characterization.

Allylic bromide ***25****c*

To a stirred solution of the allylic alcohol **24***c* (22.0 mg, 47 μmol) and CBr$_4$ (19.4 mg, 58 μmol) in 0.6 mL of CH$_2$Cl$_2$ was added, dropwise at 0°C under argon, a solution of PPh$_3$ (17.3 mg, 66 μmol) in 0.4 mL of CH$_2$Cl$_2$. The resulting mixture was allowed to warm to room temperature and then stirred for about 2 h until the starting material **24***c* was consumed. After the solvent was evaporated, the crude residue was purified by flash chromatography using a 5:1 mixture of hexane and ethyl acetate to give allylic bromide **25***c* (21.4 mg, 40 μmol, 86%) as an oil that was used immediately in the next cyclization step without further purification and characterization.

TTC macrocycle ***1****b*

General procedure I

To a stirred suspension of Cs$_2$CO$_3$ (161.0 mg, 0.493 mmol) in a mixture of DMF and THF (1:1, 20 mL) was slowly added, at 70°C under argon by automatic syringe pump over a period of 12 h, a solution of allylic chloride **25***b* (51.3 mg, 0.105 mmol) in a mixture of DMF and THF (1:1, 15 mL). After the addition was completed, the stirring was continued for 9 h longer at 70°C. The solid was removed by filtration, and the filtrate was concentrated. The crude residue thus obtained was purified by flash chromatography using a 9:1 mixture of hexane and ethyl acetate to give two products, which were further purified by recrystallization from a minimum amount of CH$_2$Cl$_2$ in hexane to afford macrocyclic monomer **1***b* (34.0 mg, 72%) and macrocyclic dimer **26***b* (10 mg, 11%).

Compound ***1****b*: mp 140–143°C; ir (CHCl$_3$): 3020, 2945, 2850, 1727, 1435, 1225 cm^{-1}; ^{1}H nmr (CDCl$_3$) δ: 1.57 (s, 3H, -CH$_2$CH$_2$C(CH_3)=), 1.62 (s, 3H, =CHCH=C(CH_3)-), 1.80–1.91 and 1.97–2.08 (2m, 8H, -CH_2CH_2C(CH$_3$)=CHCH_2CH_2-), 2.67 (d, 2H, J = 7.7 Hz, =CH-CH_2CR(CO$_2$CH$_3$)$_2$), 2.90 (s, 2H, =C(CH$_3$)CH_2CR(CO$_2$CH$_3$)$_2$), 3.72 (s, 12H, 4 × -OCH_3), 5.07 (t, 1H, J = 5.0 Hz, -CH$_2$CH=C(CH$_3$), 5.17 (dt, 1H, J = 14.1 Hz, 7.2 Hz, -CH$_2$CH=CH-), 5.92–6.11 (m, 2H, -CH=CHCH=C(CH$_3$)-); ms m/e: 450 (M$^+$). Exact Mass (M$^+$) calcd.: 450.2253; found: 450.2246. Compound **1***b* was further characterized by X-ray crystallography.

Compound ***26****b*: mp 183–185°C; ir (neat): 3020, 2955, 2858, 1728, 1438, 1220 cm^{-1}; ^{1}H nmr (CDCl$_3$) δ: 1.52 (s, 6H, -CH$_2$CH$_2$C(CH_3)-), 1.59 (s, 6H, =CHCH=C(CH_3)-), 1.76–1.95 (m, 16H, -CH_2CH_2C(CH$_3$)CHCH_2CH_2-), 2.70 (d, 4H, J = 7.4 Hz, =CHCH_2CR(CO$_2$CH$_3$)$_2$), 2.89 (s, 4H, =C(CH$_3$)CH_2-CR(CO$_2$CH$_3$)$_2$), 3.71 (s, 24H, 8 × -OCH_3), 5.02 (m, 2H, -CH$_2$CH=C(CH$_3$)-), 5.34 (dt, 2H, J = 14.9 Hz, 7.4 Hz, -CH$_2$CH=CH-), 5.91 (d, 2H, J = 10.9 Hz, -CH=CHCH=C-), 6.31 (dd, 2H, J = 14.7 Hz, 11.0 Hz, -CH=CHCH=C-); ms m/e: 900 (M$^+$), 885 (M$^+$ − CH$_3$), 869 (M$^+$ − OCH$_3$). Exact Mass (M$^+$) calcd.: 900.4507; found: 900.4502.

TTT macrocycle ***1****c*

The macrocyclization was carried out as described in the general procedure I. Thus, a solution of allylic bromide **25***c* (21.4 mg, 40 μmol) in 10 mL of DMF–THF (1:1) was added slowly to a Cs$_2$CO$_3$ (74.2 mg, 230 μmol) suspension in 14 mL of DMF–THF (1:1) at 80°C over 5 h. After the mixture was stirred for an additional 10 h, it was worked up to provide pure macrocycle **1***c* (13.1 mg, 29 μmol, 73%) and dimer **26***c* (1.0 mg, 5%).

Compound ***1****c*: ir (neat): 2960, 2860, 1738, 1450, 1220 cm^{-1}; ^{1}H nmr (CDCl$_3$) δ: 1.46 (s, 3H, -CH$_2$C(CH_3)=CH-), 1.65 (s, 3H, =CHCH=C(CH_3)-), 1.73–2.07 (m, 8H, -CH_2CH_2C(CH$_3$)=CHCH_2CH_2-), 2.66 (d, 2H, J = 7.0 Hz, -CH_2CH=CHCH=), 2.80 (s, 2H, -CH_2C(CH$_3$)=CHCH=), 3.73 (s, 12H, 4 × -OCH_3), 4.98 (t, 1H, J = 7.0 Hz, -CH$_2$CH=C(CH$_3$)-), 5.67 (dt, 1H, J = 14.9 Hz, 7.0 Hz, -CH=CHCH=C), 5.90 (d, 1H, J = 10.7 Hz, -CH=CHCH=C-), 6.11 (dd, 1H, J = 14.9 Hz, 10.8 Hz, -CH=CHCH=C); ms m/e: 450 (M$^+$).

Compound ***26****c*: ir (neat): 3020, 2950, 2860, 1735, 1440, 1200 cm^{-1}; ^{1}H nmr (CDCl$_3$) δ: 1.56 (s, 12H, 4 × =C(CH_3)-), 1.75–2.00 (m, 16H, -CH_2CH_2C(CH$_3$)=CHCH_2CH_2-), 2.72 (d, 4H, J = 7.5 Hz, -CH_2CH=CHCH=C-), 2.76 (s, 4H, =CH-CH=C(CH$_3$)CH_2-), 3.70 and 3.72 (2s, 24H, 8 × -OCH_3), 5.11 (m, 2H, -CH$_2$CH=C(CH$_3$)CH$_2$-), 5.39 (dt, 2H, J = 15.1 Hz, 7.5 Hz, -CH=CHCH=C-), 5.87 (d, 2H, J = 10.6 Hz, -CH=CHCH=C-), 6.25 (dd, 2H, J = 15.1 Hz, 10.8 Hz, -CH=CHCH=C-); ms m/e: 900 (M$^+$), 869 (M$^+$ − OCH$_3$).

Triene diether ***28***

The coupling reaction of diene and dienophile was carried out as described in the general procedure G. Thus, treatment of dimethyl malonate **4** (622.0 mg, 1.7 mmol) with NaH (89.0 mg, 60%, 2.2 mmol) in 20 mL of THF–DMF (1:1) followed by addition of allylic chloride **5***a* (507.4 mg, 2.2 mmol) afforded coupling product **28** (578.0 mg, 61%) as a colorless oil; ir (neat): 2950, 1735, 1255, 1220, 1025, 838 cm^{-1}; ^{1}H nmr (CDCl$_3$) δ: 0.04 (s, 6H, (CH_3)$_2$Si-), 0.88 (s, 9H, -(CH_3)$_3$C), 1.49–1.83 (m, 6H, -OCH$_2$(CH_2)$_3$-), 1.58 (d, 3H, J = 1.0 Hz, CH_3C=CHCH$_2$CH$_2$-), 1.67 (s, 3H, CH_3C=CHCH=CH-), 1.85–1.90 (m, 4H, -C=CH-CH_2CH_2-), 2.18 (t, 2H, J = 7.5 Hz, -CH_2CH$_2$OSi-), 2.79 (s, 2H, =CHCH=C(CH$_3$)CH_2-), 3.47–3.56 and 3.82–3.93 (2m, 2H, -OCH_2(CH$_2$)$_3$-), 3.64 (t, 2H, J = 7.5 Hz, -SiOCH_2CH$_2$-), 3.71 (s, 6H, -C(CO$_2$CH_3)$_2$), 4.11–4.21 and 4.30–4.39 (2m, 2H, -CH_2OTHP), 4.64 (t, 1H, J = 2.5 Hz, -OCHO-), 5.10 (m,

1H, -C=C*H*CH_2CH_2-), 5.55 (dt, 1H, J = 10.0 Hz, 5.0 Hz, -CH_2C*H*=CHCH=C-), 6.11 (d, 1H, -CH=CHC*H*=C-), 6.30 (ddt, 1H, J = 10.0 Hz, 11.0 Hz, 1.0 Hz, -CH=C*H*CH=C-); ms m/e: 495 ($M^+ - C_4H_9$).

Allylic alcohol ***29***

The desilylation was carried out as described in the general procedure E. Thus, treatment of silyl ether **28** (578.0 mg, 1.05 mmol) with tetrabutylammonium fluoride solution (1 M in THF, 1.93 mL, 1.93 mmol) in 10 mL of THF afforded allylic alcohol **29** (385.0 mg, 81%) as an oil; ir (neat): 3650–3200, 2950, 1735, 1440, 1270, 1220, 1117, 1025 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.47 (t, 1H, J = 5.0 Hz, -CH_2O*H*), 1.49–1.83 (m, 6H, -$OCH_2(CH_2)_3$-), 1.60 (d, 3H, J = 1.0 Hz, -(CH_3)C=$CHCH_2CH_2$-), 1.67 (d, 3H, J = 1.0 Hz, -(CH_3)C=CHCH=), 1.86–1.95 (m, 4H, -(CH_3)C=$CHCH_2CH_2$-), 2.23 (t, 2H, J = 5.0 Hz, -CH_2CH_2OH), 2.79 (s, 2H, -CH_2C(CH_3)=CHCH=CH-), 3.47–3.56 and 3.83–3.93 (2m, 2H, -$OCH_2(CH_2)_3$-), 3.66 (dt, 2H, J = 5.0 Hz, 5.0 Hz, -CH_2CH_2OH), 3.72 (s, 6H, -C(CO_2CH_3)$_2$), 4.11–4.21 and 4.30–4.39 (2m, 2H, -CH_2OTHP), 4.64 (t, 1H, J = 2.5 Hz, -OC*H*O-), 5.18 (m, 1H, -C=C*H*CH_2CH_2-), 5.55 (dt, 1H, J = 10.0 Hz, 5.0 Hz, -C*H*=CHCH=C-), 6.11 (d, 1H, J = 11.0 Hz, -CH=CHC*H*=C-), 6.30 (ddt, 1H, J = 10.0 Hz, 11.0 Hz, 1.0 Hz, -CH=C*H*CH=C-); ms m/e: 438 (M^+). Exact Mass (M^+) calcd: 438.2617; found: 438.2614.

Methanesulfonate ester ***30***

The mesylation reaction was carried out as described in the general procedure F. Thus, the alcohol **29** (380.0 mg, 0.87 mmol) was treated with methanesulfonyl chloride (84 μL, 122.0 mg, 1.06 mmol) in the presence of triethylamine (183 μL, 142.0 mg, 1.32 mmol) to afford sulfonate ester **30** (440.5 mg, 0.85 mmol), 98%) as an oil that was used immediately for the next reaction without further purification and characterization.

Tetraester ***31***

The introduction of dimethyl malonate unit into triene **30** was carried out as described in the general procedure H. Thus, the mesylate **30** (440.5 mg, 0.85 mmol) was treated with NaH (196.0 mg, 60% in oil, 4.86 mmol) in a mixture of DMF and THF (1:1, 12 mL), followed by addition of dimethyl malonate (0.61 mL, 705.0 mg, 5.4 mmol) and a catalytic amount of KI (77.0 mg) to give alkylated product **31** (338.0 mg, 0.61 mmol, 72%) as an oil; ir (neat): 2950, 1735, 1435, 1080, 1025 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.46–1.83 (m, 6H, -$OCH_2(CH_2)_3$-), 1.56 (d, 3H, J = 1.0 Hz, -(CH_3)C=$CHCH_2CH_2$-), 1.68 (s, 3H, -(CH_3)C=CHCH=CH-), 1.85–1.90 (m, 4H, -C=CHCH_2CH_2-), 1.96–2.02 (m, 4H, -CH_2CH_2CH(CO_2CH_3)$_2$), 2.79 (s, 2H, =C(CH_3)-CH_2C(CO_2CH_3)$_2$-), 3.28–3.36 (m, 1H, -CH(CO_2CH_3)$_2$), 3.46–3.56 and 3.82–3.92 (2m, 2H, -$OCH_2(CH_2)_3$-), 3.71 and 3.73 (2s, 12H, 4 × -OCH_3), 4.11–4.21 and 4.30–4.39 (2m, 2H, -CH_2OTHP), 4.64 (t, 1H, J = 2.5 Hz, -OC*H*O-), 5.09 (m, 1H, -C=C*H*CH_2CH_2-), 5.55 (dt, 1H, J = 10.0 Hz, 5.0 Hz, -C*H*=CHCH=C-), 6.11 (d, 1H, J = 11.0 Hz, -CH=CHC*H*=C-), 6.30 (ddt, 1H, J = 10.0 Hz, 11.0 Hz, 1.0 Hz, -CH=C*H*CH=C-); ms m/e: 552 (M^+). Exact Mass (M^+) calcd.: 552.2934; found: 552.2922.

Allylic alcohol ***32***

The deprotection of THP–ether was carried out in the same way as described in the general procedure D. Thus, treatment of THP–ether **31** (330.0 mg, 0.59 mmol) with pyridinium p-toluenesulfonate (17.0 mg, 0.07 mmol) in 6 mL of CH_3OH afforded alcohol **32** (268.0 mg, 97%) as a viscous oil; ir (neat): 3600–3200, 2950, 1730, 1435, 1270, 1210 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.55 (t, 1H, J = 5.0 Hz, -CH_2O*H*), 1.56 (d, 3H, J = 1.0 Hz, -(CH_3)C=$CHCH_2CH_2$-), 1.66 (s, 3H, -(CH_3)C=CHCH=CH-), 1.84–1.88 (m, 4H, -C=CHCH_2CH_2-), 1.96–2.01 (m, 4H, -CH_2CH_2CH(CO_2CH_3)$_2$), 2.78 (s, 2H, =C(CH_3)CH_2C(CO_2CH_3)$_2$-), 3.28–3.35 (m, 1H, -CH(CO_2CH_3)$_2$), 3.71 and 3.73 (2s, 12H, 4 × -OCH_3), 5.29 (dt, 2H, J = 1.0 Hz, 5.0 Hz, -CH_2OH), 5.08 (m, 1H, -C=C*H*CH_2CH_2-), 5.58 (dt, 1H, J = 10.0 Hz, 5.0 Hz, -C*H*=CHCH=C-), 6.08 (d, 1H, J = 11.0 Hz, -CH=CHC*H*=C-), 6.29 (ddt, 1H, J = 10.0 Hz, 11.0 Hz, 1.0 Hz, -CH=C*H*CH=C-); ms m/e: 450 ($M^+ - H_2O$). Exact Mass ($M^+ - H_2O$) calcd.: 450.2253; found: 450.2253.

CTT macrocycle ***1***a

The preparation of allylic chloride **33** was carried out as described in the general procedure B. Thus, treatment of allylic alcohol **33** (35.0 mg, 75 μmol) with LiCl (12.6 mg, 299 μmol), s-collidine (40 μL, 299 μmol), and methanesulfonyl chloride (23 μL, 299 μmol) in 0.5 mL of DMF yielded allylic chloride **33** (35 mg) as a crude oil that was used immediately in the next cyclization step without characterization and further purification.

The cyclization of allylic chloride **33** was carried out in as described in the general procedure I. Thus, a solution of crude oil **33** (35 mg) in a mixture of DMF and THF (1:1, 5 mL) was added at 70°C over 5 h slowly to a Cs_2CO_3 (122 mg, 375 μmol) suspension in a mixture of DMF and THF (1:1, 12 mL). The stirring was continued for an additional 8 h after completion of the addition. Work-up of the reaction mixture followed by flash chromatography and recrystallization (CH_2Cl_2–hexane) furnished a crystalline compound **1***a* (19 mg, 57% from alcohol **33**); mp 173–176°C; ^1H nmr ($CHCl_3$) δ: 1.53 (s, 3H, -(CH_3)C=CHCH=CH-), 1.59 (d, 3H, J = 1.0 Hz, -(CH_3)C=$CHCH_2CH_2$), 1.80–2.03 (m, 8H, -CH_2CH_2C(CH_3)=CHCH_2CH_2-), 2.76 (d, 2H, J = 8.0 Hz, -CH_2CH=CHCH=C-), 2.89 (s, 2H, CH=CHCH=C(CH_3)CH_2-), 3.728 and 3.730 (2s, 12H, 4 × -OCH_3), 5.05 (m, 1H, -C*H*=CHCH=C-), 5.32 (t, 1H, J = 7.5 Hz, -C=C*H*CH_2CH_2-), 5.95 (d, 1H, J = 11.0 Hz, -CH=CHC*H*=C-), 6.36 (dd, 1H, J = 10.0 Hz, 11.0 Hz, -CH=C*H*CH=C-); ms m/e: 450 (M^+). Exact Mass (M^+) calcd.: 450.2253; found: 450.2246.

Diels–Alder reaction of ***1***a

Solid macrocycle **1***a* (5.0 mg, 11 μmol) was heated in a vacuum-sealed quartz tube (20 cm long, 8 mm diameter) at 360°C for 80 min. After the tube was cooled to room temperature, the residue in the tube was dissolved in CH_2Cl_2 and then transferred into a flask. After the solvent was evaporated, the residue was purified by flash chromatography with a 12:7:1 mixture of $CHCl_3$, hexane, and Et_2O to provide a mixture (3.1 mg, 62%) that displayed only one spot on tlc but contained several tricyclic isomers as observed by gc. Attempts to separate each isomer of the mixture by flash chromatography using different solvent systems were unsuccessful. Proton nmr of the mixture is very complicated, but it does contain all the characteristic peaks for tricycle **34** whose spectral data are provided below.

The gc analysis of the reaction mixture before flash chromatography reveals four major products, each contributing between 10 and 19% yield, along with a number of minor ones (<9%).

Diels–Alder reaction of ***1***b

Solid macrocycle **1***b* (18.8 mg, 41.7 μmol) was placed in the bottom of a quartz tube, which was then sealed under vacuum. The tube was heated to 300°C for 2 h. The crude residue was transferred to a flask with CH_2Cl_2 and then purified by flash chromatography with a 97:3 mixture of hexane and ethyl acetate to give tricycle **41** (12.4 mg, 66%) as a crystalline solid; mp 119–122°C; ir (neat): 2960, 2850, 1738, 1450, 1240, 1100 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 0.92 (d, 3H, J = 6.9 Hz, CH_3CH-), 1.25–2.60 (m, 15H, all other CH_2 and C*H*), 1.62 (s, 3H, CH_3C=), 3.63–3.75 (m, 12H, 4 × -OCH_3), 5.19 (s, 1H, -C*H*=CCH_3); ^1H nmr (C_6D_6) δ: 0.82 (d, 3H, J = 6.9 Hz, C*H*CH-), 1.05–2.60 (m, 15H, all other CH_2 and C*H*), 1.62 (s, 3H, CH_3C=CH), 3.30–3.35 (m, 12H, 4 × -OCH_3), 5.20 (s, 1H, -C*H*=CCH_3). The relative stereochemistry for compound **41** was further confirmed by X-ray crystallography.

Diels–Alder reaction of ***1***c

A solution of macrocycle **1***c* (13.0 mg, 28.9 μmol) in 2 mL of toluene was heated in a vacuum-sealed quartz tube at 200°C for 17 h. After the tube was opened, the reaction mixture was trans-

ferred into a flask with CH_2Cl_2 and then evaporated. The residue was purified by flash chromatography using a 5:1 mixture of hexane and ethyl acetate to give TAC tricyclic compound **34** (12.5 mg, 27.8 μmol, 96%) as a crystalline solid; mp 146–148°C; ir (neat): 2945, 2870, 1738, 1435, 1230 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 0.88 (s, 3H, -CH_3), 0.91 (s, 3H, -CH_3), 1.10–2.23 (m, 14H, all other CH_2 and CH), 3.68, 3.70, 3.73 and 3.74 (4s, 12H, 4 × -OCH_3), 5.19 (d, 1H, J = 9.9 Hz, -CH=CHC-), 5.40 (dd, 1H, J = 9.9 Hz, 1.9 Hz, CHCH=CH-). The structure of the compound **34** was further confirmed by X-ray crystallography.

Acknowledgements

This research was supported by the Natural Sciences and Engineering Research Council of Canada (NSERCC, Ottawa) and by the "Ministère de l'Enseignement supérieur et de la Science (Fonds FCAR, Québec)." We also acknowledge the support of IBM Canada Ltd (Cooperative Project Program) and the Tripos Company that allowed us to use the Sybyl Software, and thank Professor A. Michel for helpful discussions.

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