$NaHCO_3$ (20 mL), and water (2 × 20 mL) before concentration to a syrup (9 mg) that was chromatographically homogeneous: R_f 0.28 (5:6 ethyl acetate–hexane); ^1H NMR ($CDCl_3$) δ 5.77 (dd, 1 H, J = 1.7 Hz, 3.3 Hz, H-2b), 5.45 (H-2d), 4.18 (dd, 1 H, J = 3.0, 9.0 Hz, H-3a), 4.16 (dd, 1 H, J = 3.0, 9.0 Hz, H-3b), 4.03 (H-2c), 3.82 (H-2a), 3.63 (s, OCH_3), 3.22 (dt, 1 H, ^2J = −9.5, ^3J = 6.5 Hz), 2.25 (t, 2 H, J = 7.5 Hz, CH_2COO), 2.02, 2.00 and 1.91 (each s, 3 H, $COCH_3$).

8-(Methoxycarbonyl)octyl 3,6-Bis-*O*-[2-*O*-(α-D-mannopyranosyl)-α-D-mannopyranosyl]-α-D-mannopyranoside (2). A mixture of **17** (38.5 mg, 0.019 mmol) and 5% palladium on carbon (40 mg) in 95% ethanol (2 mL) was stirred under hydrogen (1 atm) for 36 h to provide a product with R_f 0.54 in 4:1 dichloromethane–methanol that was devoid of ultraviolet absorption in TLC. The catalyst was removed by filtration and concentrated to a glass that was dried overnight over P_2O_5 and dissolved in methanol containing a trace of sodium methoxide at 0 °C. After 4 h, the mixture was neutralized with Amberlite IRC-50 (H^+), resin was removed by filtration, methanol and evaporated, and the residue was passed through a column of Bio-Gel P-2 (200–400 mesh, 50 × 2.5 cm) in 10% ethanol. The carbohydrate-containing fractions were combined, concentrated, and lyophilized to provide pentasaccharide **2** [14.6 mg (78%)] as a white powder: R_f 0.47 (4:1 2-propanol–water); $[\alpha]_D$ +66.0° (*c* 0.1, water). Anal. Calcd for $C_{40}H_{70}O_{28}\cdot 3H_2O$: C, 45.62; H, 7.28. Found: C, 45.29; H, 7.31.

8-(Methoxycarbonyl)octyl 3,6-Bis-*O*-[2-*O*-(α-D-mannopyranosyl 6-disodium phosphate)-α-D-mannopyranosyl]-α-D-mannopyranoside (3). Compound **18** (50.5 mg, 0.021 mmol) was hydrogenated over 5% palladium on carbon (50 mg) as described for the preparation of **2**. After catalyst removal and washing, the filtrate was concentrated to a gum that was redissolved in 95% ethanol (2 mL) and stirred under hydrogen (1 atm) in the presence of Adams catalyst (PtO_2, 10 mg) for 3 h. At this stage only a single non-ultraviolet-absorbing product could be detected in TLC, R_f 0.61, 2:1 2-propanol–water. The catalyst was removed by filtration, and the residue was concentrated to a glass that was dried, treated with methanolic sodium methoxide, and passed through a Biogel P-2 as described for **2**. The carbohydrate-containing fractions were concentrated, dissolved in water, and passed through Dowex 50X8 (Na^+) (10 mL), and the eluate was lyophilized to provide **3** [19.8 mg (76%)] as a white powder: R_f 0.42 in 2:1 2-propanol–water; $[\alpha]_D$ +65.7° (*c* 0.10, water). Anal. Calcd for $C_{40}H_{68}O_{34}Na_4P_2\cdot 3.5H_2O$: C, 36.67; H, 5.77. Found: C, 36.34; H, 5.53.

8-(Methoxycarbonyl)octyl 6-*O*-[2-*O*-(α-D-Mannopyranosyl)-α-D-mannopyranosyl]-3-*O*-[2-*O*-(α-D-mannopyranosyl 6-disodium phosphate)-α-D-mannopyranosyl]-α-D-mannopyranoside (4). Deprotection of **23** (45 mg, .021 mmol) as described for the preparation of **3** gave **23** [17.4 mg (71%)] as a white lyophilized powder: R_f 0.32 (4:1 2-propanol–water); $[\alpha]_D$ +81.3° (*c* 0.12, water). Anal. Calcd for $C_{40}H_{69}O_{31}PNa_2\cdot 3H_2O$: C, 40.82; H, 6.42. Found: C, 40.46; H, 6.09.

8-(Methoxycarbonyl)octyl 3-*O*-[2-*O*-(α-D-Mannopyranosyl)-α-D-mannopyranosyl]-6-*O*-[2-*O*-(α-D-mannopyranosyl 6-disodium phosphate)-α-D-mannopyranosyl]-α-D-mannopyranoside (5). Compound **24** (42 mg, 0.019 mmol) was deprotected as described for the preparation of **3** to provide the sodium salt **5** [15.5 mg (74%)] as a white lyophilized powder: R_f 0.36 (3:1 2-propanol–water); $[\alpha]_D$ +75.8° (*c* 0.12, water). Anal. Calcd for $C_{40}H_{69}O_{31}PNa_2\cdot 3H_2O$: C, 40.82; H, 6.42. Found: C, 40.41; H, 6.09.

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Registry No. **2**, 108167-16-4; **3**, 108167-17-5; **4**, 108167-18-6; **5**, 108189-44-2; **6**, 67381-29-7; **7**, 80738-49-4; **8**, 80738-50-7; **9**, 86861-46-3; **10**, 108167-19-7; **11**, 108167-20-0; **12**, 65827-59-0; **13**, 108167-21-1; **14**, 108167-22-2; **15**, 13242-53-0; **16**, 108266-23-5; **17**, 108167-23-3; **18**, 108167-24-4; **19**, 108167-25-5; **20**, 108189-45-3; **21**, 108167-26-6; **22**, 108167-27-7; **23**, 108167-28-8; **24**, 108167-29-9; **25**, 108167-30-2; 8-(methoxycarbonyl)octanol, 34957-73-8.

A General Stereocontrolled Approach to the 5–8 Fused Ring System. Application to the Total Synthesis of Marine Natural Product (±)-Precapnelladiene†

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A new and general approach to the *cis*- and *trans*-bicyclo[6.3.0]undecane system from readily available *cis,syn,cis*-triquinane bis(enones) is delineated. The key concept in our approach is the recognition of a bicyclo[3.3.0]oct-1(5)-ene moiety as a masked cyclooctane-1,5-dione equivalent. Thus, a 5–5–5 to 5–8 strategy emerges in which the stereochemical preferences of the former can be fully transcribed into the latter. A number of tricyclo[6.3.0.$0^{2,6}$]undec-1(8)-enes have been synthesized and transformed into *cis*-bicyclo[6.3.0]undecane-2,6-diones via ruthenium-catalyzed oxidation. The approach has been extended to the stereoselective synthesis of the biogenetically important marine natural product (±)-precapnelladiene (1).

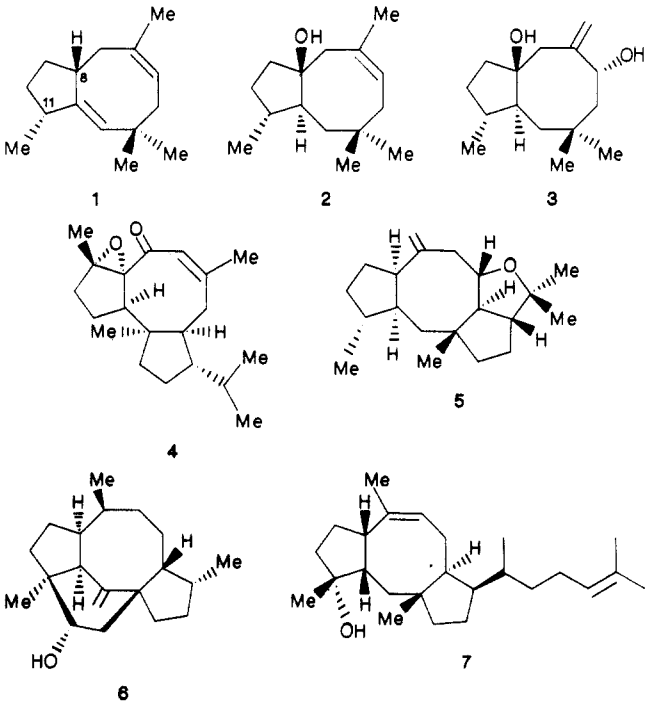
The eight-membered ring has been the latest entrant into the diverse assemblage of carbocyclic rings present among terpenoid natural products.[1] Indeed, the number of terpene carbon skeletons in which a cyclooctane ring forms a part of condensed or bridged polycyclic system has proliferated rapidly.[1] Among the more interesting carbocyclic variations that have been encountered in recent years embodying an eight-membered ring are the uncommon 5–8 and 5–8–5 fused ring systems. While the closely related sesquiterpenoids of marine origin, precapnelladiene (1),[2] dactylol (2),[3] and poitediol (3)[4] are examples of the 5–8 fused cyclopentacyclooctane nucleus, the diterpenoids

† Dedicated to Dr. Sukh Dev on the occasion of his 60th birthday.

(1) (a) Devon, T. K.; Scott, A. I. *Handbook of Naturally Occurring Compounds*; Academic: New York, 1972, Vol. II. (b) Glasby, J. S. *Encyclopaedia of the Terpenoids*; Wiley-Interscience: New York, 1982.
(2) Ayanoglu, E.; Gebreyesus, T.; Beechan, C. M.; Djerassi, C. *Tetrahedron* **1979**, *35*, 1035.
(3) Schmidt, F. J.; Hollenbeak, K. H.; Vanderah, D. J. *Tetrahedron* **1978**, *34*, 2719.
(4) Fenical, W.; Schulte, G. R.; Finer, J.; Clardy, J. *J. Org. Chem.* **1978**, *43*, 3628.

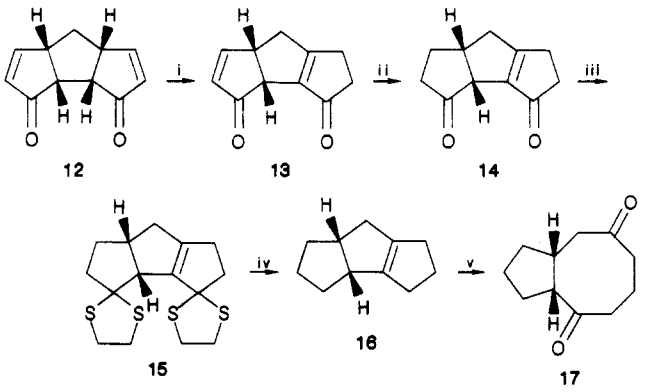
0022-3263/87/1952-2875$01.50/0

basmenone (4) from tobacco,[5] epoxydictymene (5) from brown alga,[6] longipenol (6) from a termite soldier,[7] and sesterterpene ophiobolin F (7)[8] are based on the more intricate 5–8–5 assembly. Due to the presence of the uncommon ring system, many stereogenic centers, and a complex substitution pattern, these cyclooctanoid natural products have attracted considerable attention from synthetic chemists. While there have been numerous model studies[9] for constructing the 5–8 and also 5–8–5 ring systems, the first syntheses of a natural product based on the simpler 5–8 system were reported only in 1984,[10–12] thus reflecting the nonavailability of effective methodologies for assembling and/or annulating eight-membered ring and controlling the stereochemistry in conformationally flexible 5–8 ring systems.



We describe here a general methodology for the construction of bicyclo[6.3.0]undecanes with complete control of stereochemistry. The application of this methodology to the total synthesis of (±)-precapnelladiene (1), the sesquiterpene hydrocarbon isolated[2] from soft coral *Capnella imbricata* and the biogenetic precursor of the novel polyhydroxylated "capnellanols"[13] with which it cooccurs, is described. While elucidating the structure of 1, Djerassi et al.[2] relied mainly on the IR and ^{1}H NMR data, correlation of its reduction products with those of dactylol (2), and the structure-generating computer program CONGEN. However, there was no way of assigning the relative stereochemistry at the two stereogenic centers in 1, and this question was left open.[14]

Scheme I[a]



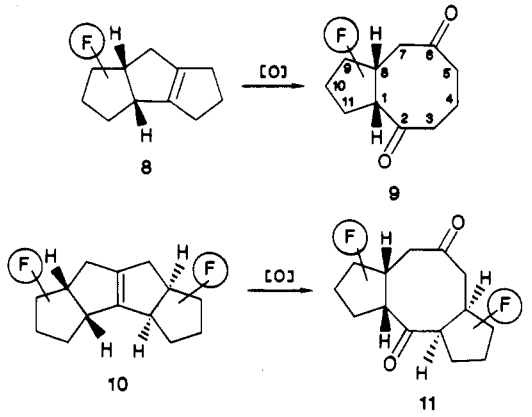
[a] Reagents and yields: (i) ref 16; (ii) H_2–10% Pd/C–EtOAc, quantitative; (iii) $HSCH_2CH_2SH$–*p*-$MeC_6H_4SO_3H$–benzene, 80%; (iv) Raney Ni (W_2)–EtOH, 79%; (v) RuO_2–$NaIO_4$–CCl_4–MeCN–H_2O, 73%.

Strategy and Model Studies

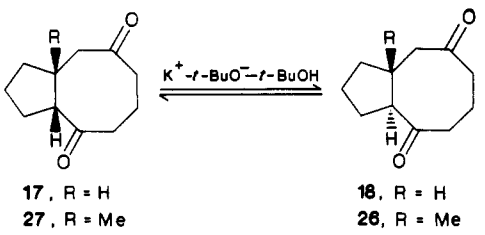
At the outset we believed that the main problem in constructing the bicyclo[6.3.0]undecanes resides in the annulation of the eight-membered ring and control of stereochemistry in the flexible 5–8 fused system. A solution therefore lay in devising a rigid substrate that is a cyclooctane equivalent and exhibits definite stereochemical preference in its reactivity. This led us to consider the bicyclo[3.3.0]oct-1(5)-ene moiety as a masked cyclooctane-1,5-dione, and triquinane 8 emerged as the equivalent of a 5–8 system 9. The latter can be unraveled through a simple oxidative scission of the double bond. The emerging C_2 and C_6 carbonyl groups provide a convenient handle for functional group manipulations in the eight-membered ring and ring junction epimerization. The extended U-shaped geometry of 8 bestows on it exclusive reactivity on the convex face, and its 5–5–5 fusion ensures cis ring junction in 9. As *cis*-bicyclo[6.3.0]undecanes can be equilibrated with the thermodynamically more stable trans isomer;[9c,f,i] the dione 9 can be used to gain entry into the trans 5–8 series also. Furthermore, the 8 → 9 theme can be readily extended to the homologous C_{14} tetraquinane 10 to provide entry into the 5–8–5 system.[15]

In opting for the tricyclo[6.3.0.0^{2,6}]undec-1(8)-ene (C_{11} triquinene 8) route to the *cis*-bicyclo[6.3.0]undecanes, we

(5) Wahlberg, I.; Eklund, A. M.; Nishid, J.; Enzell, C. R.; Berg, J. E. *Tetrahedron Lett.* **1983**, 843.
(6) Enoki, N.; Furusaki, A.; Suehiro, K.; Ishida, R.; Matsumoto, T. *Tetrahedron Lett.* **1983**, 4341.
(7) Prestwich, G. D.; Tempesta, M. S.; Turner, C. *Tetrahedron Lett.* **1984**, 1531.
(8) (a) Nozoe, S.; Morisaki, M.; Fukushima, K.; Okuda, S. *Tetrahedron Lett.* **1968**, 4457. (b) Nozoe, S.; Morisaki, M. *J. Chem. Soc. D* **1968**, 1319. (c) Cordell, G. A. *Phytochemistry* **1974**, *13*, 2343.
(9) For studies directed toward 5–8 and 5–8–5 fused systems see: (a) Birch, A. M.; Pattenden, G. *J. Chem. Soc., Chem. Commun.* **1980**, 1195. (b) Birch, A. M.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1913. (c) Begley, M. J.; Mellor, M.; Patteneden, G. *Ibid.* **1983**, 1905. (d) Coates, R. M.; Senter, P. D.; Baker, W. R. *J. Org. Chem.* **1982**, *47*, 3597. (e) Gadwood, R. C. *J. Chem. Soc., Chem. Commun.* **1985**, 123. (f) Paquette, L. A.; Ham, H. W.; Dime, D. S. *Tetrahedron Lett.* **1985**, *26*, 4983. (g) Umehara, M.; Takayanagi, H.; Ogura, H.; Hishida, S. *Bull. Chem. Soc. Jpn.* **1978**, 51, 3277. (h) Dauben, W. G.; Hart, D. J. *J. Org. Chem.* **1977**, *42*, 922. (i) Boekman, R. K., *Jr.*; Bershas, J. P.; Clardy, J.; Solheim, B. *Ibid.* **1977**, *42*, 3630. (j) Paquette, L. A.; Andrews, D. R. *Ibid.* **1985**, *50*, 201. (k) Takeshita, H.; Kato, N.; Nakanishi, K.; Tagoshi, H.; Hatsui, T. *Chem. Lett.* **1984**, 1495. (l) Grayson, G. H.; Wilson, J. R. H. *J. Chem. Soc., Chem. Commun.* **1984**, 1695. (m) Coates, R. M.; Muskopf, J. W.; Senter, P. A. *J. Org. Chem.* **1985**, *50*, 3541.
(10) One of these syntheses was reported by us in a preliminary paper.[11] Almost simultaneously Paquette[12a] and Gadwood[12b] reported syntheses of precapnelladiene (1) and poitediol (3), respectively.
(11) Mehta, G.; Murty, A. N. *J. Chem. Soc., Chem. Commun.* **1984**, 1058.
(12) (a) Kinney, W. A.; Coghlan, M. J.; Paquette, L. A. *J. Am. Chem. Soc.* **1984**, *106*, 6868; *Ibid.* **1985**, *107*, 7352. (b) Gadwood, R. C.; Lett, R. M.; Wissinger, J. E. *J. Am. Chem. Soc.* **1984**, 106, 3869; *Ibid.* **1986**, *108*, 6343.
(13) Sheik, Y. M.; Singy, G.; Kaisin, M.; Eggert, H.; Djerassi, C. *Tetrahedron Lett.* **1976**, 1171. Sheik, Y. M.; Djerassi, C. *Tetrahedron* **1977**, *33*, 2115.
(14) Birch and Pattenden[9a,b] while reporting the synthesis of (±)-*epi*-precapnelladiene correctly predicted the relative stereochemistry of the natural product as in 1 by the process of elimination. We assumed this to be correct and accordingly planned our synthetic strategy.
(15) We have recently demonstrated the 10 → 11 transformation as a viable route for constructing the 5–8–5 system: Mehta, G.; Krishnamurthy, N. *J. Chem. Soc., Chem. Commun.* **1986**, 1319.

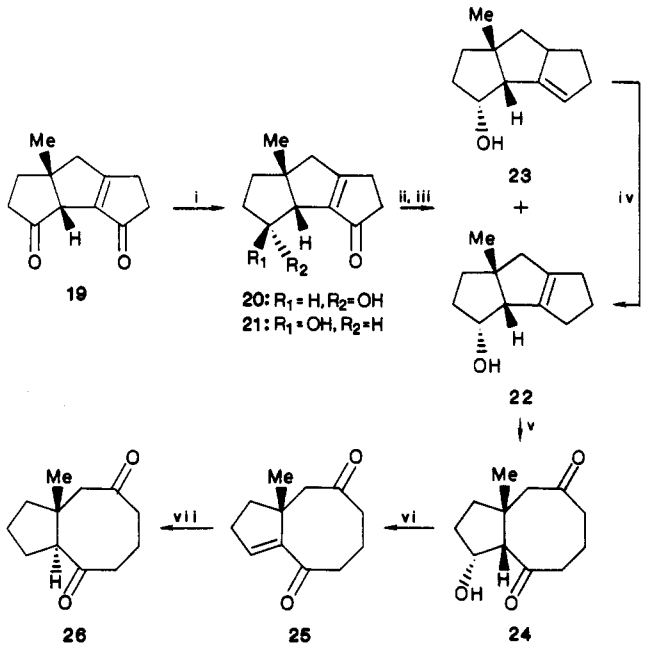


were obviously influenced by our vantage position in having developed[16] ready access to the *cis,syn,cis*-triquinane bis(enone) **12**. Indeed, **12** is available in 50–100-g quantities from 1,3-cyclopentadiene and *p*-benzoquinone in three high-yielding steps with the added flexibility of substituent control. Moreover, one of the enone moieties in **12** could be easily transposed either by thermal means or through $RhCl_3$ isomerization[17] to **13**, having one of its double bonds in the required bridgehead position.[16] Further elaboration of **13** to the C_{11} triquin-1(8)-ene **16** required shedding of the oxygen functionalities and oxidative cleavage to furnish *cis*-bicyclo[6.3.0]undecane-2,6-dione (**17**). This was accomplished in an economical sequence (Scheme I). Selective catalytic reduction of the disubstituted double bond in **13** furnished the enedione **14**, which was readily transformed into the bis(thioacetal) **15**. Reductive dethioacetalization gave the volatile triquinene **16**, containing small traces of the fully saturated C_{11} triquinane. This was directly oxidized with RuO_2–$NaIO_4$ according to the procedure of Sharpless[18] to furnish the cis dione **17**, mp 63–64 °C. The structue of **17** was fully revealed through its IR spectrum ($\nu_{C=O}$ 1700 cm^{-1}) and ^{13}C NMR resonances (δ 213.9 and 212.2 due to the two cyclooctanone carbonyl groups). Thus, *cis*-bicyclo[6.3.0]undecane-2,6-dione could be obtained from **12** in five straightforward steps in 32% overall yield. When equilibrated with potassium *tert*-butoxide in *t*-BuOH, **17** furnished a readily separable 90:10 mixture of trans dione **18**[9b] (mp 64–65 °C) and cis dione **17**, respectively.



To further extend the scope of Scheme I to bicyclo[6.3.0]undecanes bearing a quaternary center and substitution in the cyclopentane ring, C_{12} triquinane enedione **19**, previously reported by us,[19] was employed (Scheme II). Sodium borohydride reduction proceeded regioselectively as well as stereoselectively to furnish hydroxy enones **20** and **21** in a ratio of 8:1. The major endo hydroxy enone

Scheme II[a]



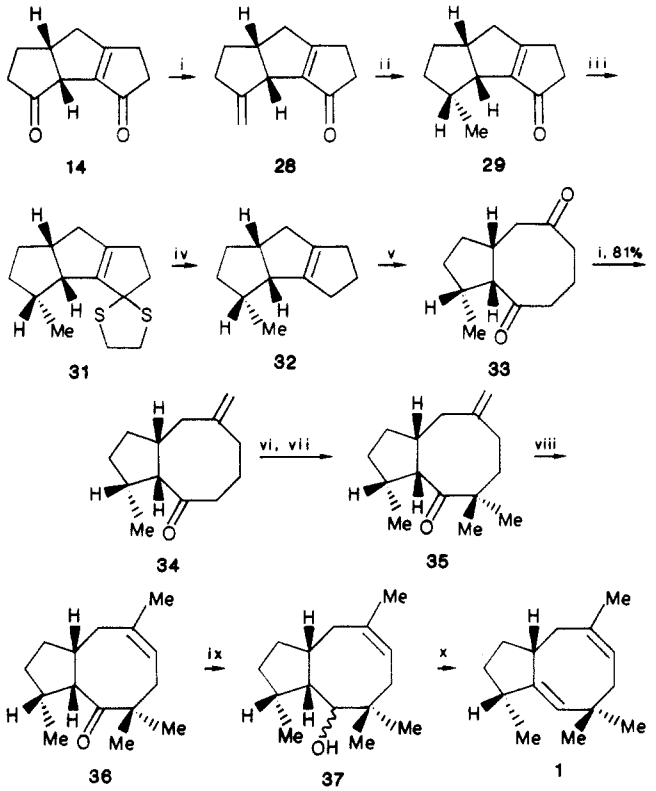
[a] Reagents and yields: (i) $NaBH_4$–MeOH, −10 °C, 80%; (ii) $HSCH_2CH_2SH$–*p*-$MeC_6H_4SO_3H$–benzene, 76%; (iii) Na–liquid NH_3, 70%; (iv) $RhCl_3 \cdot 3H_2O$–EtOH, 95%; (v) RuO_2–$NaIO_4$–CCl_4–MeCN–H_2O, 53%; (vi) *p*-$MeC_6H_4SO_3H$–benzene, 76.5%; (vii) H_2–10% Pd/C–EtOAc, 94%.

20 was converted into thioacetal and reduced with Na–liquid NH_3 to give the hydroxy olefin **22**. A small amount of the isomeric hydroxy olefin **23** was also formed in this reaction, and therefore the product from Na–liuqid NH_3 reduction was briefly treated with ethanolic $RhCl_3 \cdot 3H_2O$[17] to isomerize **23** into **22**. The hydroxy olefin **22** was oxidized with RuO_2–$NaIO_4$ to the bicyclic hydroxy dione **24**. While **24** could be characterized spectroscopically, being a β-hydroxy ketone, it showed marked propensity toward dehydration on storage. Exposure to *p*-toluenesulfonic acid resulted in smooth transformation to the enone **25** with a very useful functionality in the five-membered ring. Catalytic hydrogenation over Pd/C gave the trans bicyclic dione **26**, whose IR spectrum ($\nu_{C=O}$ 1690 cm^{-1}) and ^{13}C NMR values (δ 216.3 and 211.3) showed similarity with those of **18**. The trans dione **26** could be again equilibrated with base to furnish a 7:3 mixture of cis isomer **27** (mp 52–53 °C) and trans isomer **26**, respectively. The change in the equilibrium concentration of cis and trans isomers derived from **17** and **26**, respectively, from 9:1 to 3:7 indicates that the energy difference between the two isomers is significantly affected due to the presence of the angular methyl group.[20]

(±)-Precapnelladiene (1). Adaptation of Schemes I and II to the natural product **1** required fixing the relative stereochemistry at C_8 and C_{11} stereogenic centers and building up of the methyl substitution and olefinic bonds in the eight-membered ring. As the hydrogens at C_8 and C_{11} in **1** have a cis relationship, synthetic logic would dictate that they be preset in the triquinane precursor before the unraveling process. This could be accomplished

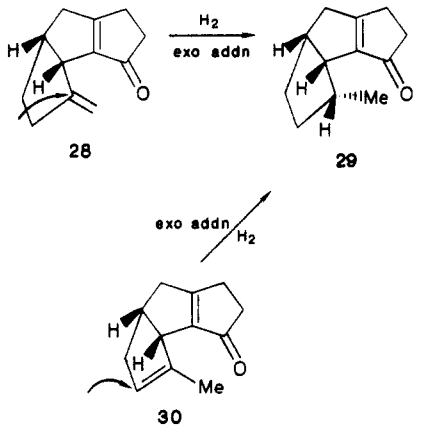
(16) Mehta, G.; Srikrishna, A.; Reddy, A. V.; Nair, M. S. *Tetrahedron* **1981**, *37*, 4543.
(17) Grieco, P. A.; Nishizawa, M.; Marinovic, N.; Ehmann, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 7102.
(18) Carlson, P. H. J.; Kalsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
(19) Mehta, G.; Reddy, D. S. K.; Murthy, A. N. *J. Chem. Soc., Chem. Commun.* **1983**, 824.
(20) A reviewer pointed out that the molecular mechanics calculations carried out by him reveal that introduction of an angular methyl group in the bicyclo[6.3.0]undecanes, indeed, makes the cis-fused system more stabe over the trans isomer. Our results on the equilibration of trans bicyclic dione **26** reported here are in agreement with the above calculations. We thank the reviewer for this helpful comment.
(21) For a general write-up on the Experimental Section see: Mehta, G.; Rao, K. S. *J. Org. Chem.* **1985**, *50*, 5537.

Scheme III[a]



[a] Reagents and yields: (i) $Ph_3P^+MeI^-$–t-$C_5H_{11}O^-Na^+$–toluene, 85%; (ii) H_2–5% Rh/C–EtOH, 90%; (iii) $HSCH_2CH_2SH$–p-$MeC_6H_4SO_3H$–benzene, 80%; (iv) Na–liquid NH_3, 65%; (v) RuO_2–$NaIO_4$–CCl_4–MeCN–H_2O, 80%; (vi) $(Me_2Si)_2NH$–n-BuLi–MeI, –78 °C, tetrahydrofuran, 92%; (vii) $(i\text{-}Pr)_2NH$–n-BuLi–MeI, –78 °C, tetrahydrofuran, 67%; (viii) $RhCl_3 \cdot 3H_2O$–EtOH, 80%; (ix) $LiAlH_4$–Et_2O, 80%; (x) $POCl_3$–1,8-diazabicyclo[5.4.0]undec-7-ene–pyridine, 70%.

through delivery of the hydrogen from the preferred convex face of the triquinanes like **28** or **30** to give **29**. The process also installs the methyl group at the desired site.



Enedione **14**, readily available as described above and having chemically differentiated carbonyl groups, was selected as the starting synthon[16] for **1**. Selective Wittig olefination of the more reactive saturated carbonyl group proceeded smoothly to give **28** (Scheme III). As planned, catalytic hydrogenation of **28** proceeded with complete stereocontrol, and crystalline enone **29** (mp 51–52 °C) with the required endo methyl group, was obtained in quantitative yield. The enone **29** was now deoxygenated via the thioacetalization to **31** and desulfurization with Na–liquid NH_3 to yield the pivotal olefin **32**. Catalytic ruthenium dioxide oxidation of **32** employing the Sharpless conditions[18] gave the bicyclic dione **33** (mp 39–40 °C), whose IR spectrum exhibited a strong carbonyl absorption at 1695 cm^{-1} and ^1H and ^{13}C NMR spectra showed signals in the expected range (see the Experimental Section).

With the acquisition of the cis bicyclic dione **33** of required stereochemistry, attention was directed toward the introduction of methyl groups and double bonds in the eight-membered ring. As per our plan, the carbonyl groups were strategically located and all the required functionality could be built around and through them. Advantage was now taken of the different steric environment prevailing around the two carbonyl groups. Chemoselective Wittig olefination of the less hindered C_6-carbonyl group furnished the keto olefin **34**: IR (neat) 1695, 1640, 890 cm^{-1}. Two successive, kinetically controlled, regioselective methylations on **34** with lithium hexamethyldisilazide–methyl iodide and lithium disopropylamide–methyl iodide, respectively, produced the *gem*-dimethylated compound **35**, mp 66–67 °C. The ^1H NMR signals [δ 1.08 (3 H, s), 1.04 (3 H, s), 0.90 (3 H, d, J = 7 Hz)] and ^{13}C NMR data left little doubt about its formulation. The stereochemical integrity at C_1 was not compromised during these alkylations. While it is not of consequence in the present context, the observation is useful in constructing other members of the 5–8 and 5–8–5 family. The C_5–C_6 double bond was now placed in its position through rhodium-catalyzed isomerization[17] of the exocyclic double bond in **35** to **36**. The presence of olefinic proton signal at δ 5.44 (dd, J = 8 Hz) in **36** established its location. The final step in the precapnelladiene synthesis required conversion of the C_2-carbonyl group into the C_1–C_2 double bond, and this was achieved through LAH reduction of **36** to the hydroxy compound **37** and dehydration with $POCl_3$–DBU in pyridine. The hydrocarbon obtained was spectroscopically identical (IR, 100-MHz ^1H NMR) with the natural product.

In summary, we have described a general approach to a functionalized *cis*- and *trans*-bicyclo[6.3.0]undecane system from the readily available *cis,syn,cis*-triquinane bis(enones). The 5–5–5 → 5–8 methodology has been extended to the total synthesis of sesquiterpene hydrocarbon (±)-precapnelladiene (**1**).

Experimental Section[20]

Tricyclo[6.3.0.0^{2,6}]undec-1(8)-ene-3,11-dione 14. A solution of isomerized dienone **13**[16] (350 mg, 2.0 mmol) was hydrogenated over 10% Pd/C catalyst (15 mg) in H_2 atmosphere (2 psi) for 15 min. Catalyst was removed by filtration and the filtrate concentrated. Crystallization from carbon tetrachloride furnished the partially hydrogenated compound **14**: 350 mg (quantitative); mp 74–76 °C; UV, λ_{max} (MeOH) 242 nm (ϵ 7000); IR (KBr) 2950, 1735, 1695, 1625 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 3.4 (2 H, br s), 1.6–3.5 (10 H, m); ^{13}C NMR (25.0 MHz, $CDCl_3$) δ 214.5, 201.8, 187.8, 144.0, 52.2, 44.6, 40.9, 38.7, 37.5, 28.5, 25.7. Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.69; H, 6.85.

3,3,11,11-Bis(ethylenedithio)tricyclo[6.3.0.0^{2,6}]undec-1-(8)-ene (15). A solution of the dihydro compound **14** (1.5 g, 8.5 mmol), ethanedithiol (2 mL), and *p*-toluenesulfonic acid (50 mg) in dry benzene (100 mL) was refluxed with a Dean–Stark water separator for 30 min. The reaction mixture was diluted with benzene (30 mL), washed with $NaHCO_3$ solution and water, and dried. The crude residue obtained after removal of the solvent was charged on a silica gel column (100 g). Elution with 5% benzene–petroleum ether removed the ethanedithiol impurities. Further elution with 10% benzene–petroleum ether furnished the dithioketal **15**: 2.25 g (80%); IR (neat) 2950, 1440, 1270, 960, 660 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.3–2.5 (8 H, m), 2.6–2.9 (4 H, m), 3.1–3.5 (8 H, m); m/e calcd (M^+) 328.59, found m/e 328.0.

(3aβ,9aβ)-Decahydro-4*H*-cyclopentacyclooctene-4,8-dione (17). Into a 250-mL round-bottomed flask were taken Raney nickel (20 g, W_2) and dithioketal **15** (2.0 g, 6.09 mmol) in absolute

ethanol (200 mL). The mixture was refluxed for 72 h and filtered. The filtrate was diluted with water (100 mL) and extracted with pentane (3 × 50 mL). The crude oily material obtained after removal of the solvent was charged on a silica gel column (10 g). Elution with pentane furnished the hydrocarbon **16** [600 mg (79%); IR (neat) 2950, 1440], which was contaminated with some fully saturated hydrocarbon.

The above hydrocarbon mixture (600 mg) was dissolved in a mixture of carbon tetrachloride (5 mL), acetonitrile (5 mL), and water (7 mL). To this mixture were added sodium periodate (1.5 g) and ruthenium dioxide (10 mg).[17] After it was stirred for 30 min, the reaction mixture was diluted and extracted with dichloromethane (3 × 20 mL). The organic layer was washed and dried. The crude material obtained after removal of the solvent was charged on a silica gel column (30 g), and elution with petroleum ether removed the saturated hydrocarbon impurities. Further elution with 10% ethyl acetate–benzene furnished dione **17**: 400 mg (73%); mp 63–64 °C; IR (KBr) 2950, 1700, 1440, 1240 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.3–2.9 (15 H, m), 3.1 (1 H, dd, J_1 = 16 Hz, J_2 = 8 Hz); ^{13}C NMR (25.0 MHz, $CDCl_3$) δ 213.9, 212.2, 63.6, 44.5, 43.1, 42.3, 39.8, 32.6, 25.2, 22.8, 22.5. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.25; H, 9.07.

(3aα,9aβ)-Decahydro-4*H*-cyclopentacyclooctene-4,8-dione (18). Into a 25-mL three-necked round-bottomed flask fitted with dry nitrogen gas inlet, rubber septum, and mercury seal were taken freshly sublimed *t*-BuOK (10 mg) and dry *t*-BuOH (3 mL). After the mixture was stirred for 5 min, the cis diketone **17** (60 mg, 0.33 mmol) in dry THF (2 mL) was added through a syringe. The reaction mixture was stirred for 1 h at room temperature and then quenched with saturated NH_4Cl solution. The mixture was extracted with ether (3 × 10 mL) and the combined organic layer washed and dried. The crude material obtained after removal of the solvent was charged on a silica gel column (10 g). Careful elution with 10% ethyl acetate–benzene furnished the starting diketone **17** [5 mg (8%)]. Further elution with the same solvent furnished the trans diketone **18** [46 mg (76%)], which was crystallized from ether–petroleum ether: mp 64–65 °C (lit.[9b] mp 64.5 °C); IR, ^1H NMR, and ^{13}C NMR, fully in agreement with the reported values.[9b]

6β-Methyl-3-hydroxytricyclo[6.3.0.0^{2,6}]undec-1(8)-en-11-ones 20 and 21. To a solution of **19** (1.6 g, 8.42 mmol) in dry methanol (150 mL) was added sodium borohydride (2.0 g (excess)) in 200-mg lots at −10 °C. Addition of sodium borohydride was stopped after the consumption of all starting material. Acetone (10 mL) was added to quench the excess borohydride. After 10 min methanol was removed under reduced pressure, and the residue was dissolved in ethyl acetate (100 mL). The organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. Removal of the solvent gave crude product (1.6 g), which was charged on a silica gel column (50 g). Elution with 25% ethyl acetate–benzene removed less polar impurities. Further elution with 50% ethyl acetate–benzene furnished the hydroxy enones **20** and **21** [1.4 g (86%)] as a mixture of hydroxy epimer (8:1), which was bulb-to-bulb distilled at 160 °C (0.3 mm). The mixture of hydroxy epimers was more conventiently separated in the next step. UV, λ_{max} (MeOH) 238 (ϵ 10580); IR (neat) 3450, 2900, 1680, 1630, 1380 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$, as a mixture of epimers) δ 1.06 (6 H, s), 1.2–1.9 (9 H, m), 2.2–2.74 (13 H, m), 3.14 (2 H, br s), 4.2 (2 H, m). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.04; H, 8.25.

6β-Methyl-3α-hydroxytricyclo[6.3.0.0^{2,6}]undec-1(8)-ene (22). A mixture of hydroxy enones **20** and **21** (800 mg, 4.2 mmol), ethanedithiol (1 mL), and *p*-toluenesulfonic acid (20 mg) in dry benzene (50 mL) was refluxed with a Dean–Stark water separator for 30 min. The reaction mixture was diluted with benzene (30 mL), washed with $NaHCO_3$ solution, and dried. The crude residue obtained after removal of the solvent was charged on a silica gel column (50 g). Elution with 50% benzene–petroleum ether removed the ethanedithiol impurities. Further elution with benzene furnished the endo hydroxy thioketal: 800 mg (76%); IR (neat) 3450, 2900, 1660, 1440, 1000, 820 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.06 (3 H, s), 1.4–1.9 (4 H, m), 2.0 (1 H, s), 2.06–2.3 (4 H, m), 2.4–2.6 (1 H, m), 2.88 (2 H, t, J = 8 Hz), 3.26 (4 H, s), 4.16 (1 H, br s); ^{13}C NMR (25.0 MHz, $CDCl_3$) δ 150.9, 144.7, 73.6, 71.0, 60.9, 55.8, 49.4, 46.7, 41.2, 40.5, 38.5, 35.5, 29.9, 28.8. Anal. Calcd for $C_{14}H_{20}OS_2$: C, 62.64; H, 7.51. Found: C, 62.83; H, 7.74. Continued elution with benzene gave the minor exo hydroxy thioketal: 100 mg (10%); IR (neat) 3450, 2900, 1660, 1440, 1020, 820 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.0 (3 H, s), 1.24–1.64 (4 H, m), 1.68–2.08 (4 H, m), 2.2 (1 H, br s), 2.44 (1 H, s), 2.64 (2 H, t, J = 8 Hz), 3.14 (4 H, s), 4.08 (1 H, m); ^{13}C NMR (25.0 MHz, $CDCl_3$) δ 147.7, 145.7, 77.3, 71.1, 62.0, 55.5, 51.1, 45.6, 40.4, 40.1, 38.6, 34.2, 29.8, 28.2.

Into a two-necked 250-mL round-bottomed flask fitted with a guard tube and stopper was taken liquid NH_3 (100 mL). To this was added freshly cut sodium metal (300 mg, 13.0 mmol) was added piece by Piece. The resulting blue solution was stirred for 5 min, and the thioketal (950 mg, 3.8 mmol) in dry ether (50 mL) was slowly added to it. The reaction mixture was quenched with NH_4Cl solution after all ammonia had evaporated. The reaction mixture was diluted and extracted with ether (3 × 50 mL), washed, and dried. The crude material obtained after removing the solvent was loaded on a small silica gel column (20 g). Elution with 50% benzene–petroleum ether gave a mixture of isomers **22** and **23** [475 mg (70%)] as revealed by the presence of an additional ^1H NMR signal at δ 5.5. The mixture of isomers **22** and **23** (475 mg, 2.7 mmol) and $RhCl_3 \cdot 3H_2O$ (50 mg) in abolute ethanol (30 mL) were refluxed for 4 h in a 50-mL round-bottom flask. The reaction mixture was passed through a small alumina (10 g) column; removal of the solvent furnished the pure hydroxy olefin [450 mg (95%)] as a single isomer, which was bulb-to-bulb distilled at 120 °C (0.4 min): IR (neat) 3350, 2950, 1440, 1040 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.1 (3 H, s), 1.18–1.28 (2 H, m), 1.46 (2 H, s), 1.5–1.7 (2 H, m), 1.9–2.2 (7 H, m), 2.4 (1 H, d, J = 7 Hz), 4.18 (1 H, m); ^{13}C NMR (25.0 MHz, $CDCl_3$) δ 148.9, 141.9, 74.9, 60.7, 55.2, 46.2, 38.5, 35.3, 29.8 (2C), 29.6, 27.9. Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.59; H, 10.21.

(3aβ,9aβ)-3a-Methyl-1-hydroxydecahydro-5*H*-cyclopentacyclooctene-5,9-dione (24). Hydroxy olefin **22** (320 mg, 1.8 mmol) was dissolved in a mixture of carbon tetrachloride (2 mL), acetonitrile (2 mL), and water (3 mL). To this mixture were added sodium periodate (900 mg) and ruthenium dioxide (8 mg). After being stirred for 5 min, the reaction mixture was diluted and extracted with dichloromethane (3 × 20 mL). The organic layer was washed and dried. The crude material obtained after removal of the solvent was loaded on a silica gel column (50 g), and elution with 30% ethyl acetate–benzene furnished hydroxy dione **24**: 200 mg (53%); IR (neat) 3450, 2950, 1680, 1450, 1080 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.08 (3 H, s), 1.2–2.8 (13 H, m), 3.0 (1 H, d, J = 6 Hz), 4.5 (1 H, m); ^{13}C NMR (25.0 MHz, $CDCl_3$) δ 215.4, 210.8, 75.8, 63.2, 51.9, 45.6, 45.1, 44.1, 38.5, 32.5, 28.2, 21.7.

(3aβ)-3a-Methyl-2,3,3a,4,6,7,8,9-octahydro-5*H*-cyclopentacyclooctene-5,9-dione (25). The above hydroxy dione **24** (200 mg, 0.952 mmol) in dry benzene (15 mL) and *p*-toluenesulfonic acid (10 mg) were refluxed for 1 h in a 25-mL round-bottomed flask. The reaction mixture was diluted with benzene (20 mL), washed with $NaHCO_3$ solution and water, and dried. The product **25** [140 mg (76.5%)] obtained after removal of the solvent was bulb-to-bulb distilled at 140 °C (0.3 mm): IR (neat) 3050, 2950, 1680, 1600, 1440, 1300, 1240 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.24 (3 H, s), 1.6–2.08 (4 H, m), 2.2–2.76 (8 H, m), 6.66 (1 H, t, J = 4 Hz); ^{13}C NMR (25.0 MHz, $CDCl_3$) δ 211.6, 202.5, 150.2, 140.4, 54.9, 47.9, 41.7, 41.3, 40.9, 29.1, 26.0, 22.0. Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.83; H, 8.6.

(3aα,9aβ)-9a-Methyldecahydro-4*H*-cyclopentacyclooctene-4,8-dione (26). The enedione **25** (100 mg, 0.52 mmol) in ethyl acetate (20 mL) and 10% Pd/C (10 mg) were taken in 250-mL Parr hydrogenation flask. After the reaction mixture was shaken in H_2 atmosphere (10 psi) for 10 min, the catalyst was filtered and the filtrate was concentrated. The product was bulb-to-bulb distilled at 140 °C (0.4 mm) to get pure trans dione **26**: 95 mg (94%); IR (neat) 2950, 1690, 1450, 1200, 1040 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.9 (3 H, s), 1.16–2.44 (14 H, m) 2.68 (1 H, m); ^{13}C NMR (25.0 MHz, $CDCl_3$) δ 216.3, 211.3, 57.7, 49.8, 45.6, 44.9, 39.9, 33.8, 28.5, 27.1, 22.1, 21.5. Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.19; H, 9.34. Found: C, 74.18; H, 9.42.

(3aβ,9aβ)-9a-Methyldecahydro-4*H*-cyclopentacyclooctene-4,8-dione (27). Into a 25-mL three-necked round-bottomed flask fitted with dry nitrogen gas inlet, rubber septum, and mercury seal were taken freshly sublimed *t*-BuOK (10 mg) and dry *t*-BuOH (3 mL). After the mixture was stirred for 5 min, trans

dione **26** (60 mg, 0.3 mmol) in dry THF (2 mL) was added through a syringe. The reaction mixture was stirred for 1 h at room temperature and then quenched with saturated NH_4Cl. The mixture was extracted with ether (3 × 10 mL), and the combined organic layer was washed and dried. The crude material obtained after removal of the solvent was charged on a silica gel column (10 g). Careful elution with 10% ethyl acetate–benzene furnished the starting trans dione **26**, 18 mg (30%). Further elution with the same solvent furnished the cis dione **27** [32 mg (53%)] and was crystallized from ether–petroleum ether: mp 52–53 °C; IR (neat) 2950, 1700, 1440, 1200, 860 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.8 (3 H, s), 1.4–2.9 (14 H, m), 3.1 (1 H, dd, J_1 = 12 Hz, J_2 = 8 Hz); ^{13}C NMR (25.0 MHz, $CDCl_3$) δ 212.2, 210.8, 56.4, 52.2, 45.6(2c), 45.1, 43.5, 27.5, 20.5, 20.0, 19.2. Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.21; H, 9.36.

Tricyclo[6.3.0.0^{2,6}]dodeca-1(8),3(12)-dien-11-one (28). Into a 50-mL three-necked round-bottomed flask fitted with dry nitrogen inlet, septum, reflux condensor, and mercury seal was introduced triphenylmethylphosphonium bromide (1.7 g, 4.77 mmol) with an addition funnel, and the solid was suspended in dry toluene (10 mL). To this suspension was added sodium *tert*-amyl oxide (420 mg, 3.81 mmol) in dry toluene (10 mL). The resulting yellow reaction mixture was stirred at ~40 °C for 5 min and then enedione **14** (560 mg, 3.18 mmol) in dry toluene (5 mL) was introduced at once. The reaction mixture was refluxed for 3.5 h, then diluted with benzene (20 mL), and washed with brine (15 mL). The organic layer was separated, washed, and dried. Removal of solvent gave an oily residue that was charged on a silica gel (50-g) column. Elution with petroleum ether removed the triphenylphosphine-derived impurities. Further elution with benzene furnished the terminal olefinic compound **28** [475 mg (85%)], which was bulb-to-bulb distilled at 110 °C (0.4 torr): UV, λ_{max} (MeOH) 238 (ϵ 14970); IR (neat) 3075, 2950, 1700, 1660, 1640, 1440, 890 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 1.2–1.4 (1 H, m), 1.7–2.8 (9 H, m), 3.0–3.4 (1 H, m), 3.4–3.6 (1 H, m), 4.75 (1 H, br s), 5.1 (1 H, br s); ^{13}C NMR (25.0 MHz, $CDCl_3$) δ 203.1, 185.0, 151.8, 148.7, 107.5, 48.2, 47.7, 41.0, 38.5, 33.6, 33.3, 25.4. Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.50; H, 8.24.

3α-Methyltricyclo[6.3.0.0^{2,6}]undec-1(8)-en-11-one (29). The *exo*-methylene compound **28** (475 mg, 2.72 mmol) was taken in ethanol (25 mL) and hydrogenated in a Parr hydrogenation apparatus over 5% Rh/C catalyst (50 mg) at 2 psi pressure. After the consumption of approximately 1 mol of hydrogen, the catalyst was filtered and the solvent was removed. The residue was filtered through a silica gel (20-g) column to give 440 mg (90%) of the *endo*-methyl compound **29** and was crystallized from petroleum ether to furnish colorless cubes: mp 51–52 °C; UV, λ_{max} (MeOH) 240 (ϵ 15560); IR (KBr) 2950, 1700, 1640, 1420, 1380 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.92 (3 H, d, J = 8 Hz), 1.36–1.72 (4 H, m), 2.04 (1 H, br s), 2.2 (1 H, br s), 2.48 (1 H, br s), 2.56–2.8 (3 H, m), 3.0–3.4 (2 H, m); ^{13}C NMR (25.0 MHz, $CDCl_3$) δ 203.9, 187.8, 148.5, 47.9, 47.8, 40.9, 40.4, 38.0, 33.9, 33.7, 25.5, 16.9. Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.57; H, 9.17.

3α-Methyl-11,11-(ethylenedithio)tricyclo[6.3.0.0^{2,6}]undec-1(8)-ene (31). A solution of enone **29** (200 mg, 1.14 mmol), ethanedithiol (0.5 mL), and *p*-toluenesulfonic acid (10 g) in dry benzene (30 mL) was refluxed with a Dean–Stark water separator for 30 min. The reaction mixture was diluted with benzene (30 mL), washed with aqueous $NaHCO_3$ and water, and dried. The crude residue obtained after removal of the solvent was charged on a silica gel (20-g) column. Elution with 20% benzene–petroleum ether removed the ethanedithiol impurities. Further elution with 50% benzene–petroleum ether furnished the thioketal **31**: 230 mg (80%); IR (neat) 2950, 1660, 1450, 810 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.90 (3 H, d, J = 8 Hz), 1.2–2.5 (10 H, m), 2.76–3.1 (3 H, m), 3.2–3.32 (4 H, m); ^{13}C NMR (25.0 MHz, $CDCl_3$) δ 158.8, 147.2, 72.2, 51.5, 50.3, 49.6, 40.6, 39.6, 39.2, 37.2, 36.4, 31.2, 28.7, 17.3.

(3aβ,9aβ)-3α-Methyldecahydro-4*H*-cyclopentacyclooctene-4,8-dione (33). Into a two-necked 100-mL round-bottomed flask, fitted with a guard tube and stopper, was taken liquid NH_3 (50 mL). To this was added freshly cut sodium metal (200 mg, 8.7 mmol) piece by piece. The resulting blue solution was stirred for 5 min, and thioacetal **31** (580 mg, 2.3 mmol) in dry ether (10 mL) was slowly added to it. The reaction mixture was quenched with saturated NH_4Cl solution after all the ammonia had evaporated. The reaction mixture was diluted, extracted with *n*-pentane (3 × 30 mL), washed, and dried over anhydrous Na_2SO_4. The crude material obtained after removing the solvent was loaded on a small silica gel column (5 g). Elution with *n*-pentane gave **32** [245 mg (65%); IR (neat, mixture of isomers) 3050, 2950, 1460, 1120 cm^{-1}] contaminated with traces of $\Delta^{1(2)}$ double-bond isomer. The above hydrocarbon mixture **32** (245 mg, 1.5 mmol) was dissolved in a mixture of carbon tetrachloride, acetonitrile, and water (each 5 mL). To this mixture were added sodium periodate (800 mg) and ruthenium dioxide (12 mg). After being stirred for 30 min, the reaction mixture was diluted and extracted with dichloromethane (3 × 10 mL). The organic layer was washed and dried. The crude material obtained after removal of the solvent was charged on a silica gel column (30 g), and elution with 10% ethyl acetate–benzene furnished dione **33**: 235 mg (80%); 39–40 °C; IR (neat) 2950, 1695, 1460, 1310, 1180 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.90 (3 H, d, J = 7 Hz), 1.6–2.6 (14 H, m), 3.10 (1 H, dd, J_1 = J_2 = 6 Hz); ^{13}C NMR (25.0 MHz, $CDCl_3$) δ 215.2, 213.9, 56.1, 47.3, 44.9, 43.9 (2C), 39.5, 31.5, 30.9, 23.1, 15.9; exact mass calcd for $C_{12}H_{18}O_2$ m/e 194.1306, found m/e 194.1307.

(3aβ,9aβ)-3α-Methyl-8-methylenedecahydro-4*H*-cyclopentacycloocten-4-one (34). Into a 25-mL three-necked round-bottomed flask fitted with dry nitrogen inlet, septum, reflux condensor, and mercury seal was introduced triphenylmethylphosphonium bromide (415 mg, 1.15 mmol) with an addition funnel, and the solid was suspended in dry toluene (5 mL). To this suspension was added sodium *tert*-amyl oxide (101 mg, 0.92 mmol) in dry toluene (5 mL). The resulting yellow reaction mixture was stirred at ~40 °C for 5 min, and then dione **33** (150 mg, 0.77 mmol) in dry toluene (5 mL) was introduced at once. The reaction mixture was refluxed for 2.5 h, then diluted with benzene (10 mL), and was with brine (15 mL). The organic layer was separated, washed, and dried. Removal of the solvent gave an oily residue that was charged on a silica gel column (30 g). Elution with petroleum ether removed triphenylphosphine-derived impurities. Further elution with 50% benzene–petroleum ether furnished the *exo*-methylene compounds **34**: 120 mg (81%); IR (neat) 3075, 2950, 1695, 1640, 1460, 1390, 890 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.86 (3 H, d, J = 7 Hz), 1.24–2.5 (14 H, m), 3.24 (1 H, dd, J = 6 Hz), 4.72 (1 H, br s), 4.88 (1 H, br s); ^{13}C NMR (25.0 MHz, $CDCl_3$) δ 215.4, 148.5, 114.3, 55.1, 48.3, 47.8, 39.3, 38.7, 37.7, 31.8, 30.8, 25.6, 15.9. Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.48; H, 10.59.

(3aβ,9aβ)-3α,5,5-Trimethyl-8-methylenedecahydro-4*H*-cyclopentacycloocten-4-one (35). Into a 25-mL three-necked round-bottomed flask fitted with a dry nitrogen gas inlet, septum, and mercury seal was added *n*-BuLi (1.2 mL, 0.4 mmol) in hexene. It was cooled to −78 °C, and hexamethyldisilazane (0.2 mL) was added. The mixture was stirred for 20 min, and then THF (2 mL) was added to dissolve the solid material formed. After 10 min the keto olefin **34** (50 mg, 0.26 mmol) in THF (1 mL) was slowly added and was stirred for 20 min. Then methyl iodide (0.2 mL, excess) was added to quench the enolate. The reaction mixture was slowly brought to room temperature and stirred for 3 h. The reaction mixture was then worked up by adding a saturated NH_4Cl solution to it, diluted, and extracted with ether (3 × 20 mL). The organic layer was washed and dried. The crude material obtained after removing the solvent was charged on a silica gel column (30 g). Elution with 10% ethyl acetate–benzene furnished monoalkylated compound: 50 mg (92%); mp 45–46 °C; IR (neat) 3075, 2950, 1700, 1640, 1460, 890 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.88 (3 H, d, J = 8 Hz), 1.0 (3 H, d, J = 8 Hz), 1.52–2.52 (13 H, m), 3.2 (1 H, t, J = 6 Hz), 4.7 (1 H, br s), 4.84 (1 H, br s); ^{13}C NMR (25.0 MHz, $CDCl_3$) δ 217.9, 148.6, 114.4, 51.7, 50.9, 48.6, 39.5, 38.2, 38.0, 34.7, 31.8, 30.5, 17.8, 16.2. Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.58; H, 10.83.

Into a 25-mL three-necked round-bottomed flask fitted with dry nitrogen gas inlet, septum, and mercury seal was introduced diisopropylamine (0.2 mL) in THF (1 mL). This mixture was cooled to −78 °C, and then *n*-BuLi (1 mL, 0.3 mmol) in hexane was slowly added to it. After 30 min monoalkylated compound (50 mg, 0.24 mmol) in THF (1 mL) was slowly introduced and stirring continued for another 25 min. The enolate was quenched with methyl iodide (0.2 mL) at the same temperature, and the reaction mixture was slowly warmed to room temperature. After 1 h, saturated NH_4Cl solution was added and the reaction mixture

was extracted with ether (3 × 20 mL). The organic layer was washed and dried. The crude product obtained after the removal of solvent was charged on a silica gel column (20 g). Elution with 5% ethyl acetate–benzene furnished the *gem*-dimethylated product **35**: 22 mg (67% based on the recovery of starting material); mp 66–67 °C; IR (KBr) 3075, 2950, 1700, 1635, 1460, 880 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.90 (3 H, d, J = 7 Hz), 1.04 (3 H, s), 1.08 (3 H, s), 1.5–1.88 (6 H, m), 2.0–2.42 (6 H, m), 3.34 (1 H, t, J = 6 Hz), 4.68 (1 H, br s), 4.84 (1 H, br s); ^{13}C NMR (25.0 MHz, $CDCl_3$) δ 218.4, 148.5, 114.5, 51.6, 49.0, 48.3, 40.6, 40.0, 37.9, 35.2, 31.9, 30.5, 27.2, 21.4, 16.3. Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.56; H, 10.99. Further elution of the column with 10% ethyl acetate–benzene resulted in the recovery of the starting material (20 mg).

(3aβ,9aβ)-3α,5,5,8-Tetramethyl-1,2,3,3a,5,6,9,9a-octahydro-4*H*-cyclopentacycloocten-4-one (36). A solution of *gem*-dimethylated compound **35** (25 mg, 0.11 mmol) and $RhCl_3 \cdot 3H_2O$ (12 mg, 0.05 mmol) in absolute ethanol (2 mL) was heated to reflux in a 5-mL round-bottomed flask fitted with reflux condensor for 6 h. The reaction mixture was passed through a short alumina column. The crude product obtained after removal of the solvent was charged on a silica gel column (5 g). Elution with 10% ethyl acetate in benzene furnished the isomerized keto olefin **36** [20 mg (80%)], which was bulb-to-bulb distilled at 110 °C (0.5 mm): IR (neat) 3050, 2950, 1695, 1660, 1460 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.86 (3 H, d, J = 7 Hz), 1.08 (3 H, s), 1.2 (3 H, s), 1.76 (3 H, s), 1.6–2.3 (10 H, m), 3.24 (1 H, dd, J = 6 Hz), 5.44 (1 H, t, J = 8 Hz); exact mass calcd for $C_{15}H_{24}O$ m/e 220.1827, found m/e 220.1817.

(3aβ,9aβ)-3α,5,5,8-Tetramethyl-4-hydroxy-1,2,3,3a,5,6,9,9a-octahydro-4*H*-cyclopentacyclooctene (37). Into a two-necked 20-mL round-bottomed flask fitted with a rubber septum and mercury seal was placed LAH (5 mg, excess) in dry ether (5 mL). To this suspension was added keto olefin **37** (20 mg, 0.09 mmol) in dry ether (5 mL) slowly through a syringe. The reaction mixture was stirred for 30 min. A few drops of ethyl acetate were then added to destroy excess hydride. The reaction mixture was diluted with water and extracted with ether (3 × 10 mL). The ethereal layer was washed and dried. Removal of solvent gave hydroxy olefin **37**: 16 mg (80%); IR (neat) 3550, 2950, 1460, 1030 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.84 (3 H, s), 0.98 (3 H, d, J = 8 Hz), 1.02 (3 H, s), 1.74 (3 H, s), 1.2–2.0 (10 H, m), 2.2–3.0 (2 H, m), 3.48 (1 H, d, J = 2 Hz), 5.36 (1 H, t, J = 8 Hz); exact mass calcd for $C_{15}H_{26}O$ m/e 222.1983, found m/e 222.1981.

(±)-Precapnelladiene (1). Hydroxy olefin **37** (15 mg, 0.06 mmol) in dry pyridine (0.5 mL) was placed in a 5-mL round-bottomed flask fitted with a drying tube. To this stirred solution was added phosphorous oxychloride (0.2 mL) at 0–5 °C, and the mixture was stirred for $4^1/_2$ days at room temperature (30 °C). DBU (0.1 mL) was added to the reaction mixture and then stirred at 60 °C for 2 h. The reaction mixture was diluted with pentane (5 mL) and slowly quenched with water (2 mL) to hydrolyze the excess phosphorous oxychloride. The reaction mixture was extracted with pentane (3 × 5 mL) and washed with dilute hydrochloric acid (20%, 3 × 5 mL) and brine. Removal of solvent gave crude diene **12** (12 mg), which was charged on a $AgNO_3$-impegnated silica gel (5 g) column. Elution with pentane removed all oily impurities. Further elution with 50% benzene–pentane furnished pure diene **1**: 9 mg (70%); IR (neat) 2900, 1440, 1370, 1360, 850 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 0.97 (6 H, s), 1.07 (3 H, d, J = 8 Hz), 1.64 (3 H, s), 1.08–1.9 (6 H, m), 2.14–2.54 (2 H, m), 2.7–3.08 (1 H, m), 3.34–3.64 (1 H, m), 5.0 (1 H, br s), 5.34 (1 H, t, J 8 Hz). These were found to be identical (IR, ^1H NMR) with naturally occurring precapnelladiene (**1**).

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A Short Synthesis of Enantiomerically Pure (2*S*,3*R*,4*R*,6*E*)-3-Hydroxy-4-methyl-2-(methylamino)-6-octenoic Acid, the Unusual C-9 Amino Acid Found in the Immunosuppressive Peptide Cyclosporine

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A new and efficient synthesis of enantiomerically pure (2*S*,3*R*,4*R*,6*E*)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoic acid (MeBmt, **2**) is reported. Reaction of (2*R*,4*E*)-2-methyl-4-hexenal (**6c**) with *p*-methoxybenzyloxycarbonylsarcosine *tert*-butyl ester (Pmz-Sar-O-*t*-Bu, **5**) gave MeBmt (**2**) in 18–20% overall yield. The lithium enolate of the *tert*-butyl ester is more stable than the corresponding methyl ester at higher temperature (room temperature vs. −78 °C) and reacts selectively with aldehydes even in the presence of impurities. Room temperature conditions were needed in order to increase the desired anti-Cram product **9a**. The Pmz group proved superior to other amino protecting groups (e.g., Cbz) because residual Pmz-sarcosine derivatives could be easily removed from products **9a** and **9b** by cleavage of the Pmz group by reaction with TFA/anisole. This procedure eliminated the need for column chromatography after the aldol reaction. Reaction of the lithium enolate of Pmz-Sar-O-*t*-Bu (**5**) with aldehyde **6c** afforded only the two trans-substituted 2-oxazolidinones **9a** and **9b** and none of the cis-substituted 2-oxazolidinones. The chemically pure diastereomeric mixture of 2-oxazolidinones **9a** and **9b** was resolved by using (1*S*,2*R*)-(+)-ephedrine to give enantiomerically and diastereomerically pure **9a** in 18–20% overall yield (from aldehyde **6c**). Hydrolysis of **9a** gave the desired MeBmt (**2**) in quantitative yield. This amino acid was incorporated into cyclosporin A (CSA, **1**) by known literature procedures. In order to demonstrate that the synthetic methodology described in this paper can be utilized in the synthesis of a number of MeBmt (**2**) analogues, 1′-desmethyl-2-oxazolidinone **10a** was also prepared by similar procedures.

The structure of the immunosuppressive agent cyclosporine A (CSA, **1**)[1] is distinguished by two novel features: the highly N-methylated cyclic undecapeptide (seven N-methyl amino acids) and the presence of the unique

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