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Total Synthesis of (±)-Momilactone A

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The first total synthesis of (±)-momilactone A was accomplished using a highly diastereoselective transannular Diels−Alder reaction on a trans-trans-cis macrocyclic triene.

Introduction

Momilactone A (**1**) was first isolated in 1973 by Kato et al. from the seed husk of *Oryza sativa* L. during studies concerning the growth-regulating substances in higher plants.[1] Originally characterized as a growth and germination inhibitor, momilactone A was subsequently identified as a phytoalexin-like compound by Cartwright et al.[2a,b] Phytoalexins are produced by plants in response to either infection by the blast fungus (*Pyricularia oryzae*) or irradiation with UV light. The fact that **1** was detectable in infected or irradiated leaf tissues but not in healthy tissue was consistent with the proposed function of momilactone as a plant phytoalexin.[2d]

Many studies have also demonstrated that this diterpene inhibits the germination of lettuce seeds as well as the growth of rice roots, and it is known to be a highly antifungal and antimicrobial compound. Moreover, momilactone A has been shown to participate in the plant defense system against pathogens.[2]

The structure of (−)-momilactone A (**1**), confirmed by X-ray crystallographic and NMR analysis, displays an unusual syn stereochemistry at C9−C10. This exhibits a similarity to the tricycle **2b** that has the same ring junction stereochemistry at C5, C9, and C10 (steroid numbering).

Our past studies on the transannular Diels−Alder (TADA) reaction have shown that 14-membered macrocycles having a trans-trans-cis olefin geometry can lead to A.B.C[6.6.6] tricycles having a trans-syn-trans (TST) ring junction stereochemistry. Thus, in one step, two rings are generated and four asymmetric centers are created with high stereoselectivity.[3] This strategy could therefore be applied to momilactone A, which represents a high level of synthetic challenge. Until now, no other synthesis has been reported.[4]

Our synthetic plan is based on the convergent assembly of fragments **4** and **5** via an aldol reaction, followed by macrocyclization and simultaneous TADA cycloaddition for the formation of the tricyclic skeleton **2b**.[5] We anticipated that this advanced intermediate (**2b**) could be converted to momilactone A (**1**) using a series of chemical transformations on ring A and C. Appropriate modifications of the malonate moiety could provide both exocyclic substituents on ring C whereas functionalized ring A could be obtained by a methylation−lactonization sequence. The subunit **4** required for the aldol condensation will be accessed by neryl acetate (**6**) modifications whereas **5** will be directly obtained by palladium cross-coupling reaction between iodide **7** and stannane **8** (Scheme 1).

We report herein the first synthesis of (±)-momilactone A (**1**) as well as the necessary studies that led to this successful endeavor.

Results and Discussion

Synthesis of Diene 5 and Dienophile 4. Synthesis of the diene **5** (Scheme 2) started with protection of 3-butyn-1-ol as a TBDMS ether followed by hydrozirconation−iodination using Schwartz's reagent[6] to give the trans vinylic iodide **10** in 88% yield as a single detectable isomer. Deprotection of the silyl ether with acidic Dowex resin[7] afforded alcohol **11**. Oxidation to carboxylic acid **12** using Jones reagent followed by esterification with chlorotrimethylsilane in MeOH[8] led

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(2) (a) Kato, T.; Tsunagawa, M.; Sasaki, N.; Aizawa, H.; Fujita, K.; Kato, Y.; Kitahara, Y.; Takahashi, N. *Phytochemistry* **1977**, *16*, 45. (b) Cartwright, D. W.; Langcake, P.; Pryce, R. J.; Leworthy, D. P.; Ride, J. P. *Phytochemistry* **1981**, 535. (c) Mohan, R. S.; Yee, N. K. N.; Coates, R. M.; Ren, Y. Y.; Stamenkovic, P.; West, C. A.; Mendez, I. *Arch. Biochem. Biophys.* **1996**, *330*, 33. (d) West, C. A.; Wickham, K. A. *Arch. Biochem. Biophys.* **1992**, *293*, 320. (e) Li, W. X.; Kodama, O.; Akatsuka, T. *Agric. Biol. Chem*. **1991**, *55*, 1041. (f) Lee, C. W.; Yoneyama, K.; Takeuchi, Y.; Konnai, M.; Tamogami, S.; Kodama, O. *Biosci. Biotechnol. Biochem*. **1999**, *63*, 1318.

(3) (a) Deslongchamps, P. *Aldrichim. Acta* **1991**, *24*, 43. (b) Deslongchamps, P. *Pure Appl. Chem*. **1992**, *64*, 1831. (c) Marsault, E.; Toró, A.; Nowak, P.; Deslongchamps, P. *Tetrahedron* **2001**, *57*, 4243.

(4) For model studies related to this subject: (a) Sicherer-Roetman, A.; Jansen, B. J. M.; de Groot, Ae. *Tetrahedron Lett*. **1984**, *25*, 2593. (b) Chu, M.; Coates, R. M. *J. Org. Chem*. **1992**, *57*, 4590.

(5) The synthesis of the tricycle **2b** has been published: Germain, J.; Deslongchamps, P. *Tetrahedron Lett.* **1999**, *40*, 4051.

(6) (a) Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl*. **1976**, *15*, 333. (b) Schwartz, J.; Hart, D. W.; Blackburn, T. F. *J. Am. Chem. Soc*. **1975**, *97*, 679. (c) Chemin, D.; Linstrumelle, G. *Synthesis* **1993**, 377.

(7) Corey, E. J.; Ponder, J. W.; Ulrich, P. *Tetrahedron Lett*. **1980**, *21*, 137.

(8) Nakao, R.; Oka, K.; Fukumoto, T. *Bull. Chem. Soc. Jpn*. **1981**, *54*, 1267.

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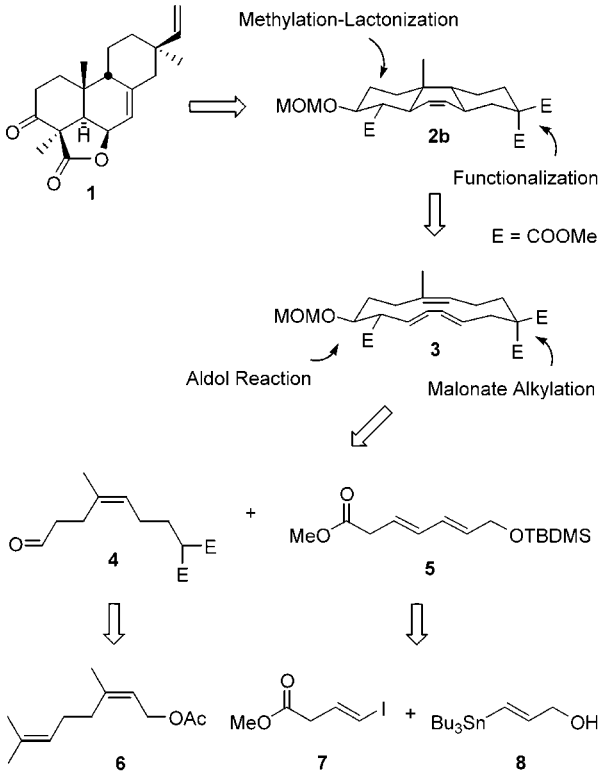
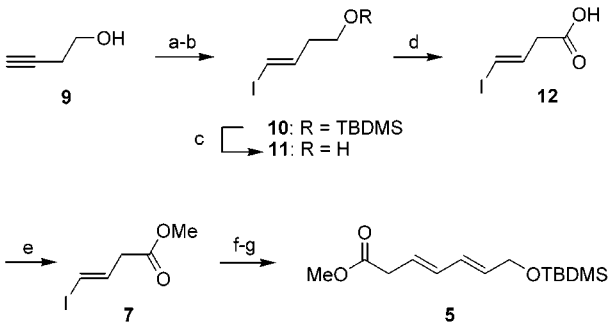
SCHEME 1



SCHEME 2[a]

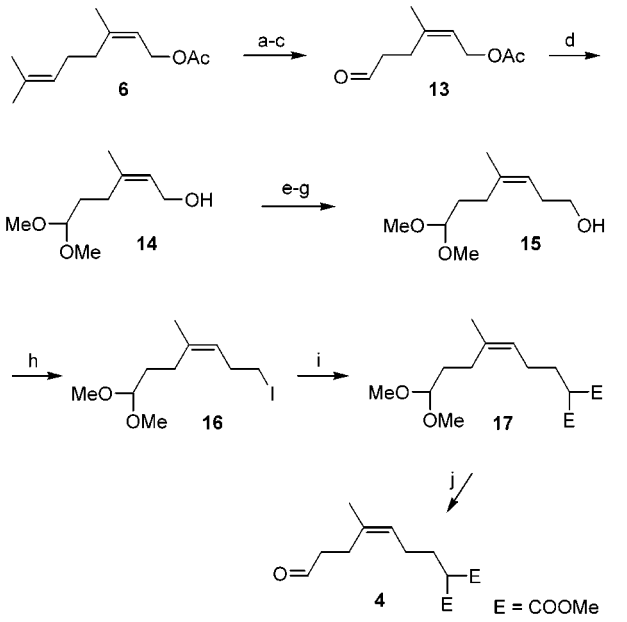


[a] Reagents and conditions: (a) TBDMSCl, imidazole, THF, 95%; (b) $Cp_2Zr(H)Cl$, I_2, THF−toluene, 88%; (c) Dowex 50WX8, MeOH, 86%; (d) Jones reagent, 91%; (e) TMSCl, MeOH, 84%; (f) *E*-$Bu_3SnCH{=}CHCH_2OH$ (**8**), $PdCl_2(CH_3CN)_2$, DMF, 50%; (g) TBDMSCl, imidazole, THF, 95%.

to ester **7** in 84% yield. Stille[9] coupling was applied between iodide **7** and (*E*)-$Bu_3SnCH{=}CHCH_2OH$ (**8**)[10] to produce the trans-trans diene exclusively in 50% yield. The resulting alcohol was then protected as a TBDMS ether to provide **5**.

Construction of the cis dienophile **4**, described in Scheme 3, began with terminal olefin epoxidation of neryl acetate **6** with *m*-chloroperoxybenzoic acid in dichloromethane.[11] The corresponding epoxide was opened in

SCHEME 3[a]



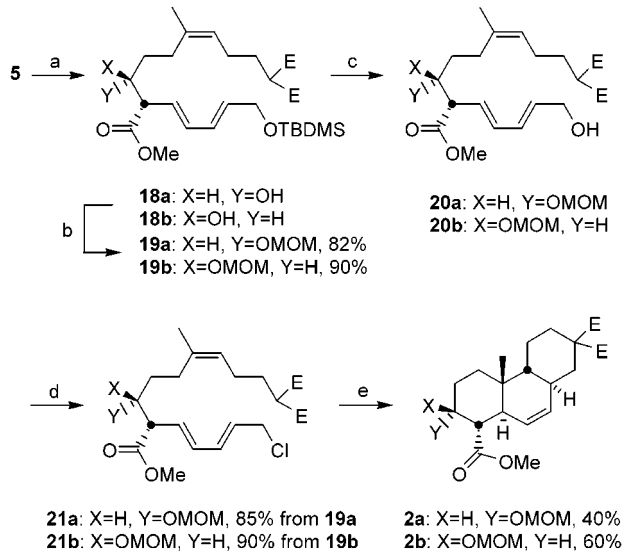
[a] Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2; (b) $HClO_4$, DME−H_2O; (c) $NaIO_4$, H_2SO_4, DME−H_2O; (d) HCl−dioxane, MeOH, then K_2CO_3, 40% over five steps; (e) TPAP, NMO, 4 Å MS, CH_2Cl_2, 95%; (f) Ph_3PMeI, PhLi, THF, 75%; (g) $(Sia)_2BH$, THF, H_2O_2−NaOH, MeOH, 80%; (h) DEAD, PPh_3, MeI, toluene, 87%; (i) NaH, CH_2E_2, THF−DMF, 70 °C, 86%; (j) TFA−H_2O, CH_2Cl_2, 99%.

acidic medium by treatment with aqueous perchloric acid in DME, and the resulting diol was cleaved using an acidic solution of sodium periodate to furnish the aldehyde **13**.[12] Exposure of this aldehyde to hydrochloric acid in methanol followed by methanolysis of the acetate with potassium carbonate afforded allylic alcohol **14** in 40% yield from **6**. To complete the dienophile, one-carbon homologation was necessary. To this end, a three-step sequence was applied by oxidation of alcohol **14** to the aldehyde using Ley[13] conditions, Wittig olefination with Ph_3PCH_2, and regioselective hydroboration with disiamylborane.[14,15] This gave rise to the homologated product **15**. The introduction of the malonate connector was accomplished by transformation of **15** into iodide **16**[16] and subsequent displacement of the latter by sodium dimethyl malonate at 70 °C. Finally, the dimethoxyacetal **17** was deprotected using a mixture of TFA−water (1:1) in dichloromethane to furnish **4** in quantitative yield.

Coupling, Macrocyclization, and TADA Reaction. Having the diene and the dienophile in hand, both units were coupled by an aldol reaction (Scheme 4). Thus, condensation of the lithium enolate of **5** with aldehyde **4** at −78 °C provided two aldol adducts **18a** and **18b** in an approximately 1.2:1 ratio for the syn and anti isomers. The aldol reaction took place at the α position of the carbonyl, and no isomerization of the double

(9) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813.
(10) Lipshutz, B. H.; Lindsley, C. *J. Am. Chem. Soc.* **1997**, *119*, 4555. The alcohol **8** was obtained by reduction of the corresponding aldehyde with $NaBH_4$ in methanol. For characterization data: Belanger, G.; Deslongchamps, P. *J. Org. Chem.* **2000**, *65*, 7070.
(11) Hashimoto, S.; Itoh, A.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 4192.
(12) Heissler, D.; Jenn, T. *Tetrahedron* **1998**, *54*, 107.
(13) Ley, S. V.; Griffith, W. P. *Aldrichim. Acta* **1990**, *23*, 13.
(14) Leopold, E. J. *Org. Synth.* **1986**, *64*, 164.
(15) (a) Brown, H. C. *Organic Synthesis via Boranes*; John Wiley and Sons: New York, 1975. (b) Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1961**, *83*, 1241.
(16) (a) Loibner, H.; Zbiral, E. *Helv. Chim. Acta* **1976**, *59*, 2100. (b) Mitsunobu, O. *Synthesis* **1981**, 1.

SCHEME 4[a]



[a] Reagents and conditions: (a) LDA, THF, −78 °C, then **4**, −78 °C, 88%; (b) MOMCl, DIPEA, CH_2Cl_2; (c) Dowex 50WX8, MeOH; (d) HCA, PPh_3, THF, −40 °C; (e) Cs_2CO_3, CH_3CN, reflux.

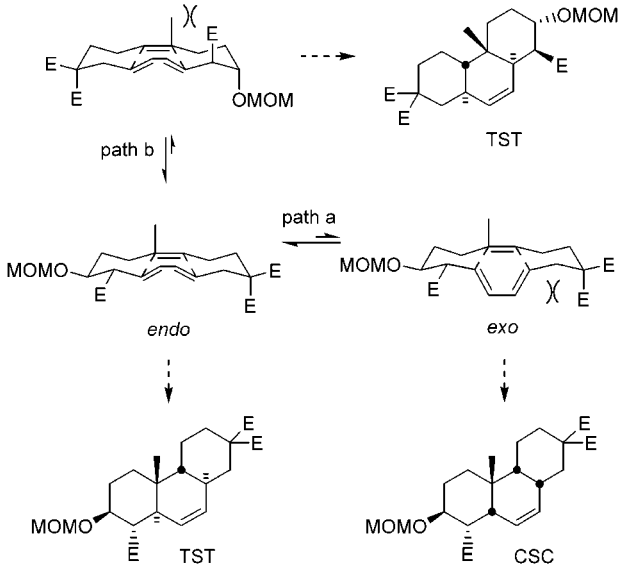
bonds was detected in the course of the reaction.[17] The diastereomeric alcohols **18a** and **18b** were easily separated by flash chromatography on silica gel. Both racemic diastereoisomers were investigated in order to find out which one would more conveniently lead to the synthesis of momilactone A.

Both isomeric alcohols were subjected to the same series of transformations. They were etherified using MOMCl in dichloromethane, and the silyl groups were removed under acidic conditions. Chlorination of the free alcohols **20a** and **20b** was performed using Magid conditions (HCA, PPh_3, THF) to yield **21a** and **21b** in good overall yield.[18]

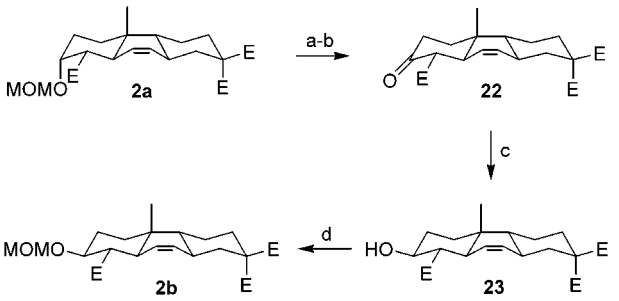
The key step of the synthesis was accomplished by slow addition of these allylic chlorides into a suspension of cesium carbonate in refluxing acetonitrile under high dilution. The macrocyclization−cycloaddition took place in a single step to afford the TST tricycles **2a** and **2b** in 40% and 60% yields, respectively.

The specific formation of the TST tricycle can be explained by the sterically favored endo transition state having a chair−boat−chair conformation as shown in Scheme 5. The exo transition state suffers from steric interactions between the pseudoaxial ester group and one double bond of the diene. Also, the face selectivity is the result of the orientation of the C4-carbomethoxy group in a pseudoequatorial position. Pseudoaxial orientation of this group leads to a steric interaction with the C10-methyl (path b). The same conclusion can be reached for the specific formation of the syn isomer **2a**. In this case, the OMOM group occupied a pseudoaxial orientation at the transition state that further disfavored the formation of the cis-syn-cis (CSC) isomer.

SCHEME 5



SCHEME 6[a]



[a] Reagents and conditions: (a) HCl, MeOH, 60 °C, 90%; (b) Jones reagent, 91%; (c) $NaBH_4$, MeOH, −78 °C, 90%; (d) Nafion-H, dimethoxymethane, reflux, 86%.

Thus, the transannular process allows complete control in the formation of the TST stereochemistry. Also, a clear advantage of such a strategy is the mild conditions by which the cycloaddition took place with a nonactivated dienophile. As a result, a tricycle containing four new chiral centers is generated in one chemical operation from an acyclic precursor in a completely stereocontrolled manner. Clearly, it can be expected as previously discussed that with a nonactivated dienophile, an intermolecular process or an intramolecular version on a simple open-chain intermediate would not take place.[19]

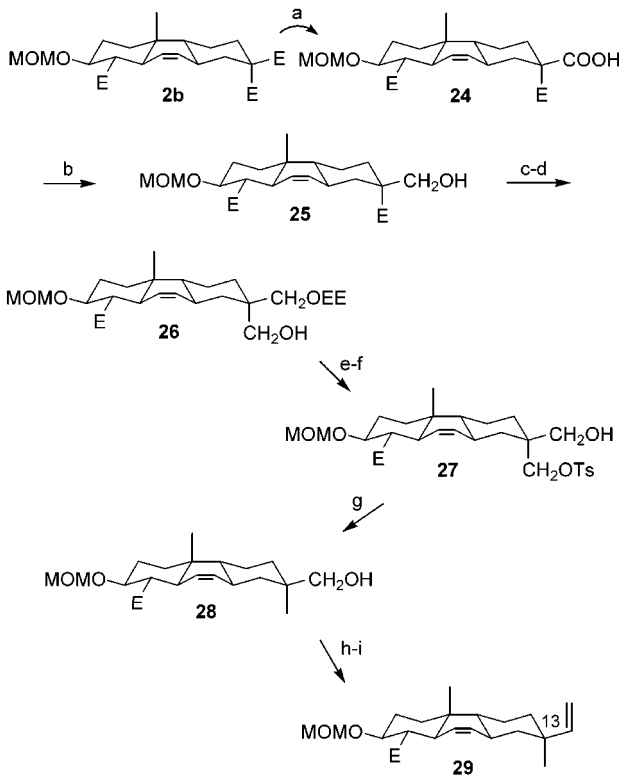
Considerable experimentation was carried out on both diastereomeric tricycles in order to determine which one would more conveniently lead to **1**. Preliminary results showed that reactions on **2b** were more selective than **2a**. Thus, we decided to recycle **2a** into **2b** (Scheme 6). For this purpose, the alcohol was liberated from its MOM ether and was oxidized to *β*-ketoester **22** with Jones reagent. Selective reduction by $NaBH_4$ in methanol afforded the equatorial alcohol **23**. Protection of the latter as a MOM ether using Nafion-H in refluxing dimethoxymethane led to **2b** in 86% yield.

(17) (a) House, H. O. *Modern Synthetic Reactions*; Benjamin: Menlo Park, CA, 1972; p 555. (b) Robertson, P. A.; Katzenellenbogen, J. A. *J. Org. Chem.* **1983**, *48*, 5288. (c) Takacs, J. M.; Jaber, M. R.; Swanson, B. J.; Mehrmen, S. J. *Tetrahedron: Asymmetry* **1998**, *9*, 4313.

(18) Magid, R. M.; Fruchey, O. S.; Johnson, W. L.; Allen, T. G. *J. Org. Chem.* **1979**, *44*, 359.

(19) Hall, D. H.; Müller, R.; Deslongchamps, P. *Tetrahedron Lett.* **1992**, *33*, 5221.

SCHEME 7[a]



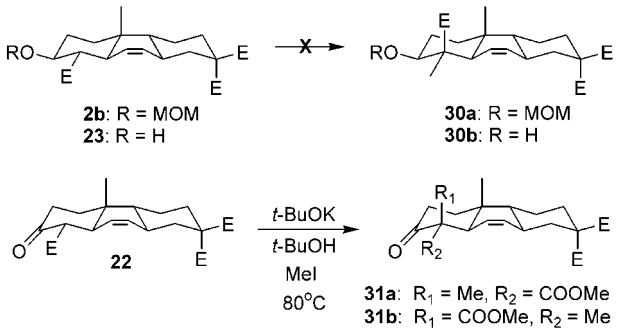
[a] Reagents and conditions: (a) KOH, MeOH, THF, 82−85%; (b) (i) MeOCOCl, Et_3N, 0 °C, THF, (ii) $NaBH_4$, THF, 0 °C, 73%; (c) ethyl vinyl ether, PPTS, CH_2Cl_2, 91%; (d) $LiAlH_4$, THF, 0 °C, 93%; (e) TsCl, Et_3N, DMAP, CH_2Cl_2, reflux, 88%; (f) 0.5 M HCl, THF, 90%; (g) $NaBH_4$, DMSO, 80 °C, 93%; (h) Dess−Martin periodinane, CH_2Cl_2; (i) Ph_3PCH_3Br, KHMDS, THF, 70% from **28**.

Model Studies on the A and C Rings. Having built the momilactone skeleton, we were ready to explore functional group manipulations on both A and C rings.

To obtain the appropriate C13 substituents, the malonate entity had to be transformed into an equatorial vinyl and an axial methyl group.

Success in the elaboration of the C ring (Scheme 7) arose from the efficient differentiation of the malonate ester. Accordingly, partial hydrolysis of the malonate **2b** produced the equatorial β monoacid **24** in 82−85% yield.[20] The malonate ester is more susceptible to hydrolysis than the ring A methyl ester due to an inductive effect of the *gem*-diester moiety. Also, the selective hydrolysis of the equatorial malonate ester must be due to less steric hindrance in the process of generating the required tetrahedral intermediate. Reduction of **24** was accomplished through its mixed anhydride with sodium borohydride at 0 °C to give alcohol **25** in 73% yield.[21] Attempts to introduce the vinyl group by conventional oxidation of the alcohol to an aldehyde followed by olefination resulted only in deformylation. Therefore, protection of alcohol **25** as an ethoxyethyl ether using standard conditions followed by selective reduction of the axial α ester with $LiAlH_4$ in THF at 0 °C furnished the acid-sensitive alcohol **26** in excellent yield. The equatorial α ester in ring A was not reduced during this process (the nonreactivity of this ester will be discussed below). Hydrogenolysis of the CH_2OH group of **26** was found to be quite difficult. Most of the reported methods were tried unsuccessfully. As an example, Barton's reaction led to the starting alcohol.[22] Success was finally achieved using a three-step sequence. First, treatment of **26** with tosyl chloride, triethylamine, and DMAP in CH_2Cl_2 at reflux for 18 h followed by hydrolysis of the ethoxyethyl ether (without removal of the MOM ether) led to tosyl alcohol **27**. Reduction of the tosylate with sodium borohydride in DMSO gave methyl alcohol **28** in 93% yield.[23,24] Interestingly, when these reduction conditions were applied to the equatorial ethoxyethyl ether only decomposition of the compound was observed. We speculate that this step must occur via an intramolecular complex of the neighboring alcohol and the boron reducing reagent. Oxidation of **28** to the corresponding aldehyde with Dess−Martin periodinane[25] followed by Wittig olefination with methyltriphenylphosphonium bromide and KHMDS afforded alkene **29**. Completion of the C ring was thus achieved in nine steps.

SCHEME 8



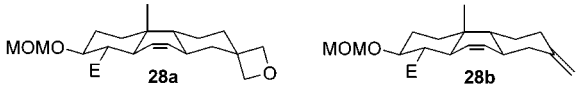
We next investigated the functional group manipulations on the A ring. We envisaged obtaining the methylated β-ketolactone by an alkylation followed by iodolactonization. Our initial approach (Scheme 8) was to introduce the methyl group at C4 from either **2b** or **23**, but all attempts (LDA, KHMDS, *t*-BuLi, NaH, etc.) failed to provide **30**. Starting material was always recovered. Attempt deuteration at C4 also failed. These results indicate that the enolate ion was not generated. One possible explanation is that the ester is probably oriented in a perpendicular fashion to the ring skeleton. In this manner, it is stereoelectronically impossible to form the enolate. The ester orientation may also explain its reluctance toward hydrolysis or hydride reduction as both

(20) The structure of monoacid **24** was confirmed by X-ray diffraction analysis. Crystallographic data (CCDC no. 115342) were deposited at the Cambridge Crystallographic Data Centre.

(21) Honda, T.; Hallinan, K. O. *Tetrahedron* **1995**, *51*, 12211.

(22) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

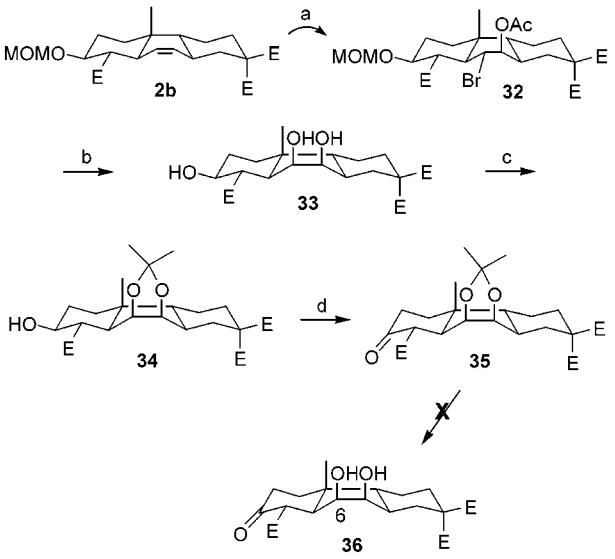
(23) This reaction was found to be very sensitive. Important byproducts (the corresponding oxetane **28a** and the deformylation product **28b**) were obtained in addition to compound **28**. To avoid these side reactions, the concentration and the purity of the $NaBH_4$ must be high.



(24) When a mesylate was used instead of a tosylate, a substantial amount of the corresponding oxetane (**28a**) was obtained during the reduction process.

(25) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

SCHEME 9[a]



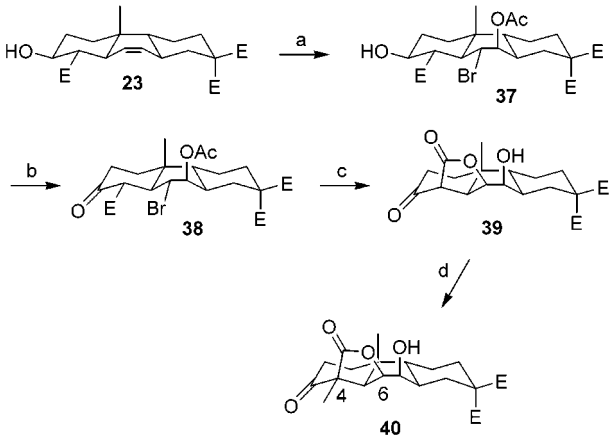
[a] Reagents and conditions: (a) NBA, AgOAc, AcOH, 85%; (b) (i) AcOH−H_2O, 90 °C, (ii) K_2CO_3, MeOH, 64%; (c) *p*-TsOH, $(MeO)_2C(CH_3)_2$, acetone, 99%; (d) Dess−Martin periodinane, CH_2Cl_2, 86%.

faces of the carbonyl ester are somewhat hindered (OMOM on one side and C6-H on the other) toward nucleophilic attack.

As an alternative strategy, we decided to investigate the methylation step using the β-ketoester **22**. Several conditions to introduce the equatorial α methyl group with high selectivity at C4 were tried unsuccessfully.[26] For instance, methylation of **22** (*t*-BuOK, *t*-BuOH, MeI, 80 °C; NaH, THF or toluene, MeI, reflux, etc.) gave a mixture of isomers **31a** and **31b** in an approximatively 1:1 ratio resulting presumably from an early transition state.

To solve this problem, we then turned our attention toward the possibility of forming the lactone before the alkylation step (Schemes 9 and 10). Methylation of the resulting β-ketolactone should then lead to perfect stereochemical control at C4. To build this lactone (cf. **39**), we must obtain the β stereochemistry for the C6-alcohol.[27] For this, we used the modified version of the Woodward reaction.[28,29] Thus, treatment of **2b** with *N*-bromoacetamide (NBA) and silver acetate in acetic acid gave rise to bromoacetate **32** with excellent stereoselectivity. By NMR analysis, we assumed that the orientation of the bromide was α and that of the acetate β but the regiochemistry was not confirmed at this stage. However, this is of no consequence for the next steps. Displacement

SCHEME 10[a]



[a] Reagents and conditions: (a) NBA, AgOAc, AcOH, 83%; (b) Dess−Martin periodinane, CH_2Cl_2, 0 °C, 70%; (c) (i) AcOH−H_2O, 90 °C, (ii) K_2CO_3, MeOH, 65%; (d) Cs_2CO_3, CH_3I, CH_3CN, 92%.

of the bromide by the neighboring acetate was realized in wet acetic acid at 90 °C, which also hydrolyzed the MOM ether. The resulting mixture of monoacetate-diols was exposed to K_2CO_3 in MeOH to give triol **33** in 64% yield. Having three alcohols on the molecule, the 1,2-diol was protected as an acetonide, and the resulting free alcohol **34** was oxidized to the ketone with Dess−Martin periodinane. The successful protection confirms the cis relationship of the 1,2-diol. Next, our plan was to remove the acetonide in order to obtain the lactone, but this strategy was abandoned as the hydrolysis of the acetonide was not successful.[30]

To avoid the use of protecting groups on the 1,2-diol, we decided to change the sequence of reactions (Scheme 10). Starting from the free alcohol **23**, obtained from **2b**, the alkene was submitted to NBA and silver acetate in acetic acid to give bromoacetate **37** in good yield. Oxidation of the alcohol to ketone **38** was accomplished with the Dess−Martin periodinane. The structure of **38** was assigned by ^{1}H NMR and selective decoupling. Thus, the C10-methyl controls the stereochemical outcome of this process. Formation of the bromonium bridge must take place on the α face (less hindered face) and the acetate ion must react away from the methyl group providing **37**. Subsequent displacement of the bromide was realized under the same conditions as reported before followed by methanolysis of the acetate to yield the lactone **39** in 65% yield. Thus, under basic conditions, epimerization at C4 must have occurred and the axial ester was trapped by the C6-alcohol to form the γ-lactone. Treatment of the latter with Cs_2CO_3 and methyl iodide in acetonitrile afforded, as expected, lactone **40** as the sole product in 92% yield.[31] The ease with which this reaction was performed results from the high reactivity of the enolate, which is almost a bridgehead. Since it cannot be completely planar and therefore less conjugated with the

(26) In the literature, introduction of a methyl group at this position on tricycles containing a β-ketoester affords mainly axial alkylation product: (a) Spencer, T. A.; Weaver, T. D.; Villarica, R. M.; Friary, R. J.; Posler, J.; Schwartz, M. A. *J. Org. Chem*. **1968**, *33*, 712. (b) Welch, S. C.; Hagan, C. P.; White, D. H.; Fleming, W. P.; Trotter, J. W. *J. Am. Chem. Soc.* **1977**, *99*, 549. (c) Czarny, M. R.; Maheshwari, K. K.; Nelson, J. A.; Spenser, T. A. *J. Org. Chem*. **1975**, *40*, 2079. (d) Afonso, A. *J. Am. Chem. Soc.* **1968**, *90*, 7375.

(27) Hydroxylation with OsO_4 leads to the diol having α stereochemistry.

(28) Woodward, R. B.; Brutcher, F. V. *J. Am. Chem. Soc.* **1958**, *80*, 209.

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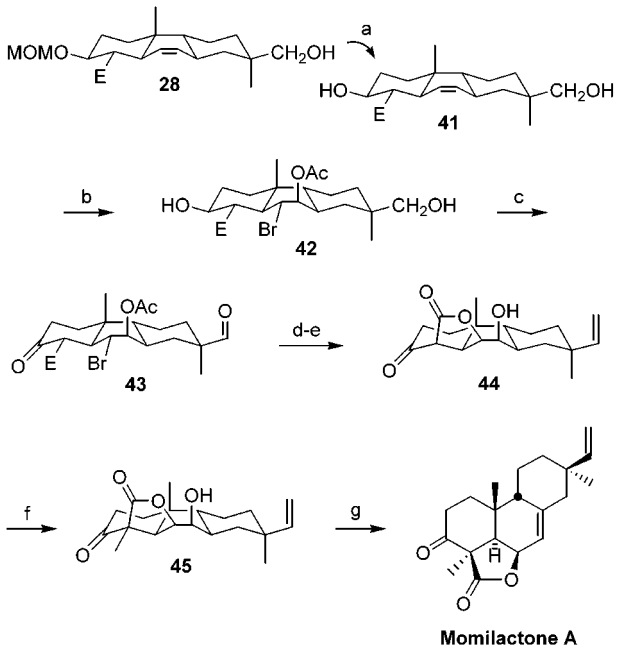
SCHEME 11[a]



[a] Reagents and conditions: (a) HCl, MeOH, 60 °C, 90%; (b) NBA, AgOAc, AcOH, 75%; (c) Dess−Martin periodinane, CH_2Cl_2, 0 °C, 83%; (d) Ph_3PCH_3Br, KHMDS, THF, 70%; (e) (i) AcOH−H_2O, 90 °C, (ii) K_2CO_3, MeOH, 65%; (f) Cs_2CO_3, CH_3I, CH_3CN, 89%; (g) Burgess reagent, toluene, reflux, 40−50%.

lactone, the reactivity is greater than that from a conventional β-ketoester. Ring A was thus completed in five steps.

During the course of these model studies, a synthetic route was developed so as to obtain the desired substituents with high stereoselectivity on both A and C rings of the momilactone core.

Final Sequence to (±)-Momilactone A. To obtain momilactone A, we had to carry out the above steps in a proper sequence. For the formation of the lactone, we needed the double bond in the B ring. Consequently, the vinyl group at C13 had to be introduced later in the synthesis. Accordingly, the completion of the synthesis is described in Scheme 11.

Starting from the methyl alcohol **28** (Scheme 7), the MOM ether was cleaved in acidic medium and formation of the bromoacetate from **41** was carried out using the conditions described above to give **42** in 75% yield and again with an excellent selectivity. Simultaneous oxidation of both alcohols produced the corresponding keto aldehyde in 83% yield. Selective Wittig homologation of the aldehyde to a vinyl group was performed with Ph_3PCH_3Br and KHMDS. Displacement of the bromide by the acetate group was accomplished followed by methanolysis to yield lactone **44**. The introduction of the methyl group was realized using Cs_2CO_3 and methyl iodide in acetonitrile. The methylated product was obtained as a single isomer in 89% yield. X-ray diffraction analysis of hydroxymomilactone A **45** rigorously established the proposed structure and relative stereochemistry.[32] To our surprise, the last step of the synthesis, the dehydration, was found to be problematic. Despite the fact that the axial β alcohol is well aligned antiperiplanar with the C8-hydrogen, trans diaxial elimination of H_2O did not proceed using most of the reported methods for dehydration (mesylation of the alcohol, Martin sulfuran, acidic conditions, $SOCl_2$, $POCl_3$, Mitsunobu conditions, etc.). In each case, starting alcohol was recovered. The nonformation of the mesylate derivative suggests that the secondary alcohol in **45** is quite hindered. An examination of a molecular model supports this idea. Fortunately, the synthesis of (±)-momilactone A was finally achieved using Burgess reagent in toluene at reflux in 40−50% yield.[33] Interestingly, this reagent is normally used for syn elimination, although examples of anti elimination are known.[34] This successful reaction is probably due to the formation of the highly reactive sulfamate ester intermediate (by addition of the Burgess reagent to the secondary alcohol) that decomposes at 110 °C to give the alkene. The ^1H NMR and ^{13}C NMR spectra ($CDCl_3$), IR, mass spectra, and HRMS of (±)-momilactone A were completely identical with the literature data of the natural compound.[1,2b]

Summary

The first total synthesis of (±)-momilactone A has been achieved in a convergent fashion in 19 steps from the two building blocks, diene **5** and dienophile **4**. The longest linear sequence is 29 steps: Scheme 3, 10 steps (**6** to **4**); Scheme 4, 5 steps (**5** to **2b**); Scheme 7, 7 steps (**2b** to **28**) and Scheme 11, 7 steps (**28** to **1**).

This synthesis has a very high degree of chemoselectivity, regioselectivity, and stereoselectivity at all the steps except for the aldol condensation, which gives two diastereoisomers. However, one isomer can be recycled into the other one. The key features of this work is the single operation for the macrocyclization and TADA steps which takes place with complete stereocontrol producing a single tricycle containing four new chiral centers from each aldol isomer. A special note is made to the fact that the TADA reaction works with a nonactivated dienophile under very mild thermal conditions. Another interesting and novel feature is the synthesis of the β-ketolactone and its stereocontrolled methylation under mild conditions. It is also interesting to point out the different chemical reactivity of the three ester functions. The transformation of the malonate ester into the desired C13 α methyl and β vinyl substituents requires several steps but is selective and efficient.

An appropriate asymmetric aldol condensation could be used to produce the natural product with complete relative and absolute stereochemical control.

Experimental Section

General Procedures. All reactions were performed under nitrogen atmosphere with oven (150 °C) or flame-dried glassware. All solvents were distilled prior to use: ether and tetrahydrofuran from sodium/benzophenone ketyl; toluene, acetonitrile, dichloromethane, and dimethyl sulfoxide were

(32) Crystallographic data of compound **45** (CCDC no. 172789) have been deposited at the Cambridge Crystallographic Data Centre.

(33) (a) Atkins, G. M., Jr.; Burgess, E. M. *J. Am. Chem. Soc.* **1968**, *90*, 4744. (b) Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26. (c) Crabbé, P.; León, C. *J. Org. Chem.* **1970**, *35*, 2594.

(34) O'Grodnick, J. S.; Ebersole, R. C.; Wittstruck, T.; Caspi, E. *J. Org. Chem.* **1974**, *39*, 2124.

distilled over calcium hydride and methanol from magnesium/iodine. Most amines were dried over calcium hydride and distilled. All other starting materials and reagents were obtained commercially and used as such. For reaction workups, all organic phases were dried over magnesium sulfate. Analytical thin-layer chromatography was carried out on precoated glass plates (0.25 mm) with 60 F-250 silica gel (Merck). Flash chromatography was performed with silica gel 60 (230−400 mesh). The following abbreviations were used for NMR data: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; br, broad. Chemical shifts are reported in ppm δ units relative to chloroform (7.26 ppm for ^{1}H NMR and 77.0 ppm for decoupled ^{13}C NMR) or benzene (128.4 ppm for decoupled ^{13}C NMR) as internal standard. When necessary, decoupling experiments were applied. Mass spectra (MS) were obtained with electronic ionization (70 eV). Melting points of crystalline compounds are uncorrected.

Methyl (±)-(5*Z*,11*E*,13*E*)-(9*R*,10*R*)-15-*tert*-Butyldimethylsilyloxy-9-hydroxy-2,10-bis(methoxycarbonyl)-6-methylpentadeca-5,11,13-trien-1-oate (18a) and Methyl (±)-(5*Z*,11*E*,13*E*)-(9*S*,10*R*)-15-*tert*-Butyldimethylsilyloxy-9-hydroxy-2,10-bis(methoxycarbonyl)-6-methylpentadeca-5,11,13-trien-1-oate (18b). To a stirred solution of the ester **5** (2.26 g, 8.75 mmol) in tetrahydrofuran (50 mL) at −78 °C was added LDA (2 M in hexane−THF−heptane, 4.2 mL, 3.0 mmol). The mixture was stirred for 20 min, and a solution of the aldehyde **4** (1.12 g, 4.38 mmol) in tetrahydrofuran (2 mL) was added. The resulting mixture was stirred at −78 °C for 3 h and was warmed to room temperature. Aqueous NH_4Cl was added, and volatiles were evaporated. Ethyl acetate was added, and the layers were separated. The aqueous phase was extracted with ethyl acetate, and the combined organic phases were dried, filtered, and evaporated. Aldolic adducts were separated by flash chromatography (ethyl acetate−hexane, 30:70) to give the adducts **18a** syn and **18b** anti (2.02 g, 88%: 1.13 g syn, 0.89 g anti).

Compound 18a: R_f = 0.22 (20% ethyl acetate−hexane); IR (film) ν 3534, 2954, 2857, 1732, 1436, 1378, 1256, 1158, 1056, 992, 838, 778 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.32−6.12 (2H, m), 5.79−5.69 (2H, m), 5.09 (1H, t, J = 6.9 Hz), 4.20 (2H, d, J = 4.8 Hz), 3.85 (1H, m), 3.72 (6H, s), 3.70 (3H, s), 3.36 (1H, t, J = 7.3 Hz), 3.06 (1H, dd, J = 9.5, 4.4 Hz), 2.75 (1H, d, J = 3.5 Hz), 2.12−1.88 (6H, 3m), 1.65 (3H, s), 1.47 (2H, m), 0.90 (9H, s), 0.06 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 169.9, 136.3, 134.9, 133.4, 128.7, 125.6, 123.9, 71.1, 63.2, 54.8, 52.5, 52.1, 51.0, 32.2, 29.1, 27.7, 25.9, 25.8, 25.5, 23.2, 18.4, −5.3; MS *m*/*e* 469 (M − C_4H_9)$^+$; HRMS calcd for $C_{23}H_{37}O_8Si$ (M − C_4H_9)$^+$ 469.2258, found 469.2260.

Compound 18b: R_f = 0.12 (20% ethyl acetate−hexane); IR (film) ν 3522, 2954, 2857, 1732, 1436, 1256, 1215, 1159, 1056, 992, 962, 838, 777 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.25−6.14 (2H, m), 5.74 (1H, m), 5.57 (1H, m), 5.09 (1H, t, J = 6.8 Hz), 4.19 (2H, d, J = 4.4 Hz), 3.75 (1H, m), 3.71 (6H, s), 3.69 (3H, s), 3.35 (1H, t, J = 7.1 Hz), 3.09 (1H, dd, J = 9.1, 8.2 Hz), 2.63 (1H, d, J = 6.4 Hz), 2.16−1.88 (6H, 3m), 1.64 (3H, s), 1.62 (1H, m), 1.36 (1H, m), 0.89 (9H, s), 0.05 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 169.9, 136.4, 134.1, 133.5, 128.6, 126.6, 123.9, 72.1, 63.2, 56.0, 52.5, 52.0, 51.0, 32.5, 29.1, 27.4, 25.9, 25.4, 23.2, 18.4, −5.3; MS *m*/*e* 469 (M − C_4H_9)$^+$; HRMS calcd for $C_{23}H_{37}O_8Si$ (M − C_4H_9)$^+$ 469.2258, found 469.2260.

Methyl (±)-(5*Z*,11*E*,13*E*)-(9*R*,10*R*)-15-*tert*-Butyldimethylsilyloxy-2,10-bis(methoxycarbonyl)-9-methoxymethoxy-6-methylpentadeca-5,11,13-trien-1-oate (19a). To a stirred solution of the alcohol **18a** (1.10 g, 2.09 mmol) in dichloromethane (10 mL) at 0 °C were added diisopropylethylamine (7.3 mL, 41.8 mmol) and chloromethyl methyl ether (2.4 mL, 31.3 mmol). The resulting mixture was stirred at 0 °C for 1 h and at room temperature for 12 h. The mixture was filtered through a silica pad, diluted in ethyl acetate, and washed with water. The organic phase was dried, filtered, and evaporated. The residue was purified by flash chromatography (ethyl acetate−hexane, 30:70) to give the protected alcohol **19a** (0.98 g, 82%) as a yellow oil: R_f = 0.55 (30% ethyl acetate−hexane); IR (film) ν 2953, 2931, 2856, 1736, 1436, 1360, 1254, 1149, 1099, 1036, 992, 837, 778 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35−6.09 (2H, m), 5.79−5.69 (2H, m), 5.07 (1H, t, J = 6.0 Hz), 4.62 (2H, s), 4.21 (2H, d, J = 4.8 Hz), 3.89 (1H, td, J = 11.2, 5.7 Hz), 3.73 (6H, s), 3.69 (3H, s), 3.36 (1H, m), 3.34 (3H, s), 3.23 (1H, dd, J = 9.5, 5.4 Hz), 2.11−1.88 (6H, m), 1.66 (3H, s), 1.55 (2H, m), 0.90 (9H, s), 0.06 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 169.8, 136.3, 133.9, 132.9, 128.9, 126.6, 123.6, 96.5, 79.0, 63.2, 55.8, 53.4, 52.4, 51.9, 50.9, 30.8, 28.9, 27.4, 25.9, 25.4, 23.3, 18.3, −5.3; MS *m*/*e* 555 (M − Me)$^+$, 513 (M − C_4H_9)$^+$; HRMS calcd for $C_{28}H_{47}O_9Si$ (M − Me)$^+$ 555.2989, found 555.2983.

Methyl (±)-(5*Z*,11*E*,13*E*)-(9*S*,10*R*)-15-*tert*-Butyldimethylsilyloxy-2,10-bis(methoxycarbonyl)-9-methoxymethoxy-6-methylpentadeca-5,11,13-trien-1-oate (19b). The procedure used for the synthesis of **19a** was applied for the protection of **18b** using alcohol **18b** (0.89 g), diisopropylethylamine (5.9 mL), chloromethyl methyl ether (1.9 mL) in dichloromethane (50 mL) to give **19b** (0.87 g, 90%) as a colorless oil: R_f = 0.50 (30% ethyl acetate−hexane); IR (film) ν 2954, 2857, 1738, 1436, 1360, 1256, 1196, 1161, 1104, 1037, 994, 838, 778 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.23−6.15 (2H, m), 5.75 (1H, m), 5.55 (1H, m), 5.05 (1H, t, J = 6.8 Hz), 4.63 (2H, s), 4.19 (2H, d, J = 4.3 Hz), 3.91 (1H, m), 3.72 (6H, s), 3.69 (3H, s), 3.35 (3H, s), 3.38−3.26 (2H, m), 2.10−1.88 (6H, m), 1.65 (3H, s), 1.56 (2H, m), 0.90 (9H, s), 0.06 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 169.8, 136.6, 134.1, 133.5, 128.6, 126.3, 123.4, 96.4, 78.5, 63.2, 55.9, 54.1, 52.4, 51.9, 50.9, 29.5, 28.9, 25.9, 25.9, 25.4, 23.3, 18.3, −5.3; MS *m*/*e* 555 (M − Me)$^+$, 513 (M − C_4H_9)$^+$; HRMS calcd for $C_{25}H_{41}O_9Si$ (M − C_4H_9)$^+$ 513.2520, found 513.2527.

Methyl (±)-(5*Z*,11*E*,13*E*)-(9*R*,10*R*)-15-Hydroxy-2,10-bis(methoxycarbonyl)-9-methoxymethoxy-6-methylpentadeca-5,11,13-trien-1-oate (20a). To a stirred solution of compound **19a** (0.85 g, 1.49 mmol) in methanol (11 mL) was added acidic resin Dowex 50WX8. The mixture was stirred at room temperature for 8 h and filtered, and solvent was evaporated. The residue was purified by flash chromatography (ethyl acetate−hexane, 1:1) to give the alcohol **20a** (0.61 g, 90%) as an oil: R_f = 0.17 (30% ethyl acetate−hexane); IR (film) ν 3466, 2954, 2861, 1732, 1436, 1351, 1288, 1239, 1200, 1151, 1098, 1035, 994, 919 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.28−6.06 (2H, m), 5.82−5.72 (2H, m), 5.03 (1H, t, J = 6.2 Hz), 4.57 (2H, s), 4.13 (2H, d, J = 5.6 Hz), 3.86 (1H, m), 3.68 (6H, s), 3.65 (3H, s), 3.31 (1H, m), 3.29 (3H, s), 3.20 (1H, dd, J = 9.4, 4.7 Hz), 2.09 (1H, br s), 2.04−1.86 (6H, m), 1.62 (3H, s), 1.52 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 169.8, 136.3, 133.7, 132.3, 130.5, 127.5, 123.6, 96.4, 79.1, 63.2, 55.8, 53.3, 52.5, 51.9, 51.0, 30.8, 29.0, 27.5, 25.4, 23.4; MS *m*/*e* 393 (M − H_2O − MOM)$^+$; HRMS calcd for $C_{21}H_{29}O_7$ (M − H_2O − MOM)$^+$ 393.1913, found 393.1920.

Methyl (±)-(5*Z*,11*E*,13*E*)-(9*S*,10*R*)-15-Hydroxy-2,10-bis(methoxycarbonyl)-9-methoxymethoxy-6-methylpentadeca-5,11,13-trien-1-oate (20b). The procedure used for the synthesis of **20a** was applied for the deprotection of **19b** (0.87 g) to give the alcohol **20b** (0.66 g, 95%) as a colorless oil: R_f = 0.14 (30% ethyl acetate−hexane); IR (film) ν 3468, 2954, 2933, 2909, 1735, 1436, 1349, 1256, 1219, 1162, 1103, 1033, 995, 920 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.29−6.15 (2H, m), 5.89 (1H, m), 5.59 (1H, m), 5.06 (1H, t, J = 6.2 Hz), 4.63 (2H, s), 4.18 (2H, t, J = 5.8 Hz), 3.93 (1H, m), 3.72 (6H, s), 3.69 (3H, s), 3.35 (3H, s), 3.34−3.25 (2H, m), 2.09−1.88 (6H, m), 1.64 (3H, s), 1.63 (1H, m), 1.45 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 169.8, 136.5, 133.9, 133.3, 129.8, 126.9, 123.4, 96.3, 78.3, 62.9, 55.8, 54.1, 52.5, 51.9, 51.0, 29.6, 28.9, 25.8, 25.4, 23.3; MS *m*/*e* 425 (M − OMe)$^+$, 407 (M − H_2O − OMe)$^+$, 393 (M − H_2O − MOM)$^+$; HRMS calcd for $C_{21}H_{29}O_7$ (M − H_2O − MOM)$^+$ 393.1913, found 393.1922.

Methyl (±)-(5*Z*,11*E*,13*E*)-(9*R*,10*R*)-15-Chloro-2,10-bis(methoxycarbonyl)-9-methoxymethoxy-6-methylpenta-

deca-5,11,13-trien-1-oate (21a). To a stirred solution of the alcohol **20a** (0.61 g, 1.3 mmol) in tetrahydrofuran (40 mL) at −40 °C were added triphenylphosphine (0.39 g, 1.5 mmol) and hexachloroacetone (0.22 mL, 0.15 mmol). The mixture was stirred at −40 °C for 25 min, and toluene (1 mL) was added. Solvents were evaporated, and the residue was purified by flash chromatography (hexane, then ethyl acetate−hexane 30:70) to give chloride **21a** (0.59 g, 85% from **19a**) as an oil: R_f = 0.49 (30% ethyl acetate−hexane); IR (film) ν 2953, 1734, 1436, 1259, 1150, 1099, 1035, 994 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.32 (1H, dd, J = 14.8, 10.3 Hz), 6.13 (1H, m), 5.92−5.70 (2H, m), 5.09 (1H, t, J = 6.2 Hz), 4.60 (2H, s), 4.09 (2H, d, J = 7.3 Hz), 3.91 (1H, q, J = 5.2 Hz), 3.73 (6H, s), 3.69 (3H, s), 3.36 (1H, m), 3.33 (3H, s), 3.22 (1H, dd, J = 9.4, 4.7 Hz), 2.10−1.86 (6H, m), 1.66 (3H, s), 1.53 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 169.7, 136.2, 133.5, 132.9, 130.4, 127.3, 123.7, 96.4, 78.9, 55.8, 53.3, 52.4, 51.9, 50.9, 44.9, 30.84, 28.9, 27.4, 25.3, 23.2; MS *m/e* 443 (M − OMe)$^+$; HRMS calcd for $C_{22}H_{32}O_7$Cl (M − OMe)$^+$ 443.1836, found 443.1841.

Methyl (±)-(5*Z*,11*E*,13*E*)-(9*S*,10*R*)-15-Chloro-2,10-bis(methoxycarbonyl)-9-methoxymethoxy-6-methylpentadeca-5,11,13-trien-1-oate (21b). The procedure used for the synthesis of **21a** was applied for chlorination of alcohol **20b** using alcohol **20b** (0.66 g), triphenylphosphine (0.42 g), and hexachloroacetone (0.24 mL) in tetrahydrofuran (45 mL) to give chloride **21b** (0.64 g, 90% from **19b**) as a colorless oil: R_f = 0.36 (30% ethyl acetate−hexane); IR (film) ν 2953, 1736, 1437, 1349, 1251, 1150, 1099, 1035, 994, 919, 665 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.31−6.12 (2H, m), 5.81 (1H, m), 5.67 (1H, dd, J = 14.5, 9.8 Hz), 5.06 (1H, t, J = 6.2 Hz), 4.64 (2H, s), 4.05 (2H, d, J = 7.3 Hz), 3.90 (1H, m), 3.73 (6H, s), 3.69 (3H, s), 3.32 (3H, s), 3.36−3.25 (2H, m), 2.05−1.89 (6H, m), 1.69 (3H, s), 1.66 (1H, m), 1.49 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 169.8, 136.5, 133.2, 133.0, 129.0, 123.6, 96.4, 78.5, 55.9, 54.0, 52.5, 51.9, 50.9, 44.8, 29.7, 28.9, 26.1, 25.4, 23.3; MS *m/e* 443 (M − OMe)$^+$, 438 (M − HCl)$^{\bullet+}$; HRMS calcd for $C_{22}H_{32}O_7$Cl (M − OMe)$^+$ 443.1836, found 443.1841.

(±)-(1*R*,2*R*,7*R*,10*R*,11*S*,12*S*)-5,5,11-Tris(methoxycarbonyl)-12-methoxymethoxy-1-methyltricyclo[8.4.0.0^{2,7}]tetradec-8-ene (2b). To a stirred suspension of cesium carbonate (1.7 g, 5.2 mmol) in acetonitrile (750 mL) at reflux was added over 15 h via syringe pump, a solution of the chloride **21b** (0.49 g, 0.70 mmol) in acetonitrile (5 mL). At the end of the addition, the mixture was stirred for an additional 3 h. The mixture was cooled to room temperature, cesium carbonate was filtered on a Celite pad, and solvent was evaporated. The residue was purified by flash chromatography (ethyl acetate−hexane, 30:70) to give tricycle **2b** (275 mg, 60%) as a yellowish foam: R_f = 0.43 (30% ethyl acetate−hexane); IR (film) ν 2952, 2892, 1730, 1435, 1374, 1237, 1152, 1095, 1035, 992, 915, 802, 732, 671 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.63−5.51 (2H, m), 4.60 (1H, d, J = 6.8 Hz), 4.49 (1H, d, J = 6.9 Hz), 3.73 (1H, m), 3.68 (3H, s), 3.63 (3H, s), 3.62 (3H, s), 3.23 (3H, s), 2.64 (1H, dd, J = 12.0, 10.4 Hz), 2.52 (1H, m), 2.39 (1H, m), 2.01−1.87 (2H, m), 1.71−1.18 (9H, m), 0.75 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 172.5, 171.2, 134.3, 129.8, 95.2, 77.6, 55.3, 54.9, 52.6, 52.5, 51.6, 51.0, 49.5, 44.5, 37.0, 36.8, 36.0, 32.3, 31.3, 27.3, 24.1, 23.9; MS *m/e* 376 (M − MOM), 406 (M − MeOH)$^+$; HRMS calcd for $C_{22}H_{30}O_7$ (M − MeOH)$^+$ 406.1991, found 406.1999.

(±)-(1*R*,2*R*,7*R*,10*R*,11*S*,12*R*)-5,5,11-Tris(methoxycarbonyl)-12-methoxymethoxy-1-methyltricyclo[8.4.0.0^{2,7}]tetradec-8-ene (2a). The procedure used for the synthesis of **2b** was applied for the macrocyclization of chloride **21a** using chloride **21a** (0.65 g), cesium carbonate (1.47 g), and acetonitrile (950 mL) to give tricycle **2a** (0.24 g, 40%) as a yellowish foam: R_f = 0.34 (30% ethyl acetate−hexane); IR (film) ν 2952, 2872, 1732, 1435, 1379, 1240, 1206, 1168, 1096, 1037, 917 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.63 (1H, m), 5.55 (1H, m), 4.65 (1H, d, J = 7.1 Hz), 4.50 (1H, d, J = 7.0 Hz), 4.15 (1H, m), 3.77 (3H, s), 3.70 (6H, s), 3.30 (3H, s), 2.78 (1H, dd, J = 12.0, 2.9 Hz), 2.62 (1H, m), 2.51−2.41 (2H, m), 1.90−1.25 (9H, m), 0.77 (3H, s), 0.85 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 172.6, 171.3, 132.9, 131.9, 94.6, 72.9, 55.4, 54.9, 52.5, 51.7, 51.4, 47.3, 37.7, 37.1, 36.9, 36.1, 32.4, 27.4, 25.6, 24.1, 23.4; MS *m/e* 406 (M − MeOH)$^{\bullet+}$; HRMS calcd for $C_{22}H_{30}O_7$ (M − MeOH)$^+$ 406.1991, found 406.1999.

(±)-(1*R*,2*R*,5*S*,7*R*,10*R*,11*S*,12*S*)-5,11-Bis(methoxycarbonyl)-12-methoxymethoxy-1-methyltricyclo[8.4.0.0^{2,7}]tetradec-8-ene-5-carboxylic Acid (24). To a stirred solution of the tricycle **2b** (0.30 g, 0.70 mmol) in THF (10 mL) was added at 0 °C a solution of KOH (1 M in MeOH, 1.7 mL). The solution was stirred at room temperature for 4 h, and the volatile compounds were evaporated. Water was added, and the mixture was extracted with ether. The aqueous phase was acidified to pH 2 and was extracted with ethyl acetate. The combined organic phases were dried, filtered, and evaporated to give monoacid **24** (241 mg, 83%) as an amorphous solid: mp 140−142 °C (ethyl acetate and hexane); IR (film) ν 3561−2500, 2951, 1731, 1720, 1436, 1377, 1288, 1269, 1211, 1099, 1036, 916, 732 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.80 (1H, br s), 5.70−5.59 (2H, m), 4.68 (1H, d, J = 6.8 Hz), 4.57 (1H, d, J = 6.8 Hz), 3.78 (3H, m), 3.76 (1H, m), 3.71 (3H, s), 3.31 (3H, s), 2.72 (1H, dd, J = 12.4, 10.4 Hz), 2.63 (1H, m), 2.51 (1H, m), 2.10−1.92 (2H, m), 1.82−1.20 (9H, m), 0.83 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 175.1, 170.9, 134.2, 129.9, 95.2, 77.7, 55.3, 54.9, 52.7, 51.7, 51.0, 49.5, 44.5, 37.1, 36.6, 36.0, 32.1, 31.3, 27.3, 24.1, 23.9; MS *m/e* 392 (M − MeOH)$^+$; HRMS calcd for $C_{21}H_{28}O_7$ (M − MeOH)$^+$ 392.1835, found 392.1825.

(±)-(1*R*,2*R*,5*S*,7*R*,10*R*,11*S*,12*S*)-5-Hydroxymethyl-5,11-bis(methoxycarbonyl)-12-methoxymethoxy-1-methyltricyclo[8.4.0.0^{2,7}]tetradec-8-ene (25). To a stirred solution of monoacid **24** (0.13 g, 0.30 mmol) in tetrahydrofuran (10 mL) was added triethylamine (43 μL, 0.30 mmol) followed by methylchloroformate (24 μL, 0.30 mmol) at 0 °C. The mixture was stirred for 20 min, and triethylamine salts were filtered. The filtrate was added to a suspension of $NaBH_4$ (0.01 g, 0.33 mmol) in THF, and the resulting mixture was stirred for 15 h at 0 °C. A saturated aqueous solution of $KHSO_4$ was added, and the mixture was stirred for 1 h. The solvent was evaporated, water was added, and the mixture was extracted with ethyl acetate. The combined organic phases were dried, filtered, and evaporated. The crude product was purified by flash chromatography (ethyl acetate−hexane, 1:1) to give the alcohol **25** (92 mg, 73%) as a yellowish oil: R_f = 0.29 (50% ethyl acetate−hexane); IR (film) ν 3478, 2948, 1731, 1435, 1204, 1154, 1098, 1036, 917, 732, 672 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69−5.60 (2H, m), 4.69 (1H, d, J = 6.9 Hz), 4.58 (1H, d, J = 6.8 Hz), 3.77 (1H, m), 3.75 (3H, m), 3.72 (3H, s), 3.56 (2H, s), 3.32 (3H, s), 2.74 (1H, dd, J = 12.4, 10.4 Hz), 2.45 (1H, m), 2.32 (1H, m), 2.10−1.95 (2H, m), 1.80−1.09 (10H, m), 0.83 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 174.9, 134.9, 129.4, 95.1, 77.6, 70.9, 55.2, 51.9, 51.8, 51.5, 49.6, 49.5, 44.4, 37.0, 36.7, 36.3, 31.8, 31.3, 27.3, 24.2, 23.8; MS *m/e* 348 (M − $C_2H_6O_2$)$^{\bullet+}$; HRMS calcd for $C_{20}H_{28}O_5$ (M − $C_2H_6O_2$)$^+$ 348.1937, found 348.1942.

(±)-(1*R*,2*R*,5*R*,7*R*,10*R*,11*S*,12*S*)-5-(1-Ethoxyethyl)oxomethyl-5-hydroxymethyl-11-methoxycarbonyl-12-methoxymethoxy-1-methyltricyclo[8.4.0.0^{2,7}]tetradec-8-ene (26). To a stirred solution of the alcohol **25** (0.10 g, 0.25 mmol) in dichloromethane (15 mL) was added ethyl vinyl ether (24 μL, 0.30 mmol) followed by PPTS (0.02 g, 0.09 mmol). The mixture was stirred at room temperature for 1 h, and an aqueous solution of $NaHCO_3$ was added. The mixture was extracted with dichloromethane, and the combined organic phases were dried, filtered, and evaporated. The crude product was purified by flash chromatography (ethyl acetate−hexane, 1:1) to give the protected alcohol (108 mg, 91%): R_f = 0.67 (50% ethyl acetate−hexane); IR (film) ν 2947, 2894, 1733, 1436, 1377, 1213, 1154, 1133, 1101, 1041, 921, 877 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70−5.56 (2H, m), 4.70−4.61 (2H, m), 4.54 (1H, d, J = 6.8 Hz), 3.78 (1H, td, J = 10.6, 5.6 Hz), 3.68 (3H, s), 3.67 (3H, s), 3.65−3.30 (4H, 3 m), 3.28 (3H, s), 2.74 (1H, dd, J = 12.4, 10.4 Hz), 2.45 (1H, m), 2.33 (1H, m), 2.08−1.94

(2H, m), 1.78−1.39 (6H, m), 1.29−1.10 (3H, m), 1.22 (3H, d, J = 5.3 Hz), 1.15 (3H, t, J = 7.0 Hz), 0.79 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 175.0, 135.1, 129.4, 99.4, 95.2, 77.7, 72.4, 60.8, 55.3, 51.8, 51.7, 51.6, 49.6, 48.5, 44.5, 37.2, 37.1, 36.4, 32.4, 31.4, 27.4, 24.3, 23.9, 19.3, 15.1; MS *m/e* 451 $(M - OMe)^+$, 437 $(M - MOM)^+$; HRMS calcd for $C_{25}H_{39}O_7$ $(M - OMe)^+$ 451.2696, found 451.2689.

To a solution of the ester (see above) (0.104 g, 0.22 mmol) in tetrahydrofuran (20 mL) was added $LiAlH_4$ (0.015 g, 0.39 mmol) at 0 °C. The mixture was stirred at 0 °C for 45 min, and acetone (2 mL) was added followed by $MgSO_4 \cdot 10H_2O$. The resulting mixture was stirred for 1 h at room temperature and filtered through a silica pad, and the solvents were evaporated. The crude product was purified by flash chromatography (ethyl acetate−hexane, 1:1) to give the alcohol **26** (91 mg, 93%) as a white foam: R_f = 0.50 (50% ethyl acetate−hexane); IR (film) ν 3496, 2935, 1738, 1437, 1378, 1196, 1134, 1100, 1042, 919 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69−5.58 (2H, m), 4.69 (1H, d, J = 6.8 Hz), 4.68 (1H, m), 4.59 (1H, d, J = 6.8 Hz), 3.81 (1H, td, J = 10.2, 5.2 Hz), 3.73 (3H, s), 3.70−3.60 (3H, m), 3.50−3.40 (2H, m), 3.32 (3H, s), 3.23 (1H, dd, J = 8.9, 4.0 Hz), 2.75 (1H, dd, J = 12.4, 10.4 Hz), 2.11−1.98 (2H, m), 1.85 (1H, m), 1.73−1.49 (6H, m), 1.32−1.20 (3H, m), 1.32 (3H, d, J = 5.3 Hz), 1.25 (3H, t, J = 7.1 Hz), 1.12−1.01 (2H, m), 0.82 (3H, s); MS *m/e* 423 $(M - OMe)^+$; HRMS calcd for $C_{24}H_{39}O_6$ $(M - OMe)^+$ 423.2746, found 423.2753.

(±)-(1*R*,2*R*,5*S*,7*R*,10*R*,11*S*,12*S*)-5-Hydroxymethyl-11-methoxycarbonyl-12-methoxymethoxy-1-methyl-5-*p*-toluenesulfonyloxymethyltricyclo[8.4.0.0^{2,7}]tetradec-8-ene (27). To a solution of the alcohol **26** (0.36 g, 0.80 mmol) in dichloromethane (50 mL) were added triethylamine (0.33 mL, 2.41 mmol) and 4-(dimethylamino)pyridine (0.3 g, 2.4 mmol) followed by *p*-toluenesulfonyl chloride (0.31 g, 1.61 mmol). The mixture was heated at reflux for 5 h and was cooled to room temperature. Water was added, and the aqueous phase was extracted with dichloromethane. The organic phases were dried, filtered, and evaporated. The crude product was purified by flash chromatography (ethyl acetate−hexane, 30:70) to give the corresponding tosylate (424 mg, 88%) as a white foam: R_f = 0.77 (50% ethyl acetate−hexane); IR (film) ν 3018, 2980, 2951, 1730, 1437, 1362, 1224, 1176, 1134, 1098, 1040, 966, 846, 666 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (2H, d, J = 8.3 Hz), 7.36 (2H, d, J = 8.0 Hz), 5.59−5.49 (2H, m), 4.69 (1H, d, J = 6.9 Hz), 4.66−4.53 (2H, m), 4.04 (1H, d, J = 9.4 Hz), 3.94 (1H, d, J = 9.4 Hz), 3.74 (1H, m), 3.73 (3H, s), 3.56 (1H, m), 3.40 (1H, m), 3.33 (3H, s), 3.26 (1H, t, J = 8.2 Hz), 3.11 (1H, t, J = 10.8 Hz), 2.69 (1H, dd, J = 12.3, 10.4 Hz), 2.46 (3H, s), 2.05 (1H, m), 1.87−1.43 (8H, m), 1.36−1.04 (9H, m), 0.78 (3H, s), 0.71 (1H, m); ^{13}C NMR (75 MHz, C_6D_6) δ 174.5, 144.3, 135.2, 133.6, 129.6, 127.8, 127.5, 99.8, 95.1, 77.4, 70.6 70.5, 69.5, 60.9, 60.8, 54.9, 51.9, 50.8, 49.6, 44.8, 38.1, 36.8, 35.9, 35.7, 34.1, 34.0, 31.2, 30.6, 30.4, 27.5, 23.6, 22.2, 22.1, 20.9, 19.6, 15.4; MS *m/e* 593 $(M - Me)^+$, 576 $(M - MeOH)^{\bullet+}$, 563 $(M - MOM)^+$; HRMS calcd for $C_{31}H_{44}O_8S$ $(M - MeOH)^+$ 576.2757, found 576.2744.

To a solution of the tosylate (see above) (0.05 g, 0.08 mmol) in tetrahydrofuran (30 mL) was added 0.5 M aqueous HCl (1.5 mL). The mixture was stirred for 4 h at room temperature, and a saturated aqueous solution of $NaHCO_3$ was added. The solvent was evaporated, and the mixture was extracted with ethyl acetate. The organic phase was dried, filtered, and evaporated. The crude product was purified by flash chromatography (ethyl acetate−hexane, 1:1) to give the alcohol **27** (39 mg, 90%) as a white foam: R_f = 0.49 (50% ethyl acetate−hexane); IR (film) ν 3480, 2945, 2948, 1738, 1598, 1436, 1360, 1244, 1188, 1176, 1098, 1039, 964, 822, 814 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (2H, d, J = 8.3 Hz), 7.35 (2H, d, J = 8.2 Hz), 5.60−5.47 (2H, m), 4.65 (1H, d, J = 6.9 Hz), 4.54 (1H, d, J = 6.9 Hz), 4.02 (1H, d, J = 10.1 Hz), 3.95 (1H, d, J = 10.1 Hz), 3.75 (1H, m), 3.69 (3H, s), 3.33 (2H, s), 3.29 (3H, s), 2.68 (1H, dd, J = 12.3, 10.4 Hz), 2.43 (3H, s), 2.14−1.95 (2H, m), 1.86−1.22 (9H, m), 1.13−0.88 (3H, m), 0.75 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 145.1, 134.8, 132.3, 129.9, 129.7, 127.9, 95.3, 77.7, 69.7, 68.7, 55.4, 52.1, 51.6, 49.5, 44.7, 39.2, 37.0, 35.3, 34.2, 31.4, 30.1, 27.4, 23.9, 22.4, 21.6; MS *m/e* 504 $(M - MeOH)^+$, 474 $(M - MOM)^+$; HRMS calcd for $C_{27}H_{36}O_7S$ $(M - MeOH)^+$ 504.2182, found 504.2163.

(±)-(1*R*,2*R*,5*R*,7*R*,10*R*,11*S*,12*S*)-5-Hydroxymethyl-11-methoxycarbonyl-12-methoxymethoxy-1,5-dimethyltricyclo[8.4.0.0^{2,7}]tetradec-8-ene (28). To a solution of the tosylate **27** (0.41 g, 0.08 mmol) in dimethyl sulfoxide (6 mL) was added $NaBH_4$ (0.04 g, 0.98 mmol). The resulting mixture was stirred at 80 °C for 4 h, and the solution was cooled to 0 °C. A saturated aqueous solution of $KHSO_4$ was added, and the mixture was stirred for 1 h and extracted with ethyl acetate. The organic phase was dried, filtered, and evaporated. The crude product was purified by flash chromatography (ethyl acetate−hexane, 30:70) to give compound **28** (260 mg, 93%) as a yellow foam: R_f = 0.51 (40% ethyl acetate−hexane); IR (film) ν 3446, 2934, 1737, 1458, 1436, 1329, 1267, 1244, 1197, 1173, 1099, 1040, 917 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.66−5.60 (2H, m), 4.69 (1H, d, J = 6.9 Hz), 4.58 (1H, d, J = 6.9 Hz), 3.81 (1H, td, J = 10.5, 5.1 Hz), 3.72 (3H, s), 3.32 (3H, s), 3.29 (2H, s), 2.74 (1H, dd, J = 12.4, 10.4 Hz), 2.10−2.02 (2H, m), 1.88 (1H, m), 1.66−1.19 (9H, m), 0.93 (3H, s), 0.81 (3H, s), 0.72 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 135.8, 129.4, 95.3, 77.8, 74.4, 55.4, 52.5, 51.6, 49.7, 44.8, 39.9, 37.2, 35.63, 34.7, 31.6, 27.5, 23.9, 22.8, 19.9; MS *m/e* 351 $(M - Me)^+$, 335 $(M - OMe)^+$; HRMS calcd for $C_{20}H_{31}O_4$ $(M - OMe)^+$ 335.2222, found 335.2227.

(±)-(1*R*,2*R*,5*R*,7*R*,10*R*,11*S*,12*S*)-12-Hydroxy-5-hydroxymethyl-11-methoxycarbonyl-1,5-dimethyltricyclo[8.4.0.0^{2,7}]-tetradec-8-ene (41). To a stirred solution of the alcohol **28** (0.1 g, 0.3 mmol) in methanol (25 mL) was added concentrated HCl (4 drops). The mixture was stirred at 60 °C for 2 h and was cooled to room temperature. An aqueous solution of $NaHCO_3$ was added, methanol was evaporated, and the residue was extracted with ethyl acetate. The combined organic phases were dried, filtered, and evaporated. The crude product was purified by flash chromatography (ethyl acetate−hexane, 1:1) to give the diol **41** (78 mg, 90%) as a white foam: R_f = 0.37 (50% ethyl acetate−hexane); IR (film) ν 3996, 2936, 2869, 1732, 1462, 1435, 1377, 1333, 1372, 1198, 1173, 1035, 912, 731 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.63 (2H, s), 3.85 (1H, m), 3.73 (3H, s), 3.28 (2H, s), 2.63 (1H, dd, J = 12.4, 10.4 Hz), 2.05−1.83 (3H, m), 1.70−1.18 (10H, m), 0.92 (3H, s), 0.81 (3H, s), 0.72 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 135.7, 129.5, 74.4, 72.3, 52.5, 51.8, 51.2, 44.3, 39.9, 37.2, 35.6, 34.7, 34.6, 31.7, 30.4, 23.9, 22.8, 19.9; MS *m/e* 322 $M^{\bullet+}$, 307 $(M - Me)^+$, 304 $(M - H_2O)^{\bullet+}$; HRMS calcd for $C_{19}H_{28}O_3$ $(M - H_2O)$ 304.2038, found 304.2033.

(±)-(1*R*,2*R*,5*R*,7*R*,8*R*,9*R*,10*R*,11*S*,12*S*)-8-Acetoxy-9-bromo-12-hydroxy-5-hydroxymethyl-11-methoxycarbonyl-1,5-dimethyltricyclo[8.4.0.0^{2,7}]tetradecane (42). To a stirred solution of the diol **41** (0.20 mg, 0.06 mmol) in acetic acid (20 mL) was added *N*-bromoacetamide (9 mg, 0.06 mmol), followed by silver acetate (10 mg, 0.06 mmol). The mixture was stirred overnight at room temperature and was filtered through a silica pad. Solvents were removed, and the crude product was purified by flash chromatography (ethyl acetate−hexane, 1:1) to give bromoacetate **42** (22 mg, 75%) as a white foam: R_f = 0.14 (50% ethyl acetate−hexane); IR (film) ν 3426, 2929, 2856, 1738, 1434, 1371, 1330, 1286, 1228, 1040 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.19 (1H, s), 3.96 (1H, d, J = 10.0 Hz), 3.82 (1H, td, J = 10.5, 4.8 Hz), 3.72 (3H, s), 3.26 (2H, s), 2.50 (1H, t, J = 11.0 Hz), 2.13 (1H, t, J = 10.3 Hz), 2.09 (3H, s), 1.86 (1H, m), 1.72 (1H, m), 1.66−1.13 (9H, m), 1.12 (3H, s), 0.93 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 170.0, 81.2, 73.9, 72.1, 54.1, 52.7, 52.4, 48.3, 45.9, 37.5, 36.7, 35.6, 34.3, 33.8, 33.0, 29.1, 23.6, 22.9, 21.0, 20.3; MS *m/e* 429 $(M - OMe)^+$; HRMS calcd for $C_{20}H_{30}O_5Br$ $(M - OMe)^+$ 429.1276, found 429.1284.

(±)-(1*R*,2*R*,5*R*,7*R*,8*R*,9*R*,10*R*,11*S*)-8-Acetoxy-9-bromo-5-formyl-11-methoxycarbonyl-1,5-dimethyltricyclo[8.4.0.0^{2,7}]-

tetradecan-12-one (43). To a stirred solution of diol **42** (0.03 g, 0.08 mmol) in dichloromethane (30 mL) at 0 °C was added Dess−Martin periodinane (0.08 g, 0.19 mmol). The mixture was stirred at room temperature for 1 h, and 1 M aqueous solution of $Na_2S_2O_3$ was added followed by a saturated aqueous solution of $NaHCO_3$. Layers were separated, and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried, filtered, and evaporated. The residue was purified by flash chromatography (ethyl acetate−hexane, 1:1) to give aldehyde **43** (25 mg, 83%) as a white foam: $R_f = 0.61$ (50% ethyl acetate−hexane); IR (film) ν 2951, 2932, 2873, 1744, 1732, 1722, 1714, 1462, 1434, 1372, 1274, 1228, 1159, 1116, 1054, 1023, 916 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.37 (1H, s), 5.48 (1H, t, $J = 5.4$ Hz), 3.98 (1H, dd, $J = 12.3$, 5.6 Hz), 3.72 (3H, s), 3.28 (1H, dd, $J = 10.8$, 0.9 Hz), 2.97 (1H, dd, $J = 12.2$, 11.0 Hz), 2.69 (1H, m), 2.50 (1H, m), 2.20 (1H, m), 2.13 (3H, s), 2.01 (1H, m), 1.76−1.63 (2H, m), 1.59−1.28 (6H, m), 1.13 (3H, s), 1.02 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.4, 204.9, 170.0, 169.7, 79.3, 60.2, 54.6, 53.1, 45.5, 45.3, 43.4, 36.9, 35.2, 32.8, 31.8, 31.1, 30.3, 21.0, 20.8, 20.7, 16.9; MS *m/e* 444; HRMS calcd for $C_{20}H_{29}O_6Br$ 444.1147, found 444.1153.

(±)-4-Desmethyl-4α,8α-dihydro-7*β*-hydroxymomilactone A (44). To a suspension of methyltriphenylphosphonium bromide (20 mg, 0.06 mmol) in THF (10 mL) was added KHMDS (0.5 M in toluene, 100 μL, 0.06 mmol). The mixture was stirred for 15 min and was cooled to −78 °C. A solution of the aldehyde **43** (12 mg, 0.02 mmol) in tetrahydrofuran (1.5 mL) was added. The resulting mixture was stirred at −78 °C for 15 min, warmed to 0 °C, and stirred for 45 min. An aqueous solution of NH_4Cl was added, and the mixture was extracted with ethyl acetate. Layers were separated, and the combined organic phases were dried, filtered, and evaporated. The residue was quickly purified by flash chromatography (ethyl acetate−hexane, 30:70) to give the vinylic compound: $R_f = 0.89$ (50% ethyl acetate−hexane); IR ($CHCl_3$) ν 2955, 2928, 2855, 1742, 1713, 1460, 1436, 1376, 1275, 1275, 1236, 1162 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.75 (1H, dd, $J = 17.5$, 10.8 Hz), 5.47 (1H, t, $J = 5.6$ Hz), 4.93 (1H, dd, $J = 17.4$, 1.1 Hz), 4.89 (1H, dd, $J = 10.6$, 1.1 Hz), 3.99 (1H, dd, $J = 12.4$, 5.8 Hz), 3.74 (3H, s), 3.31 (1H, dd, $J = 11.0$, 1.2 Hz), 2.97 (1H, dd, $J = 12.3$, 11.1 Hz), 2.69 (1H, m), 2.49 (1H, m), 2.21 (1H, dd, $J = 9.5$, 4.2 Hz), 2.12 (3H, s), 2.05 (1H, m), 1.73−1.08 (8H, m), 1.01 (3H, s), 1.00 (3H, s); MS *m/e* 426 $(M - MeOH)^{\bullet+}$; HRMS calcd for $C_{21}H_{32}O_4Br$ $(M - MeOH)^+$ 426.1406, found 426.1412.

A solution of residue (see above) in a mixture of acetic acid−water (10 mL − 1 mL) was heated overnight at 90 °C. The solution was cooled to room temperature, and solvents were evaporated. The residue was extracted with ethyl acetate, and solvent was evaporated. The mixture of hydroxyacetates was dissolved in methanol, and solid K_2CO_3 (15 mg, 0.10 mmol) was added. The mixture was stirred at room temperature for 1 h, and an aqueous saturated solution of NH_4Cl was added. Methanol was evaporated, and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried, filtered, and evaporated. The crude product was purified by flash chromatography (ethyl acetate−dichloromethane, 20:80) to give lactone **44** (5 mg, 65% for the last two steps) as an oil: $R_f = 0.36$ (20% ethyl acetate−dichloromethane); IR ($CHCl_3$) ν 3686, 3605, 2958, 2927, 1791, 1748, 1710, 1672, 1638, 1602, 1462, 1376, 1230, 1122, 1100, 1048, 925 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.82 (1H, dd, $J = 17.5$, 10.8 Hz), 4.96 (1H, dd, $J = 17.5$, 1.2 Hz), 4.89 (1H, dd, $J = 10.7$, 1.2 Hz), 4.53 (1H, dd, $J = 7.1$, 6.3 Hz), 4.14 (1H, d, $J = 7.2$ Hz), 3.34 (1H, d, $J = 8.1$ Hz), 2.79 (1H, dd, $J = 8.1$, 6.2 Hz), 2.67−2.52 (2H, m), 2.10 (1H, s), 1.90−1.72 (4H, m), 1.64−1.31 (5H, m), 1.20 (3H, s), 1.03 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.7, 170.6, 149.9, 109.5, 77.0, 67.6, 50.1, 44.1, 41.4, 40.9, 37.9, 37.3, 36.6, 35.9, 32.0, 23.8, 23.3, 22.5; MS *m/e* 318 $M^{\bullet+}$, 300 $(M - H_2O)^+$; HRMS calcd for $C_{19}H_{26}O_4$ (M^+) 318.1831, found 318.1836.

(±)-7*β*-Hydroxy-8α-hydromomilactone A (45). To a stirred solution of the lactone **44** (5 mg, 15.6 μmol) in acetonitrile (2 mL) was added iodomethane (5 μL, 78.1 μmol) followed by cesium carbonate (25 mg, 78.1 μmol). The mixture was stirred for 1.5 h at room temperature and was filtered through a Celite pad. The solvent was evaporated to give *β*-ketolactone **45** (4.6 mg, 89%) as a white solid: $R_f = 0.42$ (20% ethyl acetate−dichloromethane); mp 240 °C dec (ethyl acetate, methanol, and hexane); IR ($CHCl_3$) ν 3692, 3602, 2961, 2926, 1788, 1706, 1602, 1460, 1391, 1375, 1265, 1232, 1200, 1111, 1100, 1071, 1049 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.82 (1H, dd, $J = 17.5$, 10.7 Hz), 4.96 (1H, dd, $J = 17.5$, 1.2 Hz), 4.89 (1H, dd, $J = 10.7$, 1.2 Hz), 4.63 (1H, dd, $J = 7.2$, 6.3 Hz), 4.15 (1H, dd, $J = 7.4$, 1.3 Hz), 2.59−2.54 (2H, m), 2.37 (1H, d, $J = 6.2$ Hz), 2.09 (1H, s), 1.95−1.69 (4H, m), 1.52 (3H, s), 1.42−1.23 (5H, m), 1.17 (3H, s), 1.03 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.8, 174.1, 149.5, 109.5, 75.4, 67.6, 52.2, 48.7, 44.1, 40.9, 37.8, 37.0, 36.6, 34.3, 32.2, 31.9, 23.9, 23.8, 22.5, 22.2; MS *m/e* 332 M^+, 314 $(M - H_2O)^+$; HRMS calcd for $C_{20}H_{28}O_4$ (M^+) 332.1987, found 332.1996.

(±)-Momilactone A (1). To a solution of hydroxymomilactone A **45** (12 mg, 0.04 mmol) in toluene was added Burgess reagent (19 mg, 0.08 mmol). The mixture was heated at reflux for 12 h and was cooled to room temperature. Solvent was evaporated, and the residue was purified by flash chromatography (ethyl acetate−dichloromethane, 20:80) to give momilactone A as a white solid (4.5 mg, 40−50%): $R_f = 0.83$ (20% ethyl acetate−dichloromethane); mp 150−154 °C (ethanol and dichloromethane); IR ($CHCl_3$) ν 2937, 1770, 1702, 1602, 1458, 1378, 1331, 1184, 1137, 1038, 991 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.85 (1H, dd, $J = 17.3$, 10.7 Hz, C*H*=CHH), 5.71 (1H, d, $J = 5.2$ Hz, *H*7), 4.98 (1H, dd, $J = 17.0$, 0.9 Hz, CH=CHH_{trans}), 4.94 (1H, dd, $J = 10.7$, 0.9 Hz, CH=CH_{cis}H), 4.84 (1H, t, $J = 5.2$ Hz, *H*6), 2.66−2.58 (2H, m, *H*2), 2.32 (1H, d, $J = 4.9$ Hz, *H*5), 2.21 (1H, d, $J = 11.8$ Hz), 2.06 (1H, d, $J = 12.1$ Hz), 1.98−1.70 (3H, m), 1.66−1.50 (3H, m), 1.52 (3H, s, CH_3 at C4), 1.32 (1H, m), 1.00 (3H, s, CH_3 at C10), 0.90 (3H, s, CH_3 at C13); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.2, 174.3, 148.9, 148.0, 114.0, 110.2, 73.1, 53.5, 50.1, 47.5, 46.4, 40.1, 37.2, 34.9, 32.4, 31.2, 23.9, 21.9, 21.8, 21.4; MS *m/e* 314 M^+; HRMS calcd for $C_{20}H_{26}O_3$ (M^+) 314.1882, found 314.1886.

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Supporting Information Available: Experimental procedures and characterization data for compounds **4**, **5**, **7**, **10**−**17**, **22**, **23**, **29**, **31**−**35**, and **37**−**40**; copies of ^1H NMR spectra of compounds **1**, **2**, **4**, **5**, **18**−**29**, **31**−**35**, and **37**−**45** and ^{13}C NMR of **1**; X-ray crystal structure of **45**. This material is available free of charge via the Internet at http://pubs.acs.org.

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