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Studies Directed Towards the Total Synthesis of Aldosterone and Naturally Occurring Analogues. A Unified Approach Using the Transannular Diels-Alder Reaction.

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Abstract: A novel approach to the syntheses of aldosterone and naturally occurring analogues thereof is described. The strategy is characterized by a common and highly convergent route using the transannular Diels-Alder reaction of 14-membered TCC macrocyclic trienes as the key step. For this purpose, a novel macrocyclization procedure involving the intramolecular displacement of an α-chloroketone by a β-ketoester provided three key *trans*-fused macrocycles in high yield.

INTRODUCTION

Since its isolation in 1952 from mammalian adrenal cortex,[1] aldosterone **1a** has emerged as the most potent naturally occurring mineralocorticoid (Fig. 1). This hormone is a major regulator of sodium and potassium homeostasis and the relationship of aldosterone to different types of hypertension has been recognized for more than 40 years. Although the biochemical mechanism involved is not yet entirely clear, the link between aldosterone and the control of blood pressure is reflected in the clinical finding of hypertension in primary hyper-aldosteronism and hypotension in adrenal insufficiency.[2] High salt intake in face of high levels of aldosterone also results into cardiac hypertrophy and fibroses.[3] Apart from these pharmacological considerations, considerable efforts by organic chemists since the late 1950's have culminated to several semi[4] and total syntheses.[5] Notwithstanding its important function in maintaining electrolyte balance, aldosterone has not found any significant medical application. More recently other natural mineralocorticoids, namely 19-hydroxyaldosterone **1b** and 19-noraldosterone **1c**, have been synthesized[6] and exhibited hypertensiogenic activity while the unnatural 18-deoxy-19-noraldosterone **1d** was shown to be a more potent antagonist than the reference drug spironolactone.[7] Despite these synthetic achievements, these undertakings were rather tedious and shorter routes underlined by a common strategy would prove highly desirable for providing aldosterone and most importantly, analogs thereof for structure-activity evaluations.

Our strategic plan calls for the stereoselective elaboration of the ABC ring system via the transannular Diels-Alder reaction.[8] Incidentally, we have previously demonstrated that a 14-membered TCC (*trans-cis-cis*) macrocyclic triene leads to the TSC (*trans-syn-cis*) adduct, and provided there is a ketone or its equivalent at the pro-11 position, the former can be epimerized to the more stable TAT (*trans-anti-trans*) stereochemistry.[9] Such tactics should prove equally dependable in leading to **2a-c** (Fig. 2). On the basis of the substitution pattern

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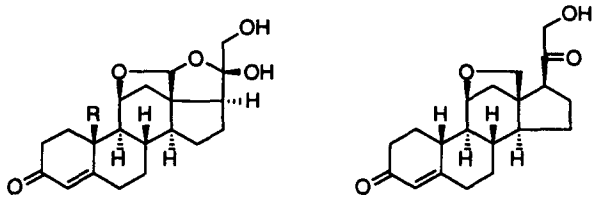
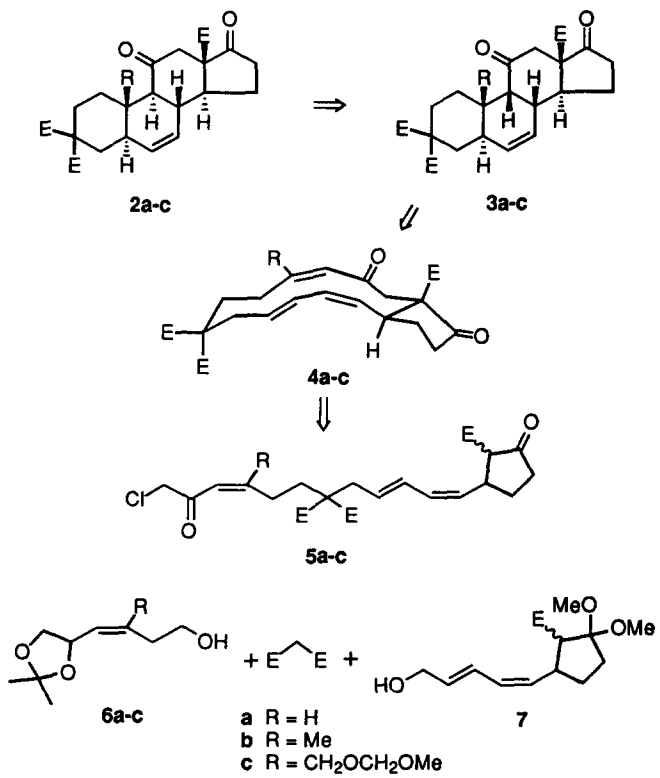


1a R = Me
1b R = CH_2OH
1c R = H

1d

Figure 1

offered by this approach, **2a-c** should be easily modified to the natural products by standard synthetic manipulations. The requisite macrocyclic trienes **4a-c** could be accessed via intramolecular alkylation from the less congested face of ketoesters **5a-c**, thereby setting the correct stereochemistry at the ring junction. The versatility of our approach is further illustrated by the choice of dienophiles **6a-c** incorporated at the convergent stage which would purposely give access to 18-noraldosterone, 18-hydroxy-aldosterone and aldosterone itself. Recourse to enantiopure **7** could eventually control the absolute stereochemistry of the impending stereogenic centers. Herein, we report progress made in this challenging endeavor and interesting observations made along the way.



2a-c **3a-c**

4a-c

5a-c

6a-c

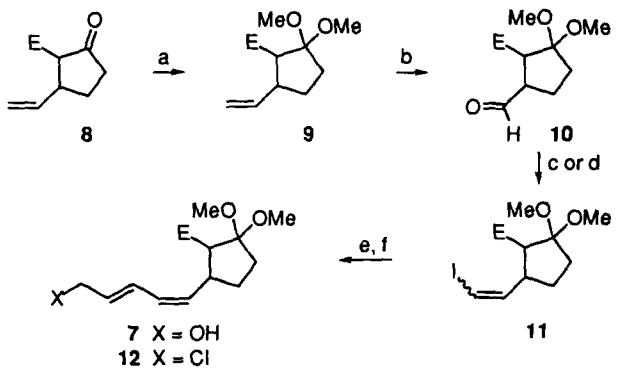
a R = H
b R = Me
c R = CH_2OCH_2OMe

7

Figure 2

RESULTS AND DISCUSSION

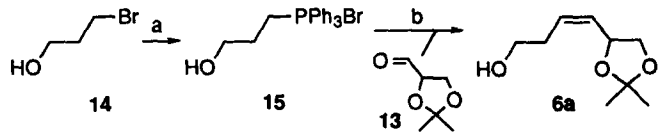
Bearing in mind the recent enantioselective synthesis of synthon **8** in both enantiomeric forms,[10] we initiated the construction of the dienophilic moiety with the racemic material which readily lends itself to large scale preparation[11] (Scheme 1). Subjected to the action of methanol and trimethylorthoformate in the presence of *p*-toluenesulfonic acid, synthon **8** gave the corresponding dimethoxyketal **9** as a 9:1 mixture of the *trans* and *cis* isomers respectively. Although possible, the separation was not of particular concern since the relative stereochemistry is inconsequential to the outcome (*vide infra*). Ozonolysis of this mixture under standard conditions proceeded smoothly providing the particularly stable aldehyde **10** in a combined yield of 89%. Upon treatment with iodomethylenetriphenylphosphorane according to Stork's protocol,[12] the vinyl iodide **11** was readily prepared in 85% yield (*Z*/*E*, 4:1). An alternative procedure using a more complex phosphorane served to deliver the pure *Z* isomer (*Z*/*E*, >100:1) but in a disappointingly low yield of 51%.[13] Moreover, the reaction was found to be more or less reproducible in our hands and considering the number of steps involved in the preparation of the requisite phosphorane, the previous procedure was considered more convenient. Gratifyingly, the pure *E*,*Z* alcohol **7** could be secured by a Stille cross-coupling[14] of the mixture of vinyl iodides **11** with (*Z*)-3-tributylstannyl-2-propenol[15] followed by simple flash chromatography. The rather labile allylic chloride **12** was then obtained by the application of Meyers' protocol.[16]



Scheme 1. (a) $CH(OMe)_3$, TsOH, MeOH, 40°C, 4 h, 91%; (b) O_3, MeOH/CH_2Cl_2 (1:5), -78°C, PPh_3, -78°C to r.t., 98%; (c) CH_2IPPh_3I, HMDSNa, THF, -78°C, 0.5 h, 85% (*Z*/*E*, 4:1); (d) CH_2IP-(*o*-MOMOPh)$_3$I, HMDSNa, THF, -78°C, 0.5 h, 51% (*Z*/*E* >98:2); (e) (*E*)-$HOCH_2CH{=}CHSn(n\text{-}Bu)_3$, $PdCl_2(MeCN)_2$, DMF, r.t., 5 h, 74%; (f) MsCl, collidine, LiCl, DMF, 0°C to r.t., 2 h, 72%. E = CO_2Me.

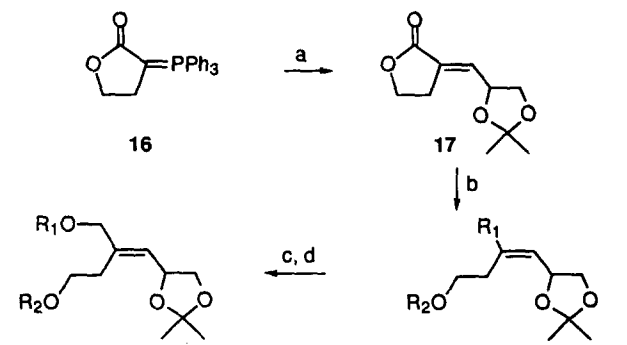
In order to demonstrate the versatility of our approach, three subsets of dienophiles were examined, all of which could potentially be accessed via a Wittig reaction between (R)-2,3-O(isopropylidene)glyceraldehyde **13**[17] and appropriately functionalized phosphoranes. Whereas the preparation of dienophile **6b** has previously been reported by our group,[9a] the stereoselective syntheses of the nor and the hydroxymethyl derivatives **6a** and **c** required investigation. In this respect, a precedent involving the reaction of phosphonium **15** with 2 equivalents of BuLi followed by the condensation with benzaldehyde was reported to yield the corresponding olefin.[18] However, little insight is gained since no comments were made on the stereochemistry of this cryptically described reaction. In our hands, a similar experiment using aldehyde **13** completely lacked selectivity in

furnishing an equal mixture of *E* and *Z* isomers. It then came to our attention that temporary masking of the alcohol should prevent an internal "Schlosser *trans*-selective Wittig" reaction which accounts for the observed stereoselectivity.[19] Thus, prior to the condensation with aldehyde **13**, the ylide was allowed to react with 1 equivalent of chlorotrimethylsilane. These highly favorable conditions did indeed provide, after acidic treatment, the homoallylic alcohol **6a** of high isomeric purity (≈90% *Z* by NMR) in an overall yield of 74% from **15** (Scheme 2). Efforts to separate the *Z*-alcohol from the minor constituent were to no avail and the enriched mixture was used as such for subsequent transformations.



Scheme 2. (a) PPh_3, $PhCH_3$, reflux, 24 h, 94%; (b) 2 eq. *n*-BuLi, THF, -20°C, 1 h, 1 eq. TMSCl, -20°C, 0.5 h *(ii)* **13**, THF, -78°C to r.t., 1 h *(iii)* citric acid, H_2O, r.t., 74% (*Z*/*E*, 9:1).

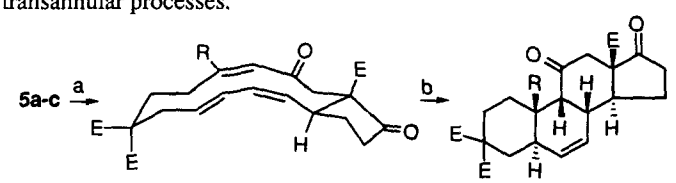
Concerning the hydroxymethyl dienophile **6c**, we were particularly attracted to the use of 1-butyrolactonylidene triphenylphosphorane **16**[20] since it has previously been shown to be highly stereoselective in providing *trans* α-alkylidene-γ-butyrolactones.[21] In the present case, its condensation with aldehyde **13** proved to be equally dependable in providing 89% of **17** as the sole product (Scheme 3). A three-step routine sequence involving partial reduction of **17** to lactol **18**, acetylation of the corresponding hydroxy aldehyde and sodium borohydride reduction led to the allylic alcohol **20** in a combined yield of 70%. It then proved an easy matter to obtain the appropriately functionalized dienophile by allylic alcohol protection as the MOM ether followed by acetate cleavage under standard conditions which provided **6c**.



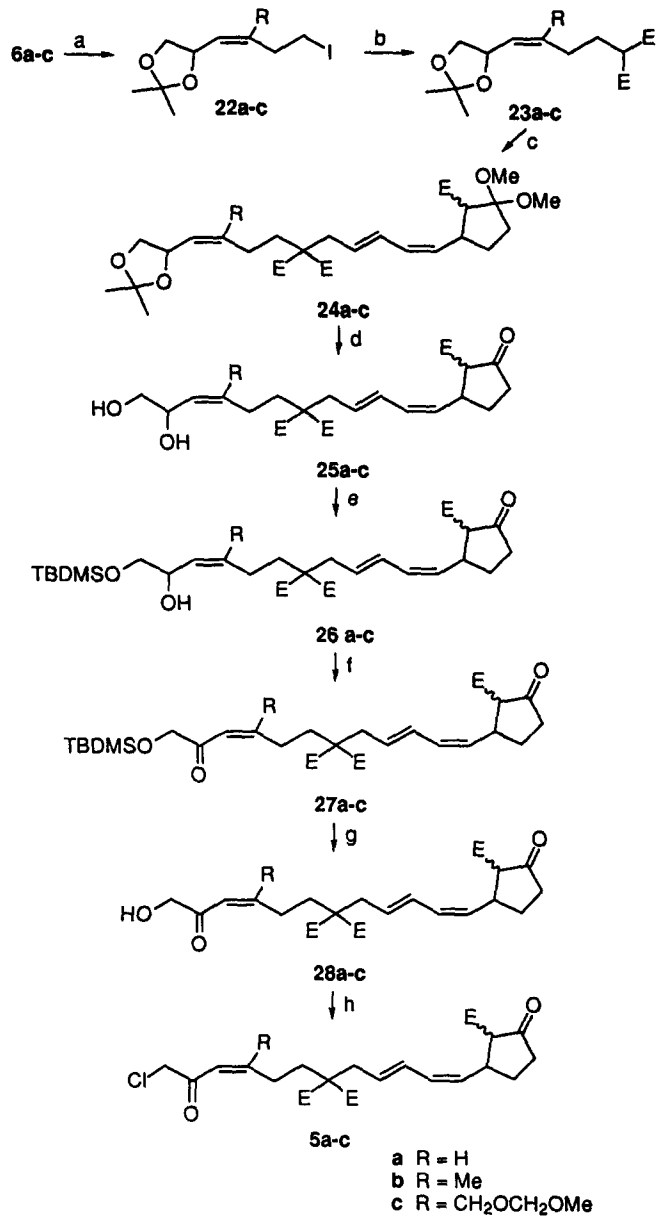
Scheme 3. (a) **13**, THF, 0°C to r.t., 1 h, 89%; (b) *(i)* DIBALH, $PhCH_3$, -78°C, 1 h, *(ii)* Et_3N, Ac_2O, DMAP, 0°C, 3 h, *(iii)* $NaBH_4$, MeOH, 0°C, 0.5 h, 70%; (c) MOMCl, DIPEA, CH_2Cl_2, r.t. 24 h, 85%; (d) K_2CO_3, MeOH, r.t., 4 h, 97%.

At the convergent stage, the choice of a connector was deemed crucial for a successful synthesis. Dimethyl malonate was considered a suitable candidate and the reasons are three-fold: (a) its acidity offers soft reaction conditions, (b) malonates also constitute umpoled acyl anions since they easily afford carbonyls by various methods,[22] (c) and most importantly, they are known to be thermally stable to the anticipated temperature of the Diels-Alder reaction.[9] Hence, the alcohols **6a-c** were activated to the corresponding iodides **22a-c** by a modified version of the Mitsunobu reaction,[23] then alkylated of the anion of dimethyl malonate to give the dienophilic synthons **23a-c** (Scheme 4). The coupling of these with allylic chloride **12** provided the TCC trienes **24a-c** which incidentally englobe the complete carbon arrangement necessary for the construction of the steroids and their six contiguous stereogenic centers. Completion of the synthesis requires the elaboration of α-chloroketone units on the dienophilic moieties and β-ketoesters as nucleophilic partners for the macrocyclization. Accordingly, concomitant hydrolysis of the acetonide and the dimethoxyketal in 80% aqueous acetic acid followed by monosilylation[24] of the primary alcohols **25a-c** gave the ketoesters **26a-c**. Dess-Martin oxidation[25] of the remaining alcohols and subsequent cleavage of the silyl protective groups led to the α-ketols **28a-c** which were then converted to the corresponding α-chloroketones **5a-c** using hexachloroacetone and triphenylphosphine.[26] It is noteworthy that the use of a full equivalent of the latter was avoided since the enone was found to isomerize via a reversible Michael addition of the phosphine. With these precautions, isomerization could be controlled to an approximate extent of 5% which was practically inevitable. The overall yields for the 5-step sequence from **24a-c** ranged between 41 and 52%.

The stage was now set to assert our basic premises. Gratifyingly, slow addition of **5a-c** to a warm suspension of cesium carbonate in acetonitrile under pseudo-high dilution afforded the *trans* ring-junctioned macrocycles **4a-c** as the sole products in high yields of 78-86% (Scheme 5). It is noteworthy that no traces of either *O*-alkylated or *cis* fused isomers were detected. As for the TCT isomers originating from scrambling of the enones (*vide supra*), the corresponding macrocycles were not observed even in trace quantities suggesting the decomposition of their precursors in the reaction medium. The key macrocyclization step thus features a novel and highly efficient method for the construction of large rings. When heated at 200-230°C for 24 h, the TCC macrocyclic trienes cleanly underwent a transannular cycloaddition to give the corresponding TSCAT tetracycles **3a-c** in yields ranging between 74 and 85%. Interestingly, the conformational restrictions in the TCC macrocycles **4a-c** circumvent the formation of the *endo* adducts which would be expected from intermolecular, intramolecular and some transannular processes.[27]



Scheme 5. (a) 1 h syringe pump addition over Cs_2CO_3, MeCN, 40°C, [ ]=2μM, 78-86%; (b) $PhCH_3$, sealed quartz tube, 200-230°C, 24 h, 74-85%.



Scheme 4. (a) DEAD, PPh_3, MeI, $PhCH_3$, r.t., 0.25 h, 81-85%; (b) E_2CH_2, NaH, DMF/THF, reflux, 1 h, 84-96%; (c) NaH, DMF/THF, r.t., 1 h, **12**, reflux, 1 h, 76-85%; (d) H_2O/HOAc (1:4), r.t., 6 h, 85-94%; (e) 1 eq. TBDMSCl, Imid., DMF, -20°C, 2 h, 72-79%; (f) Dess-Martin periodinane, CH_2Cl_2, r.t., 2-4 h, 79-87%; (g) H_2O/HOAc (1:4), r.t., 9 h, 90-94%; (h) PPh_3, HCA, THF, -40°C, 0.5 h, 88-94%. E = CO_2Me.

Rather interesting observations arose when the thermal reaction of **4b** was monitored over time. After only a few hours, the proton NMR exhibited a high degree of scrambling of the olefinic protons where only traces of the macrocyclic precursor **4b** was detected. Gratifyingly, this complex mixture slowly converged to a single adduct. *A priori*, these observations suggest that prototropic shifts occur in a reversible fashion,[28] as illustrated in Fig. 3. Indeed, compound **31** was isolated from the mother liquor of combined runs. Once the structure had been established by single crystal X-ray analysis,[29] macrocycle **31** was resubmitted to the thermal reaction conditions previously employed. Albeit in minute quantities, the adduct **3b** was observed again as part of a complex mixture. Naturally, we were concerned that epimerization at the pro C-14 position might have occurred during the thermal process leading to **32** and this could then collapse to the TSCAC adduct **33**. To our delight, X-ray analysis of the adduct unambiguously established its TSCAT stereochemistry.[29]

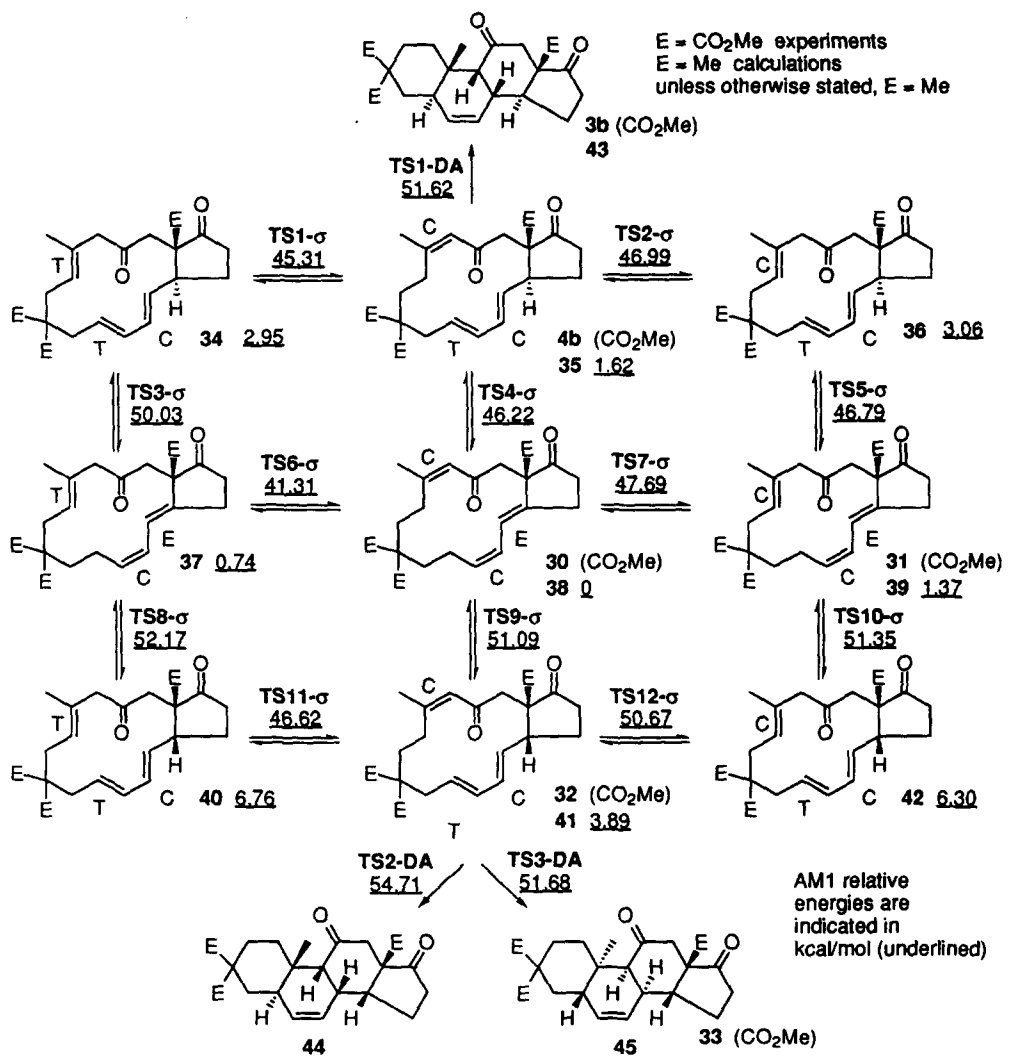


Figure 3

Clearly, the path leading to **33** is energetically unfavorable and in an effort to gain insight into this rather complex matter, recourse to molecular modeling was made. As already used in previous studies,[28] the ester groups encountered in the real molecules were replaced by methyl groups in the corresponding structures destined to be calculated by means of the semiempirical hamiltonian AM1.[30,31,32] Careful examination of all possible competing reactions to be calculated led to the identification of 9 interconverting macrocycles (Fig. 3). As a result 12 transition structures had to be located. The horizontal transformations (*e.g.* **34** to **35**) occur via 1,5-H shift reactions inside *Z*-butenone systems as shown in Fig. 4 (see also **TS1-σ** and **TS2-σ** in Fig. 5). The vertical transformations (*e.g.* **34** to **37**) take place via [1,5]sigmatropic hydrogen shift reactions at the diene sites (see **TS4-σ** in Fig. 5). Finally, since all these 9 macrocycles possess diene and dienophile in a transannular relationship, each of them could in principle yield Diels-Alder adducts. However, unactivated dienophiles like the ones found in the rings **34**, **36**, **37**, **39**, **40** and **42** usually necessitate higher temperatures than the 200-230°C experimentally used in the present case.[33] Moreover, the diene geometries in compounds **37**, **38** and **39** prevent them from adopting the reactive *cisoid* conformation; in fact they can be compared to *cis-cis* dienes which are known to rearrange rather than undergo a Diels-Alder reaction.

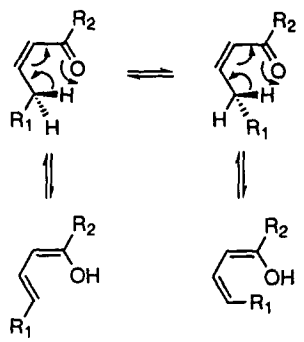


Figure 4

It ensues that only the two trienes **35** and **41** can be expected to react in a Diels-Alder electrocyclic fashion (see **TS1-DA** in Fig. 5). The corresponding transition structures were calculated; only one adduct **43** is possible from the triene **35**, whereas the isomeric triene **41** may lead to the two products **44** and **45**. The transition structure energies showed that the two tetracycles **43** and **45** should be equally formed if the starting macrocycles **35** and **41** were rapidly equilibrating. Indeed the transition structures **TS1-DA** and **TS3-DA** differ by only 0.06 kcal/mol in heat of formation.

Since only the product **3b** corresponding to **43** was experimentally observed it appeared that **35** must not be transformed into **41**. Calculations of the 12 interconverting transition structures **TS1-σ** to **TS12-σ** revealed that there exist two systems separated by 3 very high barriers, the transition-structures **TS8-σ** (52.17 kcal/mol); **TS9-σ** (51.09 kcal/mol) and **TS-10-σ** (51.35 kcal/mol). The first six macrocycles **34-39** are all more stable than the three remaining *cis*-fused bicycles **40-42**. Consequently, it is likely that the three latter macrocycles might be transformed into the former six if given enough energy. As a result submitting a compound like **32** corresponding to **41** to Diels-Alder conditions could yield mixtures of adducts **3b** and **33**, contrary to the present case where **4b** affords only **3b**. Demonstrating this hypothesis is however another project.

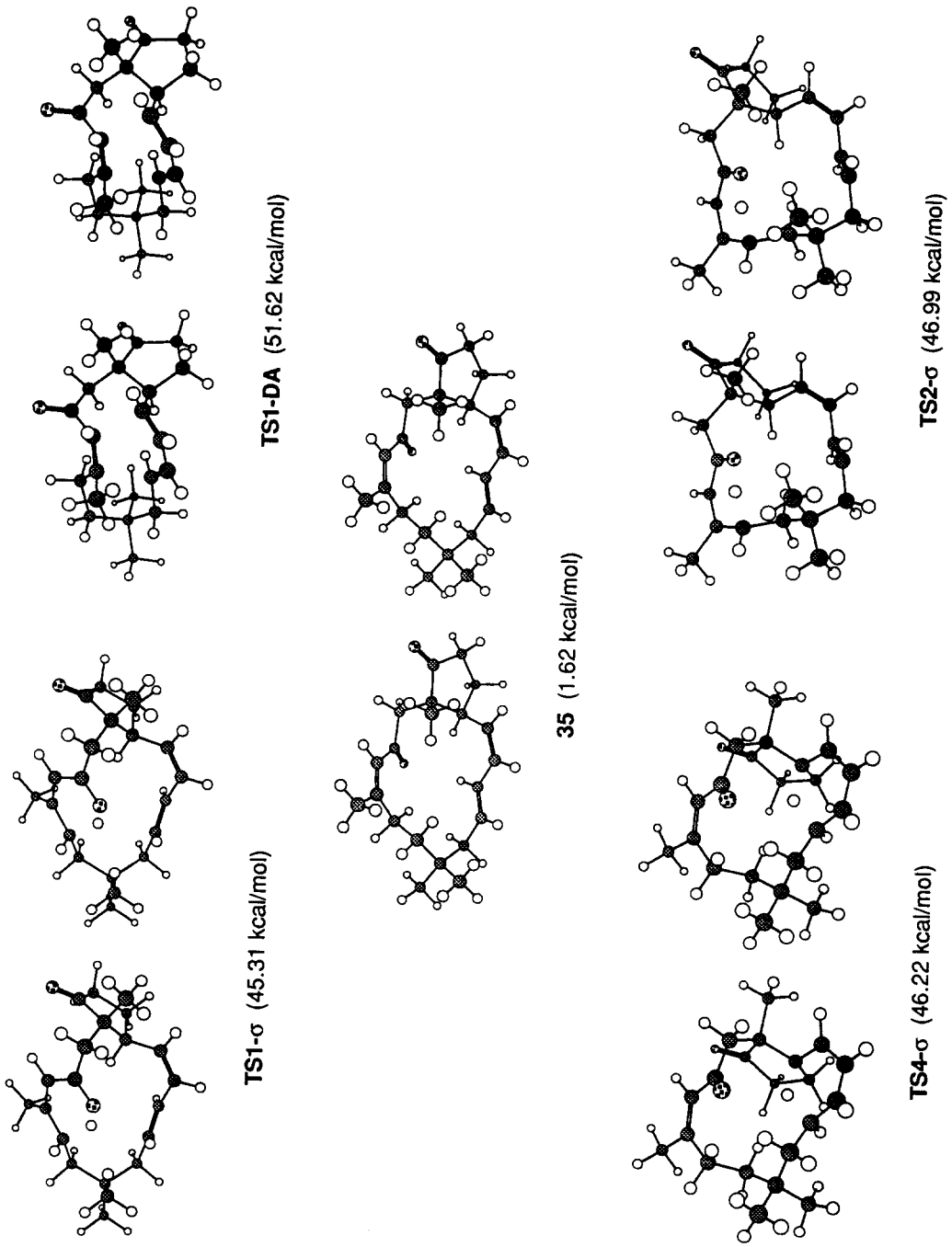
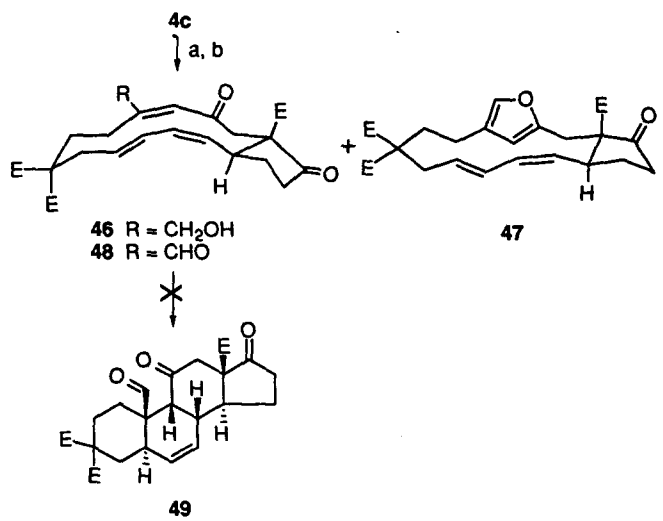


Figure 5. Stereoviews of selected structures.

It has been experimentally observed that on heating, **4b** yields first a mixture of macrocycles, then the expected Diels-Alder adduct **3b** appears; at the same time the isomeric macrocycle **31** accumulates in very small quantity in the reaction mixture. This compound was found to be transformed very slowly into the product **3b**. The calculations readily explain this matter of fact since **TS2-σ** and **TS5-σ** are two successive sigmatropic rearrangements leading to **39** (corresponding to **31**) which require a lot of energy. The alternative route via **TS7-σ** demands even more energy. On the contrary **TS1-σ** and **TS4-σ** leading to **34** and **38** respectively are easier processes. **38** can even further yield the macrocycle **37** through a very low barrier reaction (**TS6-σ**).

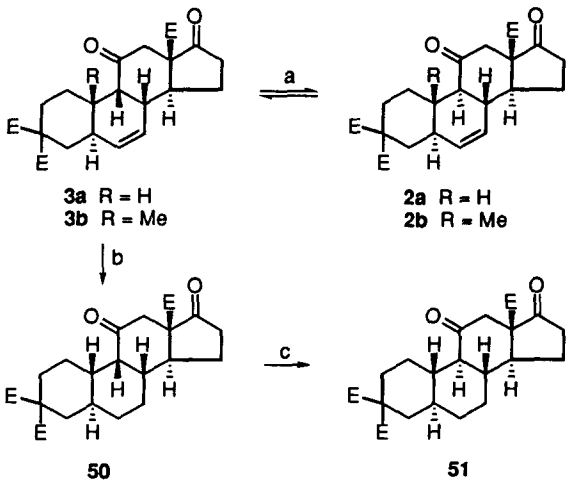
On this ground, it can be postulated that the macrocycles **34**, **35**, **37** and **38** (where E = CO_2Me) constitute mainly the mixture of products observed at the initial stage of the reaction. Obviously, some macrocycle like **39** (**31**, E = CO_2Me) eventually appears but reverts back to **35** with great difficulty for the same reason invoked for its uneasy formation, namely the high energy barriers of the reactions **TS7-σ**, **TS5-σ** and **TS2-σ**.

The next issue to be addressed was to lower the energy barrier of the cycloaddition by having recourse to Lewis acids. However, we have previously demonstrated that in 14-membered TCC macrocyclic systems involving enones as dienophiles, Lewis acids had no effect whatsoever in reducing the reaction temperature.[34] The absence of catalytic effect comes as no surprise since the enone must deconjugate in order to reach the transition state, a rationale which can be visualized by simple Dreiding molecular models (see **TS1-DA**). In the present case, we hoped that a formyl group at C-10 could freely adopt the right conformation which would modulate the previous behavior. Hence, macrocyle **4c** could serve for this purpose after adequate functionalization (Scheme 6). Deprotection of the alcohol **4c** was problematic since isomerization of the enone **46** occurred which ultimately led to the furane **47**. Efforts to avoid this side reaction met with little success and at best, the alcohol **46** was obtained in 55% yield. The formyl **48** was then prepared by allylic oxidation with the Dess-Martin periodinane. Notwithstanding the opportunity to reduce the energy barrier associated with the TADA reaction, the adduct **49** has not yet been secured. We believe that by forcefully keeping the dienophilic system in a conjugated state, Lewis acids prevent the cycloaddition.



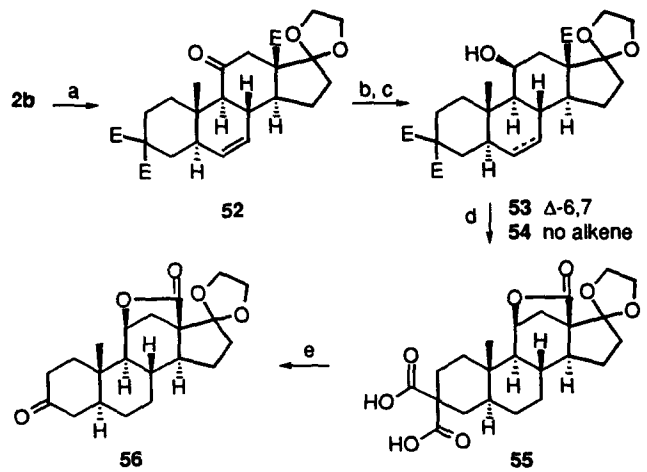
Scheme 6. (a) 3M HCl, MeOH, 65°C, 2 h, 55% of **46**, 44% of **47**; (b) Dess-Martin periodinane, CH_2Cl_2, r.t., 1 h, 84%.

Attention was then turned to the epimerization of the TSCAT adducts to the TATAT tetracyclic cores related to the major class of saturated steroids (Scheme 7). By heating **3b** with a catalytic amount of *p*-toluenesulfonic acid in benzene, the desired transformation could be accomplished in 96% yield. However, when these conditions were applied to **3a**, the reaction was far from complete. Not unexpectedly, independent resubmission of **2a** to the reaction conditions returned a 63:37 thermodynamic ratio of **2a**:**3a**. This had not been observed earlier with **3b** but careful reexamination revealed a similar equilibrium, here in a favorable 95:5 ratio. In order to skirt this difficulty, the nor adduct **3a** was hydrogenated over palladium and then submitted to similar acidic treatment. This manoeuvre proved effective in driving the ensuing epimerization to completion. This behavior can be rationalized in terms of gauche interactions which are relieved during the process.



Scheme 7. (a) TsOH, C_6H_6, reflux, 4 h, **2a** 60%, **2b** 96%; (b) 10% Pd/C, H_2, EtOAc, r.t., 2 h, 85%; (c) TsOH, C_6H_6, reflux, 4 h, 100%.

It was of further interest to probe the chemistry of **2b** (Scheme 8). Hence, selective protection of the cyclopentanone **2b** was achieved using chlorotrimethylsilane and ethylene glycol in dichloromethane.[35] Sodium borohydride reduction of the remaining ketone **52** was then directed from its less hindered face which resulted in conversion to the β-oriented alcohol **53**. Following conventional hydrogenation of the olefin, the triester **54** was completely saponified using barium hydroxide in aqueous methanol. By cyclising the lactone **55**, the carboxyl at the C-D ring junction was conveniently discriminated from the malonic acid thereby offering protection from the impending oxidative decarboxylation. Upon treatment with lead tetraacetate in pyridine, the malonic acid delightfully provided ketone **56** via the corresponding gem-diacetate.[22a] Such crafting thus leads to an appropriately functionalized pentacyclic core which opens the way to the total synthesis of aldosterone **1a** and analogues thereof.



Scheme 8. (a) $(CH_2OH)_2$, TMSCl, CH_2Cl_2, r.t., 48 h, 91%; (b) $NaBH_4$ MeOH, 0°C, 0.5 h, 75%; (c) 10% Pd/C, H_2, EtOAc, r.t., 2 h, 85%; (d) $Ba(OH)_2$, H_2O, MeOH, reflux, 2 h, 80%; (e) $Pb(OAc)_4$, pyridine, 60°C, 0.5 h, 48%.

CONCLUDING REMARKS

The synthetic efforts described above have culminated in a highly efficient and novel macrocyclization and the ensuing TADA reaction have proven highly reliable in providing 3 key intermediates. Through a highly convergent strategy, the tactics lend themselves conveniently to advanced molecular construction which should constitute a generic solution to the synthesis of a wide range of aldosterone analogues. By its inherent simplicity and versatility, this work further testifies to the potential of TADA reactions for the construction of complex polycyclic arrays. Currently, studies in our laboratories are progressive towards the enantioselective synthesis of aldosterone and will be reported in due course.

EXPERIMENTAL SECTION

All reactions were performed under N_2 atmosphere with oven (150°C) or flame dried glassware. Et_2O and THF were dried by distilling over sodium / benzophenone ketyl. Toluene, CH_2Cl_2, and DMF were dried by distilling over CaH_2. Analytical TLC were carried out on glass precoated (0.25 mm) with silica gel 60 F-250 (Merck). The chromatograms were visualized under UV (254 nm) and/or by spraying with a solution of phosphomolybdic acid (10% in ethanol) followed by heating on a hot plate. Column chromatography was performed with flash silica gel 60 (230-400 mesh, Merck). All solvents used in chromatography were distilled. Melting points were recorded on a Reichert hot plate microscope and are reported uncorrected. IR spectra were taken on a Perkin-Elmer 1600 FT-IR spectrometer. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker AC-300 instrument. Chemical shifts are reported in δ units, parts per million from the $CHCl_3$ peak as internal reference (^1H: δ = 7.26, ^{13}C: δ = 77.0). Abbreviations used are: s singlet, d doublet, t triplet, q quadruplet, qn quintet, m multiplet, br broad. Mass spectral (MS) assays were obtained with a VG Micromass ZAB-2F spectrometer (70 eV).

2-Carbomethoxy-3-vinylcyclopentanone dimethylketal (9). A solution of 2-carbomethoxy-3-vinylcyclopentanone **8** (10.4 g, 62.0 mmol) and trimethylorthoformate (19.7 g, 186 mmol) in methanol (100 mL) was treated with *p*-toluenesulfonic acid monohydrate (236 mg, 1.24 mmol) at 40°C for 1 h. The cooled solution was poured into 10% aqueous sodium bicarbonate (100 mL), then extracted with dichloromethane. Removal of solvent afforded an oil that was purified by flash chromatography (ethyl acetate / hexane, 1:9) to give the title compound as a clear oil (12.0 g, 91%); IR ($CHCl_3$) 3012, 2952, 1731, 1436, 1259, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) 5.72 (1H, ddd, J=7.5, 10.0, 17.0 Hz, C<u>H</u>=CH_2), 5.02 (1H, dt, J=1.5, 17.0 Hz, CH=CH<u>H</u> *trans*), 4.94 (1H, dt, J=1.5, 10.0 Hz, CH=CH<u>H</u> *cis*), 3.69 (3H, s, CO_2CH_3), 3.26, 3.18 (2x3H, 2s, $(OCH_3)_2$), 3.12 (1H, m, C<u>H</u>-CH=CH_2), 2.75 (1H, d, J=9.0 Hz, C<u>H</u>CO_2CH_3), 2.0-1.8 (3H, m, C<u>H</u>$_2$C<u>H</u>H), 1.51 (1H, m, CH_2CH<u>H</u>); ^{13}C NMR ($CDCl_3$) 172.02, 140.02, 114.50, 111.44, 57.17, 51.67, 49.86, 48.72, 46.09, 36.20, 29.31; MS *m/e* 214 (M^+), 183 (M^+-OMe); HRMS calcd for $C_{11}H_{18}O_4$: 214.1205; found: 214.1200.

2-Carbomethoxy-3-formylcyclopentanone dimethylketal (10). Ozone was bubbled through a solution of ketal **9** (4.29 g, 20.0 mmol) in methanol (4 mL) and dichloromethane (20 mL) at -78°C until persistence of a bluish color. Triphenylphosphine (7.87 g, 30.0 mmol) was then added and the slurry was stirred 1 h at the same temperature. The mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (ethyl acetate / hexane, 3:7) to yield aldehyde **10** as a colorless oil (4.24 g, 98%); IR ($CHCl_3$) 3020, 2952, 1727, 1437, 1260, 1049 cm^{-1}; ^1H NMR ($CDCl_3$) 9.57 (1H, s, CHO), 3.68 (3H, s, CO_2CH_3), 3.42 (1H, d, J=4.5 Hz, C<u>H</u>-CO_2CH_3), 3.20 (1H, m, C<u>H</u>-CHO), 3.19, 3.17 (2x3H, 2s, $(OCH_3)_2$), 2.13 (1H, m, CH_2-CH<u>H</u>), 2.0-1.8 (3H, m, C<u>H</u>$_2$-C<u>H</u>H); ^{13}C NMR ($CDCl_3$) 200.76, 172.00, 110.91, 52.62, 52.03, 50.58, 49.37, 48.67, 33.10, 22.57; MS *m/e* 216 (M^+), 187 (M^+-CHO); HRMS calcd for $C_{10}H_{16}O_5$ 216.0998; found: 216.0994.

2-Methoxycarbonyl-3-[(*Z*)-2-iodovinyl]cyclopentanone dimethylketal (11). To a suspension of iodomethyltriphenylphosphonium iodide (3.32 g, 6,25 mmol) in THF (20 mL) was rapidly added sodium bis(trimethylsilyl)amide (1M in THF, 6.25 mL, 6.25 mmol) and the mixture was stirred at room temperature for 1 min. The resulting dark red solution was then cooled to -78°C and a solution of aldehyde **10** (1.08 g, 5.00 mmol) in THF (5 mL) was introduced via cannula. The reaction mixture was further stirred at the same temperature for 1 h and then allowed to warm to room temperature at which point saturated aqueous ammonium chloride was added. The aqueous phase was extracted with dichloromethane and the combined organic layers were dried (Na_2SO_4) and evaporated. Purification of the residual oil by flash chromatography (ethyl acetate / hexane, 1:9) gave **11** (1.45 g, 85%, 80% isomeric purity by NMR) as a colorless oil; IR ($CHCl_3$) 3013, 2951, 1732, 1438, 1264, 1126, 1047 cm^{-1}; ^1H NMR ($CDCl_3$) 6.22 (1H, d, J=7.5 Hz, CHI), 6.11 (1H, dd, J=7.5, 8.5 Hz, C<u>H</u>=CHI), 3.72 (3H, s, CO_2CH_3), 3.26, 3.22 (2x3H, 2s, $(OCH_3)_2$), 3.44 (1H, m, C<u>H</u>-CH=CHI), 2.80 (1H, d, J=7.0 Hz, C<u>H</u>CO_2CH_3), 2.1-1.9 (3H, m, C<u>H</u>$_2$C<u>H</u>H), 1.58 (1H, m, CH_2CH<u>H</u>); ^{13}C NMR ($CDCl_3$) 171.92, 143.85, 111.49, 82.13, 56.37, 51.83, 50.26, 48.60, 46.72, 35.01, 28.28; MS *m/e* 340 (M^+), 309 (M^+-OMe); HRMS calcd for $C_{11}H_{17}IO_4$: 340.0172; found: 340.0169.

2-Methoxycarbonyl-3-[(1*Z*,3*E*)-5-hydroxypenta-1,3-dienyl]cyclopentanone dimethylketal (7). To a solution of (*E*)-3-tributylstannyl-2-propenol (2.78 g, 8.00 mmol) and vinylic iodide **11** (2.21 g, 6.5

mmol) in freshly distilled DMF (18 mL) was added a solution of bis(acetonitrile)-palladium(II) chloride (104 mg, 400 μmol) in the same solvent (2 mL) at room temperature. After 9 h the reaction mixture was cooled to 0°C, treated with saturated aqueous ammonium chloride and then extracted with a mixture of ether/hexane (1:1). The combined organic extracts were repeatedly washed with water, dried (Na_2SO_4) and concentrated. Purification of the residual oil by flash chromatography (ethyl acetate / hexane, 2:3) gave a mixture of the corresponding *Z,E* and *E,E* isomers (1.30 g, 74%) from which the title compound **7** was isolated by a second flash chromatography (ethyl acetate / toluene, 1:3) (844 mg, 48%) as a colorless oil; IR ($CHCl_3$) 3609, 3503, 3014, 2952, 1730, 1439, 1257, 1126, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) 6.61 (1H, ddq, J=15.0, 11.0, 1.5 Hz, C<u>H</u>=CH-CH_2), 5.97 (1H, t, J=11.0 Hz, CH-CH=C<u>H</u>), 5.82 (1H, dt, J=15.0, 6.0 Hz, CH=C<u>H</u>-CH_2), 5.28 (1H, t, J=10.5 Hz, CH-C<u>H</u>=CH), 4.20 (2H, dd, J=5.0, 1.5 Hz, C<u>H</u>$_2$OH), 3.68 (3H, s, CO_2CH_3), 3.58 (1H, m, C<u>H</u>-CH=CH), 3.28, 3.20 (2x3H, 2s, $(OCH_3)_2$), 2.72 (1H, d, J=8.5 Hz, C<u>H</u>-CO_2CH_3), 2.05-1.85 (3H, m, C<u>H</u>$_2$-C<u>H</u>H), 1.55-1.35 (2H, m, CH_2-CH<u>H</u>, OH); ^{13}C NMR ($CDCl_3$) 172.01, 133.97, 133.72, 133.15, 128.63, 126.15, 111.48, 63.03, 57.97, 51.76, 49.89, 48.72, 40.71, 36.24, 30.22 ; MS *m/e* 253 (M^+), 238 (M^+-MeOH); HRMS calcd for $C_{13}H_{19}O_4$ (M^+-OMe): 239.1283; found: 239.1278.

2-Methoxycarbonyl-3-[(*1Z*,*3E*)-5-chloropenta-1,3-dienyl]cyclopentanone dimethylketal (12). To an ice cold solution of **7** (2.03 g, 7.50 mmol) and 2,4,6-collidine (2.9 mL, 22.5 mmol) in DMF (60 mL) were successively added methanesulfonyl chloride (879 μL, 11.3 mmol), and a solution of lithium chloride (1.59 g, 37.5 mmol) in DMF (20 mL). After stirring at room temperature for 1.5 h, the reaction mixture was poured into ice cold water and extracted with a mixture of ether/hexane (1:1). The combined organic layers were washed with water, dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography (ethyl acetate / hexane, 2:8) yielding chloride **12** (1.64 g, 73%) as a colorless oil; IR ($CHCl_3$) 3015, 2953, 1731, 1439, 1127, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) 6.63 (1H, brdd, J=15.0, 11.0 Hz, C<u>H</u>=CH-CH_2), 5.94 (1H, t, J=11.0 Hz, CH-CH=C<u>H</u>), 5.75 (1H, dt, J=15.0, 7.5 Hz, CH=C<u>H</u>-CH_2), 5.32 (1H, t, J=10.0 Hz, CH-C<u>H</u>=CH), 4.11 (2H, brd, J=7.5 Hz, CH_2Cl), 3.67 (3H, s, CO_2CH_3), 3.54 (1H, m, C<u>H</u>-CH=CH), 3.25, 3.19 (2x3H, 2s, $(OCH_3)_2$), 2.70 (1H, d, J=8.5 Hz, C<u>H</u>-CO_2CH_3), 2.1-1.8 (3H, m, C<u>H</u>$_2$-C<u>H</u>H), 1.48 (1H, m, CH_2-CH<u>H</u>); ^{13}C NMR ($CDCl_3$) 171.77, 135.75, 129.47, 128.91, 127.79, 111.42, 57.91, 51.70, 49.89, 48.72, 45.10, 40.77, 36.17, 30.23 ; MS *m/e* 257 (M^+-OMe), 253 (M^+-Cl); HRMS calcd for $C_{13}H_{18}O_3Cl$ (M^+-OMe): 257.0944; found: 257.2953.

3-Hydroxypropyltriphenylphosphonium bromide (15). Freshly distilled 3-bromo-1-propanol (31.8 mL, 350 mmol) was added to a stirred solution of triphenylphosphine (61.3 g, 233 mmol) in toluene (100 mL) and the mixture was refluxed for 24 h. The resulting white precipitate was isolated by filtration over a fritted glass, rinsed with cold toluene and dried under vacuum thus providing the title compound (87.7 g, 94%) as white crystals: mp 240-242°C; IR ($CHCl_3$) 3325, 2946, 1439, 1238, 1113, 1059, 998, 882 cm^{-1}; ^1H NMR ($CDCl_3$) 7.85-7.6 (15H, m, Ph), 4.56 (1H, brs, OH), 4.85-4.7 (4H, m, C<u>H</u>$_2$$CH_2$C<u>H</u>$_2$), 1.83 (2H, m, CH_2C<u>H</u>$_2$$CH_2$); MS *m/e* 319 ($M^+$-$H_2Br$), 157 ($PPh_3$).

(*Z*)-1,2-*O*-Isopropylidene-3-hexen-1,2,6-triol (6a). To a cold suspension of phosphonium **15** (2.01 g, 5.00 mmol) in THF (20 mL) at -20°C was added dropwise *n*-BuLi (1.6 M in hexane, 6.25 mL, 10.0 mmol) and the mixture was stirred at the same temperature for 1 h. Freshly distilled chlorotrimethylsilane (635 μL,

5.00 mmol) was then introduced and after 30 min, the reaction mixture was cooled to -78°C. A solution of (*R*)-2,3-*O*-(ispropylidene)glyceraldehyde **13** (651 mg, 5.00 mmol) in THF (5 mL) was then added and the mixture was allowed to warm to room temperature. After 1 h, the reaction was quenched with 10% aqueous citric acid (25 mL) and extracted with dichloromethane. The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated. Purification of the residual oil by flash chromatography (ethyl acetate / hexane, 4:6) provided alcohol **6a** (1.30 g, 74%, 90% isomeric purity by NMR) as a colorless oil; IR ($CHCl_3$) 3621, 3479, 3015, 1377, 1231, 1056 cm^{-1}; ^1H NMR ($CDCl_3$) 5.66 (1H, dt, J=11.0, 7.5 Hz, CH_2CH=CH), 5.56 (1H, brdd, J=8.0, 11.0 Hz, CH_2CH=CH), 4.82 (1H, dt, J=6.0, 8.0 Hz, OCHCH$_2$O), 4.07 (1H, dd, J=6.0, 8.0 Hz, OCHCHHO), 3.63 (2H, t, J=6.5 Hz, CH_2OH), 3.53 (1H, t, J=8.0 Hz, OCHCHHO), 2.5-2.3 (2H, m, CH_2CH=CH), 2.05 (1H, brs, OH), 1.40, 1.37 (2x3H, 2s, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) 130.96, 129.41, 109.02, 71.76, 69.24, 61.35, 31.07, 26.60, 25.76 ; MS *m/e* 172 (M^+), 157 (M^+-Me); HRMS calcd for $C_9H_{16}O_3$: 172.1099; found: 172.1100.

(*E*)-3-(2,3-Dihydroxy-2,3-*O*-isopropylidenepropylidene)oxolan-2-one (17). To an ice cold solution of 1-butyrolactonylidene triphenylphosphorane **16** (20.9 g, 60.0 mmol) in THF (80 mL) was added a solution of freshly distilled (*R*)-2,3-*O*-(ispropylidene)glyceraldehyde **13** (7.80 g, 60.0 mmol) in the same solvent (20 mL). The mixture was allowed to warm to room temperature and further stirred for 1 h after which the solvent was removed under reduced pressure. After the addition of diethyl ether (100 mL), the resulting slurry was filtered through a fritted glass, rinsed with ether and the filtrate was concentrated. The crude product was purified by flash chromatography (ethyl acetate / hexane, 4:6) providing the title compound (10.6 g, 89%) as a colorless oil; IR ($CHCl_3$) 3022, 1759, 1379, 1204, 1060, 1036 cm^{-1}; ^1H NMR ($CDCl_3$) 6.67 (1H, dt, J=3.0, 7.0 Hz, C=CH), 4.72 (1H, brq, J=7.0 Hz, OCHCH$_2$O), 4.37 (2H, t, J=7.0 Hz, OCH_2CH_2), 4.18 (1H, dd, J=6.5, 8.0 Hz, OCHCHHO), 3.69 (1H, t, J=8.0 Hz, OCHCHHO), 3.1-2.9 (2H, m, OCH_2CH_2), 1.43, 1.39 (2x3H, 2s, $C(CH_3)_2$) ; ^{13}C NMR ($CDCl_3$) 170.56, 135.62, 127.73, 110.00, 73.44, 68.27, 65.42, 26.15, 25.50, 25.11; MS *m/e* 183 (M^+-Me); HRMS calcd for $C_9H_{11}O_4$ (M^+-Me): 183.0657; found: 183.0660.

(*E*)-6-Acetoxy-4-hyroxymethyl-1,2-*O*-isopropylidene-3-hexen-1,2-diol (20). Diisobutylaluminium hydride (1.5 M in toluene, 39 mL, 58 mmol) was added dropwise to a solution of lactone **17** (10.5 g, 53.0 mmol) in toluene (400 mL) at -78°C. The solution was stirred at the same temperature for 1 h after which methanol (10 mL) was added and the mixture was allowed to warm to room temperature. It was then extracted with 30% aqueous disodium tartrate (4 × 25 mL) and the combined aqueous phases were extracted several times with ether. The combined organic phases were washed with brine, dried (Na_2SO_4) and filtered over a short pad of silica gel. Without delay, the condensed material was dissolved in dichloromethane (250 mL) and cooled to 0°C. Acetic anhydride (12.5 mL, 133 mmol), triethylamine (22.2 mL, 159 mmol) and 4-dimethylaminopyridine (20 mg, cat.) were successively added and the solution was stirred for 3 h at the same temperature. Saturated aqueous ammonium chloride was then added and the mixture was extracted with dichloromethane. The combined organic layers were washed with water, dried (Na_2SO_4), filtered and concentrated. The crude unstable acetate was immediately dissolved in methanol (250 mL) and cooled to 0°C. Sodium borohydride (2.00 g, 53 mmol) was added and the mixture was stirred for 30 min at the same temperature. A solution of aqueous saturated ammonium chloride was added and the bulk of methanol was evaporated. The resulting mixture was diluted with water and extracted several times with ether. The combined ethereal phases

were dried (Na_2SO_4) filtered and concentrated. The crude product was purified by flash chromatography (ethyl acetate / hexane, 4:6) providing the title compound (9.02 g, 70%) as a colorless oil; IR ($CHCl_3$) 3609, 3494, 2991, 1734, 1377, 1237, 1055 cm^{-1}; ^1H NMR ($CDCl_3$) 5.50 (1H, brd, J=9.0 Hz, C=CH), 4.73 (1H, dt, J=6.0, 8.0 Hz, OC<u>H</u>CH_2O), 4.10 (5H, m, C<u>H</u>$_2$OAc, C<u>H</u>$_2$OH, OCHC<u>H</u>HO), 3.46 (1H, t, J=8.0 Hz, OCHCH<u>H</u>O), 2.81 (1H, brs, OH), 1.96 (3H, s, $OCOCH_3$), 1.33, 1.31 (2x3H, 2s, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) 170.88, 140.28, 125.44, 109.01, 71.95, 69.17, 65.80, 62.63, 27.64, 26.53, 25.69, 20.71; MS *m/e* 229 (M^+-Me), 226 (M^+-H_2O); HRMS calcd for $C_{11}H_{17}O_5$ (M^+-Me): 229.1076; found: 229.1074.

(*E*)-6-Acetoxy-1,2-*O*-isopropylidene-4-(methoxymethoxy)methyl-3-hexen-1,2,-diol (21). To a solution of alcohol **20** (2.93 g, 12 mmol) in dichloromethane (250 mL) were successively added diisopropylethylamine (6.3 mL, 36 mmol) and methoxymethyl chloride (1.8 mL, 24 mmol). The reaction mixture was stirred at room temperature for 24 h after which a saturated aqueous ammonium chloride solution was added. The mixture was extracted with dichloromethane and the combined organic phases were washed with water, dried (Na_2SO_4), filtered and concentrated. Purification of the residue by flash chromatography (ethyl acetate / hexane, 2:8) furnished compound **21** (2.93 g, 85%) as a colorless oil; IR ($CHCl_3$) 2992, 1735, 1376, 1238, 1049 cm^{-1}; ^1H NMR ($CDCl_3$) 5.52 (1H, brd, J=9.0 Hz, C=CH), 4.73 (1H, dt, J=6.0, 8.0 Hz, OC<u>H</u>CH_2O), 4.52 (2H, s, OC<u>H</u>$_2$$OCH_3$), 4.1-3.95 (3H, m, C<u>H</u>$_2$OAc, OCHC<u>H</u>HO), 3.92 (2H, s, CH_2OMOM), 3.46 (1H, t, J=8.0 Hz, OCHCH<u>H</u>O), 3.27 (3H, s, OCH_2OC<u>H</u>$_3$), 2.41 (2H, m, C<u>H</u>$_2$$CH_2OAc$), 1.95 (3H, s, $OCOCH_3$), 1.32, 1.30 (2x3H, 2s, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) 170.49, 136.91, 127.66, 108.97, 95.38, 71.89, 70.27, 69.17, 62.38, 55.07, 27.83, 26.53, 25.69, 20.63; MS *m/e* 288 (M^+), 273 (M^+-Me); HRMS calcd for $C_{13}H_{21}O_6$ (M^+-Me): 273.1338; found: 273.1336.

(*E*)-1,2-*O*-Isopropylidene-4-(methoxymethoxy)methyl-3-hexen-1,2,6-triol (6c). Potassium carbonate (629 mg, 4.55 mmol) was added to a solution of compound **21** (2.62 mg, 9.10 mmol) in methanol (100 mL) and the resulting mixture was stirred at room temperature for 4 h. The bulk of the methanol was evaporated and the residue was diluted with water. The mixture was extracted several times with ether and the combined organic layers were washed with brine, dried (Na_2SO_4) and condensed. The crude product was purified by flash chromatography (ethyl acetate / hexane, 1:1) providing alcohol **6c** (2.17 g, 97%) as a colorless oil; IR ($CHCl_3$) 3621, 3468, 3013, 2943, 1377, 1223, 1152, 1049 cm^{-1}; ^1H NMR ($CDCl_3$) 5.52 (1H, brd, J=8.5 Hz, C=CH), 4.71 (1H, dt, J=6.0, 8.0 Hz, OC<u>H</u>CH_2O), 4.52 (2H, s, OC<u>H</u>$_2$$OCH_3$), 3.98 (3H, dd, J=6.0, 8.0 Hz, OCHC<u>H</u>HO), 3.90 (2H, s, CH_2OMOM), 3.46 (1H, t, J=8.0 Hz, OCHCH<u>H</u>O), 3.25 (3H, s, OCH_2OC<u>H</u>$_3$), 2.93 (1H, brt, J=5.5 Hz, OH), 2.31 (2H, m, C<u>H</u>$_2$$CH_2OH$), 1.30, 1.27 (2x3H, 2s, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) 138.47, 127.34, 108.96, 95.44, 71.89, 70.78, 69.22, 60.69, 55.13, 32.16, 26.47, 25.63 ; MS *m/e* 246 (M^+), 231 (M^+-Me); HRMS calcd for $C_{11}H_{19}O_5$ (M^+-Me): 231.1232; found: 231.1226.

(*Z*)-6-Iodo-1,2-*O*-isopropylidene-3-hexen-1,2-diol (22a). To a solution of **6a** (2.19 g, 12.7 mmol) and triphenylphosphine (4.01 g, 15.2 mmol) in toluene (60 mL) at room temperature were added rapidly and successively iodomethane (1.2 mL, 19.1 mmol) and diethyl azodicarboxylate (2.41 mL, 15.2 mmol). A pale yellow paste immediately separated from the organic solution. The latter was removed and the remaining salt was washed with toluene (10 mL). The combined toluene solutions were evaporated and flash chromatography (ethyl acetate / hexane, 1:9) of the residue provided **22a** (2.91 g, 81%) as a colorless oil; IR ($CHCl_3$) 2992,

1377, 1239, 1156, 1059, 857 cm^{-1}; ^1H NMR ($CDCl_3$) 5.49 (2H, m, C<u>H</u>=C<u>H</u>), 4.71 (1H, dt, J=6.0, 8.0 Hz, OC<u>H</u>CH_2O), 4.02 (1H, dd, J=6.0, 8.0 Hz, OCHC<u>H</u>HO), 3.48 (1H, t, J=8.0 Hz, OCHCH<u>H</u>O), 3.2-3.0 (2H, m, CH_2I), 2.7-2.55 (2H, m, $C\underline{H}_2CH_2I$), 1.34, 1.31 (2x3H, 2s, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) 132.19, 129.60, 108.97, 71.56, 69.10, 31.39, 26.54, 25.76, 4.47; MS *m/e* 282 (M^+), 267 (M^+-Me); HRMS calcd for $C_9H_{15}O_2I$: 282.0117; found: 282.0122.

(*Z*)-6-Iodo-1,2-*O*-isopropylidene-4-methyl-3-hexen-1,2-diol (22b). To a solution of **6b** (1.42 g, 7.60 mmol) and triphenylphosphine (2.39 g, 9.12 mmol) in toluene (40 mL) at room temperature were added rapidly and successively iodomethane (710 µL, 11.4 mmol) and diethyl azodicarboxylate (1.44 mL, 9.12 mmol). A pale yellow paste immediately separated from the organic solution. The latter was removed and the remaining salt was washed with toluene (10 mL). The combined toluene solutions were evaporated and a flash chromatography (ethyl acetate / hexane, 1:9) of the residue provided **22b** (1.93 g, 86%) as a colorless oil; IR ($CHCl_3$) 2989, 1381, 1223, 1156, 1056, 870 cm^{-1}; ^1H NMR ($CDCl_3$) 5.37 (1H, brd, J=8.0 Hz, C=C<u>H</u>), 4.74 (1H, dt, J=6.0, 8.0 Hz, OC<u>H</u>CH_2O), 4.11 (1H, dd, J=6.0, 8.0 Hz, OCHC<u>H</u>HO), 3.54 (1H, t, J=8.0 Hz, OCHCH<u>H</u>O), 3.27 (1H, ddd, J=5.5, 8.0, 9.5 Hz, C<u>H</u>HI), 3.13 (1H, dt, J=9.5, 5.5 Hz, CH<u>H</u>I), 2.78 (1H, dt, J=14.0, 8.0 Hz, C<u>H</u>HCH_2I), 2.62 (1H, ddd, J=14.0, 8.0, 5.5 Hz, CH<u>H</u>CH_2I), 1.77 (3H, s, CH_3), 1.42, 1.39 (2x3H, 2s, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) 132.50, 125.58, 108.89, 72.21, 69.45, 36.30, 26.72, 25.89, 22.59, 2.86 ; MS *m/e* 296 (M^+), 281 (M^+-Me); HRMS calcd for $C_{10}H_{17}O_2I$: 296.0273; found: 296.0268.

(*E*)-6-Iodo-1,2-*O*-isopropylidene-4-(methoxymethoxy)methyl-3-hexen-1,2-diol (22c). To a solution of **6c** (2.17 g, 8.80 mmol) and triphenylphosphine (2.77 g, 10.6 mmol) in toluene (40 mL) at room temperature were added rapidly and successively iodomethane (825 µL, 13.2 mmol) and diethyl azodicarboxylate (1.67 mL, 10.6 mmol). A pale yellow paste immediately separated from the organic solution. The latter was removed and the remaining salt was washed with toluene (10 mL). The combined toluene solutions were evaporated and a flash chromatography (ethyl acetate / hexane, 2:8) of the residue provided **22c** (2.66 g, 85%) as a colorless oil; IR ($CHCl_3$) 2294, 1377, 1223, 1152, 1051 cm^{-1}; ^1H NMR ($CDCl_3$) 5.56 (1H, brd, J=8.5 Hz, C=CH), 4.69 (1H, dt, J=6.0, 8.0 Hz, OC<u>H</u>CH_2O), 4.52 (2H, s, $OC\underline{H}_2OCH_3$), 4.04 (3H, dd, J=6.0, 8.0 Hz, OCHC<u>H</u>HO), 3.92 (2H, s, CH_2OMOM), 3.50 (1H, t, J=8.0 Hz, OCHCH<u>H</u>O), 3.27 (3H, s, $OCH_2OC\underline{H}_3$), 3.25-3.0 (2H, m, CH_2I), 2.68 (2H, m, $C\underline{H}_2CH_2I$), 1.33, 1.31 (2x3H, 2s, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) 139.24, 127.72, 109.09, 95.39, 71.76, 69.75, 69.24, 55.19, 32.94, 26.59, 25.76, 2.85; MS *m/e* 341 (M^+-Me); HRMS calcd for $C_{11}H_{18}O_4I$ (M^+-Me): 341.0250; found: 341.0248.

(*Z*)-7,7-Bis(methoxycarbonyl)-1,2-*O*-isopropylidene-3-hepten-1,2-diol (23a). To an ice cold suspension of sodium hydride (60% dispersion in oil, 824 mg, 20.6 mmol) in *N,N*-dimethylformamide (50 mL) was added dimethyl malonate (2.36 mL, 20.6 mmol). After 1 h of stirring at room temperature, a solution of **22a** (2.91 g, 10.3 mmol) in dry tetrahydrofuran (50 mL) was introduced and the resulting mixture was refluxed for 1 h. The cooled reaction mixture was the quenched with a saturated aqueous ammonium chloride solution and extracted several times with a solution of ether and hexane (1:1). The organic extracts were washed with water, dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography (ethyl acetate / hexane, 2:8) to yield the title compound **23a** (2.84 g, 96%) as a colorless oil; IR ($CHCl_3$) 3022, 2954, 1735, 1440, 1221, 1157, 1057 cm^{-1}; ^1H NMR ($CDCl_3$) 5.49 (1H, dt, J=6.0, 8.0 Hz, $CH_2C\underline{H}$=CH),

5.49 (1H, brdd, J=8.0, 11.0 Hz, $CH_2CH=C\underline{H}$), 4.76 (1H, dt, J=6.0, 8.0 Hz, $OC\underline{H}CH_2O$), 4.06 (1H, dd, J=6.0, 8.0 Hz, $OCHC\underline{H}HO$), 3.73 (6H, s, $(CO_2CH_3)_2$), 3.50 (1H, t, J=8.0 Hz, $OCHCH\underline{H}O$), 3.37 (1H, t, J=7.0 Hz, $C\underline{H}(CO_2Me)_2$), 2.2-1.9 (4H, m, $C\underline{H}_2C\underline{H}_2$), 1.41, 1.38 (2x3H, 2s, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) 169.39, 132.91, 128.24, 108.95, 71.57, 69.17, 52.28, 50.54, 28.35, 26.53, 25.76, 25.18; MS *m/e* 286 (M^+), 271 (M^+-Me); HRMS calcd for $C_{14}H_{22}O_6$: 286.1416; found: 286.1421.

(Z)-7,7-Bis(methoxycarbonyl)-1,2-*O*-isopropylidene-4-methyl-3-hepten-1,2-diol (23b). To an ice cold suspension of sodium hydride (60% dispersion in oil, 520 mg, 13.0 mmol) in *N,N*-dimethylformamide (25 mL) was added dimethyl malonate (1.49 mL, 13.0 mmol). After 1 h of stirring at room temperature, a solution of **22b** (1.42 g, 6.50 mmol) in dry tetrahydrofuran (25 mL) was introduced and the resulting mixture was refluxed for 1 h. The cooled reaction mixture was the quenched with a saturated aqueous ammonium chloride solution and extracted several times with a solution of ether and hexane (1:1). The organic extracts were washed with water, dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography (ethyl acetate / hexane, 2:8) to yield the title compound **23b** (1.63 g, 84%) as a colorless oil; IR ($CHCl_3$) 2989, 2954, 1734, 1440, 1376, 1225, 1157, 1056 cm^{-1}; ^1H NMR ($CDCl_3$) 5.24 (1H, brd, J=9.0 Hz, C=CH), 4.69 (1H, dt, J=6.0, 8.0 Hz, $OC\underline{H}CH_2O$), 4.03 (1H, dd, J=6.0, 8.0 Hz, $OCHC\underline{H}HO$), 3.74 (6H, s, $(CO_2CH_3)_2$), 3.48 (1H, t, J=8.0 Hz, $OCHCH\underline{H}O$), 3.33 (1H, t, J=7.0 Hz, $C\underline{H}(CO_2Me)_2$), 2.3-1.9 (4H, m, $C\underline{H}_2C\underline{H}_2$), 1.75 (3H, brs, CH_3), 1.40, 1.38 (2x3H, 2s, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) 169.39, 140.34, 124.11, 108.64, 72.22, 69.31, 52.35, 50.74, 29.64, 27.17, 26.66, 25.82, 23.11; MS *m/e* 300 (M^+), 285 (M^+-OMe); HRMS calcd for $C_{15}H_{24}O_6$: 300.1573; found: 300.1567.

(*E*)-7,7-Bis(methoxycarbonyl)-1,2-*O*-isopropylidene-4-(methoxymethoxy)methyl-3-hepten-1,2-diol (23c). To an ice cold suspension of sodium hydride (60% dispersion in oil, 600 mg, 15.0 mmol) in *N,N*-dimethylformamide (25 mL) was added dimethyl malonate (1.72 mL, 15.0 mmol). After 1 h of stirring at room temperature, a solution of **22c** (2.67 g, 7.50 mmol) in dry tetrahydrofuran (25 mL) was introduced and the resulting mixture was refluxed for 1 h. The cooled reaction mixture was the quenched with saturated aqueous ammonium chloride aqueous solution and extracted several times with a solution of ether and hexane (1:1). The organic extracts were washed with water, dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography (ethyl acetate / hexane, 2:8) to yield the title compound **23c** (2.38 g, 88%) as a colorless oil; IR ($CHCl_3$) 2994, 2951, 1736, 1441, 1224, 1154, 1051 cm^{-1}; ^1H NMR ($CDCl_3$) 5.42 (1H, brd, J=8.5 Hz, C=CH), 4.65 (1H, dt, J=6.0, 8.0 Hz, $OC\underline{H}CH_2O$), 4.48 (2H, s, $OC\underline{H}_2OCH_3$), 3.96 (3H, dd, J=6.0, 8.0 Hz, $OCHC\underline{H}HO$), 3.86 (2H, s, CH_2OMOM), 3.61 (6H, s, $CH(CO_2C\underline{H}_3)_2$), 3.41 (1H, t, J=8.0 Hz, $OCHCH\underline{H}O$), 3.25 (1H, t, J=7.0 Hz, $C\underline{H}(CO_2CH_3)_2$), 3.23 (3H, s, $OCH_2OC\underline{H}_3$), 2.2-1.8 (4H, m, $C\underline{H}_2C\underline{H}_2$), 1.28, 1.26 (2x3H, 2s, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$) 169.16, 139.75, 126.11, 108.83, 95.37, 71.76, 69.83, 69.11, 55.00, 52.17, 50.73, 27.64, 26.47, 26.07, 25.63; MS *m/e* 360 (M^+), 345 (M^+-Me); HRMS calcd for $C_{17}H_{28}O_8$ (M^+-Me): 360.1784; found: 360.1779.

(3*Z*,9*E*,11*Z*)-7,7-Bis(methoxycarbonyl)-12-(2-methoxycarbonyl-3,3-dimethoxy)cyclopentyl-1,2-*O*-isopropylidenedodeca-3,9,11-trien-1,2-diol (24a). To an ice cold suspension of sodium hydride (60% dispersion in oil, 208 mg, 5.20 mmol) in DMF (40 mL) was added a solution of **23a** (1.43 g, 4.99 mmol) in THF (20 mL). After the mixture had been stirred for 1 h at room temperature, a solution of **12**

(1.43 g, 4.76 mmol) in THF (20 mL) was added and the reaction mixture was refluxed for 1 h. The mixture was then cooled to 0°C and saturated aqueous ammonium chloride solution was added. The phases were separated and the aqueous layer was extracted several times with a solution of ether and hexane (1:1). The combined organic extracts were washed with water and brine, dried (Na_2SO_4), filtered and concentrated. Flash chromatography (ethyl acetate / hexane, 2:8) of the residual material gave **24a** (2.00 g, 76%) as a colorless oil; IR ($CHCl_3$) 3017, 2953, 1731, 1440, 1231, 1208, 1054 cm^{-1}; ^1H NMR ($CDCl_3$) 6.36 (1H, dd, J=11.0, 15.0 Hz, C<u>H</u>=CHCH$_2$), 5.82 (1H, t, J=11.0 Hz, CHCH=C<u>H</u>), 5.6-5.3 (3H, m, C<u>H</u>=C<u>H</u>CO, CH=C<u>H</u>CH$_2$), 5.12 (1H, t, J=10.5 Hz, CHC<u>H</u>=CH), 4.70 (1H, q, J=8.0 Hz, OC<u>H</u>CH$_2$O), 4.00 (1H, ddd, J=3.0, 6.0, 8.0 Hz, OCHC<u>H</u>HO), 3.66, 3.65, 3.60 (3x3H, 3s, 3xCO$_2$CH$_3$), 3.55-3.4 (2H, m, OCHCH<u>H</u>O, C<u>H</u>CH=CH), 3.20, 3.13 (2x3H, 2s, C(OCH$_3$)$_2$), 2.65-2.6 (3H, m, C<u>H</u>CO$_2$Me, CH=CHC<u>H</u>$_2$), 2.05-1.7 (7H, m, C=CC<u>H</u>$_2$C<u>H</u>$_2$, C<u>H</u>$_2$C<u>H</u>H), 1.40 (1H, m, CH$_2$CH<u>H</u>), 1.34, 1.31 (2x3H, 2s, C(CH$_3$)$_2$); ^{13}C NMR ($CDCl_3$) 171.78, 171.20, 133.12, 129.59, 128.70, 128.06, 127.83, 111.42, 108.90, 71.68, 69.24, 57.91, 57.46, 52.28, 51.64, 49.89, 48.66, 40.70, 36.43, 36.18, 32.63, 30.27, 26.60, 25.82, 22.59; MS *m/e* 556 (MNH_4^+); HRMS calcd for $C_{28}H_{46}NO_{10}$ (MNH_4^+): 556.3121; found: 556.3123.

(3*Z*,9*E*,11*Z*)-7,7-Bis(methoxycarbonyl)-12-(2-methoxycarbonyl-3,3-dimethoxy)cyclopentyl-1,2-*O*-isopropylidene-4-methyldodeca-3,9,11-trien-1,2-diol (24b). To an ice cold suspension of sodium hydride (60% dispersion in oil, 120 mg, 3.00 mmol) in DMF (25 mL) was added a solution of **23b** (810 mg, 2.70 mmol) in THF (15 mL). After the mixture had been stirred for 1 h at room temperature, a solution of **12** (1.08 g, 3.60 mmol) in THF (10 mL) was added and the reaction mixture was refluxed for 1 h. The mixture was then cooled to 0°C and a saturated aqueous ammonium chloride solution was added. The phases were separated and the aqueous layer was extracted several times with a solution of ether and hexane (1:1). The combined organic layers were washed with water and brine, dried (Na_2SO_4), filtered and concentrated. Flash chromatography (ethyl acetate / hexane, 2:8) of the residual material gave **24b** (1.27 g, 85%) as a colorless oil; IR ($CHCl_3$) 2989, 2953, 1731, 1440, 1373, 1246, 1051 cm^{-1}; ^1H NMR ($CDCl_3$) 6.44 (1H, dd, J=11.0, 15.0 Hz, C<u>H</u>=CHCH$_2$), 5.89 (1H, t, J=11.0 Hz, CHCH=C<u>H</u>), 5.48 (1H, dt, J=15.0, 7.5 Hz, CH=C<u>H</u>CH$_2$), 5.2-5.1 (2H, m, CHC<u>H</u>=CH, C=C<u>H</u>CO), 4.67 (1H, dt, J=6.0, 8.0 Hz, OC<u>H</u>CH$_2$O), 4.02 (1H, ddd, J=2.5, 6.0, 8.0 Hz, OCHC<u>H</u>HO), 3.73, 3.72, 3.67 (3x3H, 3s, 3xCO$_2$CH$_3$), 3.55-3.4 (2H, m, OCHCH<u>H</u>O, C<u>H</u>CH=CH), 3.26, 3.19 (2x3H, 2s, C(OCH$_3$)$_2$), 2.75-2.6 (3H, m, C<u>H</u>CO$_2$Me, CH=CHC<u>H</u>$_2$), 2.1-1.75 (7H, m, C=CC<u>H</u>$_2$C<u>H</u>$_2$, C<u>H</u>$_2$C<u>H</u>H), 1.73 (3H, brs, C=CCH$_3$), 1.5-1.35 (1H, m, CH$_2$CH<u>H</u>), 1.40, 1.37 (2x3H, 2s, C(CH$_3$)$_2$); ^{13}C NMR ($CDCl_3$) 171.08, 170.50, 140.38, 132.75, 129.16, 128.24, 127.41, 123.06, 110.97, 107.99, 71.89, 68.85, 57.34, 57.01, 51.68, 50.99, 49.24, 48.03, 40.25, 35.82, 35.73, 31.26, 29.82, 26.53, 26.15, 25.37, 22.79; MS *m/e* 552 (M^+), 520 (M^+-MeOH); HRMS calcd for $C_{29}H_{44}O_{10}$: 552.2934; found: 552.2930.

(3*E*,9*E*,11*Z*)-7,7-Bis(methoxycarbonyl)-12-(2-methoxycarbonyl-3,3-dimethoxy)cyclopentyl-1,2-*O*-isopropylidene-4-(methoxymethoxy)methyldodeca-3,9,11-trien-1,2-diol (24c). To an ice cold suspension of sodium hydride (60% dispersion in oil, 230 mg, 5.75 mmol) in DMF (40 mL) was added a solution of **23c** (2.07 g, 5.75 mmol) in THF (20 mL). After the mixture had been stirred for 1 h at room temperature, a solution of **12** (1.65 g, 5.50 mmol) in THF (20 mL) was added and the reaction mixture was refluxed for 1 h. The mixture was then cooled to 0°C and a saturated aqueous ammonium chloride solution

was added. The phases were separated and the aqueous layer was extracted several times with a solution of ether and hexane (1:1). The combined organic extracts were washed with water and brine, dried (Na_2SO_4), filtered and concentrated. Flash chromatography (ethyl acetate / hexane, 2:8) of the residual material gave **24c** (2.78 g, 81%) as a colorless oil; IR ($CHCl_3$) 3014, 2952, 1731, 1440, 1219, 1151, 1048 cm^{-1}; ^1H NMR ($CDCl_3$) 6.36 (1H, dd, J=11.0, 15.0 Hz, C<u>H</u>=CHCH$_2$), 5.82 (1H, t, J=11.0 Hz, CHCH=C<u>H</u>), 5.5-5.35 (2H, m, C=C<u>H</u>CO, CH=C<u>H</u>CH$_2$), 5.13 (1H, t, J=10.5 Hz, CHC<u>H</u>=CH), 4.68 (1H, dt, J=6.0, 8.0 Hz, OC<u>H</u>CH$_2$O), 4.53 (2H, s, OC<u>H</u>$_2$OCH$_3$), 4.00 (1H, ddd, J=2.5, 6.0, 8.0 Hz, OCHC<u>H</u>HO), 3.89 (2H, s, CH$_2$OMOM), 3.67, 3.66, 3.60 (3x3H, 3s, 3xCO$_2$CH$_3$), 3.55-3.4 (2H, m, OCHCH<u>H</u>O, C<u>H</u>CH=CH), 3.29 (3H, s, OCH$_2$OC<u>H</u>$_3$), 3.19, 3.13 (2x3H, 2s, C(OCH$_3$)$_2$), 2.75-2.55 (3H, m, C<u>H</u>CO$_2$Me, CH=CHC<u>H</u>$_2$), 2.1-1.75 (7H, m, C=CC<u>H</u>$_2$C<u>H</u>$_2$, C<u>H</u>$_2$C<u>H</u>H), 1.45-1.35 (1H, m, CH$_2$CH<u>H</u>), 1.35, 1.32 (2x3H, 2s, C(CH$_3$)$_2$); ^{13}C NMR ($CDCl_3$) 171.85, 171.08, 140.08, 133.24, 129.54, 128.67, 127.79, 125.34, 111.42, 108.96, 95.57, 71.95, 70.02, 69.30, 57.91, 57.65, 55.17, 52.28, 51.64, 49.89, 48.66, 40.68, 36.43, 36.11, 32.33, 30.28, 26.60, 25.82, 23.43; MS *m/e* 630 (MNH_4^+); HRMS calcd for $C_{31}H_{52}NO_{12}$ (MNH_4^+): 630.3489; found: 630.3481.

(3*Z*,9*E*,11*Z*)-7,7-Bis(methoxycarbonyl)-12-(2-methoxycarbonyl-3-oxo)cyclopentyldodeca-3,9,11-trien-1,2-diol (25a). A solution of **24a** (2.00 g, 3.71 mmol) in acetic acid (10 mL) and water (3 mL) was stirred at room temperature for 6 h. The mixture was then diluted with water (250 mL), neutralized with sodium bicarbonate and extracted several times with ether. The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. Flash chromatography (ethyl acetate / dichloromethane / methanol, 70:29:1) of the residue provided **25a** (1.43 g, 85%) as a colorless oil; IR ($CHCl_3$) 3578, 3023, 2955, 1729, 1440, 1274, 1069 cm^{-1}; ^1H NMR ($CDCl_3$) 6.35 (1H, dd, J=11.0, 15.0 Hz, C<u>H</u>=CHCH$_2$), 5.93 (1H, t, J=11.0 Hz, CHCH=C<u>H</u>), 5.5-5.25 (3H, m, C<u>H</u>=C<u>H</u>COH, CH=C<u>H</u>CH$_2$), 5.17 (1H, t, J=10.0 Hz, CHC<u>H</u>=CH), 4.39 (1H, m, OC<u>H</u>CH$_2$O), 3.65 (9H, brs, 3xCO$_2$CH$_3$), 3.6-3.3 (3H, m, OCHC<u>H</u>$_2$O, C<u>H</u>CH=CH), 3.18, 2.97 (2x1H, 2brs, 2xOH), 2.89 (1H, d, J=11.5 Hz, C<u>H</u>CO$_2$Me), 2.64 (2H, d, J=7.5 Hz, CH=CHC<u>H</u>$_2$), 2.45-1.8 (7H, m, C=CC<u>H</u>$_2$C<u>H</u>$_2$, C<u>H</u>$_2$C<u>H</u>H), 1.61 (1H, m, CH$_2$CH<u>H</u>); ^{13}C NMR ($CDCl_3$) 210.67, 171.27, 169.17, 131.87, 130.58, 130.25, 129.10, 128.97, 68.20, 66.00, 61.34, 57.20, 52.35, 39.66, 37.86, 36.14, 32.21, 27.83, 22.53; MS *m/e* 470 (MNH_4^+), 452 (MNH_4^+-H_2O); HRMS calcd for $C_{23}H_{36}NO_9$ (MNH_4^+): 470.2390; found: 470.2384.

(3*Z*,9*E*,11*Z*)-7,7-Bis(methoxycarbonyl)-12-(2-methoxycarbonyl-3-oxo)cyclopentyl-4-methyldodeca-3,9,11-trien-1,2-diol (25b). A solution of **24b** (1.27 g, 2.30 mmol) in acetic acid (8 mL) and water (2 mL) was stirred at room temperature for 6 h. The mixture was then diluted with water (250 mL), neutralized with sodium bicarbonate and extracted several times with ether. The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. Flash chromatography (ethyl acetate / dichloromethane / methanol, 70:29:1) of the residue provided **25b** (981 mg, 91%) as a colorless oil; IR ($CHCl_3$) 3577, 3023, 2956, 1729, 1440, 1238, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) 6.44 (1H, dd, J=11.0, 15.0 Hz, C<u>H</u>=CHCH$_2$), 6.02 (1H, t, J=11.0 Hz, CHCH=C<u>H</u>), 5.51 (1H, m, CH=C<u>H</u>CH$_2$), 5.23 (1H, t, J=10.5 Hz, CHC<u>H</u>=CH), 5.15 (1H, d, J=9.0 Hz, C=C<u>H</u>CO), 4.35 (1H, m, OC<u>H</u>CH$_2$O), 3.72 (6H, brs, 2xCO$_2$CH$_3$), 3.71 (3H, brs, CO$_2$CH$_3$), 3.7-3.4 (3H, m, OCHC<u>H</u>$_2$O, C<u>H</u>CH=CH), 2.94 (1H, d, J=11.5 Hz, C<u>H</u>CO$_2$Me), 2.73 (2H, d, 7.5 Hz, CH=CHC<u>H</u>$_2$), 2.5-1.8 (9H, m, C=CC<u>H</u>$_2$C<u>H</u>$_2$, C<u>H</u>$_2$C<u>H</u>H, 2xOH), 1.70

(3H, brs, C=CCH$_3$), 1.63 (1H, m, CH$_2$CHH); ^{13}C NMR ($CDCl_3$) 210.56, 171.26, 169.07, 139.37, 130.61, 130.25, 129.15, 128.95, 124.73, 68.65, 66.32, 61.34, 57.34, 52.35, 39.61, 37.86, 36.23, 31.14, 27.89, 26.92, 23.04; MS *m/e* 434 (M^+), 416 (M^+-H_2O); HRMS calcd for $C_{24}H_{34}O_9$: 434.1941; found: 434.1931.

(3*E*,9*E*,11*Z*)-7,7-Bis(methoxycarbonyl)-12-(2-methoxycarbonyl-3-oxo)cyclopentyl-4-(methoxymethoxy)methyldodeca-3,9,11-trien-1,2-diol (25c). A solution of **24c** (1.23 g, 2.00 mmol) in acetic acid (10 mL) and water (3 mL) was stirred at room temperature for 6 h. The mixture was then diluted with water (250 mL), neutralized with sodium bicarbonate and extracted several times with ether. The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. Flash chromatography (ethyl acetate / dichloromethane / methanol, 70:29:1) of the residue provided **25c** (991 mg, 94%) as a colorless oil; IR ($CHCl_3$) 3570, 3020, 1729, 1441, 1272, 1219, 1045 cm^{-1}; ^{1}H NMR ($CDCl_3$) 6.39 (1H, dd, J=11.0, 15.0 Hz, CH=CHCH$_2$), 5.97 (1H, t, J=11.0 Hz, CHCH=CH), 5.49 (1H, m, CH=CHCH$_2$), 5.42 (1H, brd, J=8.5 Hz, C=CHCO), 5.20 (1H, t, J=10.0 Hz, CHCH=CH), 4.54 (2H, s, OCH$_2$OCH$_3$), 4.36 (1H, m, OCHCH$_2$O), 3.90 (2H, brs, CH$_2$OMOM), 3.68 (6H, s, 2xCO$_2$CH$_3$), 3.67 (3H, s, CO$_2$CH$_3$), 3.65-3.4 (3H, m, OCHCH$_2$O, CHCH=CH), 3.29 (3H, s, OCH$_2$OCH$_3$), 3.2-2.6 (2H, brs, 2OH), 2.92 (1H, d, J=11.5 Hz, CHCO$_2$Me), 2.68 (2H, d, J=7.5 Hz, CH=CHCH$_2$), 2.5-1.8 (7H, m, C=CCH$_2$CH$_2$, CH$_2$CHH), 1.59 (1H, m, CH$_2$CHH); ^{13}C NMR ($CDCl_3$) 210.62, 171.27, 169.20, 139.24, 130.71, 130.36, 129.21, 129.02, 127.08, 95.57, 70.21, 68.46, 66.22, 61.43, 57.52, 55.25, 52.45, 39.67, 37.92, 36.37, 31.70, 27.96, 23.30; MS *m/e* 544 (MNH_4^+), 512 (MNH_4^+-MeOH); HRMS calcd for $C_{26}H_{42}NO_{11}$ (MNH_4^+): 544.2758; found: 544.2761.

(3*Z*,9*E*,11*Z*)-7,7-Bis(methoxycarbonyl)-12-(2-methoxycarbonyl-3-oxo)cyclopentyl-1-*tert*-butyldimethylsiloxydodeca-3,9,11-trien-2-ol (26a). To a cold solution of **25a** (1.43 g, 3.16 mmol) in DMF (35 mL) at -20°C were successively added imidazole (322 mg, 4.74 mmol) and *t*-butylchlorodimethylsilane (476 mg, 3.16 mmol). After being stirred for 2 h at the same temperature, the mixture was poured into water and extracted several times with a solution of ether and hexane (1:1). The combined organic layers were then washed with water and brine. Removal of the solvents from the dried extracts (Na_2SO_4) afforded an oil which was purified by flash chromatography (ethyl acetate / hexane, 7:3) to give the title compound **26a** (1.26 g, 72%) as a clear oil; IR ($CHCl_3$) 3563, 3024, 2955, 1730, 1440, 1257, 1104 cm^{-1}; ^{1}H NMR ($CDCl_3$) 6.36 (1H, dd, J=11.0, 15.0 Hz, CH=CHCH$_2$), 5.96 (1H, t, J=11.0 Hz, CHCH=CH), 5.55-5.4 (2H, m, CH=CHCOH, CH=CHCH$_2$), 5.29 (1H, t, J=9.5 Hz, CH=CHCOH), 5.18 (1H, t, J=10.0 Hz, CHCH=CH), 4.34 (1H, m, OCHCH$_2$O), 3.66 (9H, brs, 3xCO$_2$CH$_3$), 3.65-3.3 (3H, m, OCHCH$_2$O, CHCH=CH), 2.89 (1H, d, J=11.5 Hz, CHCO$_2$Me), 2.66 (2H, d, J=7.5 Hz, CH=CHCH$_2$), 2.5-1.8 (8H, m, C=CCH$_2$CH$_2$, CH$_2$CHH, OH), 1.62 (1H, m, CH$_2$CHH), 0.84 (9H, s, C(CH$_3$)$_3$), 0.02 (3H, s, SiCH$_3$); ^{13}C NMR ($CDCl_3$) 210.44, 171.21, 168.87, 132.07, 130.58, 130.37, 129.24, 128.97, 68.06, 66.66, 61.41, 57.45, 52.29, 39.68, 37.92, 36.35, 32.51, 27.96, 25.76, 22.72, 18.19, -5.46; MS *m/e* 584 (MNH_4^+), 549 (M^+-OH); HRMS calcd for $C_{29}H_{50}NO_9Si$ (MNH_4^+): 584.3255; found: 584.3247.

(3*Z*,9*E*,11*Z*)-7,7-Bis(methoxycarbonyl)-12-(2-methoxycarbonyl-3-oxo)cyclopentyl-4-methyl-1-*tert*-butyldimethylsiloxydodeca-3,9,11-trien-2-ol (26b). To a cold solution of **25b** (979 mg, 2.10 mmol) in DMF (25 mL) at -20°C were successively added imidazole (214 mg, 3.15 mmol) and *t*-

butylchlorodimethylsilane (317 mg, 2.10 mmol). After being stirred for 2 h at the same temperature, the mixture was poured into water and extracted several times with a solution of ether and hexane (1:1). The combined organic layers were then washed with water and brine. Removal of the solvents from the dried extracts (Na_2SO_4) afforded an oil which was purified by flash chromatography (ethyl acetate / hexane, 7:3) to give the title compound **26b** (960 mg, 79%) as a clear oil; IR ($CHCl_3$) 3559, 3024, 2954, 1730, 1440, 1254, 1114 cm^{-1}; ^1H NMR ($CDCl_3$) 6.43 (1H, dd, J=11.0, 15.0 Hz, C<u>H</u>=CHCH$_2$), 6.02 (1H, t, J=11.0 Hz, CHCH=C<u>H</u>), 5.51 (1H, dt, J=15.0, 7.5 Hz, CH=C<u>H</u>CH$_2$), 5.23 (1H, t, J=10.0 Hz, CHC<u>H</u>=CH), 5.12 (1H, brd, J=8.5 Hz, C=C<u>H</u>CO), 4.29 (1H, m, OC<u>H</u>CH$_2$O), 3.74, 3.73, 3.72 (3x3H, 3s, 3xCO$_2$CH$_3$), 3.65-3.35 (3H, m, OCHC<u>H$_2$</u>O, C<u>H</u>CH=CH), 2.94 (1H, d, J=11.5 Hz, C<u>H</u>CO$_2$Me), 2.73 (2H, d, J=7.5 Hz, CH=CHC<u>H$_2$</u>), 2.5-1.8 (8H, m, C=CC<u>H$_2$</u>C<u>H$_2$</u>, C<u>H$_2$</u>C<u>H</u>H, OH), 1.71 (3H, brs, C=CCH$_3$), 1.63 (1H, m, CH$_2$CH<u>H</u>), 0.90 (9H, s, C(CH$_3$)$_3$), 0.07 (3H, s, SiCH$_3$); ^{13}C NMR ($CDCl_3$) 210.47, 171.21, 168.84, 139.63, 130.57, 130.38, 129.33, 128.95, 124.45, 68.46, 66.99, 61.41, 57.59, 52.33, 39.71, 37.98, 36.37, 31.55, 27.99, 27.12, 25.76, 23.24, 18.19, -5.46; MS *m/e* 580 (M^+), 562 (M^+-H_2O); HRMS calcd for $C_{30}H_{46}O_8Si$ (M^+-H_2O): 562.2962; found: 562.2954.

(3*E*,9*E*,11Z)-7,7-Bis(methoxycarbonyl)-12-(2-methoxycarbonyl-3-oxo)cyclopentyl-4-(methoxymethoxy)methyl-1-*tert*-butyldimethylsiloxydodeca-3,9,11-trien-2-ol (26c). To a cold solution of **25c** (1.07 g, 2.03 mmol) in DMF (30 mL) at -20°C were successively added imidazole (207 mg, 3.04 mmol) and *t*-butylchlorodimethylsilane (306 mg, 2.03 mmol). After being stirred for 2 h at the same temperature, the mixture was poured into water and extracted several times with a solution of ether and hexane (1:1). The combined organic layers were then washed with water and brine. Removal of the solvents from the dried extracts (Na_2SO_4) afforded an oil which was purified by flash chromatography (ethyl acetate / hexane, 7:3) to give the title compound **26c** (934 mg, 72%) as a clear oil; IR ($CHCl_3$) 3557, 3022, 2954, 1730, 1440, 1255, 1111 cm^{-1}; ^1H NMR ($CDCl_3$) 6.39 (1H, dd, J=11.0, 15.0 Hz, C<u>H</u>=CHCH$_2$), 5.97 (1H, t, J=11.0 Hz, CHCH=C<u>H</u>), 5.53 (1H, dt, J=15.0, 7.0 Hz, CH=C<u>H</u>CH$_2$), 5.39 (1H, d, J=8.5 Hz, C=C<u>H</u>CO), 5.18 (1H, t, J=10.0 Hz, CHC<u>H</u>=CH), 4.55 (2H, s, OC<u>H$_2$</u>OCH$_3$), 4.31 (1H, m, OC<u>H</u>CH$_2$O), 3.91 (2H, brs, CH$_2$OMOM), 3.67 (9H, s, 3xCO$_2$CH$_3$), 3.65-3.35 (3H, m, OCHC<u>H$_2$</u>O, C<u>H</u>CH=CH), 3.30 (3H, s, OCH$_2$OC<u>H$_3$</u>), 2.90 (1H, d, J=11.5 Hz, C<u>H</u>CO$_2$Me), 2.68 (2H, d, J=7.5 Hz, CH=CHC<u>H$_2$</u>), 2.6-1.8 (8H, m, C=CC<u>H$_2$</u>C<u>H$_2$</u>, C<u>H$_2$</u>C<u>H</u>H, OH), 1.59 (1H, m, CH$_2$CH<u>H</u>), 0.85 (9H, s, C(CH$_3$)$_3$), 0.03 (3H, s, SiCH$_3$); ^{13}C NMR ($CDCl_3$) 210.47, 171.14, 168.88, 139.37, 130.60, 130.38, 129.28, 128.95, 126.67, 95.51, 70.21, 68.20, 66.80, 61.41, 57.65, 55.20, 52.32, 39.68, 37.92, 36.37, 31.91, 27.96, 25.76, 23.43, 18.19, -5.43; MS *m/e* 658 (MNH_4^+), 640 (MNH_4^+-H_2O); HRMS calcd for $C_{32}H_{56}NO_{11}Si$ (MNH_4^+): 658.3622; found: 658.3613.

(3Z,9*E*,11Z)-7,7-Bis(methoxycarbonyl)-12-(2-methoxycarbonyl-3-oxo)cyclopentyl-2-oxo-1-*tert*-butyldimethylsiloxydodeca-3,9,11-triene (27a). To a solution of alcohol **26a** (760 mg, 1.19 mmol) in dichloromethane (75 mL) was added the Dess-Martin periodinane (606 mg, 1.43 mmol). After stirring at room temperature for 4 h, the reaction mixture was quenched with saturated aqueous sodium bicarbonate (50 mL). A 5% aqueous sodium thiosulfate solution (25 mL) was added to the mixture which was vigorously stirred for 1 h. The aqueous phase was extracted several times with ether and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered and condensed. The crude product was purified by flash chromatography (ethyl acetate / hexane, 3:7) to give the title compound **27a** (598 mg, 79%) as a clear oil;

IR ($CHCl_3$) 3027, 2954, 1730, 1618, 1439, 1259, 1112 cm^{-1}; ^1H NMR ($CDCl_3$) 6.38 (1H, dd, J=11.0, 15.0 Hz, C<u>H</u>=CHCH$_2$), 6.32 (1H, d, J=11.5 Hz, CH=C<u>H</u>CO), 6.10 (1H, dt, J=11.5, 4.0 Hz, C<u>H</u>=CHCO), 5.97 (1H, t, J=11.0 Hz, CHCH=C<u>H</u>), 5.54 (1H, dt, J=15.0, 7.5 Hz, CH=C<u>H</u>CH$_2$), 5.18 (1H, t, J=10.0 Hz, CHC<u>H</u>=CH), 4.13 (2H, s, CH_2OSi), 3.68, 3.67, 3.65 (3x3H, 3s, 3xCO_2CH_3), 3.65-3.5 (1H, m, C<u>H</u>CH=CH), 2.89 (1H, d, J=11.5 Hz, C<u>H</u>CO$_2$Me), 2.69 (2H, d, J=7.5 Hz, CH=CHC<u>H</u>$_2$), 2.6-2.1 (5H, m, C=CHC<u>H</u>$_2$CH$_2$, C<u>H</u>$_2$C<u>H</u>H), 1.95 (2H, t, J=8.5 Hz, C=CHCH$_2$C<u>H</u>$_2$), 1.62 (1H, m, CH_2CH<u>H</u>), 0.86 (9H, s, $C(CH_3)_3$), 0.03 (3H, s, $SiCH_3$); ^{13}C NMR ($CDCl_3$) 210.47, 199.66, 171.13, 168.80, 148.04, 130.44, 129.35, 128.95, 122.68, 69.75, 61.47, 57.53, 52.30, 39.73, 37.92, 35.91, 31.57, 27.96, 25.67, 24.33, 18.19, -5.55; MS *m/e* 564 (M^+), 533 (M^+-OMe); HRMS calcd for $C_{29}H_{44}O_9Si$: 564.2754; found: 564.2750.

(3*Z*,9*E*,11*Z*)-7,7-Bis(methoxycarbonyl)-12-(2-methoxycarbonyl-3-oxo)cyclopentyl-4-methyl-2-oxo-1-*tert*-butyldimethylsiloxydodeca-3,9,11-triene (27b). To a solution of alcohol **26b** (436 mg, 750 μmol) in dichloromethane (75 mL) was added the Dess-Martin periodinane (382 mg, 900 μmol). After stirring at room temperature for 2.5 h, the reaction mixture was quenched with saturated aqueous sodium bicarbonate (50 mL). A 5% aqueous sodium thiosulfate solution (25 mL) was added to the mixture which was vigorously stirred for 1 h. The aqueous phase was extracted several times with ether and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered and condensed. The crude product was purified by flash chromatography (ethyl acetate / hexane, 3:7) to give the title compound **27b** (376 mg, 87%) as a clear oil; IR ($CHCl_3$) 3026, 2955, 1730, 1616, 1439, 1258, 1111 cm^{-1}; ^1H NMR ($CDCl_3$) 6.41 (1H, dd, J=11.0, 15.0 Hz, C<u>H</u>=CHCH$_2$), 6.24 (1H, s, C=C<u>H</u>CO), 6.01 (1H, t, J=11.0 Hz, CHCH=C<u>H</u>), 5.65 (1H, dt, J=15.0, 7.5 Hz, CH=C<u>H</u>CH$_2$), 5.18 (1H, t, J=10.0 Hz, CHC<u>H</u>=CH), 4.10 (2H, s, CH_2OSi), 3.72, 3.71, 3.67 (3x3H, 3s, 3xCO_2CH_3), 3.65-3.55 (1H, m, C<u>H</u>CH=CH), 2.91 (1H, d, J=11.5 Hz, C<u>H</u>CO$_2$Me), 2.73 (2H, d, J=7.5 Hz, CH=CHC<u>H</u>$_2$), 2.6-1.95 (7H, m, C=CC<u>H</u>$_2$C<u>H</u>$_2$, C<u>H</u>$_2$C<u>H</u>H), 1.86 (3H, brs, C=CCH_3), 1.63 (1H, m, CH_2CH<u>H</u>), 0.88 (9H, s, $C(CH_3)_3$), 0.04 (3H, s, $SiCH_3$); ^{13}C NMR ($CDCl_3$) 210.60, 198.44, 171.20, 168.81, 159.17, 130.57, 130.29, 129.66, 128.82, 119.51, 69.75, 61.47, 57.72, 52.31, 39.74, 37.98, 35.72, 30.36, 28.67, 28.02, 25.69, 25.48, 18.25, -5.56; MS *m/e* 578 (M^+), 547 (M^+-MeO); HRMS calcd for $C_{30}H_{46}O_9Si$: 578.2911; found: 578.2905.

(3*E*,9*E*,11*Z*)-7,7-Bis(methoxycarbonyl)-12-(2-methoxycarbonyl-3-oxo)cyclopentyl-4-(methoxymethoxy)methyl-2-oxo-1-*tert*-butyldimethylsiloxydodeca-3,9,11-triene (27c). To a solution of alcohol **26c** (760 mg, 1.19 mmol) in dichloromethane (75 mL) was added the Dess-Martin periodinane (606 mg, 1.43 mmol). After stirring at room temperature for 4 h, the reaction mixture was quenched with saturated aqueous sodium bicarbonate (50 mL). A 5% aqueous sodium thiosulfate solution (25 mL) was added to the mixture which was vigorously stirred for 1 h. The aqueous phase was extracted several times with ether and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered and condensed. The crude product was purified by flash chromatography (ethyl acetate / hexane, 3:7) to give the title compound **27c** (598 mg, 79%) as a clear oil; IR ($CHCl_3$) 3025, 2954, 1730, 1627, 1440, 1259, 1152 cm^{-1}; ^1H NMR ($CDCl_3$) 6.53 (1H, s, C=C<u>H</u>CO), 6.37 (1H, dd, J=11.0, 15.0 Hz, C<u>H</u>=CHCH$_2$), 5.98 (1H, t, J=11.0 Hz, CHCH=C<u>H</u>), 5.64 (1H, dt, J=15.0, 7.5 Hz, CH=C<u>H</u>CH$_2$), 5.17 (1H, t, J=10.0 Hz, CHC<u>H</u>=CH), 4.58 (2H, s, OC<u>H</u>$_2$OCH$_3$), 4.14 (2H, s, CH_2OSi), 4.00 (2H, s, CH_2OMOM), 3.69 (6H, s, 2xCO_2CH_3), 3.65 (3H, s, CO_2CH_3), 3.65-3.5 (1H, m, C<u>H</u>CH=CH), 3.30 (3H, s, OCH$_2$OC<u>H</u>$_3$), 2.89 (1H, d,

J=11.5 Hz, C<u>H</u>CO_2Me), 2.71 (2H, d, J=7.5 Hz, CH=CHC<u>H_2</u>), 2.5-1.9 (7H, m, C=CC<u>H_2</u>C<u>H_2</u>, C<u>H_2</u>C<u>H</u>H), 1.58 (1H, m, CH_2C<u>H</u>H), 0.85 (9H, s, $C(CH_3)_3$), 0.02 (3H, s, $SiCH_3$); ^{13}C NMR ($CDCl_3$) 210.60, 198.70, 171.07, 168.80, 157.16, 130.56, 130.31, 129.54, 128.83, 117.23, 95.89, 69.89, 69.37, 61.47, 57.78, 55.32, 52.33, 39.73, 37.92, 35.73, 30.87, 27.97, 25.63, 24.85, 18.19, -5.56; MS *m/e* 638 (M^+), 607 (M^+-MeO); HRMS calcd for $C_{32}H_{50}O_{11}Si$: 638.3122; found: 638.3114.

(3*Z*,9*E*,11*Z*)-7,7-Bis(methoxycarbonyl)-12-(2-methoxycarbonyl-3-oxo)cyclopentyl-2-oxododeca-3,9,11-trien-1-ol (28a). A solution of **27a** (997 mg, 1.77 mmol) in acetic acid (10 mL) and water (3 mL) was stirred at room temperature for 9 h. The mixture was then diluted with water (250 mL), neutralized with sodium bicarbonate and extracted several times with ether. The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. Flash chromatography (ethyl acetate / hexane, 1:1) of the residue provided **28a** (720 mg, 90%) as a colorless oil; IR ($CHCl_3$) 3480, 3026, 2955, 1730, 1627, 1439, 1273 cm^{-1}; ^{1}H NMR ($CDCl_3$) 6.38 (1H, dd, J=11.0, 15.0 Hz, C<u>H</u>=CHCH_2), 6.17 (1H, dt, J=11.5, 4.0 Hz, C<u>H</u>=CHCO), 6.01 (1H, d, J=11.5 Hz, CH=C<u>H</u>CO), 5.94 (1H, t, J=11.0 Hz, CHCH=C<u>H</u>), 5.47 (1H, dt, J=15.0, 7.5 Hz, CH=C<u>H</u>CH_2), 5.16 (1H, t, J=10.0 Hz, C<u>H</u>CH=CH), 4.16 (2H, d, J=4.5 Hz, C<u>H_2</u>OH), 3.66, 3.65, 3.62 (3x3H, 3s, 3xCO_2CH_3), 3.6-3.5 (1H, m, C<u>H</u>CH=CH), 3.27 (1H, t, J=4.5 Hz, OH), 2.88 (1H, d, J=11.5 Hz, C<u>H</u>CO_2Me), 2.67 (2H, d, J=7.5 Hz, CH=CHC<u>H_2</u>), 2.65-2.05 (5H, m, C=CHC<u>H_2</u>CH_2, C<u>H_2</u>C<u>H</u>H), 1.91 (2H, t, J=8.5 Hz, C=CHCH_2C<u>H_2</u>), 1.56 (1H, m, CH_2C<u>H</u>H); ^{13}C NMR ($CDCl_3$) 210.53, 198.70, 170.95, 168.87, 149.20, 130.57, 130.26, 129.05, 122.29, 68.71, 61.33, 57.26, 52.32, 39.60, 37.80, 35.84, 31.26, 27.83, 24.59; MS *m/e* 450 (M^+), 432 (M^+-H_2O); HRMS calcd for $C_{23}H_{30}O_9$: 450.1890; found: 450.1884.

(3*Z*,9*E*,11*Z*)-7,7-Bis(methoxycarbonyl)-12-(2-methoxycarbonyl-3-oxo)cyclopentyl-4-methyl-2-oxododeca-3,9,11-trien-1-ol (28b). A solution of **27b** (415 mg, 715 μmol) in acetic acid (4 mL) and water (1 mL) was stirred at room temperature for 9 h. The mixture was then diluted with water (100 mL), neutralized with sodium bicarbonate and extracted several times with ether. The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. Flash chromatography (ethyl acetate / hexane, 1:1) of the residue provided **28b** (311 mg, 94%) as a colorless oil; IR ($CHCl_3$) 3471, 3025, 1730, 1625, 1439, 1279, 1220 cm^{-1}; ^{1}H NMR ($CDCl_3$) 6.46 (1H, dd, J=11.0, 15.0 Hz, C<u>H</u>=CHCH_2), 6.02 (1H, t, J=11.0 Hz, CHCH=C<u>H</u>), 5.94 (1H, s, C=C<u>H</u>CO), 5.60 (1H, dt, J=15.0, 7.5 Hz, CH=C<u>H</u>CH_2), 5.21 (1H, t, J=10.0 Hz, CHC<u>H</u>=CH), 4.17 (2H, s, C<u>H_2</u>OH), 3.75, 3.73, 3.69 (3x3H, 3s, 3xCO_2CH_3), 3.65-3.55 (1H, m, C<u>H</u>CH=CH), 3.30 (1H, brs, OH), 2.93 (1H, d, J=11.5 Hz, C<u>H</u>CO_2Me), 2.76 (2H, d, J=7.5 Hz, CH=CHC<u>H_2</u>), 2.6-1.9 (7H, m, C=CC<u>H_2</u>C<u>H_2</u>, C<u>H_2</u>C<u>H</u>H), 1.90 (3H, brs, $C=CCH_3$), 1.61 (1H, m, CH_2C<u>H</u>H); ^{13}C NMR ($CDCl_3$) 210.54, 197.27, 171.02, 168.81, 160.99, 130.39, 129.21, 129.09, 119.19, 68.47, 61.34, 57.52, 52.34, 52.23, 39.67, 37.86, 35.58, 30.28, 28.99, 27.90, 25.30; MS *m/e* 464 (M^+), 446 (M^+-H_2O); HRMS calcd for $C_{24}H_{31}O_9$: 464.2046; found: 464.2038.

(3*E*,9*E*,11*Z*)-7,7-Bis(methoxycarbonyl)-12-(2-methoxycarbonyl-3-oxo)cyclopentyl-4-(methoxymethoxy)methyl-2-oxododeca-3,9,11-trien-1-ol (28c). A solution of **27c** (738 mg, 1.15 mmol) in acetic acid (10 mL) and water (3 mL) was stirred at room temperature for 9 h. The mixture was then diluted with water (250 mL), neutralized with sodium bicarbonate and extracted several times with ether.

The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. Flash chromatography (ethyl acetate / hexane, 1:1) of the residue provided **28c** (564 mg, 93%) as a colorless oil; IR ($CHCl_3$) 3474, 3025, 1730, 1635, 1440, 1276, 1051 cm^{-1}; ^1H NMR ($CDCl_3$) 6.44 (1H, dd, J=11.0, 15.0 Hz, C<u>H</u>=CHCH$_2$), 6.24 (1H, s, C=C<u>H</u>CO), 6.00 (1H, t, J=11.0 Hz, CHCH=C<u>H</u>), 5.59 (1H, dt, J=15.0, 7.5 Hz, CH=C<u>H</u>CH$_2$), 5.20 (1H, t, J=10.0 Hz, CHC<u>H</u>=CH), 4.61 (2H, s, OC<u>H$_2$</u>OCH$_3$), 4.14 (2H, d, J=4.5 Hz, C<u>H$_2$</u>OH), 4.05 (2H, s, CH$_2$OMOM), 3.71 (6H, s, 2xCO$_2$CH$_3$), 3.67 (3H, s, CO$_2$CH$_3$), 3.65-3.55 (1H, m, C<u>H</u>CH=CH), 3.32 (3H, s, OCH$_2$OC<u>H$_3$</u>), 2.91 (1H, d, J=11.5 Hz, C<u>H</u>CO$_2$Me), 2.73 (2H, d, J=7.5 Hz, CH=CHC<u>H$_2$</u>), 2.5-1.9 (7H, m, C=CC<u>H$_2$</u>C<u>H$_2$</u>, C<u>H$_2$</u>C<u>H</u>H), 1.61 (1H, m, CH$_2$CH<u>H</u>); ^{13}C NMR ($CDCl_3$) 210.60, 197.73, 171.01, 168.93, 159.10, 130.54, 129.19, 116.61, 96.02, 69.11, 68.91, 61.47, 57.66, 55.46, 52.41, 39.73, 37.92, 35.72, 30.88, 28.02, 25.25; MS *m/e* 542 (MNH_4^+); HRMS calcd for $C_{26}H_{40}NO_{11}Si$: 542.2601; found: 542.2596.

(3*Z*,9*E*,11*Z*)-7,7-Bis(methoxycarbonyl)-1-chloro-12-(2-methoxycarbonyl-3-oxo)cyclopentyl-2-oxododeca-3,9,11-triene (5a). To a solution of alcohol **28a** (14 mg, 675 µmol) in tetrahydrofuran (35 mL) at -40°C was added hexachloroacetone (205 µL, 1.35 mmol) immediately followed by a cold solution (-40°C) of triphenylphosphine (177 mg, 675 µmol) dissolved in THF (5 mL). After stirring for 30 min, the mixture was allowed to warm to room temperature and the solvent was removed under reduced pressure. The residue was then diluted with carbon tetrachloride (4 mL) and directly transferred to a silica gel column. A rapid flash chromatography (ethyl acetate / hexane, 1:9 then 4:6) provided allylic chloride **5a** (306 mg, 94%) as a colorless oil; IR ($CHCl_3$) 3027, 2956, 1730, 1620, 1439, 1273, 1117 cm^{-1}; ^1H NMR ($CDCl_3$) 6.39 (1H, dd, J=11.0, 15.0 Hz, C<u>H</u>=CHCH$_2$), 6.26 (1H, d, J=11.5 Hz, CH=C<u>H</u>CO), 6.20 (1H, dt, J=11.5, 4.0 Hz, C<u>H</u>=CHCO), 5.95 (1H, t, J=11.0 Hz, CHCH=C<u>H</u>), 5.48 (1H, dt, J=15.0, 7.5 Hz, CH=C<u>H</u>CH$_2$), 5.17 (1H, t, J=10.0 Hz, CHC<u>H</u>=CH), 4.05 (2H, s, C<u>H$_2$</u>Cl), 3.67, 3.66, 3.64 (3x3H, 3s, 3xCO$_2$CH$_3$), 3.65-3.5 (1H, m, C<u>H</u>CH=CH), 2.88 (1H, d, J=11.5 Hz, C<u>H</u>CO$_2$Me), 2.67 (2H, d, J=7.5 Hz, CH=CHC<u>H$_2$</u>), 2.65-1.9 (7H, m, C=CHC<u>H$_2$</u>C<u>H$_2$</u>, C<u>H$_2$</u>C<u>H</u>H), 1.61 (1H, m, CH$_2$CH<u>H</u>); ^{13}C NMR ($CDCl_3$) 210.54, 191.59, 170.98, 168.79, 150.04, 130.55, 130.31, 129.06, 123.00, 61.35, 57.26, 52.34, 48.92, 39.67, 37.86, 35.84, 31.25, 27.89, 24.33; MS *m/e* 468 (M^+), 437 (M^+-OMe); HRMS calcd for $C_{23}H_{29}O_8Cl$: 468.1551; found: 468.1557.

(3*Z*,9*E*,11*Z*)-7,7-Bis(methoxycarbonyl)-1-chloro-12-(2-methoxycarbonyl-3-oxo)cyclopentyl-4-methyl-2-oxododeca-3,9,11-triene (5b). To a solution of alcohol **28b** (601 mg, 1.33 mmol) in tetrahydrofuran (60 mL) at -40°C was added hexachloroacetone (404 µL, 2.66 mmol) immediately followed by a cold solution (-40°C) of triphenylphosphine (330 mg, 1.26 mmol) dissolved in THF (15 mL). After stirring for 30 min, the mixture was allowed to warm to room temperature and the solvent was removed under reduced pressure. The residue was then diluted with carbon tetrachloride (5 mL) and directly transferred to a silica gel column. Rapid flash chromatography (ethyl acetate / hexane, 1:9 then 4:6) provided allylic chloride **5b** (520 mg, 88%) as a colorless oil; IR ($CHCl_3$) 3026, 2955, 1730, 1617, 1440, 1275, 1222 cm^{-1}; ^1H NMR ($CDCl_3$) 6.47 (1H, dd, J=11.0, 15.0 Hz, C<u>H</u>=CHCH$_2$), 6.22 (1H, brs, C=C<u>H</u>CO), 6.03 (1H, t, J=11.0 Hz, CHCH=C<u>H</u>), 5.62 (1H, dt, J=15.0, 7.5 Hz, CH=C<u>H</u>CH$_2$), 5.21 (1H, t, J=10.0 Hz, CHC<u>H</u>=CH), 4.03 (2H, s, C<u>H$_2$</u>Cl), 3.75, 3.74, 3.70 (3x3H, 3s, 3xCO$_2$CH$_3$), 3.7-3.55 (1H, m, C<u>H</u>CH=CH), 2.93 (1H, d, J=11.5 Hz, C<u>H</u>CO$_2$Me), 2.76 (2H, d, J=7.5 Hz, CH=CHC<u>H$_2$</u>), 2.55-1.95 (7H,

m, C=CC$\underline{H}_2$C$\underline{H}_2$, C$\underline{H}_2$C$\underline{H}$H), 1.92 (3H, brs, C=CCH_3), 1.65 (1H, m, CH_2C$\underline{H}$H); ^{13}C NMR ($CDCl_3$) 210.73, 190.60, 171.26, 168.93, 162.08, 130.64, 130.51, 129.49, 129.15, 120.15, 61.60, 57.73, 52.47, 52.23, 49.12, 39.81, 38.04, 36.49, 35.85, 30.35, 28.87, 28.10, 25.56; MS *m/e* 482 (M^+), 467 (M^+-Me); HRMS calcd for $C_{24}H_{31}O_8Cl$: 482.1707; found: 482.1702.

(3*E*,9*E*,11*Z*)-7,7-Bis(methoxycarbonyl)-1-chloro-12-(2-methoxycarbonyl-3-oxo)cyclopentyl-4-(methoxymethoxy)methyl-2-oxododeca-3,9,11-triene (5c). To a solution of alcohol **28c** (447 mg, 850 μmol) in tetrahydrofuran (40 mL) at -40°C was added hexachloroacetone (258 μL, 1.70 mmol) immediately followed by a cold solution (-40°C) of triphenylphosphine (212 mg, 808 μmol) dissolved in THF (10 mL). After stirring for 30 min, the mixture was allowed to warm to room temperature and the solvent was removed under reduced pressure. The residue was then diluted with carbon tetrachloride (4 mL) and directly transferred to a silica gel column. Rapid flash chromatography (ethyl acetate / hexane, 1:9 then 4:6) provided allylic chloride **5c** (388 mg, 88%) as a colorless oil; IR ($CHCl_3$) 3026, 2954, 1730, 1628, 1440, 1277, 1154 cm^{-1}; ^{1}H NMR ($CDCl_3$) 6.47 (1H, s, C=C$\underline{H}$CO), 6.41 (1H, dd, J=11.0, 15.0 Hz, C$\underline{H}$=CHCH_2), 5.98 (1H, t, J=11.0 Hz, CHCH=C$\underline{H}$), 5.58 (1H, dt, J=15.0, 7.5 Hz, CH=C$\underline{H}$CH_2), 5.18 (1H, t, J=10.0 Hz, CHC$\underline{H}$=CH), 4.60 (2H, s, OC$\underline{H}_2$OCH_3), 4.06 (2H, d, J=4.5 Hz, C$\underline{H}_2$Cl), 4.05 (2H, brs, CH_2OMOM), 3.69 (6H, s, 2xCO_2CH_3), 3.65 (3H, s, CO_2CH_3), 3.65-3.5 (1H, m, C$\underline{H}$CH=CH), 3.31 (3H, s, OCH_2OC$\underline{H}_3$), 2.90 (1H, d, J=11.5 Hz, C$\underline{H}$CO_2Me), 2.71 (2H, d, J=7.5 Hz, CH=CHC$\underline{H}_2$), 2.5-1.9 (7H, m, C=CC$\underline{H}_2$C$\underline{H}_2$, C$\underline{H}_2$C$\underline{H}$H), 1.60 (1H, m, CH_2C$\underline{H}$H); ^{13}C NMR ($CDCl_3$) 210.60, 190.74, 171.01, 168.86, 159.72, 130.50, 129.29, 129.08, 117.69, 96.02, 69.24, 61.47, 57.72, 55.45, 52.36, 39.73, 37.92, 35.79, 30.81, 27.99, 24.99 ; MS *m/e* 560 (MNH_4^+); HRMS calcd for $C_{26}H_{29}NO_{10}ClSi$ (MNH_4^+): 560.2262; found: 560.2259.

(4*Z*,10*E*,12*Z*)-[1*R,14*S**]-1,8,8-Tris(methoxycarbonyl)-3,17-dioxobicyclo[12.3.0]heptadeca-4,10,12-triene (4a).** To a vigorously stirred suspension of cesium carbonate (1.63 g, 5.00 mmol) in dry acetonitrile (490 mL) at 40°C was slowly added a solution of allylic chloride **5a** (470 mg, 1.00 mmol) in the same solvent (10 mL) via syringe pump during an hour (final concentration = 2μM). After an additional hour of stirring at the same temperature, the solvent was evaporated and the residue was filtered through a fritted glass using dichloromethane. Removal of the solvent afforded an oil which was purified by flash chromatography (ethyl acetate / hexane, 4:6) to give the title compound **4a** (365 mg, 85%) as a white solid: mp 175-176°C; IR ($CHCl_3$) 3029, 2956, 1730, 1636, 1443, 1267, 1221 cm^{-1}; ^{1}H NMR ($CDCl_3$) 6.33 (1H, dd, J=11.0, 15 Hz, C$\underline{H}$=CHCH_2), 6.09 (1H, t, J=11.0 Hz, CHCH=C$\underline{H}$), 6.04 (1H, d, J=12.0 Hz, CH=C$\underline{H}$CO), 5.67 (1H, dt, J=4.0, 12.0 Hz, C$\underline{H}$=CHCO), 5.34 (1H, ddd, J=15.0, 11.0, 4.5 Hz, CH=C$\underline{H}$CH_2), 5.11 (1H, t, J=11.0 Hz, CHC$\underline{H}$=CH), 4.23 (1H, dt, J=11.0, 8.5 Hz, C$\underline{H}$CH=CH), 3.68, 3.67, 3.64 (3x3H, 3s, 3xCO_2CH_3), 3.13 (1H, d, J=20.0 Hz, C=C-C(O)-C$\underline{H}$H), 2.83 (1H, d, J=20.0 Hz, C=C-C(O)-CH$\underline{H}$), 2.78 (1H, brdd, J=4.0, 14.0 Hz), 2.6-2.35 (4H, m) 2.1-1.9 (3H, m), 1.6-1.35 (2H, m); ^{13}C NMR ($CDCl_3$) 212.93, 201.34, 171.14, 170.76, 169.33, 137.88, 131.34, 130.16, 129.99, 128.68, 128.05, 61.15, 56.29, 52.61, 52.22, 42.19, 40.84, 37.47, 35.14, 31.43, 26.08, 22.72; MS *m/e* 432 (M^+), 400 (M^+-MeOH); HRMS calcd for $C_{23}H_{28}O_8$: 432.1784; found: 432.1779.

(4*Z*,10*E*,12*Z*)-[1*R,14*S**]-1,8,8-Tris(methoxycarbonyl)-5-methyl-3,17-dioxobicyclo[12.3.0]heptadeca-4,10,12-triene (4b).** To a vigorously stirred suspension of cesium

carbonate (1.04 g, 3.18 mmol) in dry acetonitrile (310 mL) at 40°C was slowly added a solution of allylic chloride **5b** (306 mg, 635 μmol) in the same solvent (10 mL) via syringe pump during an hour (final concentration = 2μM). After an additional hour of stirring at the same temperature, the solvent was evaporated and the residue was filtered through a fritted glass using dichloromethane. Removal of the solvent afforded an oil which was purified by flash chromatography (ethyl acetate / hexane, 4:6) to give the title compound **4b** (245 mg, 86%) as a white solid: mp 203-204°C; IR ($CHCl_3$) 3015, 2955, 1750, 1731, 1690, 1644, 1435, 1220 cm^{-1}; ^1H NMR ($CDCl_3$) 6.39 (1H, dd, J=11.0, 15.0 Hz, C<u>H</u>=CHCH$_2$), 6.13 (1H, t, J=11.0 Hz, CHCH=C<u>H</u>), 5.91 (1H, s, C=C<u>H</u>CO), 5.34 (1H, ddd, J=15.0, 11.0, 4.5 Hz, CH=C<u>H</u>CH$_2$), 5.17 (1H, t, J=11.0 Hz, CHC<u>H</u>=CH), 4.43 (1H, dt, J=11.0, 7.5 Hz, C<u>H</u>CH=CH), 3.73, 3.72, 3.68 (3x3H, 3s, 3xCO_2CH_3), 3.17 (1H, d, J=20.0 Hz, C=C-C(O)-C<u>H</u>H), 2.82 (1H, d, J=20.0 Hz, C=C-C(O)-CH<u>H</u>), 2.9-2.5 (5H, m) 2.3-2.0 (3H, m), 1.77 (3H, s, CH_3), 1.46 (1H, dt, J=6.0, 13.5 Hz), 1.30 (1H, brt, J=13.5 Hz); ^{13}C NMR ($CDCl_3$) 212.99, 201.68, 171.19, 170.68, 169.37, 147.33, 131.41, 130.39, 128.82, 127.79, 127.25, 61.41, 56.62, 52.56, 52.16, 42.82, 40.77, 37.47, 34.91, 30.22, 26.53, 26.01, 22.91; MS *m/e* 446 (M^+), 415 (M^+-MeO); HRMS calcd for $C_{24}H_{30}O_8$: 446.1941; found: 446.1946.

(4*E*,10*E*,12*Z*)-[1*R,14*S**]-1,8,8-Tris(methoxycarbonyl)-5-(methoxymethoxy)methyl-3,17-dioxobicyclo[12.3.0]heptadeca-4,10,12-triene (4c).** To a vigorously stirred suspension of cesium carbonate (1.43 g, 4.38 mmol) in dry acetonitrile (430 mL) at 50°C was slowly added a solution of allylic chloride **5c** (476 mg, 875 μmol) in the same solvent (10 mL) via syringe pump during an hour (final concentration = 2μM). After an additional hour of stirring at the same temperature, the solvent was evaporated and the residue was filtered through a fritted glass using dichloromethane. Removal of the solvent afforded an oil which was purified by flash chromatography (ethyl acetate / hexane, 4:6) to give the title compound **4c** (345 mg, 78%) as a white solid: mp 144-146°C; IR ($CHCl_3$) 3028, 2955, 1750, 1731, 1651, 1443, 1220, 1157 cm^{-1}; ^1H NMR ($CDCl_3$) 6.33 (1H, dd, J=11.0, 15.0 Hz, C<u>H</u>=CHCH$_2$), 6.16 (1H, brs, C=C<u>H</u>CO), 6.08 (1H, t, J=11.0 Hz, CHCH=C<u>H</u>), 5.28 (1H, ddd, J=15.0, 11.0, 4.5 Hz, CH=C<u>H</u>CH$_2$), 5.12 (1H, t, J=11.0 Hz, CHC<u>H</u>=CH), 4.55 (2H, s, CH_2OCH_3), 4.36 (1H, dt, J=11.0, 8.0 Hz, C<u>H</u>CH=CH), 3.98, 3.91 (2x1H, 2d, J=14.5 Hz, C<u>H</u>HOMOM), 3.67, 3.66, 3.62 (3x3H, 3s, 3xCO_2CH_3), 3.28 (3H, s, $OCH_2OC\underline{H}_3$), 3.18 (1H, d, J=20.0 Hz, C=C-C(O)-C<u>H</u>H), 2.8-2.4 (6H, m) 2.15-1.9 (3H, m) 1.5-1.3 (2H, m); ^{13}C NMR ($CDCl_3$) 212.92, 202.26, 171.01, 170.56, 169.26, 145.91, 131.40, 130.38, 128.83, 127.79, 126.17, 95.83, 68.07, 61.47, 56.61, 55.27, 52.58, 52.15, 41.93, 40.89, 37.47, 34.69, 30.38, 26.02, 22.78; MS *m/e* 506 (M^+), 415 (M^+-MeOH); HRMS calcd for $C_{26}H_{34}O_{10}$: 506.2152; found: 506.2149.

***rac*-3,3-Bis(methoxycarbonyl)-18-methoxy-19-nor-18-oxo-5α,9β-androst-6-en-11,17-dione (3a).** A solution of **4a** (5.0 mg, 12 μmol) in toluene (500 μL) was degassed and sealed under nitrogen in a quartz tube. After being heated in a temperature controlled oven at 200°C for 30 h, the tube was cooled and the contents evaporated. The resulting residue was filtered over a small pad of silica gel (ethyl acetate / hexane, 3:7) yielding **3a** (4.2 mg, 85%) as a white solid: mp 151-154°C; IR ($CHCl_3$) 3030, 2956, 1753, 1727, 1453, 1436, 1243, 1157 cm^{-1}; ^1H NMR ($CDCl_3$) 5.58 (1H, dt, J=10.0, 2.0 Hz), 5.52 (1H, d, J=10.0 Hz), 3.80, 3.79, 3.68 (3x3H, 3s), 3.16 (1H, d, J=18.0 Hz), 2.96 (1H, brt, J=9.5 Hz), 2.88 (1H, dd, J=9.5, 3.5 Hz), 2.75 (1H, m), 2.6-2.15 (7H, m), 2.03 (1H, dq, J=3.5 Hz), 1.65-1.5 (2H, m), 1.4-1.1 (3H, m); ^{13}C NMR ($CDCl_3$) 210.80, 209.18, 172.69, 171.13, 170.17, 132.77, 125.72, 59.21, 55.39, 53.06, 52.61, 51.96, 47.63, 46.08,

40.12, 38.29, 37.86, 32.03, 31.26, 25.23, 23.75; MS *m/e* 432 (M^+), 401 (M^+-MeO); HRMS calcd for $C_{23}H_{28}O_8$: 432.1784; found: 432.1774.

***rac*-3,3-Bis(methoxycarbonyl)-18-methoxy-18-oxo-5α,9β-androst-6-en-11,17-dione (3b).** A solution of **4b** (5.0 mg, 11 μmol) in toluene (500 μL) was degassed and sealed under nitrogen in a quartz tube. After being heated in a temperature controlled oven at 225°C for 24 h, the tube was cooled and the contents evaporated. The resulting residue was filtered over a small pad of silica gel (ethyl acetate / toluene, 1:9) yielding **3b** (4.0 mg, 80%) as a white solid: mp 198-200°C; IR ($CHCl_3$) 3014, 2955, 1753, 1727, 1435, 1256, 1149 cm^{-1}; ^1H NMR ($CDCl_3$) 5.59 (1H, dt, J=10.0, 2.5 Hz), 5.52 (1H, dt, J=10.0, 1.5 Hz), 3.82, 3.80, 3.69 (3x3H, 3s), 3.15 (1H, d, J=17.5 Hz), 3.0-2.7 (3H, m), 2.67 (1H, d, J=7.0 Hz), 2.45-2.1 (7H, m), 1.96 (1H, m), 1.74 (1H, t, J=13.5 Hz), 1.59 (1H, dt, J=6.5, 12.0 Hz), 1.08 (1H, m) 0.86 (3H, s); ^{13}C NMR ($CDCl_3$) 210.67, 209.31, 172.75, 171.40, 170.20, 131.74, 124.96, 59.14, 55.65, 53.12, 52.63, 50.87, 46.91, 38.31, 36.82, 34.17, 33.39, 31.90, 30.02, 26.72, 23.75, 17.73; MS *m/e* 446 (M^+), 415 (M^+-MeO); HRMS calcd for $C_{24}H_{30}O_8$: 446.1941; found: 446.1951.

***rac*-3,3-Bis(methoxycarbonyl)-18-methoxy-19-(methoxymethoxy)-18-oxo-5α,9β-androst-6-en-11,17-dione (3c).** A solution of **4c** (5.0 mg, 10 μmol) in toluene (500 μL) was degassed and sealed under nitrogen in a quartz tube. After being heated in a temperature controlled oven at 230°C for 24 h, the tube was cooled and the contents evaporated. The resulting residue was filtered over a small pad of silica gel (ethyl acetate / hexane, 4:6) yielding **3c** (3.7 mg, 74%) as a white solid: mp 171-173° ; IR ($CHCl_3$) 3019, 2955, 1753, 1729, 1435, 1214, 1148 cm^{-1}; ^1H NMR ($CDCl_3$) 5.63 (1H, dt, J=10.0, 2.5 Hz), 5.52 (1H, brd, J=10.0 Hz), 4.59, 4.56 (2x1H, 2d, J=6.5 Hz), 3.84, 3.76, 3.69 (3x3H, 3s), 3.64 (1H, d, J=10.0 Hz), 3.38 (1H, d, J=10.0 Hz), 3.36 (3H, s), 3.23 (1H, d, J=17.0 Hz), 3.18 (1H, d, J=9.0 Hz), 3.1-2.9 (2H, m), 2.75 (1H, m), 2.45-2.1 (7H, m), 1.90 (1H, dt, J=4.0, 13.5 Hz), 1.7-1.55 (3H, m ; ^{13}C NMR ($CDCl_3$) 210.68, 209.70, 172.57, 171.26, 169.67, 130.64, 126.11, 96.99, 64.03, 59.21, 55.39, 52.93, 52.79, 52.67, 50.80, 47.22, 46.98, 38.30, 37.73, 36.43, 32.61, 31.71, 26.40, 24.00, 23.75; MS *m/e* 506 (M^+), 474 (M^+-MeO); HRMS calcd for $C_{26}H_{34}O_{10}$: 506.2152; found: 506.2149.

***rac*-3,3-Bis(methoxycarbonyl)-18-methoxy-19-nor-18-oxo-5α-androst-6-en-11,17-dione (2a).** To a solution of **3a** (5.0 mg, 12 μmol) in benzene (1 mL) was added *p*-toluenesulfonic acid monohydrate (a few crystals, cat.) and the mixture was heated at reflux for 4 h. At this stage, GC analysis of an aliquot revealed a thermodynamic ratio of 63:37 for the TATAT and TACST compounds respectively. The solvent was evaporated and the residue was triturated with dichloromethane (5 × 1mL). Removal of the solvent afforded an oil which was purified by flash chromatography (ethyl acetate / hexane, 3:7) to give the starting material (2 mg) immediately followed by the title compound **2a** (3 mg, 60%) as a white solid: mp 163-165°C; IR ($CHCl_3$) 3036, 2956, 1731, 1454, 1436, 1266, 1244, 1161 cm^{-1}; ^1H NMR ($CDCl_3$) 5.62 (1H, dt, J=10.0, 2.0 Hz), 5.52 (1H, brd, J=10.0 Hz), 3.73 (3H, 3s), 3.70 (2x3H, s), 2.9-2.7 (4H, m), 2.5-1.85 (9H, m), 1.75 (1H, dt, J=6.0, 13.5 Hz), 1.65-1.5 (2H, m), 0.99 (1H, dq, J=3.0, 12 Hz); ^{13}C NMR ($CDCl_3$) 209.64, 206.34, 172.37, 171.66, 169.85, 132.58, 125.27, 62.77, 55.65, 55.26, 52.70, 52.54, 51.25, 45.43, 40.64, 39.28, 37.79, 37.02, 31.38, 25.76, 22.27; MS *m/e* 432 (M^+), 400 (M^+-MeOH); HRMS calcd for $C_{23}H_{28}O_8$: 432.1784; found: 432.1774.

***rac*-3,3-Bis(methoxycarbonyl)-18-methoxy-19-nor-18-oxo-5α,9β-androstan-11,17-dione (50).** A stirred solution of **3a** (17.6 mg, 40.7 μmol) in ethyl acetate (1.5 mL) was treated with palladium (catalytic amount, 10% on activated carbon) under hydrogen for 2 h. The mixture was then filtered over a small pad of silica gel and rinsed with ethyl acetate (2 mL). Evaporation of the solvent under reduced pressure provided compound **50** (15 mg, 85%) as a white solid: mp 176-177°C; IR ($CHCl_3$) 3029, 2955, 1752, 1723, 1454, 1435, 1258, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) 3.80, 3.79, 3.67 (3x3H, 3s), 3.16 (1H, d, J=18.0 Hz), 2.75-2.6 (2H, m), 2.45-1.5 (11H, m), 1.3-0.8 (5H, m); ^{13}C NMR ($CDCl_3$) 210.35, 209.77, 172.89, 171.27, 169.91, 61.22, 55.26, 53.07, 52.55, 49.96, 47.30, 42.00, 38.63, 38.45, 37.53, 32.58, 31.71, 31.32, 25.11, 23.5 ; MS *m/e* 434 (M^+), 412 (M^+-MeOH); HRMS calcd for $C_{23}H_{30}O_8$: 434.1941; found: 434.1935.

***rac*-3,3-Bis(methoxycarbonyl)-18-methoxy-19-nor-18-oxo-5α-androstan-11,17-dione (51).** To a solution of **50** (10 mg, 24 μmol) in benzene (2 mL) was added *p*-toluenesulfonic acid monohydrate (a few crystals, cat.) and the mixture was heated at reflux for 4 h. The solvent was evaporated and the residue was triturated with dichloromethane (5 × 1mL). Removal of the solvent afforded an oil which was purified by flash chromatography (ethyl acetate / hexane, 4:6) to give the title compound **51** (10 mg, 100%) as a white solid: mp 155-156°C; IR ($CHCl_3$) 3030, 2955, 1753, 1731, 1435, 1269, 1250, 1158 cm^{-1}; ^1H NMR ($CDCl_3$) 3.72 (3H, 3s), 3.69 (2x3H, s), 2.79 (1H, d, J=13.5 Hz), 2.71 (1H, dd, J=9.0, 19.5 Hz), 2.45 (1H, dq, J=13.5, 3.5 Hz), 2.4-1.6 (12H, m), 1.51 (1H, t, J=12.5 Hz), 1.36 (1H, dq, J=2.5, 10.0 Hz), 1.2-0.95 (3H, m), 0.80 (1H, m); ^{13}C NMR ($CDCl_3$) 210.13, 206.72, 172.56, 171.84, 169.85, 62.64, 58.56, 55.13, 52.61, 52.42, 51.96, 45.56, 40.77, 40.18, 38.60, 38.18, 37.73, 31.70, 31.08, 29.71, 27.44, 22.25; MS *m/e* 434 (M^+), 402 (M^+-MeOH); HRMS calcd for $C_{23}H_{30}O_8$: 434.1941; found: 434.1935.

***rac*-3,3-Bis(methoxycarbonyl)-18-methoxy-18-oxo-5α-androst-6-en-11,17-dione (2b).** To a solution of **3b** (5.0 mg, 11 μmol) in benzene (1 mL) was added *p*-toluenesulfonic acid monohydrate (a few crystals, cat.) and the mixture was heated at reflux for 4 h. At this stage, GC analysis of an aliquot revealed a thermodynamic ratio of 95:5 for the TATAT and TACST compounds respectively. The solvent was evaporated and the residue was triturated with dichloromethane (5 × 1mL). Removal of the solvent afforded an oil which was purified by flash chromatography (ethyl acetate / hexane, 4:6) to give the title compound **2b** (4.8 mg, 96%) as a white solid: mp 175-177°C; IR ($CHCl_3$) 3014, 2955, 1752, 1729, 1436, 1244, 1168 cm^{-1}; ^1H NMR ($CDCl_3$) 5.59 (1H, dt, J=10.0, 2.5 Hz), 5.42 (1H, dt, J=10.0, 2.0 Hz), 3.73, 3.71, 3.70 (3x3H, 3s), 2.85-2.6 (4H, m), 2.4-1.8 (5H, m), 1.16 (1H, dt, J=4.0, 13.5 Hz), 1.00 (3H, s); ^{13}C NMR ($CDCl_3$) 209.97, 205.04, 172.45, 171.72, 170.23, 132.19, 124.95, 61.73, 55.20, 52.66, 52.55, 50.99, 45.47, 42.45, 37.86, 34.23, 32.16, 31.13, 26.65, 22.52, 11.33; MS *m/e* 446 (M^+), 415 (M^+-MeO); HRMS calcd for $C_{24}H_{30}O_8$: 446.1941; found: 446.1946.

(4*Z*,10*E*,12*Z*)-[1*R,14*S**]-1,8,8-Tris(methoxycarbonyl)-5-hydroxymethyl-3,17-dioxobicyclo[12.3.0]heptadeca-4,10,12-triene (46).** To a solution of **4c** (203 mg, 400 μmol) in methanol (17 mL) was added hydrochloric acid (3M, 3mL) and the resulting solution was stirred at 65°C for 2 h. The cooled reaction mixture was then quenched with saturated aqueous sodium bicarbonate and extracted with ether. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. Flash chromatography (ethyl acetate / hexane, 1:1) of the residue first provided the solid furan **47** (81 mg, 44%) fol-

lowed by the title compound **46** (102 mg, 55%) as a white solid: mp 210-211°C; IR ($CHCl_3$) 3607, 3535, 3028, 2955, 1750, 1731, 1651, 1443, 1220, 1157 cm^{-1}; ^1H NMR ($CDCl_3$) 6.35 (1H, dd, J=11.0, 15.0 Hz, C<u>H</u>=CHCH$_2$), 6.18 (1H, brs, C=C<u>H</u>CO), 6.10 (1H, t, J=11.0 Hz, CHCH=C<u>H</u>), 5.31 (1H, ddd, J=15.0, 11.0, 4.5 Hz, CH=C<u>H</u>CH$_2$), 5.13 (1H, t, J=11.0 Hz, CHC<u>H</u>=CH), 4.35 (1H, dt, J=11.0, 8.0 Hz, C<u>H</u>CH=CH), 4.10, 3.99 (2x1H, 2brd, J=16.0 Hz, C<u>H</u>HOH), 3.69, 3.68, 3.64 (3x3H, 3s, 3xCO$_2$CH$_3$), 3.21 (1H, d, J=20.0 Hz, C=C-C(O)-C<u>H</u>H), 2.85-2.4 (7H, m), 2.1-1.9 (3H, m), 1.55-1.3 (2H, m); ^{13}C NMR ($CDCl_3$) 213.44, 202.91, 171.08, 170.75, 169.25, 149.33, 131.41, 130.38, 128.82, 127.85, 124.94, 63.93, 61.54, 56.68, 52.67, 52.22, 52.06, 40.96, 37.53, 34.67, 30.42, 26.03, 22.55; MS *m/e* 462 (M^+), 431 (M^+-MeO); HRMS calcd for $C_{24}H_{30}O_9$: 462.1890; found: 462.1883.

(4*Z*,10*E*,12*Z*)-[1*R,14*S**]-5-Formyl-1,8,8-tris(methoxycarbonyl)-3,17-dioxobicyclo[12.3.0]heptadeca-4,10,12-triene (48).** To a solution of alcohol **46** (102 mg, 220 μmol) in dichloromethane (10 mL) was added the Dess-Martin periodinane (112 mg, 264 μmol). After stirring at room temperature for 1 h, the reaction mixture was quenched with saturated aqueous sodium bicarbonate (10 mL). A 5% aqueous sodium thiosulfate solution (5 mL) was added to the mixture which was vigorously stirred for 1 h. The aqueous phase was extracted several times with ether and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered and condensed. The crude product was purified by flash chromatography (ethyl acetate / hexane, 3:7) to give the title compound **48** (85.3 mg, 84%) as a white solid: mp 204-205°C; IR ($CHCl_3$) 3028, 2956, 1731, 1702, 1444, 1275, 1222, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) 9.35 (1H, s, CHO), 6.18 (1H, s, C=C<u>H</u>CO), 6.31 (1H, dd, J=11.0, 15.0 Hz, C<u>H</u>=CHCH$_2$), 6.12 (1H, t, J=11.0 Hz, CHCH=C<u>H</u>), 5.32 (1H, ddd, J=15.0, 11.0, 4.5 Hz, CH=C<u>H</u>CH$_2$), 5.12 (1H, t, J=11.0 Hz, CHC<u>H</u>=CH), 4.18 (1H, dt, J=11.0, 8.0 Hz, C<u>H</u>CH=CH), 3.78, 3.69, 3.67 (3x3H, 3s, 3xCO$_2$CH$_3$), 3.38 (1H, d, J=20.0 Hz, C=C-C(O)-C<u>H</u>H), 2.87 (1H, d, J=20.0 Hz, C=C-C(O)-CH<u>H</u>), 2.78 (1H, dd, J=4.5, 14.0 Hz), 2.65-2.45 (3H, m), 2.3-1.8 (5H, m), 1.39 (1H, dt, J=4.5, 13.5 Hz); ^{13}C NMR ($CDCl_3$) 212.99, 201.22, 192.75, 170.82, 170.49, 168.90, 145.18, 131.67, 129.79, 128.62, 128.50, 61.48, 56.55, 52.66, 52.35, 42.34, 41.48, 37.53, 34.30, 29.90, 26.15, 19.00; MS *m/e* 460 (M^+), 429 (M^+-MeO); HRMS calcd for $C_{24}H_{28}O_9$: 460.1733; found: 460.1727.

***rac*-3,3-Bis(methoxycarbonyl)-17-ethylenedioxy-18-methoxy-18-oxo-5α-androst-6-en-11-one (52).** To a solution of **2b** (50 mg, 112 μmol) in dichloromethane (2.0 mL) were successively added ethylene glycol (500 μL) and chlorotrimethylsilane (1.0 mL). The resulting heterogeneous mixture was vigorously stirred at room temperature for 48 h. The reaction was carefully quenched by a dropwise addition of saturated aqueous sodium bicarbonate and extracted several times with dichloromethane. The combined extracts were washed with water, dried (Na_2SO_4) and condensed. The crude product was purified by flash chromatography (ethyl acetate / hexane, 4:6) providing the title compound **52** (50 mg, 91%) as a white mossy solid; IR ($CHCl_3$) 3013, 2954, 1727, 1435, 1248, 1169, 909 cm^{-1}; ^1H NMR ($CDCl_3$) 5.51 (1H, dt, J=10.0, 2.5 Hz), 5.42 (1H, brd, J=10.0 Hz), 4.0-3.8 (4H, m), 3.71, 3.68, 3.67 (3x3H, 3s), 2.7-1.7 (15H, m), 1.11 (1H, dt, J=4.0, 13.5 Hz), 0.88 (3H, s); ^{13}C NMR ($CDCl_3$) 207.44, 172.57, 171.86, 171.66, 131.36, 126.24, 116.79, 65.62, 65.03, 63.80, 61.73, 55.26, 52.60, 52.49, 51.77, 50.28, 45.69, 42.26, 39.09, 36.49, 34.04, 32.09, 31.06, 26.66, 22.99, 11.33; MS *m/e* 490 (M^+); HRMS calcd for $C_{26}H_{34}O_9$: 490.2203; found: 490.2206.

***rac*-3,3-Bis(methoxycarbonyl)-17-ethylenedioxy-11β-hydroxy-18-methoxy-18-oxo-5α-androst-6-ene (53).** To an ice cold solution of **52** (50.0 mg, 102 μmol) in methanol (2.5 mL) was added sodium borohydride (19 mg, 510 μmol) and the resulting mixture was stirred for 30 min at the same temperature. A solution of aqueous saturated ammonium chloride was added and the bulk of methanol was evaporated. The resulting mixture was diluted with water and extracted several times with ether. The combined ethereal phases were dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash chromatography (ethyl acetate / hexane, 1:1) providing the title compound (37.5 mg, 75%) as a white solid: mp 198-200°C; IR ($CHCl_3$) 3588, 2954, 1728, 1436, 1248, 1167, 909 cm^{-1}; ^1H NMR ($CDCl_3$) 5.51 (1H, brd, J=10.0 Hz), 5.42 (1H, brd, J=10.0 Hz), 4.28 (1H, brs), 4.0-3.85 (4H, m), 3.73, 3.72, 3.70 (3x3H, 3s), 2.65 (1H, m), 2.43 (1H, dd, J=3.0, 14.0 Hz), 2.35-1.7 (13H, m), 1.29 (1H, dt, J=4.0, 13.5 Hz), 1.08 (1H, brd, J=12.0 Hz), 0.98 (3H, s); ^{13}C NMR ($CDCl_3$) 174.50, 172.68, 171.78, 130.44, 128.49, 117.37, 66.71, 65.47, 65.09, 58.37, 56.29, 55.45, 52.60, 51.63, 51.06, 43.74, 37.66, 35.14, 34.30, 34.17, 32.49, 30.99, 26.60, 23.04, 12.70; MS *m/e* 492 (M^+), 460 (M^+-MeOH); HRMS calcd for $C_{26}H_{36}O_9$: 492.7171; found: 492.7174.

***rac*-3,3-Bis(methoxycarbonyl)-17-ethylenedioxy-11β-hydroxy-18-methoxy-18-oxo-5α-androstane (54).** A stirred solution of **53** (14.0 mg, 28.4 μmol) in ethyl acetate (1.0 mL) was treated with palladium (catalytic amount, 10% on activated carbon) under hydrogen atmosphere for 2 h. The mixture was then filtered over a small pad of silica gel and rinsed with ethyl acetate (2 mL). Evaporation of the solvent under reduced pressure provided compound **54** (13.0 mg, 85%) as a white solid: mp 201-204°C; IR ($CHCl_3$) 3602, 2954, 1728, 1434, 1250, 1167, 1042 cm^{-1}; ^1H NMR ($CDCl_3$) 4.25 (1H, brs), 4.0-3.85 (4H, m), 3.72, 3.69, 3.67 (3x3H, 3s), 2.65 (1H, m), 2.38 (1H, dd, J=3.0, 13.5 Hz), 2.25-1.45 (13H, m), 1.3-1.05 (4H, m), 0.97 (3H, s), 0.90 (1H, m), 0.67 (1H, dd, J=2.0, 11.0 Hz); ^{13}C NMR ($CDCl_3$) 174.44, 172.89, 171.84, 117.50, 66.77, 65.42, 65.03, 58.43, 57.07, 55.20, 52.60, 52.40, 51.44, 43.16, 38.18, 35.40, 35.01, 34.75, 32.68, 31.45, 31.26, 27.55, 26.60, 22.78, 14.63; MS *m/e* 494 (M^+), 462 (M^+-MeOH); HRMS calcd for $C_{26}H_{38}O_9$: 494.2516; found: 494.2509.

***rac*-3,3-Bis(carboxyl)-17-ethylenedioxy-11β-hydroxy-5α-androstan-18-oic acid 18,11-lactone (55).** To a solution of **54** (13.0 mg, 26.3 μmol) in methanol (4.75 mL) was added barium hydroxide (250 mg) and the solution was stirred until the latter had completely dissolved. Water (250 μL) was then added and the mixture was heated to reflux for 2 h. Thereafter, the heterogeneous reaction mixture was cooled to 0°C, neutralized with hydrochloric acid (1M) and extracted several times with ethyl acetate. The combined organic phases were washed with brine, dried (Na_2SO_4), filtered and concentrated. The solid residue was dissolved in a few drops of methanol and chromatographied over silicic acid (dichloromethane/ethyl acetate, 1:1) furnishing diacid **55** (9.2 mg, 80%) as a white solid: mp 213-215°C; IR ($CHCl_3$) 3504, 2933, 1767, 1714, 1460, 1252, 1154 cm^{-1}; ^1H NMR (CD_3OD) 4.85 (1H, d, J=6.0 Hz), 3.95-3.85 (4H, m), 2.44 (1H, dd, J=6.0, 11.0 Hz), 2.4-2.2 (2H, m), 2.0-1.1 (17H, m), 0.90 (3H, s); ^{13}C NMR ($CDCl_3$) 177.30, 175.88, 174.91, 116.68, 76.57, 67.00, 65.18, 60.97, 56.57, 56.31, 43.89, 39.60, 39.50, 36.46, 33.93, 31.79, 29.26, 27.76, 25.26, 12.94; MS *m/e* 390 (M^+-CO_2); HRMS calcd for $C_{22}H_{30}O_6$ (M^+-CO_2): 390.2042; found: 390.2048.

***rac*-17-Ethylenedioxy-11β-hydroxy-3-oxo-5α-androstan-18-oic acid 18,11-lactone (56).** A solution of **54** (5.0 mg, 11.5 μmol) in freshly distilled pyridine (1.5 mL) was treated with recrystallized lead tetraacetate (25.5 mg, 57.5 μmol) and the mixture was gently warmed to 60°C under argon. After 30 min, the reaction mixture was cooled to 0°C and sufficient hydrochloric acid (1M) was added to neutralize the solvent. The mixture was extracted several times with ether and the combined organic layers were washed with sodium bicarbonate, dried (Na_2SO_4), filtered and evaporated. The crude product was purified by flash chromatography (ethyl acetate / hexane, 1:1) providing the title compound (2.0 mg, 48%) as a white solid: mp 228-231°C; IR ($CHCl_3$) 2988, 2933, 1771, 1710, 1457, 1366, 1148, 1033 cm^{-1}; ^1H NMR (CD_3OD) 4.83 (1H, d, J=6.0 Hz), 4.0-3.85 (4H, m), 2.55-1.05 (20H, m), 1.11 (3H, s); ^{13}C NMR ($CDCl_3$) 210.67, 174.63, 115.36, 74.73, 66.06, 63.99, 59.40, 55.20, 48.01, 46.20, 44.00, 38.43, 38.31, 38.02, 37.66, 35.55, 34.73, 30.41, 28.41, 24.20, 12.17; MS *m/e* 360 (M^+); HRMS calcd for $C_{21}H_{28}O_5$ (M^+): 360.1937; found: 360.1928.

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