Multiple Asymmetric Cyclopropanation: Synthesis and X-Ray Crystallographic Studies of a Prototype Coronane and all *anti-trans*-1,15-Quinquecyclopropanedimethanol

Anthony G. M. Barrett,* Tim Gross, Dieter Hamprecht, Mitsuru Ohkubo, Andrew J.P. White, David J. Williams
Department of Chemistry, Imperial College of Science, Technology and Medicine, London, SW7 2AY, U.K.
Fax +44(171)5945805; E-mail: m.stow@ic.ac.uk
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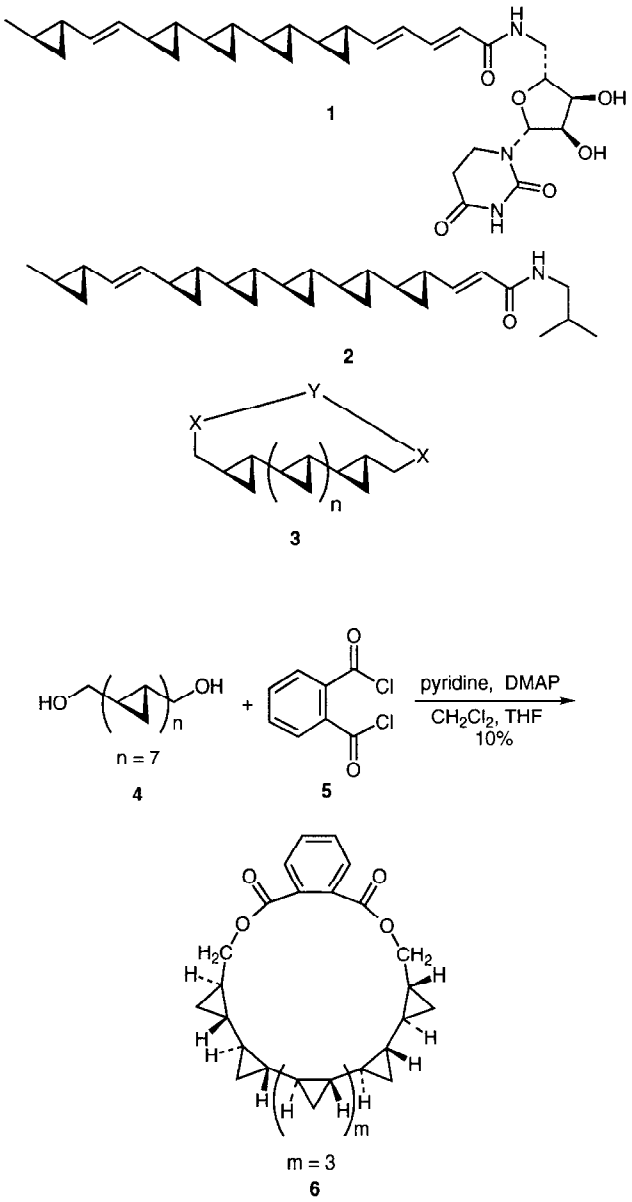
Abstract: Stepwise macrocyclization of the all *syn-trans*-1,15-quinquecyclopropanedimethanol (**9**) and the all *syn-trans*-1,21-septecyclopropanedimethanol (**4**) with phthalic acid gave the corresponding coronanes **16** and **6**, dilactones with 18- and 22-membered rings respectively. The structure of **16** was confirmed by an X-ray crystallographic study. Bidirectional asymmetric cyclopropanation of dienediol **17** was used to elaborate the corresponding all *anti-trans*-1,15-quinquecyclopropanedimethanol **21** which was shown by X-ray crystallography to adopt an extended rigid-rod conformation.

Key words: FR-900848, coronanes, multiple cyclopropane systems, asymmetric cyclopropanation

In 1990, Yoshida et al. in the Fujisawa laboratories in Japan, reported the isolation and partial structural elucidation of FR-900848 (**1**) from a fermentation broth of *Streptoverticillium fervens*.[1] The full stereochemical assignment of this substance was proven both by degradation[2] and total synthesis.[3] FR-900848 (**1**) shows potent, selective activity against filamentous fungi such as *Aspergillus niger, Mucor rouxianus, Aureobasidium pullans*, various *Trichophyton sp., etc*.[1] The fatty acid side chain of FR-900848 (**1**) bears a striking resemblance to the side chain of U-106305 (**2**) a cholesteryl ester transfer protein inhibitor isolated from *Streptomyces sp*. by workers at Upjohn Laboratories[4] and also first synthesized in our laboratories.[5] Both fatty acid side chains of FR-900848 (**1**) and U-106305 (**2**) contain all *syn-trans*-disubstituted quarter- and quinquecyclopropane systems which undoubtedly conformationally restrict these lipophilic domains. Indeed, we have shown by extensive crystallography that all-*syn-trans*-disubstituted cyclopropane oligomers with 3–7 rings are helical, at least in the solid state.[2,5] We questioned whether the preference for an extended helical structure was principally dictated by crystal packing since examination of molecular models shows considerable conformational mobility. Indeed we were intrigued by the possibility of utilizing an all *syn-trans*-cyclopropene oligomer to conformationally restrict a macrocyclic ring system as generically depicted by structure **3** and this would clearly not be possible with an extended helical conformation. In addition, we sought to examine the conformations of all *anti-trans*-cyclopropene oligomers with the expectation of finding a preference for an extended rigid-rod conformation. Herein we report the synthesis and full characterization of an all *anti-trans*-1,15-quinquecyclopropanedimethanol and the first synthesis of two coronanes as prototypes for a novel class of macrocyclic compounds.

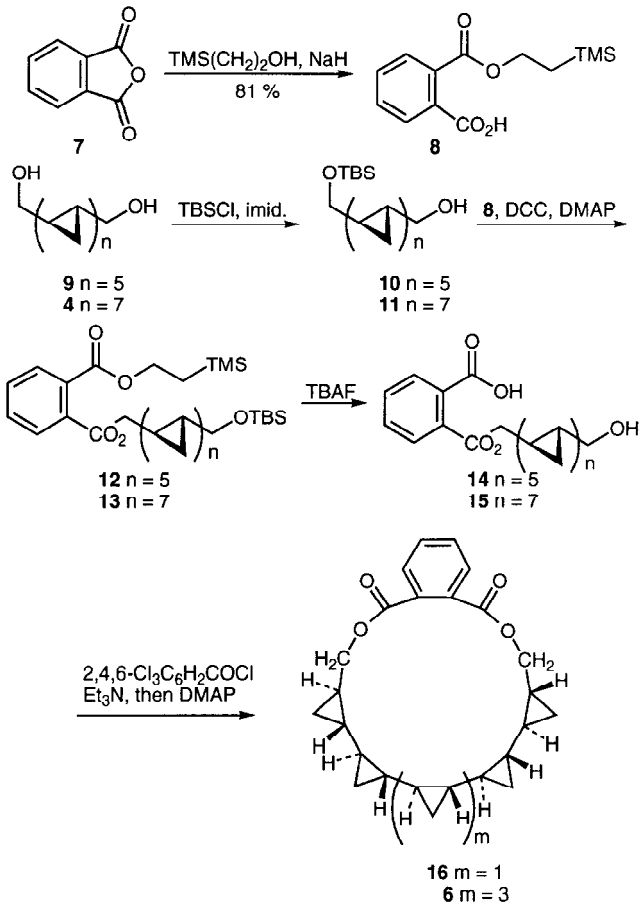
Condensation of phthaloyl chloride with the septecyclopropanedimethanol (**4**)[5b] in the presence of pyridine and DMAP under high dilution conditions gave the corresponding coronane[6] **6** in poor yield (10%) (Scheme 1). Alternatively, the same macrocyclic dilactone was prepared in superior yield using a stepwise approach (Scheme 2). Thus Steglich-esterification[7] of (2-trimethyl-



Scheme 1

silylethyl) phthalate (**8**) with alcohol **11** gave the unsymmetrical diester **13**. Following double deprotection, the resultant hydroxy acid was macrocyclized under Yamaguchi conditions[8] to provide **6** in superior yield (67% overall). The stepwise approach was extended to synthesis of the corresponding 18-membered coronane **16** starting from 1,15-quinquecyclopropanedimethanol **9**[5b] which was also obtained in excellent yield (74%).

The coronane **6** showed a remarkable affinity for the solvent diethyl ether. After dissolving a sample in this solvent and drying under high vacuum for 2 hours, it still contained 0.5 equivalent of diethyl ether as revealed by NMR spectroscopy. ES-MS analysis of this compound showed a weak $[M+H]^+$ peak and an intense $[M+H_2O]^+$ peak. No complexes were observed with Et_2O, benzene, EtOH, CH_2Cl_2 or MeCN by mass spectrometry, however, upon addition of methylamine in aqueous THF, the ES-MS spectrum displayed an intense $[M+MeNH_3]^+$ peak. In the same way, the ES-MS spectrum of a mixture of 4-(dimethylamino)pyridine and macrocycle **6** showed an intense $[M+HDMAP]^+$ ion. In both cases the macrocycle appeared intact after these observations in TLC control experiments thus excluding the possibility of covalent adducts. It is possible that the interactions are host-guest in nature but full characterization must await further studies.



Scheme 2

Much to our delight, the smaller coronane **16** was obtained as a crystalline solid suitable for an X-ray crystallographic study. The crystals were found to contain two independent macrocycles in the asymmetric unit.[9,10] Both macrocycles have essentially the same "chaise-longue" like conformation, Figure 1. One of the molecules exhibits a 65:35 disorder involving a ca. 180° "flip" about bond **e** of the orthogonally oriented ester group. In both molecules the other ester group is essentially coplanar with the aromatic ring (ca. 3° rotation about bond **f**). Four of the five cyclopropyl rings have all-*anti* H–C–C–H linkages between them (**a** to **c**) whereas that to the fifth is *gauche* (bond **d**), a consequence of satisfying the macrocyclic ring constraints. The observed conformation clearly indicates that for a system containing cyclopropyl rings all of the same chirality it should be possible to construct a relatively unstrained all-*anti* cyclocyclopropane containing just *six* cyclopropane units.

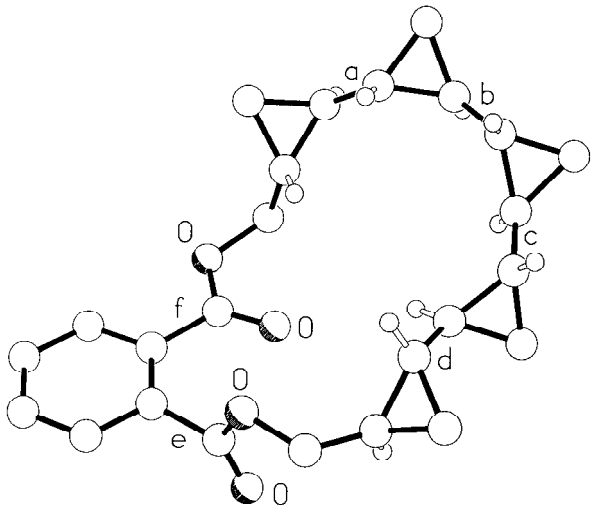
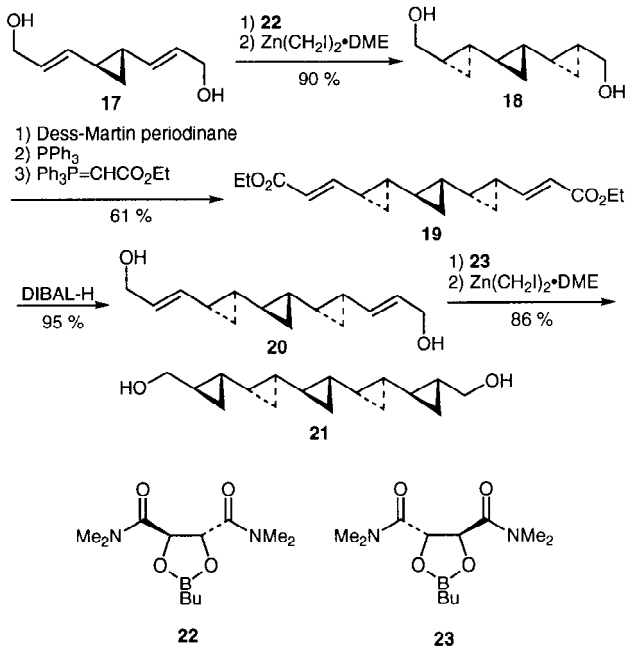


Figure 1. Molecular Structure of One of the Macrocyclic Rings Present in the Crystals of **16**

Secondly, we have examined the synthesis of a representative cyclopropene oligomer with the all *anti-trans* stereochemistry. We expected such compounds to adopt an extended rigid-rod conformation rather than the helix of the all *syn-trans* stereoisomers. Following our standard bidirectional methodology[3,5] dienediol **17**[5b] was cyclopropanated using Charette conditions[11] utilizing the boron auxiliary **22** to produce the all *anti*-tercyclopropanedimethanol **18**[12,13] (90%). Sequential Dess–Martin oxidation,[14] Wittig homologation, and DIBAl-H reduction gave dienediol **20** which was cyclopropanated in the presence of auxiliary **23** to yield the all *anti-trans*-quinquecyclopropanedimethanol **21** (Scheme 3). A single crystal X-ray analysis[10,15] shows the molecule to adopt an extended rod-like conformation with the methylene portions of the *syn* cyclopropanes eclipsing, *i.e.* the H–C–C–H linkages **a** to **d** in Figure 2 are all-*anti*. It is interesting to note that the change from a system containing linked cyclopropyl units all of the same chirality to one of alternat-

ing chiralities, but retaining an all-*trans* geometry for the linkages, produces a change from a helical to a linear conformation for the product. Molecules of **21** exhibit a lamella packing motif, the ends of adjacent chains being cross-linked by O–H···O hydrogen bonds.



Scheme 3

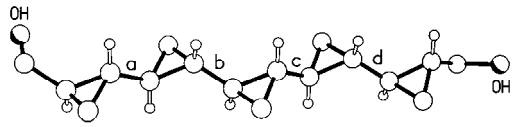


Figure 2. Molecular Structure of **21**

Further studies on related multiple cyclopropane systems will be reported in due course.

All reactions were carried out in an atmosphere of dry N_2 or argon at r.t. unless otherwise stated. Reaction temperatures other than r.t. were recorded as bath temperatures unless otherwise stated. Chromatography was carried out on BDH silica 60, 230-400 mesh ASTM, using flash techniques[16] (eluants are quoted in parenthesis). Analytical TLC was performed on Merck precoated silica 60 F_{254} plates. Petroleum ether, bp 40–60 °C (hexanes) used as a chromatography eluant was distilled; all other chromatography eluants were BDH GPR grade and undistilled. The following reaction solvents/reagents were purified by distillation: benzene (PhH) (P_2O_5, N_2), CH_2Cl_2 (CaH_2, N_2), 1,2-dimethoxyethane (DME) (CaH_2, N_2), pyridine (CaH_2, N_2), and THF (Ph_2CO/K, N_2). All other organic solvents and reagents were obtained from commercial sources and used without further purification. Organic extracts were concentrated using a rotary evaporator at ≤ 40 °C bath temperature. Involatile oils and solids were vacuum dried at < 2 Torr. Optical rotations were measured at 25 °C.

2-(Trimethylsilyl)ethyl Hydrogen Phthalate (8):
2-(Trimethylsilyl)ethanol (0.58 mL, 4.05 mmol) was added to NaH (60 % in oil, 120 mg, 4.05 mmol) in THF (5.0 mL), the mixture was stirred for 3 h when a solution of anhydride **7** (500 mg, 3.38 mmol) in THF (5.0 mL) was added and further stirred overnight. The mixture was quenched with 1 N HCl and extracted with EtOAc, the extract was evaporated and chromatographed (hexanes/EtOAc, 1:1) to give **8** (730 mg, 81%) as a colorless oil which was used directly without further purification; R_f 0.43 (CH_2Cl_2/MeOH, 9:1).
IR (film): ν = 2955, 1727, 1704, 1412, 1289, 1252, 1125, 1073, 933, 857 839 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.13 (br, 1H), 7.93 (dd, J = 1.8, 7.0 Hz, 1 H), 7.72 (dd, J = 1.8, 7.0 Hz, 1 H), 7.69–7.28 (m, 2 H), 4.48–4.42 (m, 2 H), 1.17–1.11 (m, 2 H), 0.07 (s, 9H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.1, 168.3, 133.6, 132.1, 130.8, 130.2, 129.9, 128.8, 64.4, 17.1, –1.5.
MS (CI, NH_4^+): m/z = 284 $(M+NH_4)^+$, 267 $(M+H)^+$.

(1*R*,3*S*,4*R*,6*S*,7*R*,9*S*,10*R*,12*R*,13*S*,15*R*,16*S*,18*R*,19*S*,21*R*)-1-[(*tert*-Butyldimethylsilyloxy)methyl]-21-septecyclopropanemethanol (11):
To diol **4** (81 mg, 0.24 mmol) in CH_2Cl_2 (5 mL) were added imidazole (18 mg, 0.26 mmol) and *t*-$BuMe_2SiCl$ (37 mg, 0.24 mmol). After stirring for 1.5 h, H_2O was added, and the mixture extracted with EtOAc (3 × 10 mL). The extract was dried (Na_2SO_4), rotary evaporated, and chromatographed (hexanes/EtOAc, 5:1 to 0:1) to give recovered diol **4** (25 mg, 30%) and ether **11** (57 mg, 52%) as a colorless oil; R_f 0.51 (hexane/EtOAc, 2:1); $[\alpha]_D$ –177.7 (c =1.1, $CHCl_3$).
IR (film): ν = 3064, 2996, 1470, 1255, 1088, 1027, 837, 775 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.46–3.39 (m, 4 H), 0.90 (s, 9 H), 0.86–0.65 (m, 4 H), 0.53–0.47 (m, 10 H), 0.30–0.17 (m, 4 H), 0.11–0.02 (m, 10 H), 0.05 (s, 6 H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 66.9, 66.7, 26.0, 19.8, 19.6, 18.7, 18.6, 18.50, 18.47, 18.42, 18.37, 18.27, 18.25, 18.1, 8.44, 8.39, 8.3, 8.24, 8.16, –5.09, –5.12.
MS (CI, NH_4^+): m/z = 474 $(M+NH_4)^+$, 457 $(M+H)^+$.
HRMS (FAB, NaI): [$C_{29}H_{48}O_2SiNa$, $(M + Na)^+$], m/z calcd 479.3321, found 479.3339.

(1*R*,3*S*,4*R*,6*S*,7*R*,9*S*,10*R*,12*R*,13*S*,15*R*,16*S*,18*R*,19*S*,21*R*)-1-[(*tert*-Butyldimethylsilyloxy)methyl]-21-septecyclopropanemethyl 2-(Trimethylsilyl)ethyl Phthalate (13):
A mixture of acid **8** (39 mg, 0.14 mmol), alcohol **11** (57 mg, 0.12 mmol), DCC (50 mg, 0.24 mmol) and DMAP (7 mg, 0.057 mmol) in CH_2Cl_2 was stirred overnight, when CH_2Cl_2 (10 mL) and H_2O (2 mL) were added. The organic layer was separated, dried (Na_2SO_4), rotary evaporated, and chromatographed (hexanes/Et_2O, 1:0 to 9:1) to give diester **13** (76 mg, 90 %) as a colorless oil; R_f = 0.43 (hexanes/EtOAc, 9:1); $[\alpha]_D$ –111.9 (c =2.3, $CHCl_3$).
IR (film): ν = 2996, 2954, 1728, 1284, 1122, 1070, 838 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74–7.72 (m, 2 H), 7.56–7.53 (m, 2 H), 4.44–4.38 (app t J = 8.7 Hz, 2 H), 4.15–4.08 (m, 2 H), 3.46–3.42 (m, 2 H), 1.12 (app t J = 8.7 Hz, 2 H), 0.96–0.84 (m, 2 H), 0.93 (s, 9 H), 0.74–0.01 (m, 26 H), 0.09 (s, 9 H), 0.05 (s, 6 H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.7, 132.5, 132.3, 130.9, 128.9, 128.8, 69.7, 66.7, 64.0, 26.0, 19.6, 18.9, 18.5, 18.4, 18.2, 17.8, 17.3, 15.7, 8.8, 8.3, 8.23, 8.16, –1.5, –5.1.
MS (FAB, NaI): m/z = 727 $(M+Na)^+$.
HRMS (FAB, NaI): [$C_{42}H_{64}O_5Si_2Na$, $(M + Na)^+$], m/z calcd 727.4190, found 727.4194.

Coronane 6:
A solution of the diester **13** (90 mg, 128 μmol) and Bu_4NF (1 M in THF, 638 μL) in THF (1.5 mL) was stirred for 1 h, when Et_2O (15 mL) and satd aq NH_4Cl were added. After a few min, 1N HCl was added, the organic layer was separated and the aqueous layer extracted with Et_2O (3 × 10 mL). The combined organic layer was dried (Na_2SO_4), rotary evaporated, and the residue was dissolved in THF (8 mL). Et_3N (25 μL, 179 μmol) and 2,4,6-trichlorobenzoyl chloride (26 μL, 166 μmol) were added, the mixture was stirred for 2 h and diluted with toluene (60 mL). The resultant solution was added dropwise over 4.5 h (syringe pump) to 4-(dimethylamino)pyridine (94 mg, 766 μmol) in toluene (15 mL) at reflux. After cooling to r.t., satd aq

NH_4Cl was added and the mixture was extracted with EtOAc. The separated organic layer was dried (Na_2SO_4), rotary evaporated, and chromatographed (hexanes/Et_2O, 10:1 to 1:1) to give **6** (45 mg, 74%) as a colorless oil:
R_f 0.54 (EtOAc/hexanes, 1:3); $[\alpha]_D$ –67.9 (*c* = 0.76, *t*-BuOMe).
IR (film from $CDCl_3$): ν = 3063, 2994, 1725, 1283, 1119, 1064, 954, 874 cm^{-1}.
^1H NMR ($CDCl_3$, 400 MHz): δ = 7.76–7.70 (m, 2 H), 7.56–7.50 (m, 2 H), 4.81 (dd, *J* = 11.2, 5.0 Hz, 2 H), 3.55 (dd, *J* = 11.2, 9.7 Hz, 2 H), 1.29–1.20 (m, 2 H), 0.59–0.50 (m, 4 H), 0.46–0.29 (m, 12 H), 0.27–0.15 (m, 10 H).
^{13}C NMR ($CDCl_3$, 101 MHz): δ = 167.8 (2 C), 132.4 (2 C), 130.9 (2 C), 129.0 (2 C), 69.9 (2 C), 22.1 (2 C), 21.7 (4 C), 21.6 (4 C), 19.9 (2 C), 17.2 (2 C), 10.8 (2 C), 10.6 (2 C), 9.9 (2 C), 9.3.
MS (FAB): *m/z* = 473 $[M + H]^+$, 393, 322, 149.
HRMS (FAB): [$C_{31}H_{37}O_4$, $(M + H)^+$], *m/z* calcd 473.2692, found 473.2737.

(1*R*,3*S*,4*R*,6*S*,7*R*,9*R*,10*S*,12*R*,13*S*,15*R*)-1-[(*t*-Butyldimethylsilyloxy)methyl]-15-quinquecyclopropane-methyl 2-(Trimethylsilyl)ethyl Phthalate (12):
Compound **12** (81 mg, 100%), which was prepared by condensation of **8** and **10**[5b] according to the procedure for **11**, was obtained as a colorless oil; R_f 0.46 (hexanes/EtOAc, 9:1); $[\alpha]_D$ –78.9 (*c* =1.1, $CHCl_3$).
IR (film): ν = 2997, 2952, 2931, 1728, 1284, 1253, 1122, 1070, 837 cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.71 (m, 2 H), 7.57–7.53 (m, 2 H), 4.44–4.39 (m, 2 H), 4.16 (dd, *J* = 11.4, 7.2 Hz, 1 H), 4.08 (dd, *J* = 11.4, 7.4 Hz, 1 H), 3.47 (dd, *J* = 10.8, 6.2 Hz, 1 H), 3.42 (dd, *J* = 10.8, 6.4 Hz, 1 H), 1.15–1.10 (m, 2 H), 0.97–0.84 (m, 2 H), 0.91 (s, 9 H), 0.75–0.47 (m, 7 H), 0.44–0.40 (m, 1 H), 0.36–0.32 (m, 1 H), 0.28–0.18 (m, 2 H), 0.09 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H), 0.18–0.03 (m, 7 H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7, 132.5, 132.2, 130.9, 130.8, 128.8, 128.7, 69.7, 66.7, 64.0, 26.0, 19.5, 18.8, 18.5, 18.4, 18.2, 18.1, 17.7, 17.3, 15.6, 8.7, 8.2, 8.1, 8.0, –1.5, –5.09, –5.12.
MS (FAB, NaI): *m/z* = 647 $(M+Na)^+$.
HRMS (FAB, NaI): [$C_{36}H_{56}O_5Si_2Na$, $(M+Na)^+$], *m/z* calcd 647.3564, found 647.3530.

Coronane 16:
16 (28 mg, 74 %), which was prepared from **12** in a similar manner to that of **6** without purification of intermediate **14**, was obtained as a white crystalline solid; mp 110–112 °C (Et_2O/EtOH); R_f 0.57 (hexanes/EtOAc, 4:1); $[\alpha]_D$ +87.0 (*c* =1.4, $CHCl_3$).
IR (film): ν = 3062, 2995, 1726, 1279, 1265, 1116, 1063, 941 cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.68 (m, 2 H), 7.53–7.48 (m, 2 H), 4.47 (dd, *J* = 6.7, 11.1 Hz, 2 H), 3.89 (dd, *J* = 7.4, 11.1 Hz, 2 H), 1.38–1.28 (m, 2 H), 0.78–0.69 (m, 4 H), 0.51–0.47 (m, 2 H), 0.44–0.35 (m, 6 H), 0.33–0.28 (m, 2 H), 0.05 to –0.06 (m, 4 H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9, 132.9, 130.7, 128.7, 70.1, 23.5, 21.9, 21.5, 18.9, 17.6, 10.5, 10.0, 9.4.
MS (CI, NH_4^+): *m/z* = 393 $(M+H)^+$.
HRMS (CI, NH_4^+): [$C_{25}H_{29}O_4$, $(M+H^+)$], *m/z* calcd 393.2066, found 393.2073.

(1*S*,3*R*,4*R*,6*R*,7*R*,9*S*)-1,9-Tercyclopropanedimethanol (18):
DME (1.6 mL, 15.0 mmol) and CH_2Cl_2 (15 mL) were stirred and cooled to –20 °C when Et_2Zn (1.5 mL, 15.0 mmol) was added dropwise at a rate that the temperature remained at –20 °C. CH_2I_2 (2.4 mL, 30.1 mmol), was also slowly added at –20 °C and the resultant zinc complex was added to a precooled (–78 °C) stirred solution of dienediol (**17**)[5b] (0.386 mL, 2.5 mmol) and the boronate **22** (1.421g, 5.3 mmol) in CH_2Cl_2 (19 mL). After 3 h at –78 °C, the mixture was allowed to warm to r.t. with continued stirring overnight and then quenched with satd aq NH_4Cl (33 mL) and *iso*-PrOH (7 mL) followed by vigorous stirring for 30 min. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 and *iso*-PrOH (5:1, 5 × 60 mL). The combined organic layers were dried (Na_2SO_4), filtered, rotary evaporated, and chromatographed (EtOAc/hexanes/*iso*-PrOH, 5:5:1) to yield the known[12] tercyclopropanedimethanol **18** (0.4105 g, 90%); R_f 0.35 (EtOAc).
HRMS (CI, NH_3): [$C_{11}H_{22}NO_2$, $(M + NH_4)^+$], calcd 200.1651, found 200.1651.
Anal calcd for $C_{11}H_{18}O_2$: C, 72.44; H, 9.96; found C, 72.35; H, 9.88.

(1*S*,3*R*,4*R*,6*R*,7*R*,9*S*)-1,9-Bis[(*E*)-3-hydroxyprop-1-en-1-yl]tercyclopropane (20):
Dienediol **20** (0.1966g, 0.84 mmol, 95%), which was prepared from tercyclopropanedimethanol **18** without purification of intermediates, via diester **19** [(0.2893g, 61%): R_f 0.16 (EtOAc/hexanes, 9:91)] and using the general procedure of Dess–Martin oxidation, Wittig homologation and DIBAl-H reduction described in detail elsewhere,[5b] was obtained as a colorless oil; R_f 0.56 (EtOAc).
IR (film): ν = 3330, 3066, 2999, 2922, 2866, 1666, 1086, 1003, 962 cm^{-1}.
^1H NMR ($CDCl_3$, 300 MHz): δ = 5.68 (dt, *J* = 15.3, 5.9 Hz, 2 H), 5.25 (dd, *J* = 8.8, 15.3 Hz, 2 H), 4.08 (t, *J* = 5.9 Hz, 4 H), 1.3–1.1 (m, 4 H), 0.83 (m, 2 H), 0.60 (m, 2 H), 0.53–0.47 (m, 4 H), 0.25 (m, 2 H).
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 136.7, 126.2, 63.7, 22.4, 19.8, 17.9, 12.3.
CIMS (NH_3): *m/z* (%) = 252 (4, $M + NH_4)^+$, 234 (7, $M + NH_4 - H_2O)^+$, 199 (33), 157 (45), 145 (48), 131 (65), 119 (67).
HRMS (FAB): [$C_{15}H_{26}NO_2$, $(M + NH_4)^+$], calcd 252.1964, found 252.1964.

(1*R*,3*S*,4*S*,6*R*,7*R*,9*R*,10*R*,12*S*,13*S*,15*R*)-1,15-quinquecyclopropanedimethanol (21):
Cyclopropanation of diene **20** as described above for **17** and using ligand **23** gave the diol **21** (0.1326 g, 86%) as colorless crystals; R_f 0.49 (EtOAc); mp 76–78 °C (EtOAc/hexanes); $[\alpha]_D$ –7.3 (*c* = 0.64, EtOH).
IR (film): ν = 3350, 3066, 2997, 2918, 2870, 1452, 1414, 1309, 1024, 910, 870, 733 cm^{-1}.
^1H NMR ($CDCl_3$, 400 MHz): δ = 3.39 (m, 4 H), 1.32 (s, 2 H), 0.79 (m, 2 H), 0.67 (m, 2 H), 0.54–0.42 (m, 6 H), 0.28 (m, 4 H), 0.09 (m, 6 H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 66.9, 19.6, 18.5, 18.4, 18.3, 17.9, 8.9, 8.7, 8.4.
CIMS (NH_3): *m/z* (%) = 280 (10, $M + NH_4)^+$, 262 (2, $M + NH_4 - H_2O)^+$, 105 (64), 93 (85), 91 (100).
HRMS (CI, NH_3): [$C_{17}H_{30}NO_2$, $(M + NH_4)^+$], calcd 280.2277, found 280.2279.
Anal calcd for $C_{17}H_{26}O_2$: C, 77.80; H, 10.00; found C, 77.81; H, 9.84.

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(9) Crystal data for **16**: $C_{25}H_{28}O_4$, M = 392.5, monoclinic, space group $P2_1$ (no. 4), a = 19.146(2), b = 5.215(1), c = 23.478(2) Å, β = 110.28(1)°, V = 2199.0(4) Å^3, Z = 4 (there are two crystallographically independent molecules in the asymmetric unit), D_c = 1.185 g cm^{-3}, μ(Cu-Kα) = 0.63 mm^{-1}, F(000) = 840, T = 293 K.

(10) For **16** (**21**) data for a clear needle of dimensions 0.50 × 0.08 × 0.07 mm (thin clear plate of dimensions 1.00 × 0.73 × 0.01 mm) were measured on a Siemens P4/RA diffractometer with graphite monochromated Cu-Kα radiation using ω-scans. Of the 4088 (1475) independent reflections measured [$2\theta \leq 124$ (124)°], 2986 (1247) had $|F_o| > 4\sigma(|F_o|)$ and were considered to be observed. The structures were solved by direct methods and in **21** disorder was found in the positions of one of the hydroxyl oxygen atoms—this was resolved into two partial occupancy orientations, both of which were refined anisotropically. In **16** disorder was found in the position of the *o*-phthalate moiety of one of the independent molecules; two partial occupancy orientations were identified, the atoms of the major occupancy orientation being refined anisotropically, those of the minor occupancy orientation isotropically. The remaining full occupancy non-hydrogen atoms in both structures were refined anisotropically (with the C–H hydrogen atoms placed in calculated positions—the hydroxyl hydrogen atoms could not be located) by full-matrix least squares based on F^2 to give R_1 = 0.067 (0.056), wR_2 = 0.162 (0.152) for the observed data and 572 (183) parameters. The chiralities of both structures were assigned by internal reference. Computations were carried out using the SHELXTL PC program system version 5.03 and atomic coordinates, bond lengths and angles, and thermal parameters have been deposited with the Cambridge Crystallographic Data Centre.

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