a viscous oil (2.86 g). The IR and ^{1}H NMR (60 MHz) spectra of the volatile material were identical with those of cyclopentadiene contaminated with a small amount of dicyclopentadiene. The viscous oil was chromatographed on silica gel (33 × 5.5 cm i.d.) and eluted with benzene followed by chloroform. Chloroform elution gave 2.265 g of the product mixture, which was separated into two components **9** (R_f 0.38, 1.707 g, 62%) and **10** (R_f 0.45, 463 mg, 17%) by preparative thin-layer chromatography developed with hexane–ethyl acetate (9:1). Each component was collected and recrystallized from ethanol to give colorless prisms **9** and **10**.

9: mp 80–81 °C; IR (KBr) ν_{max} 3055 (w), 3040 (w), 3025 (w), 2955 (w), 2930 (m), 2230 (vs), 1640 (m), 1615 (vs), 1435 (m), 1380 (m), 1335 (m), 1260 (m), 924 (m), 835 (m), 770 (m), 730 (vs), 619 (m), 588 (m) cm^{-1}; UV–vis λ_{max} (EtOH) 230 (log ϵ 3.91), 272 nm (3.92); EI-MS (75 eV) *m/z* (relative intensity) 221 (M^+ + 1, 11), 220 (M^+, 62), 219 (22), 192 (22), 179 (17), 165 (14), 155 (95), 154 (100), 142 (54), 128 (52), 127 (19), 115 (18), 101 (11), 91 (16), 79 (26), 78 (16), 77 (26), 66 (15), 65 (17), 51 (12), 39 (23). Anal. Calcd for $C_{15}H_{12}N_2$: C, 81.79; H, 5.49; N, 12.72. Found: C, 81.84; H, 5.28; N, 12.64.

10: mp 96–97 °C; IR (KBr) ν_{max} 3060 (w), 3050 (w), 2970 (s), 2950 (m), 2235 (vs), 1585 (vs), 1407 (m), 1328 (m), 778 (s), 740 (m), 709 (s), 695 (s) cm^{-1}; UV–vis λ_{max} (EtOH) 237 (log ϵ 4.05), 285 nm (3.73); EI-MS (75 eV) *m/z* (relative intensity) 221 (M^+ + 1, 10), 220 (M^+, 48), 219 (17), 192 (13), 179 (11), 165 (4), 155 (100), 154 (88), 142 (17), 128 (50), 127 (12), 115 (16), 101 (16), 91 (18), 79 (17), 78 (16), 77 (27), 66 (16), 65 (17), 51 (13), 39 (18). Anal. Calcd for $C_{15}H_{12}N_2$: C, 81.79; H, 5.49; N, 12.72. Found: C, 81.86; H, 5.34; N, 12.76.

Reaction of 8,8-Dicyanoheptafulvene (1) with Sodium Cyclopentadienide-d_5. In a similar way, a solution of 2.02 g (13.1 mmol) of 8,8-dicyanoheptafulvene in 100 mL of anhydrous THF was reacted with sodium cyclopentadienide-d_5 [generated from 2.0 mL (22.3 mmol) of cyclopentadiene-d_6 and 600 mg of sodium hydride in 20 mL of anhydrous THF] at −30 °C for 3 h. Workup and purification as described above gave 1.903 g (64.5%) of the main product **9**-d_5 and 0.744 g (25%) of the minor one **10**-d_5.

9-d_5: mp 76–77 °C; IR (KBr) ν_{max} 3040 (w), 2980 (w), 2935 (w), 2830 (w), 2230 (vs), 1640 (m), 1615 (vs), 1430 (m), 1380 (m), 1280 (m), 810 (m), 770 (m), 720 (m), 700 (s), 610 (w), 580 (vs) cm^{-1}; UV–vis λ_{max} (EtOH) 230 (log ϵ 3.91), 272 nm (3.92); EI-MS (75 eV) *m/z* (relative intensity) 226 (M^+ + 1, 5), 225 (M^+, 30), 224 (14), 197 (3), 184 (2), 170 (2), 160 (4), 155 (61), 154 (100), 142 (31), 128 (31), 127 (5), 115 (3), 101 (5), 91 (2), 84 (14), 83 (11), 78 (3), 77 (9), 71 (9), 70 (11), 51 (4), 42 (6).

10-d_5: mp 97–98 °C; IR (KBr) ν_{max} 3045 (m), 2970 (s), 2955 (m), 2235 (vs), 1585 (vs), 1407 (s), 1334 (m), 1305 (m), 775 (m), 755 (m), 726 (vs), 715 (s), 695 (m), 685 (m) cm^{-1}; UV–vis λ_{max} (EtOH) 237 (log ϵ 4.05), 285 nm (3.73); EI-MS (75 eV) *m/z* (relative intensity) 226 (M^+ + 1, 10), 225 (M^+, 53), 224 (27), 223 (11), 197 (7), 184 (5), 170 (4), 160 (7), 155 (100), 154 (97), 142 (16), 128 (68), 127 (12), 120 (9), 103 (15), 96 (16), 79 (11), 78 (35), 77 (10), 71 (23), 70 (11), 51 (8), 44 (21).

Computational Methods. MO calculations were performed on a HITAC M-680H computer at the Institute for Molecular Science, Okazaki, Japan. MNDO calculations were also carried out with an ACOS 430-70 computer of the Computer Center, Nara University, Japan. Geometry optimizations were done with the MNDO MO method[37] implemented in the AMPAC program package.[38]

Acknowledgment. The authors thank the Institute for Molecular Science for the allotment of CPU time of the HITAC M-680H computer. Support of this work by Scientific Grants-in-Aid from the Ministry of Education, Science, and Culture, Japan is gratefully acknowledged.

Supplementary Material Available: NMR spectral charts for the reported compounds **9**, **9**-d_5, **10**, and **10**-d_5 [400-MHz ^{1}H NMR (Lorentz-transformed spectra and those resolution-enhanced with Gaussian and sine-bell wind functions, separately), 2D NMR ^{1}H–^{1}H COSY and ^{1}H–^{1}H COLOC, 100.6-MHz ^{13}C NMR with CPD, gated decoupling (Lorentz-transformed and resolution-enhanced with Gaussian wind function), 2D NMR ^{13}C–^{1}H COSY and ^{13}C–^{1}H COLOC, and ^{13}C NMR with LSPD spectra] and Z-matrices of MNDO optimized geometries of **1**, **6**, **11**, **12**, **13**, TS (**13** → **10**), TS(**12** → **9**), **9**, and **10** (120 pages). Ordering information is given on any current masthead page.

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Access to Naturally Occurring Cyclooctanoids by Two-Carbon Intercalation. Total Synthesis of (+)-Ceroplastol I†

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Abstract: An enantioselective synthesis of the complete dicyclopenta[*a*,*d*]cyclooctane array represented by the sesterterpene (+)-ceroplastol-I is reported. Conversion of the readily accessible optically pure keto ketal **7** (>99% ee) to the α-methoxy derivative **9** was accomplished by adaptation of a protocol developed earlier by Patel and Reusch. Once the transposed enone **10** became available, its peracid oxidation and thermal activation afforded the lactone aldehyde **11**. Sequential Wittig and Tebbe olefination of this intermediate set the stage for Claisen rearrangement and the generation of **13**. Epimerization to set the trans B/C ring geometry was followed by a four-step carbonyl transposition to furnish the pivotal intermediate **17**. Application of the Piers cyclopentannulation scheme to **17** made **19** conveniently available. Kinetic deprotonation of **19**, formation of the less substituted enol triflate, and exposure to lithium dimethyl cuprate gave **20**. To introduce the remaining side chain, **20** was converted by conventional means into **21**, and this enone was subjected to 1,4-addition with the appropriately functionalized cuprate. Reductive removal of the cyclopentanone carbonyl in **22** delivered the target molecule **4**. The more significant developments made in the course of this undertaking are associated with the Claisen ring expansion, the carbonyl transposition in a 4-cyclooctenone without concurrent transannular bonding, and the stereocontrol attainable in bond constructions involving the α,β-unsaturated ketone functionality in **17**.

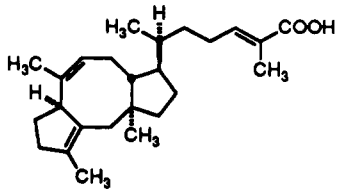
The discovery as early as 1965 of a class of closely related di- and sesterterpenes constituted of the structurally unusual dicyclopenta[*a*,*d*]cyclooctane ring system has provided considerable impetus for the development of new synthetic strategies in medium ring chemistry.[1] The ceroplastins represented by albolic acid (**1**),[2]

† This paper is dedicated to Professor Melvin S. Newman on the occasion of his 85th birthday.

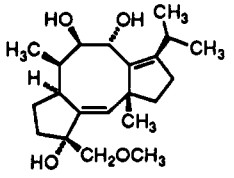
(1) Review: Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757.

0002-7863/93/1515-1676$04.00/0

the fusicoccins exemplified by cotylenol (**2**),[3] and the ophiobolins typified by ophiobolin C (**3**)[4] have been isolated from sources as widely varied as pathogenic fungi and the scale insect *Ceroplastes albolineatus*. The biological and physiological effects of these natural substances are equally diverse.[5]



1



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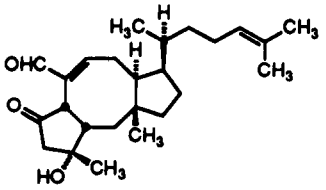
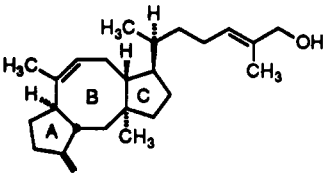


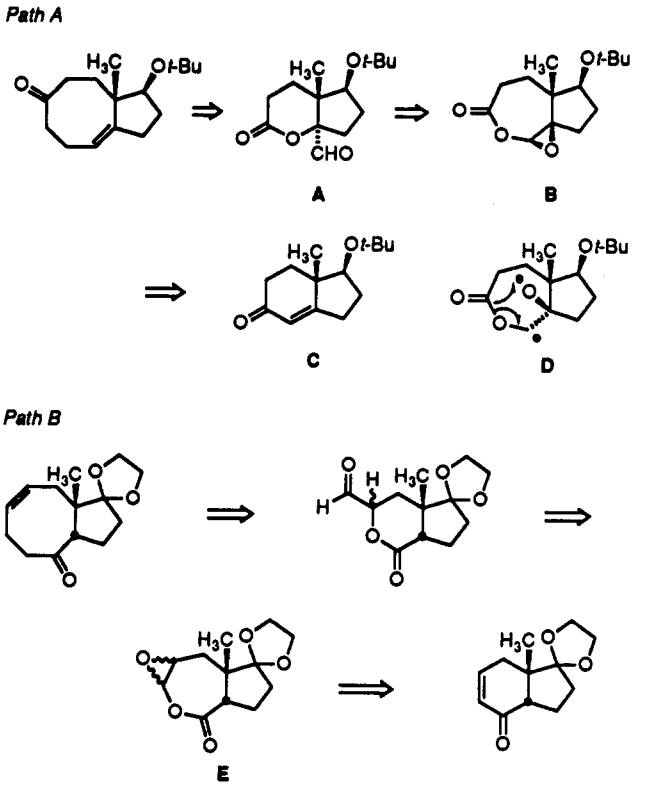
3



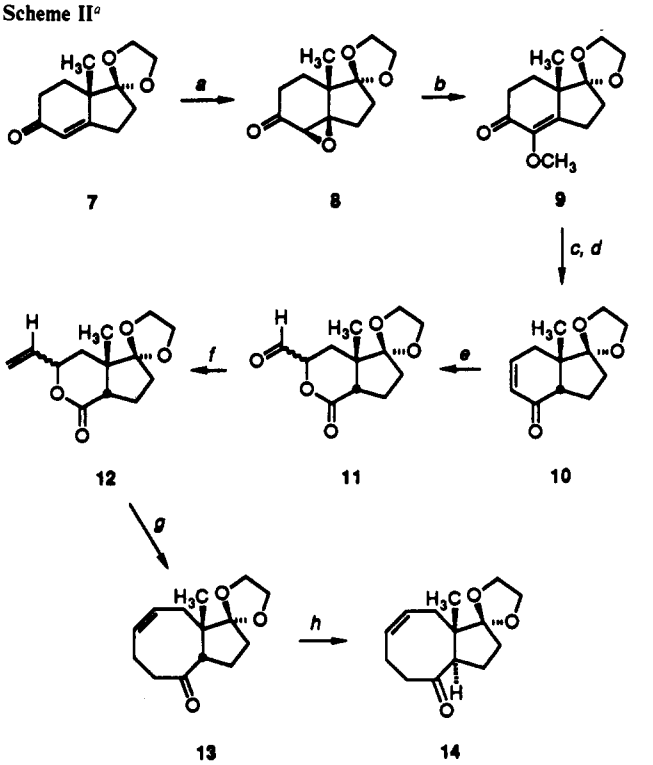
4

The possibility of exploiting several tactics in the elaboration of these targets[6] has recently culminated in successful de novo approaches to **1**, ceroplastol II, and cycloaraneosene by Kato and Takeshita,[7] to (+)-**3** by Kishi,[8] and to (±)-ceroplastol I (**4**) by Boeckman.[9] Efforts to elucidate the potentially intriguing biosynthetic origins of these isoprenoid metabolites have similarly progressed well.[10]

Scheme I



Scheme II[a]



[a] (a) $NaBH_4$, $CeCl_3$; MCPBA; PDC. (b) $NaOCH_3$, CH_3OH, (H_2O). (c) $TsNHNH_2$, CH_3OH, rt. (d) CH_3Li, THF, Et_2O; NH_4Cl, H_2O; HOAc, H_2O, reflux. (e) MCPBA, $NaHCO_3$, CH_2Cl_2, reflux; 175–180 °C, C_6H_6, sealed tube. (f) $Ph_3PCH_3^+Br^-$, $KN(SiMe_3)_2$, THF/ether. (g) $Cp_2Ti(Cl)(CH_2)Al(CH_3)_2$, THF, (py); 200 °C in KOH-coated tubes. (h) K_2CO_3, CH_3OH, reflux.

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Herein we describe a total synthesis of the natural dextrotatory enantiomer of **4**. The showcase transformation of this undertaking is the concise two-carbon intercalation protocol recently developed in these laboratories.[11] This tactic, which reliably and conveniently achieves the enlargement of 6-ring conjugated ketones as exemplified by **5** → **6**, makes tandem use of the Tebbe olefination[12] and Claisen ring expansion processes.[13,14] We have adapted this

5 **6**

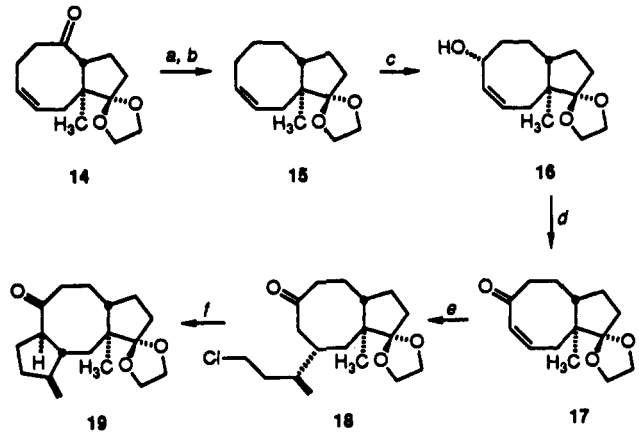
overall transformation to construction of the B and C rings of (+)-**4**. More broadly, we have addressed and defined those stereocontrol elements of significance during the ensuing progression to these targets. Several observations relevant to the regio- and stereochemical response of cyclooctanoid intermediates have emerged in the course of this undertaking.

Results and Discussion

Access to the B/C Subunit by Two-Carbon Intercalation. The two retrosynthetic strategies shown in Scheme I were given consideration in the early planning stages. Ultimately, path A was not pursued because of the untoward stereochemical features of aldehyde **A**. Thus, the thermal activation of epoxy lactone **B**, earlier recognized to be formed stereoselectively upon peracid oxidation of **C**,[15] must give rise transiently to biradical **D** or its zwitterionic equivalent.[16] Subsequent rebonding, as indicated, necessarily positions the aldehyde on the α-face, thereby generating a thermodynamically unfavorable trans-fused ring junction in **A**. Prior experience has shown this feature to be a strong deterrent to operation of this ring-contractive rearrangement.[15] A comparable complication does not materialize in either isomer of **E** since the existing cis stereochemistry is not perturbed during analogous structural isomerization. Consequently, path B was selected as the route to be pursued.

The starting keto ketal **7**, conveniently available by monoketalization[17] of the well-known optically pure (>99% ee) dike-

Scheme III[a]



14 **15** **16** **17** **18** **19**

[a] (a) $LiAlH_4$; *n*-BuLi, $ClP(O)(NMe_2)_2$. (b) Li, $C_2H_5NH_2$, *t*-BuOH, ether, 0 °C. (c) SeO_2, KH_2PO_4, toluene, reflux. (d) PDC. (e) $(ClCH_2CH_2C{=}CH_2)_2CuLi$; THF, −78 °C. (f) KH, THF.

tone,[18] proved to be unusually sluggish in its reactivity toward several epoxidizing agents. Consequently, the desired **8** was produced by sequential reduction to the β-alcohol, exposure to MCPBA, and reoxidation with PDC (Scheme II). By taking advantage of the hydrogen-bonding capacity of the allylic hydroxyl substituent in this way,[19] respectable yields of **8** could be reproducibly realized. The transformation of **8** into **10** was patterned after the studies of Patel and Reusch.[20] Thus, heating the epoxy ketone with sodium methoxide in methanol containing a small amount of water promoted addition-elimination with the formation of **9**. Application of the Shapiro reaction[21] to **9** furnished the methoxy diene, direct acidic hydrolysis of which gave **10**.[22]

The transformation of **10** into ring-expanded epoxy lactone and subsequently into **11** by heating at 175–180 °C in benzene (sealed tube) proved to be uneventful steps. Since the lactone aldehyde is a somewhat sensitive substance, it was generally taken directly into the Wittig olefination step. The overall yield for conversion of the epoxy lactone to **12** was 91%. Although the Tebbe reagent[14] acts smoothly on **12** to give the vinyl ether, this product must be freed as completely as possible of organometallic impurities prior to the Claisen rearrangement in order to realize reproducibly good conversion to **13**.[23] In our experience, elution of this precursor through three short columns of basic alumina is adequate ultimately to provide **13** in 50–60% yield for the two steps. Although the [3,3] sigmatropic event is performed in sealed, KOH-coated glass tubes at 200 °C, ketone **13** does not experience epimerization under these conditions. Conversion to the more thermodynamically favored **14** can be accomplished efficiently by heating **13** with potassium carbonate in methanol.

Synthesis of Advanced Tricyclic Intermediate 19. At this stage, the plan called for the implementation within **14** of a 1,3-carbonyl

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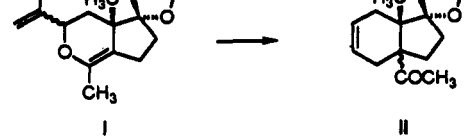
(21) (a) Shapiro, R. H. *Org. React.* **1976**, *23*, 405. (b) Chamberlin, A. R.; Bloom, S. H. *Org. React.* **1990**, *39*, 1.

(22) The diketone corresponding to **10** had earlier been elaborated in racemic form via a rather lengthy route involving intramolecular nitrone–olefin cycloaddition technology: Stanssens, D.; DeKeukeleire, D.; Vandewalle, M. *Bull. Soc. Chim. Belg.* **1987**, *96*, 813.

(23) Failure to take this precaution resulted in internalization of the exocyclic double bond to give i and subsequent Claisen rearrangement of this byproduct to deliver ii competitively:

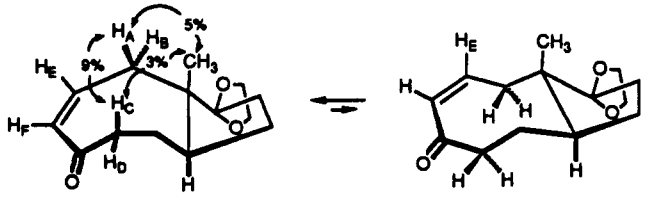


i **ii**

transposition that would neither jeopardize the positional integrity of the double bond nor induce transannular cyclization. Since processes of the latter type are recognized to proceed with exceptional facility in related 4-cyclooctenones,[6e,24] the latent potential for inducing this unwanted phenomenon had to be purposefully circumvented. Mindful of the carbonyl reduction technology that had been introduced by Ireland,[25] we proceeded to reduce **14** with lithium aluminum hydride. The epimeric mixture of alcohols so produced was esterified with bis(dimethylamino)phosphorochloridate, and the resultant phosphorodiamidates were subjected to reduction at 0 °C with lithium in ethylamine containing *tert*-butyl alcohol. In this way, it was possible to skirt both pitfalls and to generate **15** in 75% overall yield (Scheme III).

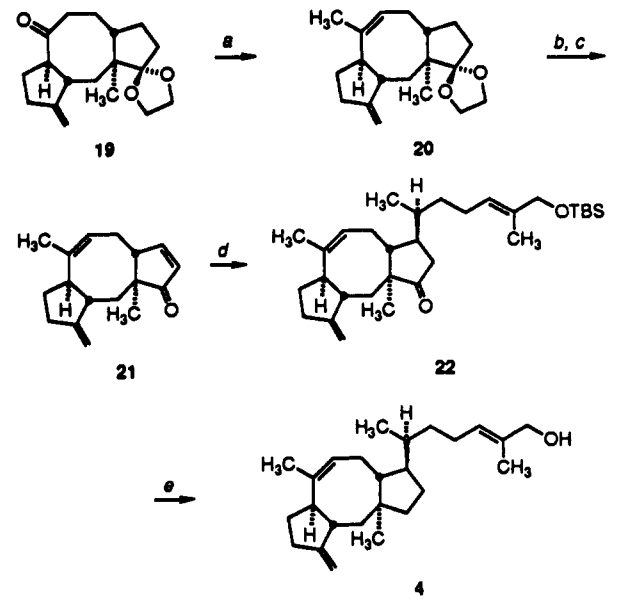
It was anticipated that the allylic oxidation of **15** would proceed regioselectively to produce **16** and/or **17** because of the steric congestion resident in the vicinity of the alternative (neopentyl) reaction site. Quite unexpectedly, however, recourse to the chromium trioxide–dimethylpyrazole complex[26] gave rise to a mixture of two enones in low yield, epoxidation of the double bond being the major reaction. Also noteworthy was the finding that selenium dioxide acts on **15** in various solvents to promote deketalization exclusively. However, the desired transformation can be achieved very effectively by buffering the latter oxidant with KH_2PO_4 and heating mixtures of **15** in refluxing toluene for a few hours. Under these conditions, one isomer of **16** was isolated (61%) alongside a lesser amount of ketone **17** (9%). No serious attempt has been made to confirm the stereochemical assignment accorded to the carbinol carbon in **16** since its oxidation with PDC follows immediately. Suffice it to suggest that the α-hydroxy stereoisomer is expected if the oxidant abstracts the more sterically accessible, stereoelectronically better aligned allylic proton available in the thermodynamically more stable tublike conformer of **15** and forms the C–O–Se bond via a least-motion pathway.

Following this successful effort to arrive at **17**, attention was directed to the annulation of ring A. The adaptation of Piers's cuprate process[27] was considered especially promising. Since two ring junction stereocenters are introduced during this sequence, trajectory considerations surrounding incorporation of the five-membered ring had to be carefully weighed. If the usual control elements operate,[28] the stereoselectivity of the conjugate addition to **17** will be governed by steric accessibility to the β-carbon of the conjugated enone. Although **17** can, in principal, adopt either of the two conformations **F** and **G**, it proved possible by ^1H–^1H



decoupling studies and NOE experiments to ascertain the more stable conformation to be **F**. Certain of the more relevant NOE enhancements are given in the illustrative formula. It is important to recognize that no NOE enhancement was observed to suggest that the methyl group and vinyl proton H_E are in close spatial proximity, as would be expected if the eight-membered ring were folded as in **G**. Consequently, **17** is believed to prefer a ground-state topography which provides more open access to entry of a cuprate reagent from that direction cis to the angular methyl

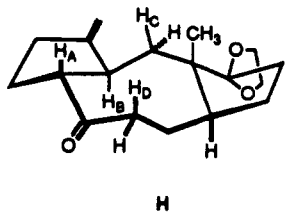
Scheme IV[a]



[a] (a) $KN(SiMe_3)_2$, Tf_2NPh; $(CH_3)_2CuLi$, THF, −20 °C. (b) (TsOH), acetone, H_2O, rt. (c) $LiN(SiMe_3)_2$, $(CH_3)_3SiCl$; $Pd(OAc)_2$, CH_3CN. (d) $TBSOCH_2(CH_3)C{=}CHCH_2CH_2CH(Cl)CH_3$ (**23**); Mg; $CuBr{\cdot}Me_2S$, HMPA, THF, Me_3SiCl, −78 °C. (e) $TsNHNH_2$, $(CO-OH)_2$, C_2H_5OH; $NaBH_3CN$, $ZnCl_2$, CH_3OH, 90 °C.

substituent. Should **F** be the reactive conformer as well, the nonepimerizable allylic center in **19** would be properly installed. The correctness of this proposition would soon be proven.

Initial probes of the conjugate addition of 4-chloro-2-(trimethylstannyl)-1-butene to **17** according to the various reaction conditions delineated by Piers[27] proved singularly unsuccessful. This complication appeared to stem from the instability of the mixed cuprate reagents (ligands such as SPh and CN) since recourse to the simpler homocuprate resulted in smooth condensation to give two diastereomers in the approximate ratio of 15:1. Adduct **18**, easily separated from its less prevalent epimer by column chromatography, underwent high-yield intramolecular cyclization when exposed to potassium hydride in THF. The identity of **19** was convincingly established by means of ^1H decoupling and NOE measurements. The heightened conformational rigidity resident in **19** that is implicit in the three-dimensional representation **H** is particularly well accommodated by the need to position H_A, H_C, and H_D in close proximity on the same surface of the molecule as that occupied by the methyl group.



H

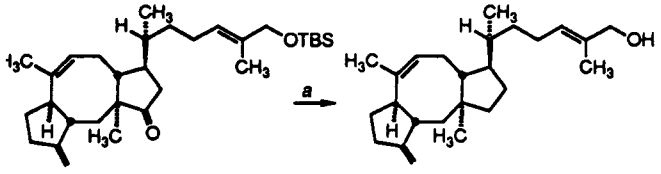
NOE enhancements:

CH_3, H_C	9%
CH_3, H_D	4%
H_C, H_D	4%
H_A, H_D	6%
H_A, H_B	0%

Final Stages of the Synthesis. The ultimate acquisition of **4** requires the introduction of a methyl group in ring B and attachment of an eight-carbon side chain to ring C. Toward this end, **19** was transformed regioselectively into its less substituted enolate anion and condensed with *N*-phenyltriflimide.[29] The success of this conversion is highly dependent upon the proper choice of base and experimental conditions. For example, no deprotonation was observed when $LiN(SiMe_3)_2$ was utilized. With $LiN(i\text{-}Pr)_2$, partial reduction (ca. 20%) and decomposition (ca. 40%) were seen, and unreacting starting material was invariably recovered (ca. 40%). Importantly, maximized yield of the enol

(24) Cope, A. C.; Martin, M. M.; McKervey, M. A. *Quart. Rev.* **1966**, *20*, 119.
(25) Ireland, R. E.; Muchmore, D. C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098.
(26) (a) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057. (b) Kok, P.; DeClercq, P. J.; Vandewalle, M. E. *J. Org. Chem.* **1979**, *44*, 4553.
(27) Piers, E.; Karunaratne, V. *J. Chem. Soc., Chem. Commun.* **1983**, 935.
(28) Sonnet, P. *Synth. Commun.* **1976**, *6*, 21.
(29) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.

Scheme V[a]



24 25

[a] $TsNHNH_2$, $(COOH)_2$, C_2H_5OH; $NaBH_3CN$, $ZnCl_2$, CH_3OH, 90 °C.

triflate was realized only when the $KN(SiMe_3)_2$ and *N*-phenyltriflimide were introduced *simultaneously*. The complication is therefore believed to reside in the relative instability of the enolate anion following its generation.

The action of lithium dimethylcuprate[30] on the enol triflate provided **20** in 68% overall yield (Scheme IV). Deketalization of **20** furnished a tricyclic dienone whose high-field ^1H and ^{13}C NMR spectra showed it to be identical to the intermediate prepared by the Boeckman group.[9] This match-up provided confirmation that our earlier spectroscopically-based stereochemical formulations constitute hard structural data.

Modifications of the original Boeckman route[9] were next implemented to reach (+)-ceroplastol-I (**4**). Once the application of organoselenium methodology was recognized to produce **21** only in very low yield, the silyl enol ether was prepared instead and oxidized with $Pd(OAc)_2$ in acetonitrile.[31] Although we came to favor this procedure as the means for delivering **21**, it was not possible despite the implementation of many variants to increase its efficiency above the 40% level.

With this conjugated enone in hand, the 1,4-addition of **23** was best accomplished by making recourse to the derived Grignard reagent in the presence of a catalytic quantity of the copper(I) bromide–dimethyl sulfide complex. Nucleophilic attack was found to occur exclusively from the β-face with formation of a 3:2 mixture of **22** and **24**. The separation of these diastereomers was accomplished by conventional MPLC. Although the 300-MHz ^1H NMR spectra of **22** and **24** are expectedly quite similar, they are most readily distinguished on the basis of the signals attributable to the two sp^3-bound methyl groups. While this pair of signals is well separated in **22** (δ 0.98 and 0.86 in $CDCl_3$), near overlap is observed in **24** (δ 1.04 and 0.99). These differences, which are obviously diagnostic of the differing preferred relative orientations of the side chain in the respective series, are useful diagnostic tools for distinguishing the two series.

Reduction of the carbonyl oxygen in **22** was achieved by conversion to the tosylhydrazone and its subsequent treatment with sodium cyanoborohydride in the presence of zinc chloride.[32] Desilylation was achieved concurrently, and ceroplastol-I was obtained in 55% yield. The identity of our synthetic dextrorotatory **4**, $[\alpha]^{25}_D$ +72.8° (*c* 1.0, $CHCl_3$), was confirmed by careful comparison of its high-field ^1H NMR spectrum with that of the authentic natural material again generously provided by Professor Boeckman.

The optical rotation of **4** has not previously been recorded. Its crystalline *p*-bromobenzoate and 3,5-dinitrobenzoate esters are both dextrorotatory,[2a] as is ceroplasteric acid (**4**).[2a] While it was therefore likely that our synthetic effort had produced the proper enantiomer, confirmatory proof was desired. Consequently, **4** was derivatized with 3,5-dinitrobenzoyl chloride to give an ester, the optical rotation of which, $[\alpha]^{25}_D$ +68° (*c* 1.17, $CHCl_3$), was found to compare favorably with previously documented data, $[\alpha]^{25}_D$ +73°.[2a]

Synthesis of the C-15 Epimer of Ceroplastol-I. The efficiency with which **24** could be separated from **22** prompted its conversion to **25** for the sake of completeness as well as for spectral comparison. Scheme V outlines the fact that the pathway followed was identical. Entirely comparable yields were secured. Direct comparison of the ^1H NMR spectra of **4** and **25** confirmed that the trend mentioned earlier does indeed persist. In $CDCl_3$ solution, the upfield methyl singlets of **4** are separated by $\Delta\delta$ = 0.12 (δ 0.90, 0.78), while for **25** the gap is much smaller ($\Delta\delta$ = 0.02; 0.90, 0.88).

Summary. A highly stereoselective total synthesis of ceroplastol-I has been achieved in enantiospecific fashion. The approach proved to be enlightening with regard to several stereochemical issues involving the eight-membered B ring. The total extent to which equilibrium is shifted away from **13** to the trans epimer **14** is noteworthy. Another significant observation is the high fidelity with which a methylenecyclopentane ring can be laterally fused to **17** to give predominantly trans-locked **19**. Other useful observations include the effectiveness of potassium hexamethyldisilazide in deprotonating **19** and the facility with which the Grignard reagent derived from **23** adds to **21** under Cu(I) catalysis. In a global sense, adaptation of the two-carbon intercalation process to the acquisition of **4** proceeded with an overall yield of 0.13%.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 1320 spectrometer. ^1H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at 75 MHz on a Bruker AC-300 instrument. Mass spectra were recorded on a Kratos MS-30 instrument at The Ohio State University Instrument Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark. The chromatographic separations were carried out either under flash conditions on Fluka silica gel H or gravimetrically on Woelm silica gel 63-200. The organic extracts were dried over anhydrous magnesium sulfate. Solvents were reagent grade and in many cases dried prior to use.

(3′a*R*,4′*R*,7′a*S*)-3′a,4′-Epoxytetrahydro-7′a-methylspiro[1,3-dioxolane-2,1′-indan]-5′(4′*H*)-one (8). To a solution of **7** (87.8 g, 0.42 mol) in methanol (430 mL) was added cerium trichloride heptahydrate (155 g, 0.42 mol) dissolved in 1 L of the same solvent. The resulting solution was cooled to 0 °C, sodium borohydride (15.3 g, 0.42 mol) was introduced in small portions during 15 min, and stirring was maintained 15 min longer. After the addition of water (300 mL) and saturated NH_4Cl solution (300 mL), most of the methanol was removed on a rotary evaporator. The residue was diluted with water and saturated NH_4Cl solution and extracted with CH_2Cl_2 (3 × 500 mL). The combined organic phases were washed with brine (2×), dried, and evaporated to leave 84 g of oily alcohol that was dissolved in CH_2Cl_2 (1.3 L).

Sodium bicarbonate (50 g, 0.6 mol) and MCPBA (78 g, 0.45 mol) were introduced sequentially into the above solution. After the mixture was stirred for 40 min, a solution of sodium thiosulfate (20.0 g, 80.6 mmol) in water (300 mL) was added. The mixture was stirred for 40 min before being transferred to a separatory funnel, and the separated organic phase was washed with saturated $NaHCO_3$ solution and brine prior to drying and concentration.

The yellow solid (80 g) so produced was dissolved in CH_2Cl_2 (1500 mL) and treated in turn with $MgSO_4$ (44 g, 367 mmol) and PDC (200 g, 532 mmol). The mixture was stirred for 51 h before being diluted with ether (1000 mL), filtered through a column of silica gel, and concentrated. Solid impurities were removed by dissolution in ethyl acetate–petroleum ether (1:3), refiltration through silica gel, and solvent evaporation. The residual yellow oil was purified by chromatography on silica gel (elution with 20% ethyl acetate in petroleum ether to give 53.7 g (57% overal) of **8** as a colorless oil. A sample of the epoxy alcohol was comparably purified (elution with 50% ethyl acetate in petroleum) for characterization purposes.

For the epoxy alcohol: IR (neat, cm^{-1}) 3580; ^1H NMR (300 MHz, $CDCl_3$) δ 3.87 (m, 5 H), 3.16 (d, *J* = 1.0 Hz, 1 H), 2.36 (br s, 1 H), 2.09–1.81 (m, 2 H), 1.79–1.55 (m, 4 H), 1.36–1.23 (m, 1 H), 1.06 (s, 3 H), 1.03–0.96 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 117.5, 71.2, 69.3, 65.2, 64.6, 63.5, 42.1, 31.1, 27.2, 25.9, 24.4, 18.2 ppm; MS *m/z* (M^+) calcd 226.1205, obsd 226.1166; $[\alpha]^{25}_D$ −32.9° (*c* 1.12, $CHCl_3$).

For **8**: IR ($CHCl_3$, cm^{-1}) 1720; ^1H NMR (300 MHz, $CDCl_3$) δ 3.97–3.85 (m, 4 H), 3.08 (s, 1 H), 2.67 (dd, *J* = 13.8, 4.6 Hz, 1 H), 2.61 (dd, *J* = 13.8, 4.6 Hz, 1 H), 2.25–1.77 (m, 5 H), 1.35 (m, 1 H), 1.27 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 208.1, 116.8, 76.3, 65.4, 64.7, 61.5, 42.9, 31.8, 31.4, 29.6, 26.9, 18.3 ppm; MS *m/z* ($M^+ - CH_3$) calcd 209.0814, obsd 209.0867; $[\alpha]^{25}_D$ +46.5° (*c* 1.04, $CHCl_3$).

(*S*)-7′,7′a-Dihydro-4′-methoxy-7′a-methylspiro[1,3-dioxolane-2,1′-indan]-5′(6′*H*)-one (9). To a solution of **8** (43.39 g, 194 mmol) in methanol (4.0 L) was added 21.96 g (407 mmol) of sodium methoxide,

(30) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1980**, *21*, 4313.
(31) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
(32) Kim, S.; Oh, C. H.; Ko, J. S.; Ahn, K. H.; Kim, Y. J. *J. Org. Chem.* **1985**, *50*, 1927.

and the mixture was refluxed for 18 h. The volume was reduced to ca. 1 L under reduced pressure, water (1.5 L) was added, and the product was extracted into CH_2Cl_2 (5 × 500 mL). The combined organic layers were dried and concentrated to leave a residue that was purified chromatographically (silica gel, elution with 20% ethyl acetate in petroleum ether) to furnish 30.12 g (65%) of **9** as a colorless crystalline solid: mp 86–87 °C; IR ($CHCl_3$, cm^{-1}) 1665; ^1H NMR (300 MHz, $CDCl_3$) δ 3.87 (m, 4 H), 3.59 (s, 3 H), 2.58–2.32 (m, 4 H), 2.37–1.78 (series of m, 3 H), 1.46 (ddd, J = 12.7, 5.2, 2.1 Hz, 1 H), 1.20 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 194.0, 156.1, 146.3, 117.4, 65.5, 64.7, 59.2, 48.0, 34.3, 31.7, 26.4, 22.7, 20.1 ppm; MS m/z (M^+) calcd 238.1205, obsd 238.1196; $[\alpha]^{25}_D$ −47.2° (c 1.02, $CHCl_3$).

Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.23; H, 7.57.

(3′a*S*,7′a*S*)-7′,7′a-Dihydro-7′a-methylspiro[1,3-dioxolane-2,1′-indan]-4′(3′a*H*)-one (10). A solution of **9** (28.8 g, 121 mmol) in methanol (180 mL) was treated with *p*-toluenesulfonyl hydrazide (24 g, 129 mmol), stirred under N_2 for 17 h, freed of methanol under reduced pressure, and dried azeotropically with benzene to give 54 g of the tosylhydrazone: IR (CCl_4, cm^{-1}) 3220 (br), 1660, 1600; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 8.2 Hz, 2 H), 7.26 (d, J = 8.2 Hz, 2 H), 3.85 (m, 4 H), 3.52 (s, 3 H), 2.63–2.33 (m, 7 H), 2.28–1.75 (m, 4 H), 1.40 (m, 1 H), 1.03 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) 149.2, 144.1, 143.9, 143.0, 135.5, 129.4, 128.1, 118.0, 65.5, 64.7, 59.3, 46.9, 31.8, 25.1, 22.5, 21.9, 21.5, 20.5 ppm; MS m/z (M^+) calcd 406.1562, obsd 406.1560.

The hydrazone was dissolved in ether (1.2 L) and THF (300 mL), cooled to 0 °C, treated with methyllithium (300 mL of 1.5 M in ether, 450 mmol), stirred at room temperature for 2 h, and returned to 0 °C prior to slow quenching with saturated NH_4Cl solution (300 mL). The separated organic phase was washed with water and brine, dried, and concentrated. Chromatography of the residue on silica gel (elution with 10% ethyl acetate in petroleum ether) afforded 20 g of the methoxy diene as a pale yellow liquid: IR ($CHCl_3$, cm^{-1}) 1680; ^1H NMR (300 MHz, $CDCl_3$) δ 5.86 (dd, J = 9.9, 3.4 Hz, 1 H), 5.70 (m, 1 H), 3.86 (m, 4 H), 3.55 (s, 3 H), 2.68–2.35 (m, 3 H), 2.05 (m, 1 H), 1.74 (m, 2 H), 1.02 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 145.1, 125.8, 122.1, 120.5, 118.3, 65.3, 64.5, 56.6, 46.7, 32.4, 28.9, 21.4, 19.5 ppm; MS m/z (M^+) calcd 222.1256, obsd 222.1280; $[\alpha]^{25}_D$ +74.0° (c 1.03, $CHCl_3$).

The above sample was taken up in THF (200 mL), acetic acid (45 mL), and water (45 mL), refluxed under N_2 for 9 h, and carefully neutralized with aqueous NaOH (30 g in 200 mL of H_2O) at 0 °C. The mixture was extracted with ether, and the combined organic layers were washed with saturated $NaHCO_3$ solution and brine prior to drying and concentration. The residue was crystallized from ethyl acetate–petroleum ether to give 10.3 g of colorless crystals. The mother liquor was chromatographed to afford another 5.4 g of **10** (62% overall): mp 57–58 °C; IR ($CHCl_3$, cm^{-1}) 1670; ^1H NMR (300 MHz, $CDCl_3$) δ 6.77 (ddd, J = 10.1, 5.5, 2.7 Hz, 1 H), 5.91 (d, J = 10.1 Hz, 1 H), 3.86 (m, 4 H), 2.54–2.37 (m, 2 H), 2.12–1.70 (m, 5 H), 0.98 (s, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$) 200.2, 147.5, 127.1, 118.7, 65.2, 64.4, 53.5, 48.8, 34.0, 31.1, 23.4, 19.1 ppm; MS m/z (M^+) calcd 208.1100, obsd 208.1093; $[\alpha]^{25}_D$ +32.8° (c 1.64, $CHCl_3$).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.07; H, 7.70.

(4a*S*,7a*S*)-Hexahydro-4a-methyl-1-oxospiro[cyclopenta[*c*]pyran-5-(1*H*),2′-[1,3]dioxolane]-3-carboxaldehyde (11). A solution of **10** (16.51 g, 79.33 mmol) in CH_2Cl_2 (1.6 L) was treated with $NaHCO_3$ (39.98 g, 476 mmol) followed by MCPBA (51.34 g of 80%, 238 mmol) and heated at gentle reflux for 5 days. After cooling, saturated $NaHCO_3$ (500 mL) and 10% $Na_2S_2O_3$ solutions (500 mL) were added, the mixture was stirred for 2 h, and the separated organic phase was washed with saturated $NaHCO_3$ solution and water prior to drying and evaporation. Purification of the residue by silica gel chromatography (elution with 30% ethyl acetate in petroleum ether) to give 10.51 g (55%) of epoxy lactone as colorless crystals: mp 157–158 °C (from ethyl acetate–petroleum ether); IR ($CHCl_3$, cm^{-1}) 1755; ^1H NMR (300 MHz, $CDCl_3$) δ 5.09 (d, J = 2.4 Hz, 1 H), 3.94–3.78 (m, 5 H), 3.36 (ddd, J = 9.0, 5.4, 2.4 Hz, 1 H), 2.89 (dd, J = 8.3, 2.1 Hz, 1 H), 2.51–2.41 (m, 1 H), 2.06–1.76 (m, 4 H), 1.30 (d, J = 0.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 170.3, 117.0, 75.5, 65.3, 65.0, 54.1, 50.9, 50.3, 32.4, 30.3, 24.1, 20.3 ppm; MS m/z (M^+) calcd 240.0997, obsd 240.0979; $[\alpha]^{25}_D$ +14.2° (c 1.29, $CHCl_3$).

Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.93; H, 6.73.

A solution of the epoxy lactone (2.00 g, 8.32 mmol) was dissolved in benzene (10 mL), placed in a heavy-walled tube, degassed by the freeze–thaw technique, sealed, and heated at 175–180 °C for 1 day. The cooled mixture was evaporated to give **11**, which was used directly because of its sensitivity to chromatographic adsorbents: IR ($CHCl_3$, cm^{-1}) 1740; ^{13}C NMR (75 MHz, C_6D_6) (major isomer) 198.8, 171.5, 118.3, 81.0, 64.8, 64.5, 48.6, 44.0, 32.7, 30.2, 26.1, 24.2 ppm; MS m/z (M^+) calcd 240.0997, obsd 240.0981.

(4a*S*,7a*S*)-Hexahydro-4a-methyl-3-vinylspiro[cyclopenta[*c*]pyran-5-(1*H*),2′-[1,3]dioxolan]-1-one (12). A stirred mixture of methyltriphenylphosphonium bromide (5.21 g, 14.2 mmol), anhydrous ether (200 mL), and dry THF (200 mL) was cooled to 0 °C, basified with KN($SiMe_3$)$_2$ (25 mL of 0.5 M in THF, 12.5 mmol), and allowed to warm to room temperature during 30 min. After being recooled to 0 °C, the mixture was treated with a solution of the unpurified **11** in THF (20 mL), stirred for 1 h at room temperature, and quenched with saturated NH_4Cl solution. After the mixture was diluted with ether, the separated organic phase was washed with brine, dried, and evaporated. The resulting residue was chromatographed on silica gel (elution with 20% ethyl acetate in petroleum ether) to give 1.81 g (91% overall) of **12** as a 1:1 mixture of epimers: colorless oil; IR ($CHCl_3$, cm^{-1}) 1740; ^1H NMR (300 MHz, $CDCl_3$) δ 5.89 (m, 1 H), 5.42–5.18 (m, 2 H), 5.00 (m, 0.5 H), 4.75 (m, 0.5 H), 3.92 (m, 4 H), 2.68 (m, 0.5 H), 2.46 (dd, J = 9.9, 4.8 Hz, 0.5 H), 2.35–2.10 (m, 1 H), 2.34–1.75 (m, 4 H), 1.50 (dd, J = 14.1, 2.2 Hz, 0.5 H), 1.36 (dd, J = 14.6, 10.4 Hz, 0.5 H), 1.25 (s, 1.5 H), 1.11 (s, 1.5 H); ^{13}C NMR (75 MHz, $CDCl_3$) 174.4, 174.0, 136.3, 135.8, 118.5, 117.4, 116.9, 116.4, 77.7, 76.6, 65.3, 64.9, 48.8, 46.7, 45.3, 44.3, 36.9, 35.1, 33.6, 31.8, 26.7, 25.4, 23.6, 21.2 (2 carbon signals not observed) ppm; MS m/z (M^+) calcd 238.1205, obsd 238.1238.

(3a*S*,9a*S*)-3,3a,5,6,9,9a-Hexahydro-9a-methylspiro[1*H*-cyclopentacyclooctene-1,2′-[1,3]dioxolan]-4(2*H*)-one (13). To a solution of **12** (1.95 g, 8.6 mmol) in dry THF (12 mL) and toluene (12 mL) containing 0.1 mL of pyridine and cooled to −40 °C was added Tebbe reagent (18 mL of 0.5 M in toluene, 9.0 mmol). After being stirred at −40 °C for 30 min, the red-colored mixture was allowed to warm to room temperature for 2 h, cooled to 0 °C, and treated with 20% NaOH solution (2.8 mL). Once gas evolution ceased, the mixture was diluted with ether (100 mL), *briefly* dried over $MgSO_4$, and filtered through a short column of activity III basic alumina (elution with ether). The concentrated filtrate was twice chromatographed on activity III basic alumina (elution with 4% ether in petroleum ether) to remove all metal-containing impurities.

The resulting faintly yellow oil (1.4 g) was dissolved in xylenes (20 mL), sealed in a KOH-coated Pyrex tube under vacuum, and heated at 200 °C for 26 h. After being cooled, the solution was diluted with ether and washed with saturated NH_4Cl solution, water, and brine prior to drying and solvent evaporation. Chromatographic purification (silica gel, elution with 20% ethyl acetate in petroleum ether) afforded **13** (1.2 g, 61% overall) and traces of trans isomer **14**.

For **13**: colorless oi; IR ($CHCl_3$, cm^{-1}) 1700; ^1H NMR (300 MHz, $CDCl_3$) δ 5.83–5.74 (m, 1 H), 5.70–5.62 (m, 1 H), 3.89 (m, 4 H), 2.80–2.70 (m, 2 H), 2.65–2.55 (m, 1 H), 2.42 (m, 2 H), 2.25–1.75 (m, 6 H), 1.05 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 213.6, 130.6, 129.4, 118.5, 65.5, 64.6, 58.7, 50.4, 45.0, 33.1, 30.0, 23.0, 21.7, 20.7 ppm; MS m/z (M^+) calcd 236.1413, obsd 236.1411; $[\alpha]^{25}_D$ +25.4° (c 2.58, $CHCl_3$).

(3a*R*,9a*S*)-3,3a,5,6,9,9a-Hexahydro-9a-methylspiro[1*H*-cyclopentacyclooctene-1,2′-[1,3]dioxolan]-4(2*H*)-one (14). A solution of **13** (1.26 g, 5.3 mmol) in methanol (70 mL) was treated with K_2CO_3 (630 mg, 4.6 mmol), heated at reflux for 31 h, cooled, diluted with water, and extracted with ether. The organic phase was washed with water and brine, dried, and evaporated. The residue was purified by silica gel chromatography (elution with 20% ethyl acetate in petroleum ether) to give 1.06 g (93%) of **14** and return 124 mg of unisomerized **13**.

For **14**: colorless oil; IR ($CHCl_3$, cm^{-1}) 1705; ^1H NMR (300 MHz, $CDCl_3$) δ 5.75 (m, 1 H), 5.56 (m, 1 H), 3.93 (m, 4 H), 3.46 (dd, J = 10.2, 2.0 Hz, 1 H), 2.95 (m, 1 H), 2.63 (dd, J = 13.4, 7.8 Hz, 1 H), 2.50–2.32 (m, 2 H), 2.15–1.55 (m, 6 H), 0.80 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 212.9, 131.2, 129.3, 119.9, 65.7, 64.2, 53.7, 50.8, 46.1, 31.5, 30.3, 21.8, 21.7, 15.8 ppm; MS m/z (M^+) calcd 236.1413, obsd 236.1417; $[\alpha]^{25}_D$ −40.9° (c 2.27, $CHCl_3$).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.35; H, 8.66.

(3a*R*,9a*S*)-2,3,3a,4,5,6,9,9a-Octahydro-9a-methylspiro[1*H*-cyclopentacyclooctene-1,2′-[1,3]dioxolane] (15). A solution of **14** (484 mg, 2.05 mmol) in ether (4 mL) and THF (4 mL) was treated at 0 °C with lithium aluminum hydride (170 mg, 4.5 mmol) and stirred at room temperature for 20 min, and the reaction was quenched by slow addition of saturated NH_4Cl solution until the solids turned white. The salts were filtered and washed repeatedly with a 1:1 ether/THF mixture. The combined filtrates were dried and evaporated. Chromatography of the residue on silica gel (elution with 30% ethyl acetate in petroleum ether) gave 400 mg (83%) of the alcohol as a colorless oil: IR ($CHCl_3$, cm^{-1}) 3650 (br); ^1H NMR (300 MHz, $CDCl_3$) δ 5.65–5.50 (m, 2 H), 3.90 (m, 5 H), 2.50–2.10 (m, 5 H), 2.05–1.70 (m, 4 H), 1.65 (m, 1 H), 1.50 (s, 1 H), 1.15 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 129.8, 127.6, 120.1,

74.9, 65.2, 63.7, 50.3, 44.4, 33.8, 32.54, 32.46, 26.4, 22.2, 20.0 ppm; MS m/z (M^+) calcd 238.1569, obsd 238.1554.

A cold (0 °C), magnetically stirred solution of this alcohol (480 mg, 2.0 mmol) in THF (20 mL) and TMEDA (5 mL) was treated with *n*-butyllithium (2 mL of 1.3 M in hexane, 2.6 mmol) and stirred for 15 min. After bis(dimethylamino)phosphorochloridate (1.73 g, 10.0 mmol) was introduced, stirring was maintained at room temperature for 4 h, at which point saturated $NaHCO_3$ solution (12 mL) was slowly added. The mixture was agitated for 2 h, diluted with ethyl acetate, and washed with water, saturated NH_4Cl, and brine. The combined aqueous layers were extracted with ethyl acetate, and the assimilated organic solutions were dried and concentrated. Chromatography of the residue (silica gel, elution with 10% methanol in ethyl acetate) afforded 750 mg (98%) of the phosphoroamidate as a colorless oil, which was directly reduced with a solution of lithium (250 mg, 36 mmol) in dry ethylamine (freshly distilled from lithium) containing ether (6 mL) and *tert*-butyl alcohol (0.2 mL). The blue solution was stirred for 30 min at 0 °C, the reaction was quenched with saturated NH_4Cl solution, and the solution was allowed to stand overnight. The product was taken up in ether and water. The organic phase was washed with saturated NH_4Cl and $NaHCO_3$ solutions and brine, dried, and concentrated. Silica gel chromatography (elution with 5% ethyl acetate in petroleum ether) gave 330 mg (73%) of **15** as a colorless oil: IR (neat, cm^{-1}) 1660, 1470, 1300, 1160, 1065; ^1H NMR (300 MHz, C_6D_6) δ 5.78 (dt, J = 10.5, 8.1 Hz, 1 H), 5.63 (m, 1 H), 3.47 (s, 4 H), 2.58 (dd, J = 13.1, 8.1 Hz, 1 H), 2.37 (m, 1 H), 2.16 (m, 1 H), 1.98–1.09 (m, 10 H), 0.99 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) 130.8, 129.5, 120.6, 65.3, 64.0, 50.3, 43.3, 32.9, 30.7, 28.3, 27.8, 26.2, 24.9, 15.4 ppm; MS m/z (M^+) calcd 222.1620, obsd 222.1633; $[\alpha]^{25}_D$ −78.5° (c 1.77, $CHCl_3$).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.86; H, 10.10.

(3a*R*,6*R*,9a*S*)-2,3,3a,4,5,6,9,9a-Octahydro-9a-methylspiro[1*H*-cyclopentacyclooctene-1,2′-[1,3]dioxolan]-6-ol (16). A mixture of **15** (143 mg, 0.64 mmol), potassium dihydrogen phosphate (275 mg, 2.02 mmol), and selenium dioxide (159 mg, 1.43 mmol) in toluene (9 mL) was refluxed under N_2 for 3 h. The cooled mixture was diluted with ether, washed with saturated $NaHCO_3$ solution and brine, dried, and concentrated. The residue was chromatographed on silica gel (elution with 35% ethyl acetate in petroleum ether) to furnish 90 mg (61%) of **16** and 14 mg (9%) of **17**.

For **16**: colorless oil; IR (neat, cm^{-1}) 3410; ^1H NMR (250 MHz, $CDCl_3$) δ 5.68 (m, 1 H), 5.53 (m, 1 H), 3.89 (s, 4 H), 3.71 (m, 1 H), 2.28 (dd, J = 13.1, 8.1 Hz, 1 H), 2.02–1.15 (m, 11 H), 0.83 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) 136.3, 127.2, 120.4, 67.6, 65.3, 64.0, 50.3, 44.1, 37.1, 32.4, 31.4, 28.5, 24.7, 15.0 ppm; MS m/z (M^+) calcd 238.1569, obsd 238.1570; $[\alpha]^{25}_D$ −110.8° (c 1.12, $CHCl_3$).

(3a*R*,9a*S*)-3,3a,4,5,9,9a-Hexahydro-9a-methylspiro[1*H*-cyclopentacyclooctene-1,2′-[1,3]dioxolan]-6(2*H*)-one (17). A solution of **16** (51 mg, 0.21 mmol) in dry CH_2Cl_2 (6 mL) was treated with pyridinium dichromate (150 mg, 0.40 mmol) and $MgSO_4$ (30 mg), stirred for 15 h, and diluted with ether. Filtration through a short path of silica gel and concentration of the filtrate left a yellow oil, which was purified chromatographically (silica gel, elution with 30% ethyl acetate in petroleum ether). There was isolated 41 mg (80%) of **17** as a colorless oil: IR (neat, cm^{-1}) 1660; ^1H NMR (300 MHz, $CDCl_3$) δ 6.40 (ddd, J = 12.3, 9.1, 7.4 Hz, 1 H), 6.16 (dt, J = 12.2, 1.5 Hz, 1 H), 3.92 (m, 4 H), 2.98 (m, 1 H), 2.50–2.26 (m, 3 H), 1.80–1.53 (m, 5 H), 1.40–1.25 (m, 2 H), 1.01 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) 200.4, 143.2, 135.6, 119.5, 65.1, 63.6, 47.2, 40.9, 39.1, 34.6, 32.6, 26.1, 25.9, 17.0 ppm; MS m/z (M^+) calcd 236.1413, obsd 236.1417; $[\alpha]^{25}_D$ +160.5° (c 1.47, $CHCl_3$).

(3a*R*,8*S*,9a*S*)-8-[1-(2-Chloroethyl)vinyl]octahydro-9a-methylspiro-[1*H*-cyclopentacyclooctene-1,2′-[1,3]dioxolan]-6(2*H*)-one (18). To a solution of 4-chloro-2-trimethylstannyl-1-butene (255 mg, 1.0 mmol) in ether (5 mL) and THF (4 mL) at −78 °C was added methyllithium (0.8 mL of 1.5 M in ether, 1.2 mmol). After 15 min, copper(I) bromide–dimethyl sulfide (115 mg, 0.57 mmol) was introduced, and the mixture was stirred for 25 min while being warmed to −65 °C to form an orange solution. A solution of **17** (53 mg, 0.22 mmol) in ether (3 mL) was added dropwise at −78 °C, and stirring was maintained for 1 h at −78 °C before saturated NH_4Cl solution (4 mL) was dropped in. The mixture was warmed to room temperature, diluted with ether, and washed with water and brine prior to drying and concentration. Chromatography of the residue on silica gel (elution with 10% ethyl acetate in petroleum ether furnished 57 mg (78%) of **18** and 4 mg (5%) of its epimer.

For **18**: colorless crystals, mp 58.5–60 °C; IR (neat, cm^{-1}) 1712; ^1H NMR (300 MHz, $CDCl_3$) δ 4.89 (s, 1 H), 4.77 (s, 1 H), 3.88 (m, 4 H), 3.61 (t, J = 7.5 Hz, 2 H), 2.75 (m, 2 H), 2.50 (br t, J = 6.7 Hz, 2 H), 2.39–1.25 (series of m, 12 H), 0.92 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) 212.4, 152.2, 121.0, 110.1, 64.8, 63.1, 53.9, 46.8, 42.9, 41.1, 39.1, 38.93, 38.87, 37.6, 32.3, 29.0, 26.8, 18.6 ppm; MS m/z (M^+) calcd 326.1649, obsd 326.1651; $[\alpha]^{25}_D$ −43.1° (c 1.59, cyclohexane).

For the epimer: ^1H NMR (300 MHz, C_6D_6) δ 4.77 (s, 1 H), 4.58 (s, 1 H), 3.40 (m, 4 H), 3.26 (t, J = 7.2 Hz, 2 H), 2.48–1.97 (series of m, 8 H), 1.71–0.91 (series of m, 8 H), 0.86 (s, 3 H).

(3a*R*,6a*R*,9a*S*,10a*S*)-Dodecahydro-10a-methyl-9-methylenespiro[dicyclopenta[*a*,*d*]cyclooctene-1(6*H*),2′-[1,3]dioxolan]-6-one (19). To a suspension of KH (165 mg, 4.1 mmol) in dry THF was added **18** (389 mg, 1.2 mmol) dissolved in the same solvent (7 mL), followed by a trace amount of methanol. The mixture was stirred for 5 h before the reaction was quenched with saturated NH_4Cl solution, diluted with ether, washed with water and brine, and dried. Chromatography of the residue on silica gel (elution with 10% ethyl acetate in petroleum ether) afforded 315 mg (90%) of **19** as a colorless oil: IR (neat, cm^{-1}) 1710; ^1H NMR (300 MHz, $CDCl_3$) δ 4.83 (m, 2 H), 3.92 (m, 4 H), 2.78 (td, J = 12.4, 5.3 Hz, 1 H), 2.65–1.25 (series of m, 16 H), 0.96 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) 212.5, 155.5, 121.1, 103.5, 65.0, 63.7, 63.2, 46.6, 46.4, 39.6, 39.5, 38.0, 32.4, 30.7, 29.0, 26.8, 24.3, 18.5 ppm; MS m/z (M^+) calcd 290.1882, obsd 290.1880; $[\alpha]^{25}_D$ −55.0° (c 1.13, cyclohexane).

Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02. Found: C, 74.38; H, 9.09.

(3a*S*,6a*R*,9a*S*,10a*S*)-3,3a,4,6a,7,8,9,9a,10,10a-Decahydro-6,10a-dimethyl-9-methylenespiro[dicyclopenta[*a*,*d*]cyclooctene-1(2*H*),2′-[1,3]dioxolane] (20). A solution of **19** (119 mg, 0.42 mmol) in dry THF (7 mL) at −78 °C was treated dropwise with potassium hexamethyldisilazide (1.7 mL of 0.5 M in toluene, 0.85 mmol) during 5 min while *N*-phenyltrifluoromethanesulfonimide (300 mg, 0.85 mmol) in 3.5 mL of dry THF was introduced via a syringe pump over 1 h. After the reaction mixture was stirred for 30 min, the reaction was quenched with saturated NH_4Cl solution, warmed to room temperature, diluted with ether, and washed with water and brine prior to drying. The concentrate was purified by silica gel chromatography (elution with 7.5% ethyl acetate in petroleum ether) to give 173 mg of somewhat impure enol triflate: ^1H NMR (300 MHz, C_6D_6) δ 5.65 (dd, J = 8.6, 8.1 Hz, 1 H), 5.03 (dd, J = 5.0, 2.5 Hz, 1 H), 4.92 (dd, J = 4.8, 2.3 Hz, 1 H), 3.45 (m, 4 H), 2.69 (m, 2 H), 2.33–1.06 (series of m, 13 H), 0.83 (s, 3 H).

A suspension of the copper(I) bromide–dimethyl sulfide complex (300 mg, 1.5 mmol) in THF (20 mL) at −40 °C was treated with methyllithium (2 mL of 1.5 M in ether, 3 mmol) and stirred until an almost colorless solution resulted. The enol triflate (173 mg, 0.42 mmol) dissolved in dry THF (10 mL) was next added, and stirring was maintained for 40 min at −20 °C. After the addition of saturated NH_4Cl solution and warming to room temperature, the usual workup and chromatographic purification followed (elution with 5% ethyl acetate in petroleum ether). There was isolated 81 mg (68% overall) of **20** as a colorless oil: IR (neat, cm^{-1}) 2970, 1305, 1155, 1070, 1055; ^1H NMR (300 MHz, C_6D_6) δ 5.58 (dd, J = 7.7, 6.7 Hz, 1 H), 5.17 (d, J = 2.4 Hz, 1 H), 5.07 (d, J = 2.2 Hz, 1 H), 3.49 (m, 4 H), 2.97 (td, J = 12.4, 5.5 Hz, 1 H), 2.49–2.06 (series of m, 6 H), 1.83–1.13 (m, 8 H), 1.57 (s, 3 H), 1.09 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) 154.4, 137.1, 126.8, 121.4, 104.2, 65.5, 63.9, 50.5, 50.3, 48.2, 44.7, 32.2, 32.0, 29.1, 28.0, 27.7, 27.0, 18.6, 14.3 ppm; MS m/z (M^+) calcd 288.2089, obsd 288.2088; $[\alpha]^{25}_D$ −26.5° (c 1.59, cyclohexane).

(3a*R*,6a*R*,9a*S*,10a*S*)-4,6a,7,8,9,9a,10,10a-Octahydro-6,10a-dimethyl-9-methylenedicyclopenta[*a*,*d*]cycloocten-1(3a*H*)-one (21). A solution of **20** (81 mg, 0.28 mmol) and *p*-toluenesulfonic acid (7 mg, 0.036 mmol) in acetone (4 mL) and water (1 mL) was stirred for 13 h and concentrated on a rotary evaporator. The product was taken up in ether, washed with water and brine, dried, freed of solvent, and purified chromatographically (silica gel, elution with 5% ethyl acetate in petroleum ether). There was obtained 56 mg (84%) of the ketone as a colorless solid: mp 71.5–73 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 5.57 (t, J = 7.8 Hz, 1 H), 5.03 (br d, J = 2.4 Hz, 1 H), 4.93 (br d, J = 2.3 Hz, 1 H), 2.87 (td, J = 12.6, 5.5 Hz, 1 H), 2.62 (d, J = 15.4 Hz, 1 H), 2.58–2.29 (m, 6 H), 2.07 (dd, J = 19.1, 9.7 Hz, 1 H), 1.91–1.49 (m, 5 H), 1.63 (s, 3 H), 1.21 (dd, J = 15.3, 7.4 Hz, 1 H), 0.86 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 220.5, 153.7, 137.8, 125.6, 104.5, 53.0, 52.8, 47.3, 44.5, 34.8, 31.6, 30.8, 27.5, 27.1, 25.2, 18.4, 13.3 ppm; MS m/z (M^+) calcd 244.1827, obsd 244.1822; $[\alpha]^{25}_D$ +111.7° (c 1.42, cyclohexane).

The ^1H and ^{13}C NMR spectra of our sample were identical to those provided to us by Professor Boeckman.

A solution of this ketone (62 mg, 0.25 mmol) in dry THF (8 mL) was treated with lithium hexamethyldisilazide (0.32 mL of 1.0 M in THF) at −78 °C. The mixture was stirred for 40 min before chlorotrimethylsilane (70 μL, 0.52 mmol) was introduced. After 5 min, the mixture was allowed to warm to room temperature, freed of volatiles under reduced pressure, taken up in petroleum ether (2 mL), and filtered through a pad of Celite. Concentration of the filtrate gave 80 mg of the silyl enol ether as a colorless oil. This material was dissolved in deoxygenated acetonitrile (2.5 mL) under nitrogen, cooled to 0 °C, treated with

a solution of palladium(II) acetate (65 mg, 0.29 mmol) in the same solvent (2.5 mL), stirred at room temperature for 1.5 h, and partitioned between benzene and saturated NH_4Cl solution. The organic phase was washed with brine, dried, and evaporated. Chromatography of the residue on silica gel (elution with 5% ethyl acetate in petroleum ether) afforded 18 mg of **21** and returned 17 mg of starting ketone. The yield based on recovered starting material is 40%: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (dd, J = 5.8, 1.8 Hz, 1 H), 6.0 (dd, J = 5.8, 3.0 Hz, 1 H), 5.67 (t, J = 7.2 Hz, 1 H), 4.98 (dd, J = 4.5, 2.3 Hz, 1 H), 4.92 (dd, J = 4.5, 2.3 Hz, 1 H), 2.94 (td, J = 11.4, 5.9 Hz, 1 H), 2.64 (dt, J = 10.2, 1.4 Hz, 1 H), 2.53–2.29 (m, 5 H), 2.13 (dd, J = 8.2, 14.6 Hz, 1 H), 1.67 (s, 3 H), 1.79–1.50 (m, 4 H), 1.11 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 213.2, 165.0, 154.5, 138.7, 129.4, 126.6, 104.7, 57.4, 55.2, 47.3, 44.5, 31.8, 31.7, 28.3, 25.9, 21.4, 19.7 ppm; MS m/z (M^+) calcd 242.1671, obsd 242.1667; $[\alpha]^{25}_D$ +22.0° (c 1.73, cyclohexane).

(3*R*,3a*R*,6a*R*,9a*S*,10a*S*)-3-[(1*S*,4*E*)-6-(*tert*-Butyldimethylsiloxy)-1,5-dimethyl-4-hexenyl]-3,3a,4,6a,7,8,9,9a,10,10a-decahydro-6,10a-dimethyl-9-methylenedicyclopenta[*a*,*d*]cycloocten-1(2*H*)-one (22). Chloride **23** was prepared according to the Boeckman protocol[9] and purified by Kugelrohr distillation (115 °C/1.5 Torr): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.35 (tq, J = 7.3, 1.3 Hz, 1 H), 4.01 (m, 2 H), 2.20 (m, 2 H), 1.76 (m, 2 H), 1.62 (s, 3 H), 1.51 (d, J = 6.6 Hz, 3 H), 0.91 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) 135.7, 122.7, 68.4, 58.3, 40.1, 26.0, 25.4, 24.7, 18.4, 13.4, −5.3 ppm.

Conversion of the chloride (440 mg, 1.6 mmol) to the Grignard reagent was achieved by stirring with magnesium turnings (75 mg, 3.1 mmol) in dry THF (2 mL) for 40 min. The extent of conversion was approximately 80%.

To a suspension of $CuBr{\cdot}Me_2S$ (8.5 mg, 0.041 mmol) in cold (−78 °C) anhydrous THF (1 mL) was added the above Grignard reagent (0.35 mL of 0.65 M, 0.22 mmol), followed by HMPA (50 μL, 0.28 mmol). This mixture was stirred for 10 min before **21** (18 mg, 0.074 mmol) and trimethylsilyl chloride (30 μL, 0.24 mmol) dissolved in THF (1 mL) was introduced dropwise. The resulting yellow suspension was stirred for 30 min, and the reaction was quenched with saturated NH_4Cl solution (1 mL) and hydrolyzed with 5% HCl (2 mL) for 1.5 h. The products were isolated by ether extraction and silica gel chromatography (elution with 3% ethyl acetate in petroleum ether) to give 30 mg (83%) of a diastereomeric mixture, the components of which were separated by MPLC (silica gel, elution with 2.5% ethyl acetate in petroleum ether). There was obtained 11 mg (30%) of the less polar epimer **24** and 17 mg (47%) of **22**.

For **24**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.56 (br t, J = 7.6 Hz, 1 H), 5.32 (br t, J = 6.8 Hz, 1 H), 5.04 (d, J = 2.2 Hz, 1 H), 4.95 (d, J = 1.9 Hz, 1 H), 3.98 (s, 2 H), 2.90 (td, J = 12.6, 5.4 Hz, 1 H), 2.62–1.67 (series of m, 13 H), 1.63 (s, 3 H), 1.57 (s, 3 H), 1.54–1.08 (m, 5 H), 1.04 (d, J = 6.6 Hz, 3 H), 0.99 (s, 3 H), 0.90 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) 222.5, 153.6, 137.5, 134.7, 126.3, 124.1, 104.6, 68.5, 57.8, 52.6, 47.8, 44.4, 44.0, 42.7, 36.5, 35.2, 33.9, 31.8, 27.5, 26.3, 26.0, 24.8, 20.3, 18.41, 18.38, 16.7, 13.4, −5.3 ppm; MS m/z (M^+) calcd 484.3737, obsd 484.3731; $[\alpha]^{25}_D$ +62.2° (c 1.9, cyclohexane).

For **22**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.56 (br t, J = 7.8 Hz, 1 H), 5.36 (br t, J = 7.8 Hz, 1 H), 5.03 (d, J = 2.2 Hz, 1 H), 4.94 (d, J = 1.8 Hz, 1 H), 4.00 (s, 2 H), 2.88 (td, J = 12.2, 5.5 Hz, 1 H), 2.58–1.91 (series of m, 12 H), 1.75–1.50 (m, 4 H), 1.63 (s, 3 H), 1.59 (s, 3 H), 1.25 (m, 2 H), 0.98 (s, 3 H), 0.91 (s, 9 H), 0.86 (d, J = 6.7 Hz, 3 H), 0.06 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) 222.0, 153.7, 137.6, 134.6, 126.1, 124.2, 104.6, 68.5, 57.0, 52.6, 47.6, 44.5, 42.2, 40.3, 38.3, 33.6, 32.8, 31.8, 27.6, 26.0, 25.2, 25.0, 18.5, 18.4, 18.3, 16.7, 13.4, −5.3 ppm; MS m/z (M^+) calcd 484.3737, obsd 484.3735; $[\alpha]^{25}_D$ +89.4° (c 1.12, cyclohexane).

(2*E*,6*S*)-6-[(3*R*,3a*R*,6a*R*,9a*S*,10a*S*)-1,2,3,3a,4,6a,7,8,9,9a,10,10a-Dodecahydro-6,10a-dimethyl-9-methylenedicyclopenta[*a*,*d*]cycloocten-3-yl]-2-methyl-2-hepten-1-ol. Ceroplastol-I (4). A solution of **22** (35 mg, 0.072 mmol) in ethanol (1.5 mL) was treated with *p*-toluenesulfonylhydrazide (20 mg, 0.11 mmol) and oxalic acid dihydrate (35 mg, 0.28 mmol), stirred at room temperature for 24 h, taken up in ethyl acetate, and washed with saturated $NaHCO_3$ solution and brine prior to drying and concentration. Silica gel chromatography of the residue (elution with 40% ethyl acetate in petroleum ether) gave 34 mg (88%) of the tosylhydrazone, to which was added a solution of sodium cyanoborohydride (34 mg, 0.54 mmol) and zinc chloride (34 mg, 0.25 mmol) dissolved in methanol (2 mL). The resulting solution was heated in a sealed tube at 90 °C for 3 h, cooled, diluted with ether, washed sequentially with 5% HCl, saturated $NaHCO_3$ solution, and brine, dried, and concentrated. Chromatography of the residual oil on silica gel (elution with 10% ethyl acetate in petroleum ether) produced 11 mg (55%) of **4**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.54 (m, 1 H), 5.40 (m, 1 H), 4.90 (s, 1 H), 4.81 (d, J = 2.1 Hz, 1 H), 4.00 (s, 2 H), 2.96 (td, J = 12.5, 5.4 Hz, 1 H), 2.55–1.73 (series of m, 8 H), 1.67 (s, 3 H), 1.67 (s, 3 H), 1.71–1.06 (series of m, 14 H), 0.90 (s, 3 H), 0.78 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 155.0, 136.8, 134.4, 127.6, 126.8, 103.6, 69.1, 57.1, 48.4, 46.5, 46.2, 44.42, 44.35, 39.5, 36.9, 32.9, 32.1, 27.7, 25.9, 23.6, 22.5, 19.0, 18.5, 16.7, 13.6 ppm; MS m/z (M^+) calcd 356.3079, obsd 356.3073; $[\alpha]^{25}_D$ +72.8° (c 1.0, $CHCl_3$).

The 3,5-dinitrobenzoate of **4** was isolated as a pale yellow foamy solid: mp 107–109 °C (lit.[2a] mp 111–112 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.22 (t, J = 2.1 Hz, 1 H), 9.16 (d, J = 2.1 Hz, 2 H), 5.62 (br t, 1 H), 5.48 (br t, 1 H), 4.90 (s, 1 H), 4.84 (s, 2 H), 4.81 (s, 1 H), 2.94 (td, J = 12.4, 5.4 Hz, 1 H), 2.55–1.80 (series of m, 9 H), 1.77 (s, 3 H), 1.60 (s, 3 H), 1.72–1.24 (m, 11 H), 0.90 (s, 3 H), 0.78 (d, J = 6.8 Hz, 3 H); $[\alpha]^{25}_D$ +68° (c 1.17, $CHCl_3$) (lit.[2a] $[\alpha]_D$ +73°).

The less polar isomer **24** (11 mg) was similarly reduced to give 3 mg of **25**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.53 (br t, 1 H), 5.39 (br t, 1 H), 4.90 (s, 1 H), 4.81 (d, J = 2.2 Hz, 1 H), 3.99 (s, 2 H), 2.96 (td, J = 12.4, 5.4 Hz, 1 H), 2.55–1.78 (series of m, 9 H), 1.66 (s, 3 H), 1.62 (s, 3 H), 1.70–1.03 (series of m, 13 H), 0.90 (s, 3 H), 0.88 (d, J = 6.7 Hz, 3 H); MS m/z (M^+) calcd 356.3079, obsd 356.3072.

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