A Stereospecific Transannular Diels–Alder Approach to the [6.6.7] Tricyclic Skeleton Related to Aphidicolin and Scopadulan Natural Products

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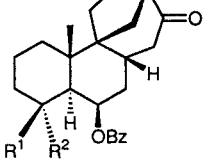
Model *trans-cis-cis* (TCC) macrocyclic triene **7** was synthesized using a convergent approach. Upon heating at 200 °C, a 1,5-hydrogen-shift on the diene moiety was found to compete with the transannular Diels–Alder (TADA) reaction, thus leading to a mixture of tricyclic products. However, the diene rearrangement could be avoided by using boron trifluoride–diethyl ether complex as catalyst at reduced temperature (60 °C). The exclusive formation of the *trans-syn-cis* [6.6.7] (TSC) tricyclic product **8** through an *endo* approach was observed. This result demonstrates the feasibility of a TADA strategy for synthesizing the title compounds and analogs.

Since its recent development, the transannular Diels–Alder (TADA) reaction is showing considerable promise in organic synthesis.[1,2] This is attributable to its capacity to generate a tricyclic array containing four asymmetric centers in a single step from a macrocyclic triene. Accordingly, a large number of polycyclic natural products and analogs are potentially accessible through this synthetic strategy. For instance, members of the scopadulan family[3] (**1** and **2**) and aphidicolin (**3**),[4] which stand among the most challenging targets, share a similar ABC [6.6.7] tricyclic subunit with a *trans-syn-cis* (TSC) ring junction stereochemistry (Scheme 1). Their biological properties and complex tetracyclic structures have attracted the interest of the scientific community for many years. As a result, extensive work toward the total synthesis of **1**–**3** has culminated in some successful approaches.[5]

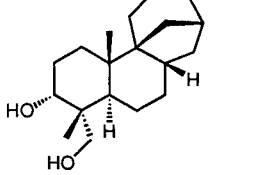


scopadulcic acid A (**1**)

$R^1 = CO_2H$, $R^2 = CH_2OH$

scopadulcic acid B (**2**)

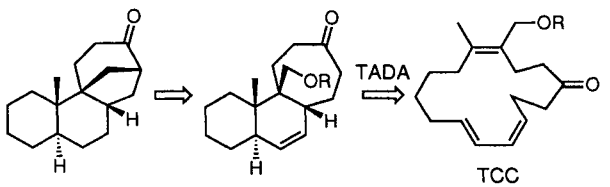
$R^1 = CH_3$, $R^2 = CO_2H$



aphidicolin (**3**)

Scheme 1

We envisaged that a stereocontrolled TADA approach to a TSC [6.6.7] skeleton of type **5** (Scheme 2) could indeed be performed on a *trans-cis-cis* (TCC)[6] 15-membered macrocyclic triene **6**.[7] Further retrosynthetic analysis, as exemplified for aphidicolin (**3**), would include an intramolecular C–C bond closure to insure formation of the C/D bridged system **4**.



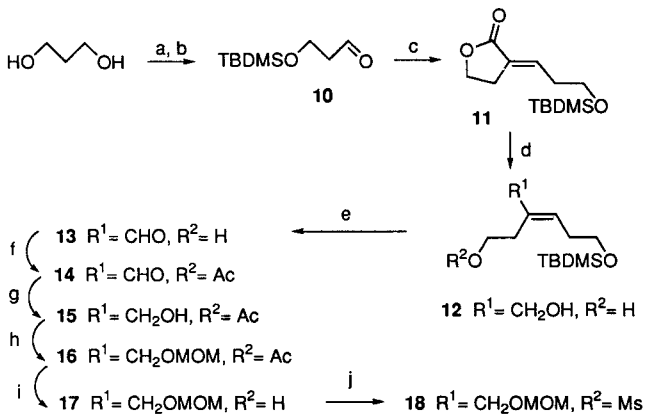
4 TSC [6.6.7] **5** cyclopentadecatriene **6**

Scheme 2

At first sight, this particular TADA transformation is associated with two fundamental difficulties of organic synthesis: 1) the [4 + 2] cycloaddition of an open-chain *trans-cis* diene,[8] and 2) the concurrent formation of a 7-membered carbocycle.[9] However, entropy and proximity effects[1] brought by the transannular nature of the reaction are favorable factors that could help in overcoming such impediments. In order to test this challenging opportunity, we have prepared model TCC macrocycle **7** (Scheme 5). Based on previous studies[1] and molecular model analysis, stereoselective formation of the TSC [6.6.7] tricylic product **8** through an *endo* approach is expected. Actually, the alternative *exo* approach leads to a highly strained *trans*-diaxial B/C ring junction at transition state level, making the formation of the corresponding CST tricycle **9** a most unlikely pathway for the TADA reaction. Moreover, the transition state discrimination favoring the formation of **8** could be further substantiated by the *endo* effect originating from the formyl group.[10]

Our standard convergent approach using preformed dienophile and diene building blocks with malonate connectors was chosen to prepare **7**. The synthesis of the trisubstituted dienophilic component **18** (Scheme 3) starts with a Horner–Emmons condensation of α-diethylphosphono-γ-butyrolactone anion[11] on aldehyde **10**, giving the *E*-alkylidene lactone **11** after chromatographic separation. A four step routine sequence furnished the diprotected triol **15** in high yield. Allylic alcohol protection as a MOM (methoxymethyl) ether was followed by acetate cleavage, affording the alcohol **17** on which mesylation resulted in the coupling synthon **18**.

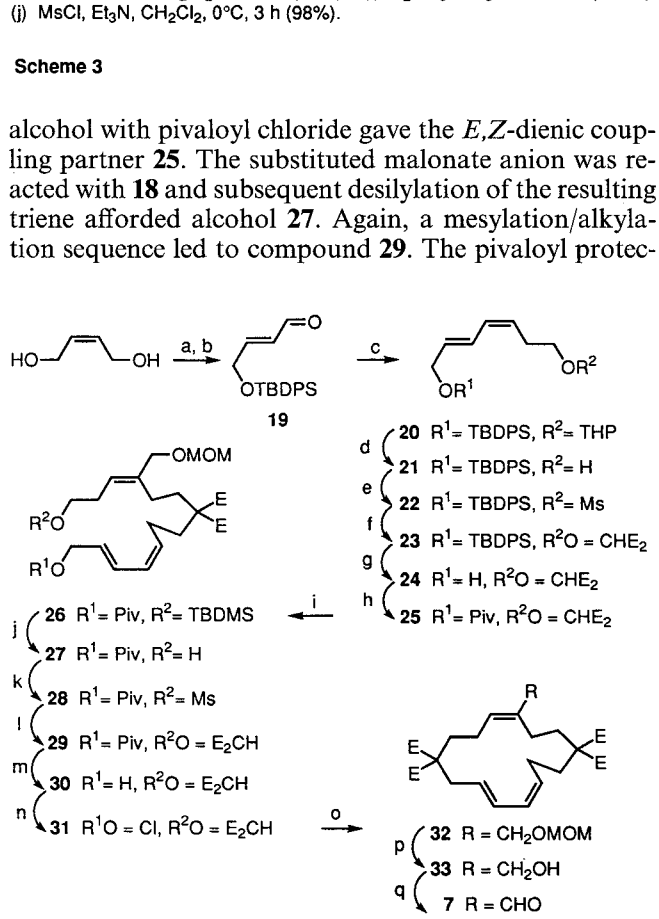
The diene partner was elaborated from aldehyde **19** (Scheme 4) upon treatment with a known phosphorane,[12] furnishing the *E,Z*-isomer after chromatographic separation of the corresponding mixture of alcohols. Mesylation of **21** was followed by displacement with the sodium anion of dimethyl malonate, resulting in compound **23**. Silyl ether cleavage and esterification of the resulting



(a) TBDMSCl, imidazole, THF, r t, 36 h (85%). (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C to rt (88%). (c) NaH, α-diethylphosphono-γ-butyrolactone, C_6H_6, r t to 60°C, then **10**, 60°C, 0.5 h (43% (Z), 38% (E)). (d) DIBALH, Et_2O, -78°C, 1 h. (e) MnO_2, $CHCl_3$, r t, 3 h. (f) Ac_2O, Et_3N, DMAP (cat.); CH_2Cl_2, 0°C, 2 h. (g) $NaBH_4$, CH_3OH, 0°C, 1 h (63% over 4 steps). (h) MOMCl, DIPEA, CH_2Cl_2, r t, 20 h (79%). (i) K_2CO_3, CH_3OH, r t, 3 h (100%). (j) MsCl, Et_3N, CH_2Cl_2, 0°C, 3 h (98%).

Scheme 3

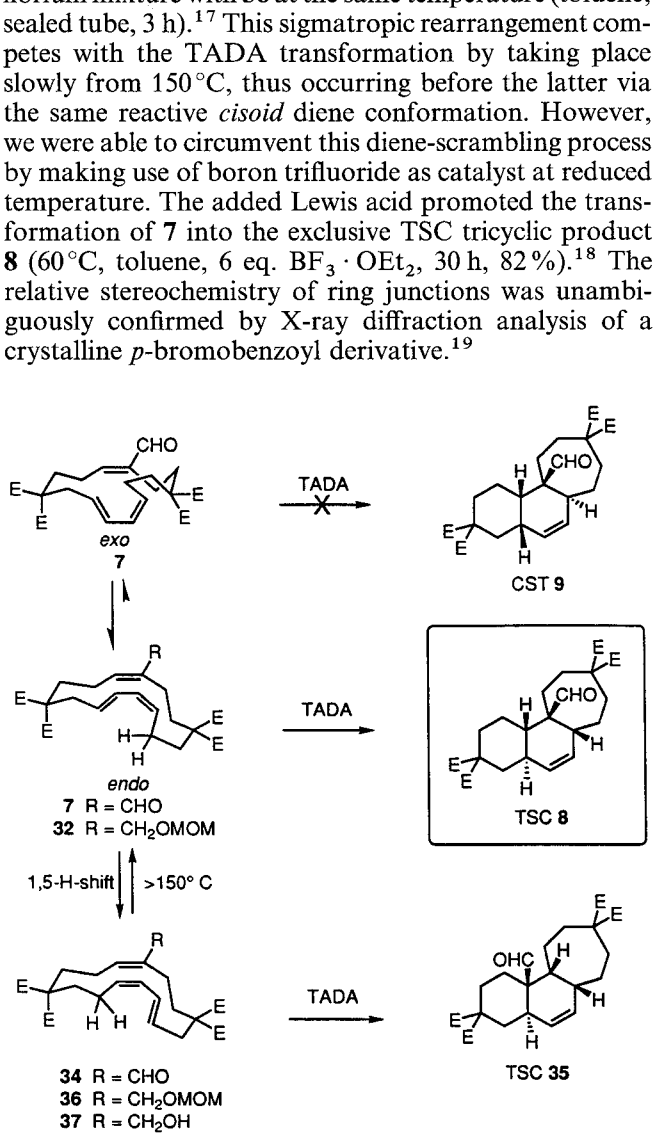
alcohol with pivaloyl chloride gave the *E,Z*-dienic coupling partner **25**. The substituted malonate anion was reacted with **18** and subsequent desilylation of the resulting triene afforded alcohol **27**. Again, a mesylation/alkylation sequence led to compound **29**. The pivaloyl protecting group was removed and Meyers chlorination[13] of the corresponding alcohol **30** gave the allylic chloride **31**. Macrocyclization of this chlorotriene proceeded smoothly in pseudo-high dilution conditions to afford TCC cyclopentadecatriene **32**. Finally, the analogous formyl-substituted macrocycle **7**[14] was obtained quantitatively through allylic alcohol deprotection and Dess–Martin oxidation.[15]



E = CO_2CH_3. (a) TBDPSCl, imidazole, THF, r t, 15 h (82%). (b) PCC, 4Å mol. sieves, CH_2Cl_2, r t, 1.5 h (85%). (c) $THPO(CH_2)_3$-PPh_3Br, THF, 0°C, then *n*-BuLi, 0°C, 30 min, go to -78°C, then **19**, -78°C to rt, 2 h (97% (E,Z)/(E,E) =7:1). (d) PPTS, *i*-PrOH, 80°C,1.5h (67% of pure (E,Z) **21**). (e) MsCl, Et_3N, CH_2Cl_2, 0°C, 1h (95%.). (f) NaH, DMF, r t, then $(CH_3O_2C)_2CH_2$, then **22** / THF and KI, 70°C, 6h (78%). (g) TBAF, THF, rt, 5.5h (74%). (h) PivCl, Et_3N, DMAP (cat.), CH_2Cl_2, 0°C to rt, 4.5h (96%). (i) NaH, DMF, rt, then **25**, 40°C, 1h, then **18** /THF and KI, 65°C, 6h. (j) TBAF, THF, r t, 6h (46% over 2 steps). (k) MsCl, Et_3N, CH_2Cl_2, 0°C, 3 h (100%). (l) NaH, DMF, r t, then $(CH_3O_2C)_2CH_2$, then **28**/THF and KI, 70°C, 9h (93%). (m) $NaOCH_3$, CH_3OH, rt, 2h (79%). (n)LiCl, MsCl, 2,4,6-collidine, DMF, 0°C, 3h (96%). (o) Cs_2CO_3, DMF/THF 1:1, 75°C, then **31** via syringe pump over 15 h, final: [0.003 M], (83%). (p) HCl conc. / H_2O / CH_3OH 0.5:1:8.5, 65°C, 2h (100%). (q) Dess-Martin periodinane, CH_2Cl_2, rt, 1 h (100%).

Scheme 4

Model TCC macrocyclic triene **7** was unreactive at 150°C (neat, sealed tube, 3 h) and showed little hope for a clean thermal noncatalyzed conversion to the desired TSC tricycle **8**. Upon heating at 200°C (neat, sealed tube, 1 h), a nonseparable mixture of two tricyclic compounds, assigned structures **8** and **35**, along with starting material **7** and isomeric macrocycle **34** were obtained (Scheme 5). A 1,5-hydrogen shift on the *trans-cis* diene moiety[16] presumably accounts for this observation since the parent unactivated macrocycle **32** gave an inseparable 1:1 equilibrium mixture with **36** at the same temperature (toluene, sealed tube, 3 h).[17] This sigmatropic rearrangement competes with the TADA transformation by taking place slowly from 150°C, thus occurring before the latter via the same reactive *cisoid* diene conformation. However, we were able to circumvent this diene-scrambling process by making use of boron trifluoride as catalyst at reduced temperature. The added Lewis acid promoted the transformation of **7** into the exclusive TSC tricyclic product **8** (60°C, toluene, 6 eq. $BF_3 \cdot OEt_2$, 30 h, 82%).[18] The relative stereochemistry of ring junctions was unambiguously confirmed by X-ray diffraction analysis of a crystalline *p*-bromobenzoyl derivative.[19]



Scheme 5

Thus, the TADA strategy allows the successful cycloaddition of a diene component with a *trans-cis* geometry.

Moreover, the stereospecific formation of the key TSC [6.6.7] tricycle **8** described herein demonstrates the feasibility of a TADA approach toward the synthesis of natural products such as aphidicolin and scopadulcic acids. This could be achieved through construction of functionalized macrocyclic trienes which would incorporate a tetrasubstituted dienophile in view of introducing the requisite angular methyl group. Suitable chiral substituents along the chain should insure chirality transfer thus controlling the absolute stereochemistry in the TADA transformation. Work toward the realization of these objectives is currently in progress.

All reactions were performed under Ar or N_2 atmosphere with oven- (150 °C) or flame-dried glassware. Et_2O and THF were dried by distilling over sodium/benzophenone ketyl. Benzene, CH_2Cl_2 and DMF were dried by distilling over CaH_2. Analytical and preparative TLC were carried out on glass plates precoated (0.25 mm) with silica gel 60 F-250 (Merck). Materials were detected by visualization under an ultraviolet lamp and/or by spraying with a solution of phosphomolybdic acid (10% in EtOH) followed by heating on a hot plate. Column chromatography was performed with 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 uncorrected. IR spectra were taken on a Perkin-Elmer 681 spectrophotometer or a Perkin-Elmer 1600 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker WM-250 or AC-300 instrument. Chemical shifts are reported in δ units, parts per million from the $CHCl_3$ peak as internal reference (^{1}H: $\delta = 7.26$, ^{13}C: $\delta = 77.0$). Where necessary, COSY, *J*-resolved and H-correlation experiments were performed. Abbreviations used are: s singlet, d doublet, t triplet, q quartet, qn quintet, m multiplet, br broad. Mass spectral (MS) assays were obtained with a VG Micromass ZAB-2F spectrometer (70 eV).

3-*tert*-Butyldimethylsiloxypropanol:
Imidazole (7.69 g, 0.113 mol) and *tert*-butyldimethylchlorosilane (17.00 g, 0.113 mol) were successively added to a solution of propane-1,3-diol (40.8 mL, 0.565 mol) in THF (250 mL) at 0 °C. The cloudy mixture was stirred 14 h at r.t. and diluted with CH_2Cl_2 (1.3 mL). The resulting mixture was washed with water (5 × 100 mL) and the organic phase was dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography (20% EtOAc in hexanes), yielding 18.96 g (88%) of the title alcohol as a clear oil.

IR (neat): $\nu = 3360$ (br), 2990–2820 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 3.82$ (4 H, m, $HOC\underline{H}_2CH_2OTBS$), 2.60 (1 H, t, $J = 5.5$ Hz, HO), 1.76 (2 H, qn, $J = 5.5$ Hz, $CH_2C\underline{H}_2CH_2$), 0.90 [9 H, s, $SiC(CH_3)_3$], 0.08 [6 H, s, $Si(CH_3)_2$].

MS: $m/z = 133$ [$M^+ - (CH_3)_3C$].

HRMS: m/z calc. for $C_5H_{13}O_2Si$: 133.0685; found: 133.0684 ± 0.0004.

3-*tert*-Butyldimethylsiloxypropan-1-al (10):
To a solution of oxalyl chloride (0.75 mL, 8.73 mmol) in CH_2Cl_2 (23 mL) at −78 °C was added DMSO (1.25 mL, 17.6 mmol) in CH_2Cl_2 (7 mL). After stirring for 0.25 h, the above mono-protected alcohol (1.4421 g, 7.59 mmol) in CH_2Cl_2 (23 mL) was added to the reaction mixture. After stirring for 1.25 h, Et_3N (3 mL, 21.6 mmol) was added to the mixture, which was allowed to warm to r.t. during 2 h, quenched with water and extracted several times with CH_2Cl_2. The combined organic phases were washed with 1% HCl, water, 5% aq $NaHCO_3$, water, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (hexanes/EtOAc, 5:1) to afford aldehyde **10** (1.2572 g, 88%, colourless oil).

IR (neat): $\nu = 2980$–2820, 2730, 1725 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 9.81$ (1 H, t, $J = 2.0$ Hz, C_1-H), 3.99 (2 H, t, $J = 6.0$ Hz, C_3-H_2), 2.61 (2 H, dt, $J = 6.0$, 2.0 Hz, C_2-H_2), 0.88 [9 H, s, $SiC(CH_3)_3$], 0.06 [6 H, s, $Si(CH_3)_2$].

MS: $m/z = 188$ (M^+), 131 [$M^+ - C(CH_3)_3$].

HRMS: m/z calc. for $C_5H_{11}O_2Si$: 131.0528; found: 131.0515 ± 0.0004.

(*Z*)-3-(3′-*tert*-Butyldimethylsiloxy)propylideneoxolan-2-one (11) and (*E*)-3-(3′-*tert*-Butyldimethylsiloxy)propylideneoxolan-2-one (11):
To a suspension of NaH (0.906 g, 22.6 mmol, 60% dispersion in mineral oil) in benzene (130 mL) was added dropwise α-diethylphosphono-γ-butyrolactone (5.0 g, 22.6 mmol). After completion of the H_2 evolution, the clear reaction mixture was heated to 60 °C for 0.5 h and a solution of 3-*tert*-butyldimethylsiloxypropanal (**10**; 2.84 g, 15.1 mmol) in benzene (15 mL) was added dropwise. The solution was stirred at 60 °C for 0.5 h and aq sat. NH_4Cl (100 mL) was added. The mixture was extracted with Et_2O (1 × 200 mL, 3 × 50 mL) and the organic phases were washed with brine (25 mL), dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (10% → 20% EtOAc in hexanes), affording lactones (*Z*)-**11** (1.65 g, 43% colourless oil) and (*E*)-**11** (1.47 g, 38%, colourless oil).

trans-isomer (*Z*)-**11** (less polar):

IR ($CHCl_3$): $\nu = 2980$–2880, 1750, 1670 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.32$ (1 H, tt, $J = 7.5$, 3 Hz, =CH), 4.28 (2 H, t, $J = 7.3$ Hz, CH_2OCO), 3.68 (2 H, t, $J = 6.0$ Hz, $C\underline{H}_2OTBS$), 2.95–2.83 (4 H, m, $C\underline{H}_2CH_2OCO$ and $=CHC\underline{H}_2$), 0.85 [9 H, s, $SiC(CH_3)_3$], 0.02 [6 H, s, $Si(CH_3)_2$].

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.94$, 140.70, 124.60, 65.24, 62.01, 30.90, 29.03, 25.80, 18.22, −5.43.

MS: $m/z = 241$ ($M^+ - CH_3$), 226 ($M^+ - 2CH_3$).

HRMS: m/z calc. for $C_{12}H_{21}O_3Si$: 241.1260; found: 241.1256 ± 0.0007.

cis-isomer (*E*)-**11** (more polar):

IR ($CHCl_3$): $\nu = 2980$–2880, 1750, 1680 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.67$ (1 H, tt, $J = 7.5$, 3.0 Hz, =CH), 4.30 (2 H, t, $J = 7.4$ Hz, CH_2OCO), 3.68 (2 H, t, $J = 6.3$ Hz, $C\underline{H}_2OTBS$), 2.90–2.80 (2 H, m, $CO_2CH_2C\underline{H}_2$), 2.40–2.28 (2 H, m, $=CHC\underline{H}_2$), 0.80 [9 H, s, $SiC(CH_3)_3$], −0.03 (6 H, s, $Si(CH_3)_2$].

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.88$, 137.28, 126.78, 65.24, 61.01, 33.64, 25.61, 24.99, 18.03, −5.61.

MS: $m/z = 241$ ($M^+ - CH_3$), 226 ($M^+ - 2CH_3$).

HRMS: m/z = calc. for $C_{12}H_{21}O_3Si$: 241.1260; found: 241.1256 ± 0.0007.

(*E*)-1-Acetoxy-6-*tert*-butyldimethylsiloxy-3-hydroxymethylhex-3-ene (15):
Diisobutylaluminium hydride (DIBALH, 45 mL, 67.2 mmol, 1.5 M in toluene) was added over a few minutes to a solution of lactone (*E*)-**11** (7.83 g, 30.6 mmol) in Et_2O (220 mL) at −78 °C. The solution was stirred for 1 h after which MeOH (15 mL) was added and the mixture allowed to warm to r.t. It was then extracted with a 30% solution of disodium tartrate (4 × 25 mL) and the combined aqueous phases were extracted with Et_2O (4 × 50 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$) and filtered over a short pad of silica gel. Concentration of the solvents left a crude mixture of diol **12** along with aldehyde **13**, originating from incomplete reduction. This sensitive material was immediately used for the next step by dilution with $CHCl_3$ (330 mL). MnO_2 (26.6 g, 306 mmol) was added and the mixture was stirred for 3 h (more MnO_2 might be needed depending on its activity), after which it was filtered over a pad of Celite (rinsed with $CHCl_3$). The filtrate was concentrated to give the crude aldehyde **13** (homogeneous by TLC). Without delay, **13** was dissolved in CH_2Cl_2 (500 mL) and the solution was cooled to 0 °C. Ac_2O (8.7 mL, 91.8 mmol), Et_3N (12.8 mL, 91.8 mmol) and 4-dimethylaminopyridine (a few crystals, cat.) were successively added. The solution was stirred for 3 h at 0 °C and aq sat. NH_4Cl (100 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic layers were washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered and concentrated. The crude unstable acetate **14** was immediately used in the following step. It was dissolved

in MeOH (425 mL) and the solution was cooled to 0 °C. $NaBH_4$ (0.75 g, 19.8 mmol) was added and the mixture was stirred for 1 h at 0 °C. A solution of sat. NH_4Cl (25 mL) was added and the bulk of MeOH was evaporated. The resulting mixture was diluted with water (15 mL) and extracted with Et_2O (4 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash chromatography (8% → 20% EtOAc in hexanes), affording *E*-allylic alcohol **15** (5.80 g, 63% overall from (*E*)-**11**, colourless oil).

IR ($CHCl_3$): ν = 3450, 2970, 1745 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 5.58 (1 H, t, J = 7 Hz, $=CHCH_2$), 4.15 (2 H, t, J = 7 Hz, CH_2OAc), 4.07 (2 H, s, CH_2OH), 3.62 (2 H, t, J = 7.0 Hz, CH_2OTBS), 2.47 (2 H, t, J = 7 Hz, CH_2CH_2OAc), 2.30 (2 H, dt, J = 7, 7 Hz, CH_2CH_2OTBS), 2.03 (3 H, s, CH_3CO_2), 1.65 (1 H, br, HO^-), 0.88 [9 H, s, $SiC(CH_3)_3$], 0.05 [6 H, s, $Si(CH_3)_2$].

MS: m/z = 303 (MH^+), 285 ($M^+ - OH$), 245 [$M^+ - C(CH_3)_3$].

HRMS: m/z calc. for $C_{11}H_{21}O_4Si$: 245.1209; found: 245.1208 ± 0.0007.

(*E*)-1-Acetoxy-6-*tert*-butyldimethylsiloxy-3-(methoxymethoxy)methylhex-3-ene (16):

To a solution of the *E*-allylic alcohol **15** (5.80 g, 19.2 mmol) in CH_2Cl_2 (400 mL) were successively added diisopropylamine (10.12 mL, 58.2 mmol) and methoxymethyl chloride (2.95 mL, 38.8 mmol). The reaction mixture was stirred for 20 h at r.t. after which a sat. solution of NH_4Cl (100 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 150 mL) and the combined organic layers were washed with water (15 mL) and brine (15 mL), dried ($MgSO_4$), filtered and concentrated. Purification of the residue by flash chromatography (20% EtOAc in hexanes) furnished compound **16** (5.24 g, 79% yellowish oil).

IR ($CHCl_3$): ν = 2930, 2860, 1742 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.58 (1 H, t, J = 6 Hz, $=CHCH_2$), 4.60 (2 H, s, OCH_2O), 4.11 (2 H, t, J = 7.5 Hz, CH_2OAc), 3.97 (2 H, s, CH_2OMOM), 3.62 (2 H, t, J = 7.5 Hz, CH_2OTBS), 3.35 (3 H, s, OCH_3), 2.44 (2 H, t, J = 7.5 Hz, CH_2CH_2OAc), 2.30 (2 H, dt, J = 7.5, 7.5 Hz, CH_2CH_2OTBS), 2.02 (s, 3 H, CH_3CO_2), 0.87 [9 H, s, $SiC(CH_3)_3$], 0.03 [6 H, s, $Si(CH_3)_2$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.93, 133.20, 128.16, 95.36, 71.55, 62.88, 62.61, 55.28, 31.43, 27.81, 25.88, 20.95, 18.30, − 5.28.

MS: m/z = 289 [$M^+ - C(CH_3)_3$], 285 ($M^+ - AcOH_2$).

HRMS: m/z = calc. for $C_{13}H_{25}O_5Si$: 289.1471; found: 289.1466 ± 0.0008.

(*E*)-6-*tert*-Butyldimethylsiloxy-3-(methoxymethoxy)methylhex-3-en-1-ol (17):

K_2CO_3 (420 mg, 3.03 mmol) was added to a solution of compound **16** (5.24 g, 15.2 mmol) in MeOH (170 mL). The solution was stirred 3 h at r.t. and then diluted with Et_2O (525 mL). The resulting mixture was filtered over a short column of silica gel (rinsed with Et_2O) and the filtrate was concentrated to give pure alcohol **17** (4.62 g, 100%, slightly yellowish oil).

IR ($CHCl_3$): ν = 3440, 3930, 2860 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.58 (1 H, t, J = 7 Hz, $=CHCH_2$), 4.62 (2 H, s, OCH_2O), 3.97 (2 H, s, CH_2OMOM), 3.65 (4 H, m, CH_2OH, CH_2OTBS), 3.35 (3 H, s, OCH_3), 2.61 (1 H, s, OH), 2.42–2.27 (4 H, m, $CH_2C=CHCH_2$), 0.87 [9 H, s, $SiC(CH_3)_3$], 0.02 [6 H, s, $Si(CH_3)_2$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.59, 129.15, 95.38, 72.21, 62.58, 61.22, 55.33, 32.26, 31.23, 25.83, 18.37, − 5.40.

MS: m/z = 243 (M^+ − MOMO).

HRMS: m/z = calc. for $C_{13}H_{27}O_2Si$: 243.1780; found: 243.1785 ± 0.0007.

(*Z*)-4-*tert*-Butyldiphenylsiloxybut-2-en-1-ol:

To a solution of *cis*-but-2-ene-1,4-diol (46.46 g, 528 mmol) and imidazole (7.2 g, 106 mmol) in THF (315 mL) at 0 °C was added *tert*-butyldiphenylsilyl chloride (TBDPSCl, 29 g, 106 mmol). After stirring for 19 h at r.t., the reaction mixture was diluted with CH_2Cl_2 (1800 mL), washed several times with water, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (hexanes/EtOAc, 4:1), yielding mono-protected alcohol (26.48 g, 77%, colourless oil).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.69 (6 H, m) and 7.42 (4 H, m) (2 × C_6H_5), 5.69 (2 H, m, C_2-H, C_3-H), 4.27 (2 H, m, C_4-H_2), 4.02 (2 H, m, C_1-H_2), 1.58 (1 H, m, OH), 1.06 [9 H, s, $SiC(CH_3)_3$].

(2*E*)-4-*tert*-Butyldiphenylsiloxybut-2-en-1-al (19):

To a solution of mono-protected alcohol (3.50 g, 10.7 mmol) (Scheme 4) and molecular sieves 3 Å (7.0 g) in CH_2Cl_2 (80 mL) was added pyridinium chlorochromate (3.47 g, 16.0 mmol). After stirring for 1.5 h at r.t., the reaction mixture was diluted with Et_2O (350 mL), filtered through silica gel and concentrated. The crude product was purified by flash chromatography (hexanes/EtOAc, 9:1), yielding aldehyde **19** (2.97 g, 85%, white crystals, mp 83–86 °C).

IR ($CHCl_3$): ν = 3010, 2960, 2935, 2860, 1685 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 9.62 (1 H, dd, J = 7.5, 0.5 Hz, C_1-H), 7.68 (6 H, m) and 7.45 (4 H, m) (2 × C_6H_5), 7.20–6.80 (2 H, m, C_2-H), C_3-H), 4.47 (2 H, dd, J = 3.0, 1.5 Hz, C_4-H_2), 1.10 [9 H, s, $SiC(CH_3)_3$].

(3*Z*,5*E*)-7-*tert*-Butyldiphenylsiloxyhepta-3,5-dien-1-ol (21):

To a solution of triphenyl(3-tetrahydroxypyranyloxy)propylphosphonium bromide (1.4 g, 2.9 mmol) in THF (6 mL) at 0 °C was added BuLi (1.6 mL, 2.56 mmol, 1.6 M in hexane). After stirring for 0.5 h, the temperature was lowered to − 78 °C and a solution of the aldehyde **19** (0.792 g, 2.3 mmol) in THF (25 mL) was added. The mixture was then allowed to warm to r.t. during 2 h, quenched with sat. aq NH_4Cl and extracted three times with Et_2O. The combined organic phases were washed with water, brine, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (hexanes/EtOAc, 20:1) yielding the two possible isomers (0.95 g, *Z,E*/*E,E*: 7:1, 97%) which were separated at the alcohol stage. To a solution of both isomers in *i*-PrOH (17 mL) was added pyridinium *p*-toluenesulfonate (PPTS, 60 mg, 0.24 mmol). After stirring for 1.5 h at 80 °C, the mixture was allowed to cool to r.t. and K_2CO_3 (5.5 mg, 0.4 mmol) was added to the solution. The mixture was then filtered through a fritted glass and concentrated. The crude product was purified by flash chromatography (hexanes/EtOAc, 9:1) yielding (*Z,E*)-alcohol-**21** (0.533 g, 67% colourless oil).

IR ($CHCl_3$): ν = 3615, 2960, 2930 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 7.68 (6 H, m) and 7.40 (4 H, m) (2 × C_6H_5), 6.58 (1 H, m, C_5-H), 6.17 (1 H, dd, J = 11, 11 Hz, C_4-H), 5.79 (1 H, dt, J = 15.0, 5.0 Hz, C_6-H), 5.43 (1 H, m, C_3-H), 4.27 (2 H, d, J = 5.0 Hz, C_7-H_2), 3.68 (2 H, t, J = 6.5 Hz, C_1-H_2), 2.44 (2 H, dt, J = 6.5, 6.5 Hz, C_2-H_2), 1.38 (1 H, m, OH), 1.07 [9 H, s, $SiC(CH_3)_3$].

MS: m/z = 309 [$M^+ - C(CH_3)_3$].

HRMS: m/z calc. for $C_{19}H_{21}O_2Si$: 309.1311; found: 309.1317 ± 0.0009.

(4*Z*,6*E*)-8-*tert*-Butyldiphenylsiloxy-1,1-bis(methoxycarbonyl)octa-4,6-diene (23):

To a solution of alcohol **21** (2.75 g, 7.5 mmol) and Et_3N (1.60 mL, 11.3 mmol) in CH_2Cl_2 (90 mL) at 0 °C was added $MeSO_2Cl$ (0.62 mL, 7.9 mmol). After stirring at 0 °C for 1 h, the mixture was poured into water, extracted with CH_2Cl_2 and the extracts were washed with brine, dried ($MgSO_4$), and concentrated, to give the crude mesylate **22** (3.23 g, yellowish oil). To a suspension of NaH (1.363 g, 34.0 mmol, 60% dispersion in mineral oil) in DMF (75 mL) were added dropwise dimethyl malonate (4.33 mL, 37.9 mmol) and, after the bubbling had stopped, a solution of the above crude mesylate in THF (75 mL), and KI (251 mg, 1.5 mmol). The reaction mixture was stirred for 15 h at 70–75 °C, then quenched with sat. aq NH_4Cl and extracted with hexanes/Et_2O (2:1). The combined organic layers were dried ($MgSO_4$), concentrated, and the residue was chromatographed (silica gel, hexanes/EtOAc, 4:1), yielding the alkylation product **23** (2.877 g, 80%, colourless oil).

IR (neat): $\nu = 3060, 3040, 1750, 1735\ cm^{-1}$.

^1H NMR (250 MHz, $CDCl_3$): $\delta = 7.65-7.71$ (4H, m, aromatic), 7.34–7.46 (6H, m, aromatic), 6.50 (1H, m, $J = 15, 11, \approx 1$ Hz, H-C_6), 6.05 (1H, app. t, $J = 11$ Hz, H-C_5), 5.76 (1H, dt, $J = 15.0, 5$ Hz, H-C_7), 5.34 (1H, dt, $J = 11, 7.5$ Hz, H-C_4), 4.25 (1H, m, H-C_8), 3.71 (6H, s, $2 \times CO_2CH_3$), 3.39 (1H, t, $J = 7.5$ Hz, H-C_1), 2.22 (2H, m, H-C_3), 2.00 (2H, m, H-C_2), 1.06 [9H, s, $SiC(CH_3)_3$].

^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 169.7, 135.5, 134.8, 133.7, 132.9, 129.6, 129.2, 127.7, 124.7, 63.3, 52.4, 50.9, 28.6, 26.8, 25.3, 19.2$.

MS: $m/z = 480\ (M^+)$, 423 ($M^+ - t$-Bu).

HRMS: m/z calc. for $C_{28}H_{36}O_5Si$: 480.2332; found: 480.2324 ± 0.0014.

(4*Z*,6*E*)-1,1-Bis(methoxycarbonyl)octa-4,6-dien-8-ol (24):
To a solution of silyl ether **23** (6.96 g, 14.5 mmol) and 2 drops of Et_3N in THF (150 mL) at r.t. was added Bu_4NF (15.97 mL, 16.0 mmol). After stirring for 5.5 h, the reaction mixture was quenched with sat. aq NH_4Cl and extracted three times with Et_2O. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (hexanes/EtOAc, 3:1) yielding alcohol **24** (2.5772 g, 74%, colourless oil).

IR ($CHCl_3$): $\nu = 3520, 3010, 2960, 1730\ cm^{-1}$.

^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.44$ (1H, m, C_6-H), 6.04 (1H, dd, $J = 11, 11$ Hz, C_5-H), 5.82 (1H, dt, $J = 15, 6$ Hz, C_7-H), 5.38 (1H, m, C_4-H), 4.19 (2H, d, $J = 8$ Hz, C_8-H_2), 3.72 (6H, s, $2 \times CO_2CH_3$), 3.38 (1H, t, $J = 7$ Hz, C_1-H), 2.21 (2H, dt, $J = 8, 8$ Hz, C_3-H_2), 1.98 (2H, dt, $J = 8, 8$ Hz, C_2-H_2), 1.82 (1H, s, OH).

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.7, 132.7, 129.9, 129.3, 125.9, 63.2, 52.5, 50.8, 30.9, 28.5$.

MS: $m/z = 224\ (M^+ - H_2O)$.

HRMS: m/z calc. for $C_{12}H_{16}O_4$: 224.1049; found: 224.1037 ± 0.0006.

(4*Z*,6*E*)-1,1-Bis(methoxycarbonyl)-8-pivaloyloxyocta-4,6-diene (25):
To a solution of alcohol **24** (2.568 g, 10.6 mmol) in CH_2Cl_2 (125 mL) at 0 °C were added Et_3N (4.43 mL, 31.8 mol, 4-dimethylaminopyridine (26 mg, 0.21 mmol) and trimethylacetyl chloride (3.92 mL, 31.8 mmol). After stirring for 2 h at 0 °C and 2.5 h at r.t., the reaction mixture was quenched with sat. aq NH_4Cl and extracted several times with CH_2Cl_2. The combined organic phases were washed with water and brine, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (hexanes/EtOAc, 4:1) yielding pivaloyl ester **25** (3.458 g, 96%, yellowish oil).

IR ($CHCl_3$): $\nu = 2960, 2875, 1735\ cm^{-1}$.

^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.46$ (1H, m, C_6-H), 6.03 (1H, dd, $J = 11, 11$ Hz, C_5-H), 5.72 (1H, dt, $J = 15, 10$ Hz, C_7-H), 5.40 (1H, m, C_4-H), 4.60 (2H, d, $J = 7.5$ Hz, C_8-H_2), 3.72 (6H, m, $2 \times CO_2CH_3$), 3.48 (1H, t, $J = 7$ Hz, C_1-H), 2.23 (2H, m, C_3-H_2), 2.00 (2H, m, C_2-H_2), 1.19 [9H, s, $(CH_3)_3CCO_2$].

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 178.3, 169.5, 130.9, 129.1, 128.4, 127.7, 64.6, 52.5, 50.8, 38.8, 28.5, 27.2, 25.4$.

MS: $m/z = 241\ [M^+ - COC(CH_3)_3]$.

HRMS: m/z calc. for $C_{12}H_{17}O_5$: 241.1076; found: 241.1074 ± 0.0007.

(3*E*,10*Z*,12*E*)-7,7-Bis(methoxycarbonyl)-4-(methoxymethoxy)methyl-14-pivaloyloxytetradeca-3,10,12-trien-1-ol (27):
To a solution of alcohol **17** (4.3259 g, 14.2 mmol) in CH_2Cl_2 (120 mL) at 0 °C were added Et_3N (2.79 mL, 19.9 mmol) and $MeSO_2Cl$ (1.29 mL, 16.1 mmol). After stirring for 3 h at 0 °C, the reaction mixture was quenched with water and extracted four times with CH_2Cl_2. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated to obtain the crude mesylate **18** (5.3347 g, 99%). To a suspension of NaH (0.47 g, 11.7 mmol, 60% in oil) in DMF (29 mL) was added malonate **25** (3.3173 g, 10.2 mmol). After stirring for 1 h at 40 °C, the above mesylate **18**, in THF (29 mL), and KI (1.10 g, 6.6 mmol) were added to the reaction mixture. After stirring for 6 h at 65 °C, the reaction was quenched with sat. aq NH_4Cl, extracted several times with petroleum ether (bp 65–110 °C)/Et_2O (2:1). The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (hexanes/EtOAc, 7:1) yielding a mixture of silyl ether **26** and some inseparable dimethyl malonate (3.685 g). To a solution of this mixture in THF (52 mL), were added one drop of Et_3N and Bu_4NF (6.33 mL, 6.32 mmol). After stirring for 6 h r.t., the reaction mixture was quenched with sat. aq NH_4Cl and extracted several times with Et_2O. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (hexanes/EtOAc, 1:1) yielding alcohol **27** (2.2845 g, 46% overall from **25**, colourless oil).

IR ($CHCl_3$): $\nu = 3470, 2960, 2880, 1730\ cm^{-1}$.

^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.50$ (1H, m, C_{12}-H), 6.00 (1H, dd, $J = 11$ Hz, C_{11}-H), 5.74 (1H, m, C_{13}-H), 5.45 (2H, m, C_{10}-H, C_3-H), 4.60 (4H, m, C_{14}-H_2, OCH_2O), 3.98 (2H, s, CH_2OMOM), 3.74 (6H, s, $2 \times CO_2CH_3$), 3.67 (2H, t, $J = 7.5$ Hz, C_1-H_2), 3.37 (3H, s, OCH_3), 2.33 (2H, dt, $J = 7$ Hz, C_2-H_2), 2.18–1.94 (8H, m, C_5-H_2, C_6-H_2, C_8-H_2, C_9-H_2), 1.61 (1H, s, OH), 1.20 [9H, s, $(CH_3)_3CCO_2$].

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 178.3, 171.8, 137.9, 131.6, 128.7, 128.3, 127.5, 125.6, 95.6, 71.3, 64.8, 62.1, 57.4, 55.4, 52.4, 38.7, 32.7, 31.8, 27.2, 23.2, 22.8$.

MS: $m/z = -466\ (M^+ - CH_3OH)$, 436 ($M^+ - MOM$).

HRMS: m/z calc. for $C_{25}H_{38}O_8$: 466.2566; found: 466.2557 ± 0.0014.

(4*E*,11*Z*,13*E*)-5-(Methoxymethoxy)methyl-15-pivaloyloxy-1,1,8,8-tetrakis(methoxycarbonyl)pentadeca-4,11,13-triene (29):
To a solution of alcohol **27** (2.2845 g, 4.59 mmol) in CH_2Cl_2 (54 mL) at 0 °C were added, Et_3N (0.9 mL, 6.43 mmol) and $MeSO_2Cl$ (0.39 mL, 5.05 mmol). After stirring for 3 h, the reaction mixture was quenched with water and extracted four times with CH_2Cl_2. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated, yielding crude mesylate **28** (2.6430 g, 100%). To a suspension of NaH (0.89 g, 22 mmol, 60% suspension in oil) in DMF (21 mL) was added dimethyl malonate (2.73 mL, 23.9 mmol). After stirring for 0.5 h at 40 °C, the crude mesylate **28** in THF (21 mL), and KI (0.4 g) were added to the reaction mixture. After stirring for 9 h at 70 °C, the mixture was quenched with sat. aq NH_4Cl and extracted four times with petroleum ether (bp 65–110 °C)/Et_2O (2:1). The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (hexanes/EtOAc, 3:1) yielding compound **29** (2.6043 g, 93%, colourless oil).

IR ($CHCl_3$): $\nu = 2955, 2880, 1735\ cm^{-1}$.

^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.49$ (1H, m, C_{13}-H), 5.98 (1H, dd, $J = 11, 11$ Hz, C_{12}-H), 5.73 (1H, m, C_{14}-H), 5.41 (2H, m, C_{11}-H), 4.59 (4H, m, C_{15}-H_2, OCH_2O), 3.94 (2H, s, CH_2OMOM), 3.74 (12H, m, $4 \times CO_2CH_3$), 3.35 (4H, m, OCH_3, C_1-H), 2.18–1.90 (12H, m, C_2-H_2, C_3-H_7, C_6-H_2, C_7-H_2, C_9-H_2, C_{10}-H_2), 1.19 [9H, s, $(CH_3)_3CCO_2$].

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 178.3, 171.9, 169.9, 137.1, 131.8, 128.8, 128.5, 127.8, 127.7, 95.6, 71.2, 65.0, 57.4, 55.4, 52.6, 51.1, 39.0, 32.9, 32.0, 28.7, 27.8, 25.2, 23.2, 23.0$.

MS: $m/z = 581\ (M^+ - OCH_3)$.

HRMS: m/z calc. for $C_{30}H_{44}O_{11}$: 581.2960; found: 581.2956 ± 0.0023.

(4*E*,11*Z*,13*E*)-5-(Methoxymethoxy)methyl-1,1,8,8-tetrakis(methoxycarbonyl)pentadeca-4,11,13-trien-15-ol (30):
To a solution of pivaloyl ester **29** (34.3 mg, 0.06 mmol) in MeOH (0.5 mL) was added a solution of NaOMe in MeOH (1.7 mL, 0.1 M, 0.18 mmol). After stirring for 2 h at r.t., the reaction mixture was quenched with sat. aq NH_4Cl, extracted several times with Et_2O and once with EtOAc. The combined organic phases were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (hexanes/EtOAc, 1:1) yielding alcohol **30** (23.3 mg, 79% colourless oil).

IR ($CHCl_3$): $\nu = 3540, 2955, 1735\ cm^{-1}$.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.54 (1 H, m, C_{13}-H), 5.97 (1 H, t, J = 9 Hz, C_{12}-H), 5.41 (3 H, m, C_{14}-H, C_{11}-H, C_8-H), 4.52 (2 H, m, OCH_2O), 3.87 (2 H, m, CH_2OMOM), 3.71 (2 H, m, C_{15}-H_2), 3.70 (13 H, m, 4 × CO_2CH_3 and C_1-H), 3.31 (3 H, m, OCH_3), 1.78–2.11 (13 H, m, HO, C_2-H_2, C_3-H_2, C_6-H_2, C_7-H_2, C_9-H_2, C_{10}-H_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.7, 169.7, 136.4, 132.9, 130.4, 128.6, 127.8, 125.6, 95.4, 71.0, 63.2, 57.3, 55.4, 52.5, 50.9, 32.3, 31.2, 28.5, 25.0, 23.0, 22.6.

MS: m/z = 510 ($M^+ - H_2O$).

HRMS: m/z calc. for $C_{26}H_{38}O_{10}$: 510.2465; found: 510.2471 ± 0.0015.

(4*E*,11*Z*,13*E*)-5-(Methoxymethoxy)methyl-1,1,8,8-tetrakis(methoxycarbonyl)cyclopentadeca-4,11,13-triene (32):

$MeSO_2Cl$ (0.26 mL, 3.30 mmol) was added to a cooled (0 °C) solution of alcohol **30** (1.42 g, 2.72 mmol), 2,4,6-collidine (0.45 mL, 3.40 mmol) and LiCl (0.14 g, 3.13 mmol, vacuum dried with a heat gun) in DMF (7 mL). The reaction mixture was stirred at 0 °C for 4 h (a thick white precipitate appeared after 10 min). The reaction mixture was then poured into ice/water (75 mL) and extracted with Et_2O/petroleum ether (bp 65–110 °C) (1:1, 4 × 150 mL). The combined organic layers were successively washed with aqueous sat. $Cu(NO_3)_2$ (100 mL) and brine (2 × 50 mL), dried ($MgSO_4$), filtered over a fritted glass wih a small pad of silica gel, affording the unstable allylic chloride **31** (1.40 g, 95%, yellowish oil). This material was used without delay for the following macrocyclization.

To a vigorously stirred suspension of Cs_2CO_3 (5.00 g, 15.36 mol, vacuum dried with a heat gun) in DMF/THF (500 mL: 500 mL) at 75 °C was slowly added the above allylic chloride **31** in DMF/THF (5 mL: 5 mL) via syringe pump within 13 h (final concentration: 3×10^{-3} M). After additional stirring for 2 h, the reaction mixture was allowed to cool to r.t., filtered through a fritted glass and concentrated (the rotary evaporator was connected to an oil pump for removing DMF). The residue was purified by flash chromatography (25% EtOAc in hexanes), giving pure TCC macrocyclic triene **32** (1.09 g, 83%, mossy solid).

IR ($CHCl_3$): ν = 2950, 1735 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.54 (1 H, dd, J = 15.0 Hz, 10.5 Hz, C_{13}-H), 5.93 (1 H, dd, J = 10.5 Hz, 10.5 Hz, C_{12}-H), 5.50–5.30 (3 H, m, C_{11}-H, C_{14}-H, C_5-H), 4.50 (2 H, s, OCH_2O), 3.81 (2 H, s, CH_2OMOM), 3.68 (6 H, s, 2 × CO_2CH_3), 3.67 (6 H, s, 2 × CO_2CH_3), 3.28 (3 H, s, OCH_3), 2.68 (2 H, d, J = 7.5 Hz, C_9-H_2), 2.10–1.70 (12 H, m, C_2-H_2, C_3-H_2, C_6-H_2, C_7-H_2, C_{14}-H_2, C_{15}-H_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.57, 171.34, 135.69, 130.51, 129.73, 127.59, 127.33, 127.07, 95.18, 70.53, 57.20, 56.94, 55.13, 52.54, 52.42, 35.14, 30.73, 30.29, 28.86, 22.23, 21.76, 21.63.

MS: m/z = 510 (M^+), 478 ($M^+ - CH_3OH$), 448 (M^+ – MOMOH).

HRMS: m/z calc. for $C_{26}H_{38}O_{10}$: 510.2465; found: 510.2461 ± 0.0015.

(4*E*,11*Z*,13*E*)-5-Hydroxymethyl-1,1,8,8-tetrakis(methoxycarbonyl)-cyclopentadeca-4,11,13-triene (33):

A 0.5:1:8.5 solution of conc. HCl/H_2O/MeOH (40 mL) was added to the macrocycle **32** (0.7433 g, 1.46 mmol). After stirring at 65 °C for 2 h, the reaction mixture was quenched with sat. aq $NaHCO_3$, extracted three times with Et_2O and once with EtOAc. The combined organic phases were dried ($MgSO_4$) and concentrated, yielding the pure alcohol **33** (680 mg, ~ 100%, white mossy solid mp 145–150 °C).

IR ($CHCl_3$): ν = 3600, 3545, 2955, 2870, 1725 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.54 (1 H, d, J = 15.0 Hz, 10.5 Hz, C_{13}-H), 5.90 (1 H, dd, J = 10.5, 10.5 Hz, C_{12}-H), 5.45–5.25 (3 H, m, C_{11}-H, C_{14}-H, C_5-H), 3.89 (2 H, s, CH_2OH), 3.66 (6 H, s, 2 × CO_2CH_3), 3.65 (6 H, s, 2 × CO_2CH_3), 2.66 (2 H, d, J = 7.5 Hz, C_9-H_2), 2.15–1.65 (13 H, m, C_2-H_2, C_3-H_2, C_6-H_2, C_7-H_2, C_{14}-H_2, C_{15}-H_2, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.59, 171.28, 138.93, 130.51, 129.65, 127.21, 126.95, 124.69, 66.08, 57.18, 56.88, 52.48 (br), 35.03, 30.74, 30.21, 29.40, 28.80, 21.95, 21.60.

MS: m/z = 466 (M^+), 448 ($M^+ - H_2O$).

HRMS: m/z calc. for $C_{24}H_{34}O_9$: 466.2203; found: 466.2196 ± 0.0014.

(4*E*,11*Z*,13*E*)-5-Formyl-1,1,8,8-tetrakis(methoxycarbonyl)cyclopentadeca-4,11,13-triene (7):

To a solution of alcohol **33** (350 mg, 0.75 mmol) in CH_2Cl_2 (7 mL) was added the Dess–Martin periodinane (0.38 g, 0.9 mmol). After stirring at r.t. for 1 h, the reaction mixture was diluted with Et_2O (25 mL) and quenched with sat. aq $NaHCO_3$. Pentahydrated $Na_2S_2O_3 \cdot 5H_2O$ (2.4 g, 9.7 mmol) was added to the mixture which was stirred for 15 min. The organic phase was washed with sat. aq $NaHCO_3$, water, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (hexanes/EtOAc, 3:1) yielding aldehyde **7** (348 mg, ~ 100%, white powder (mp 166–169 °C)). A sample could be recrystallized (CH_2Cl_2/hexanes), giving monocrystals from which a suitable one was submitted to X-ray diffraction analysis, confirming the structure of **7**.

IR ($CHCl_3$): ν = 2990–2800, 1730, 1680, 1640 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.31 (1 H, s, CHO), 6.59 (1 H, dd, J = 15.0, 10.5 Hz, C_{13}-H), 6.48 (1 H, t, J = 7.5 Hz, C_5-H), 5.97 (1 H, dd, J = 10.5, 10.5 Hz, C_{12}-H), 5.46 (2 H, m, C_{11}-H, C_{14}-H), 3.77 (6 H, s, 2 × CO_2CH_3), 3.76 (6 H, s, 2 × CO_2CH_3), 2.77 (2 H, d, J = 7.7 Hz, C_9-H_2), 2.27 (2 H, dt, J = 7.5, 7.5 Hz, C_6-H_2), 2.10–1.85 (10 H, m, C_2-H_2, C_3-H_2, C_7-H_2, C_{14}-H_2, C_{15}-H_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.04, 171.59, 171.14, 152.12, 143.30, 131.02, 129.86, 127.21, 127.02, 57.01, 56.82, 52.67, 35.39, 30.29, 29.77, 29.38, 23.05, 21.60, 18.25.

MS: m/z = 464 (M^+), 449 ($M^+ - CH_3$), 446 ($M^+ - H_2O$).

HRMS: m/z calc. for $C_{24}H_{32}O_9$: 464.2086; found: 464.2080 ± 0.0014.

***rac*-(1*S*,2*S*,7*R*,10*R*)-(8*Z*)-1-Formyl-5,5,13,13-tetrakis(methoxycarbonyl)tricyclo[8.5.0.0^{2,7}]pentadec-8-ene (8):**

To a solution of the formyl-substituted macrocycle **7** (0.127 g, 0.27 mmol) in toluene (5 mL) was added $BF_3 \cdot OEt_2$ (0.20 mL, 1.64 mmol). After stirring for 30 h at 60 °C, the reaction mixture was diluted with Et_2O (15 mL), poured into aqueous sat. $NaHCO_3$ (10 mL) and extracted three times with Et_2O. The combined organic phases were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (hexanes/EtOAc, 4:1) yielding the tricyclic product **8** (0.104 g, 82%, colourless oil).

IR ($CHCl_3$): ν = 2990–2800, 1730 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.50 (1 H, s, CHO), 5.54 (1 H, ddd, J = 10.0, 2.0, 2.0 Hz, CH=CH), 5.39 (1 H, ddd, J = 10.0, 2.0, 2.0 Hz, CH=CH), 3.76 (3 H, s, CO_2CH_3), 3.68 (6 H, s, 2 × CO_2CH_3), 3.66 (3 H, s, CO_2CH_3), 2.97 (1 H, br s, C_{10}-H), 2.45 (2 H, m) and 2.32 (1 H, dd, J = 14.0, 6.5 Hz) and 2.13 (1 H, dd, J = 15.0, 8.0 Hz) and 1.93 (2 H, dd, J = 15.0, 9.0 Hz) and 1.80 (2 H, dd, J = 15.0, 10.0 Hz) and 1.78–1.35 (8 H, m) (C_2-H, C_3-H_2, C_4-H_2, C_6-H_2, C_7-H, C_{11}-H_2, C_{12}-H_2, C_{14}-H_2, C_{15}-H_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.11, 172.90, 172.67, 172.13, 171.16, 131.04, 129.87, 57.15, 54.89, 54.71, 52.70, 52.56, 44.80, 39.69, 37.42, 32.57, 31.22, 27.55, 26.49, 26.06, 22.74, 19.76.

MS: m/z = 464 (M^+), 446 ($M^+ - H_2O$), 435 (M^+ – CHO).

HRMS: m/z calc. for $C_{24}H_{32}O_9$: 464.2046; found: 464.2035 ± 0.0014.

(4*E*,10*E*,12*Z*)-5-Hydroxymethyl-1,1,8,8-tetrakis(methoxycarbonyl)-cyclopentadeca-4,10,12-triene (37):

TCC macrocyclic triene **32** (24.0 mg, 0.047 mmol) was heated in a vacuum sealed Pyrex tube for 3 h at 200 °C. The tube was opened at r.t. and the content transferred to a flask and concentrated, yielding an inseparable 1:1 mixture of **32** and **36** (~ 24 mg, ~ 100%). This mixture was treated following the procedure employed for the preparation of **33** from pure **32**, giving pure **33** (8.6 mg, 40%) and pure CTC macrocyclic trienol **37** (8.5 mg, 39%,

colourless oil) after preparative TLC on silica gel (20 × 20 cm, 0.50 mm thickness, eluent: 40% EtOAc in hexanes, 8 elutions, desorption with EtOAc).

IR (neat): ν = 3450 (br), 2955, 1730 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.53 (1 H, dd, J = 15.0 Hz, 10.5 Hz, C_{11}-H), 5.99 (1 H, dd, J = 10.5 Hz, 10.5 Hz, C_{12}-H), 5.48 (2 H, m, C_{10}-H, C_{13}-H), 5.37 (1 H, t, J = 7.5 Hz, C_4-H), 3.98 (2 H, s, CH_2OH), 3.74 (6 H, s, 2 × CO_2CH_3), 3.71 (6 H, s, 2 × CO_2CH_3), 2.71 (2 H, d, J = 8.0 Hz, C_9-H_2), 2.10–1.80 (12 H, m, C_1-H_2, C_2-H, C_6-H_2, C_7-H_2, C_{14}-H_2, C_{15}-H_2), 1.60 (1 H, br s, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.81, 171.33, 138.86, 130.56, 129.92, 127.73, 127.20, 125.26, 66.84, 57.58, 56.75, 52.74, 52.61, 34.43, 30.87, 30.29, 29.71, 22.52, 22.33, 22.00.

MS: m/z = 466 (M^+), 448 ($M^+ - H_2O$).

HRMS: m/z calc. for $C_{24}H_{34}O_9$: 466.2203; found: 466.2196 ± 0.0014.

(4*E*,10*E*,12*Z*)-5-Formyl-1,1,8,8-tetrakis(methoxycarbonyl)cyclopentadeca-4,10,12-triene (34):
Using the procedure employed for the preparation of **7** from **33**, CTC macrocyclic trienol **37** (7.4 mg, 0.016 mmol) was oxidized (reaction time: 1 h) to give pure aldehyde **34** (6.3 mg, 85%, white mossy solid).

IR (neat): ν = 2955, 2850, 2720, 1730, 1685 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 9.34 (1 H, s, CHO), 6.51 (1 H, dd, J = 15.5, 10.5 Hz, C_{11}-H), 6.43 (1 H, t, J = 7.5 Hz, C_4-H), 5.99 (1 H, dd, J = 10.5, 10.5 Hz, C_{12}-H), 5.47 (1 H, br dt, J = 10.5, 8.0 Hz, C_{13}-H), 5.38 (1 H, dt, J = 15.5, 8.0 Hz, C_{10}-H), 3.79 (6 H, s, 2 × CO_2CH_3), 3.74 (6 H, 2 × CO_2CH_3), 2.75 (2 H, d, J = 8.0 Hz, C_9-H_2), 2.38–1.72 (12 H, m, C_{11}-H_2, C_2-H_2, C_7-H_2, C_8-H_2, C_{14}-H_2, C_{15}-H_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.82, 171.47, 171.14, 152.37, 142.99, 130.25, 129.73, 127.72, 127.28, 57.14, 56.58, 52.77 (br), 34.36, 30.89, 29.71, 29.32, 23.95, 22.01, 17.87.

MS: m/z = 464 (M^+), 446 ($M^+ - H_2O$), 433 ($M^+ - CH_3O$).

HRMS: m/z calc. for $C_{24}H_{32}O_9$: 464.2047; found: 464.2042 ± 0.0014.

Pyrolysis of **7**: TCC Macrocyclic triene **7** (1.0 mg, 0.0022 mmol) was heated in a vacuum sealed Pyrex tube for 1 h at 200 °C. The tube was opened at r.t. and the content transferred to a flask and concentrated, yielding a ~1 mg 39:38:11:12 crude mixture of **7/34/8/35**. Purification of this material by preparative TLC on silica gel (10 × 10 cm, 0.25 mm thickness, eluent: 50% EtOAc in hexanes, desorption with EtOAc) gave a mixture of isomeric macrocycles **7** and **34** (< 1 mg) and a mixture of inseparable tricyclic products **8** and *rac*-(1*R*,2*R*,7*R*,10*R*)-(8*Z*)-2-formyl-5,5,13,13-tetrakis(methoxycarbonyl)tricyclo[8.5.0.0^{2,7}]pentadec-8-ene **35**:**8**/**35**:

^1H NMR (250 MHz, $CDCl_3$): δ = 9.50 [1 H, s, CHO **(8)**], 9.34 [1 H, d, J = 1 Hz, CHO **(35)**], 5.70–5.66 [2 H, m, C_8-H and C_9-H **(35)**], 5.55 and 5.41 [parts A and B of a XABY system, $J_{A,B}$ = 10 Hz, C_8-H and C_9-H **(8)**], 3.76 [6 H, s, CO_2CH_3 **(8)**, CO_2CH_3 **(35)**], 3.73 [3 H, s, CO_2CH_3 **(35)**], 3.70 [3 H, s, CO_2CH_3 **(35)**], 3.68 [6 H, s, 2 × CO_2CH_3 **(8)**], 3.66 [3 H, s, CO_2CH_3 **(8)**], 2.98 [1 H, m, C_{10}-H **(8)**], 2.80–1.10 [m, 16 H **(8)**, 17 H **(35)**].

***rac*-(1*S*,2*S*,7*R*,10*R*)-(8*Z*)-1-*p*-Bromobenzoyloxymethyl-5,5,13,13-tetrakis(methoxycarbonyl)tricyclo[8.5.0.0^{2,7}]pentadec-8-ene (8′):**
To a cooled solution (0 °C) of formyl tricycle **8** (0.051 g, 0.11 mmol) in MeOH/THF (1 mL/1 mL) was added $NaBH_4$ (5.0 mg, 0.11 mmol) and the solution was stirred 1 h. A solution of aqueous sat. NH_4Cl (10 mL) was added and the resulting mixture was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated to give the crude neopentylic alcohol (0.051 g, 98%). This compound was dissolved in CH_2Cl_2 and the solution was cooled to 0 °C. Et_3N (40 µL, 0.25 mmol), a few crystals of 4-dimethylaminopyridine and *p*-bromobenzoyl chloride (50 mg, 0.22 mmol) were successively added and the mixture was allowed to warm to r.t. and stirred for 2.5 h. A solution of aqueous sat. NH_4Cl (10 mL) was added and the mixture was extracted with CH_2Cl_2 (4 × 15 mL). The combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated. The residue was purified by preparative TLC on silica gel (20 × 20 cm, 0.5 mm thickness, eluent: 35% EtOAc in hexanes, extraction with EtOAc), yielding the *p*-bromobenzoyl derivative **8′** (0.063 g, 88%, mossy solid). This compound was recrystallized from MeOH, giving the monocrystals (mp 123–126 °C) from which a suitable one was submitted to X-ray diffraction analysis, confirming the structure of this derivative and hence that of **8**.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.84 (2 H, m) and 7.59 (2 H, m) (*p*-Br-Ar), 5.56 (1 H, br d, J = 10.0 Hz, CH=CH), 5.35 (1 H, br d, J = 10.0 Hz, CH=CH), 4.39 (1 H, d, J = 11.5 Hz, HCHOCOAr), 4.13 (1 H, d, J = 11.5 Hz, HCHOCOAr), 3.77 (3 H, s, CO_2CH_3), 3.68 (9 H, s, 3 × CO_2CH_3), 2.50–1.25 (17 H, m, C_2-H, C_3-H_2, C_4-H_2, C_7-H, C_{10}-H, C_{11}-H_2, C_{12}-H_2, C_{14}-H_2, C_{15}-H_2).

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(18) The use of more than 4 equiv of $BF_3 \cdot OEt_2$ was necessary, since the β-diester moieties of our model substrate could form strong chelates. Other Lewis acids were tried, but showed lower reactivity and/or yields: a) 3 equiv $SnCl_4$, toluene, 110 °C, 12 h: 61 %; b) 6 equiv $BF_3 \cdot OEt_2$, CH_2Cl_2, 40 °C, 30 h: 77 %.
(19) The *p*-bromobenzoyl derivative **8'** was obtained through esterification of the alcohol resulting from reduction of the bridgehead formyl group in **8** with $NaBH_4$. X-ray data will be submitted as a communication to *Acta Cryst.*