flux/3 min)[19,20] gave the primary alcohol **12** in 52% overall yield from **11**. The stereoselectivity of the enone reduction was approximately 4:1, favoring the desired diastereomer.

The primary alcohol was protected [*t*-Bu(Me)$_2$SiCl/imidazole/DMF/room temperature] not only to differentiate it from the alcohol produced in the next reaction but also to protect the β-silyloxyketone from elimination upon treatment with Grignard reagents.[21] The ketone was then treated with methylmagnesium bromide (Et_2O/0 °C → room temperature) to give a 13:1 mixture of tertiary alcohols favoring the desired **13** in 68% overall yield from **12**. At this stage, and in the earlier tin hydride reduction, the relative stereochemistry of the products was assigned by analogy to the model system[4] and was proven correct by successful conversion to ophiobolin C.

Swern oxidation, Wittig reaction [$(Me)_2C{=}P(Ph)_3$ (30 equiv)/THF/−78 °C → 0 °C], deprotection (*n*-Bu_4NF/THF/room temperature/2 h), and Swern oxidation furnished synthetic ophiobolin C (**1c**; mp 118–120 °C) in 46% overall yield from **13**. On comparison of spectroscopic (^1H and ^{13}C NMR, IR, UV, $[\alpha]_D$, MS) and chromatographic data, the synthetic substance was superimposed on an authentic sample.[22] In addition, no depression was observed on mixed melting point determination.

Acknowledgment. Financial support from the National Science Foundation (CHE 86-105050) is gratefully acknowledged.

Supplementary Material Available: ^1H NMR spectra of key intermediates and ^1H and ^{13}C NMR spectra of (+)-ophiobolin C (18 pages). Ordering information is given on any current masthead page.

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(22) We are grateful to Professor S. Nozoe, Tohoku University, for providing us with a very generous sample of natural ophiobolin C.

Synthetic Studies Directed toward Naturally Occurring Cyclooctanoids. 1. Total Synthesis of (±)-Ceroplastol I

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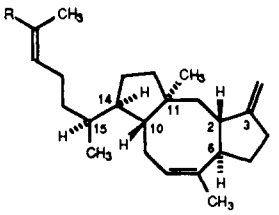
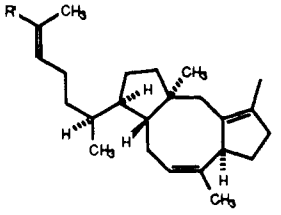
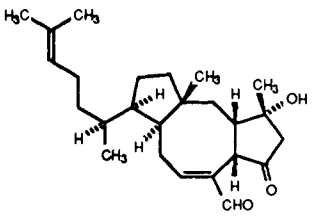
Our interest in the development of general protocols for the highly stereoselective construction of natural substances which contain functionalized eight-membered rings led us to consider the relatively small group of sesterterpenes exemplified by ceroplastol I (**1**),[1] the closely related structures ceroplastol II (**2**),[2] albolic acid (**3**),[3] and the ophiobolins, such as ophiobolin C (**4**).[4] A number of the ophiobolins show biological and potent phytological effects.[5-7] The challenges associated with the construction of these systems have stimulated a number of synthetic approaches;[8] however, only very recently has the first report of successful assembly of a naturally occurring member of the class appeared.[9,10]



1 R = CH_2OH
25 R = $CH_2OCOPh[3,5\text{-}(NO_2)_2]$



2 R' = CH_2OH
3 R' = CO_2H



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The central feature of our strategy is the construction of the eight-membered ring via fragmentation of an appropriately functionalized bicyclo[3.3.1]nonanone system as was described in our prior model studies.[11] The choice of this strategy was dictated by the need to minimize the potential for isomerization of the exocyclic olefin and transannular reactions involving the highly reactive trisubstituted eight-membered ring olefin. We felt establishment of the required relative stereochemistry about the eight-membered ring could be conveniently achieved utilizing the rigid template provided by the bicyclic precursors to the medium ring. Herein we describe the implementation of this strategy to a concise and overall highly stereoselective total synthesis of (±)-**1**.

Base-catalyzed Michael addition of the known racemic β-ketolactone **5**[12] to enone **6**[11] and acid-induced cyclization of the intermediate diketone afforded an inconsequential mixture (4.5:1) of crystalline epimeric tricyclic lactones **7** (mp 89–90 °C) in 60% yield (Scheme I).[13] The mixture of lactones **7** underwent decarboxylation upon base treatment, and the resulting hydroxy enones were directly transformed to the related methoxymethyl ethers **8** in 70% overall yield (twice distilled Kugelrohr, 110–130 °C at 0.5 mm).[14]

Introduction of the C_{11} quaternary center in **1** with complete stereoselectivity was then achieved by alkylation of the α′ enolate derived from **1** with (*Z*)-2-chloroacrylate **9**.[11,15] Alkaline hydrolysis and exposure of the resulting *Z* enone acrylate to TFAA provided the δ trienol lactone **10**, possessing the required stereodefined framework for introduction of the C_{10} ring junction center in **1**, in 63% overall yield.[16] The C_2 and C_{10} centers were

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(10) See: Rowley, M.; Tsukamoto, M.; Kishi, Y. *J. Am. Chem. Soc.* **1989**, *111*, the preceding paper in this issue, reporting the first synthesis of a natural ophiobolin (ophiobolin C).
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(12) Boeckman, R. K., Jr.; Naegely, P. C.; Arthur, S. D. *J. Org. Chem.* **1980**, *45*, 752. Both enantiomers of **5** have been prepared in our laboratories by this protocol by using appropriate chiral auxiliaries: (3*R*,7*R*)-**5** (α^{25}_D −89.0° and (3*S*,7*S*)-**5** (α^{25}_D +89.7°). See: Boeckman, R. K., Jr.; Napier, J. J.; Thomas, E. W.; Sato, R. I. *J. Org. Chem.* **1983**, *48*, 4152.
(13) All new substances exhibited spectroscopic data (IR, NMR (300 or 500 MHz), and MS) in accord with the assigned structure and provided acceptable combustion or high resolution analytical data.
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(15) All compounds reported are racemic unless otherwise stated. The stereochemical frame of reference changes from Scheme I (six-membered ring) to Scheme II (eight-membered ring) which accounts for the apparent stereochemical changes in Scheme II.

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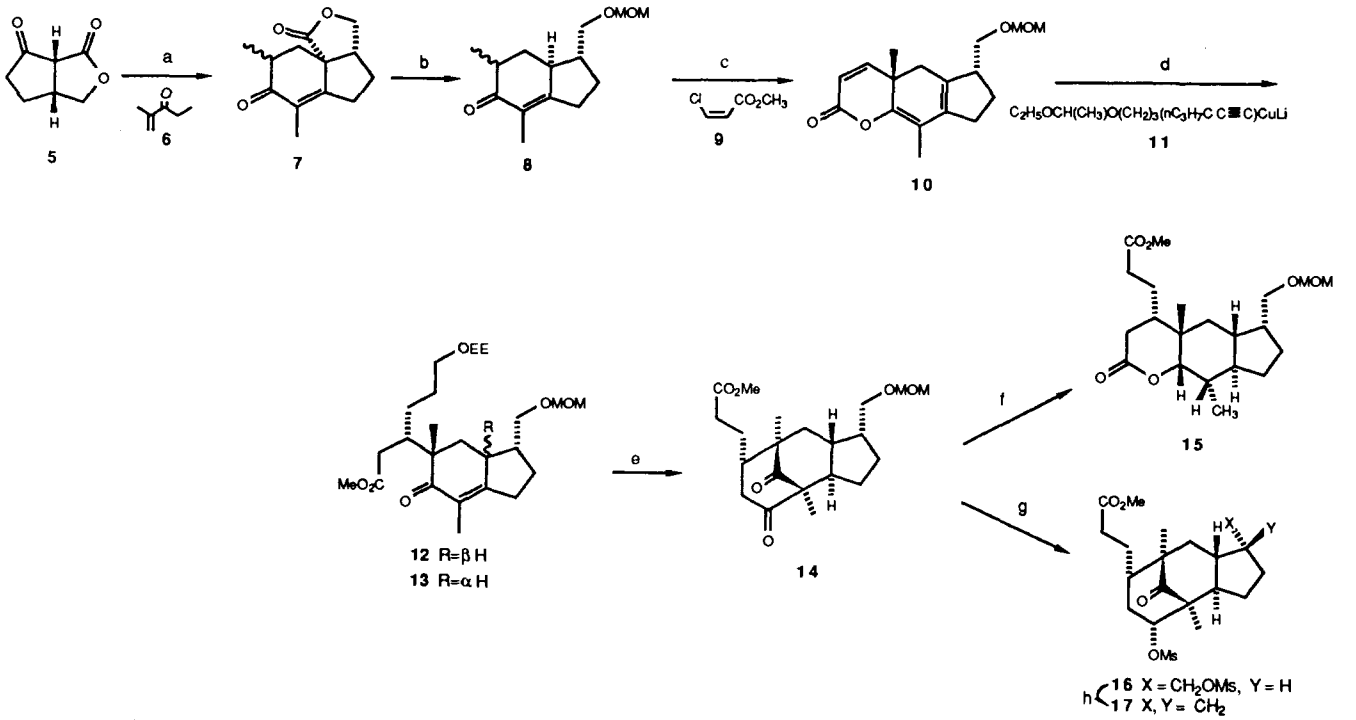
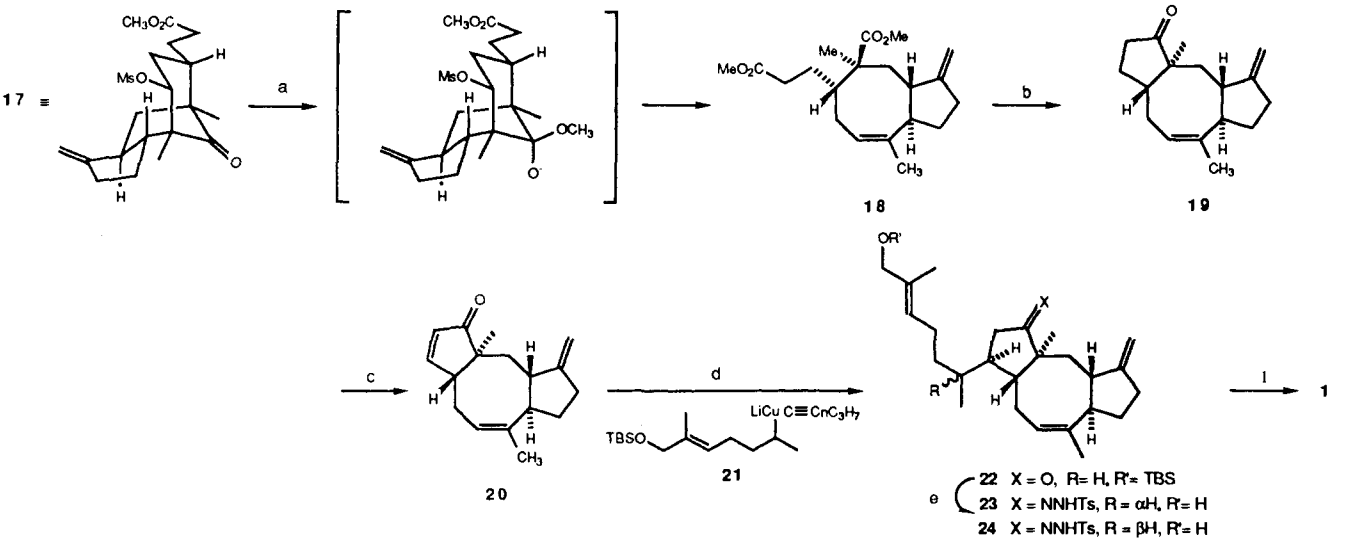
Scheme I[a]



[a] Reagents: (a) **6** (1.5 equiv), DBN (0.7 mol %), Et_3N (0.7 mol %), 25 °C, 48 h then pTsOH (catalytic), PhH, Δ, 48 h; (b) KOH (1 equiv), DMSO, H_2O (1.2 equiv), 137 °C, 4 h then P_2O_5 (1 equiv), $CH_2(OCH_3)_2/CHCl_3$ (1:1, v/v), 25 °C, 8 h; (c) LiICA (1.1 equiv), **9** (1.3 equiv), −23 °C, 2 h then KOH (1.1 equiv), CH_3OH/H_2O (2:1), 25 °C, 24 h followed by TFAA (1.2 equiv), NaOAc (1 equiv), CH_2Cl_2, 0 °C (1 h) → 25 °C (0.5 h); (d) $C_2H_5OCH(CH_3)O(CH_2)_3(C{\equiv}CC_3H_7)CuLi$ (**11**), Et_2O, −23 °C, 1 h then $LiOCH_3$ (0.6 equiv), CH_3OH, 0 °C, 3 h; (e) Na (25 equiv), *t*BuOH (9 equiv), $NH_3(l)/THF$ (4:1), −78 °C (0.5 h) → −33 °C (0.66 h) then $NaBrO_3$ (1 equiv), $(NH_4)_2Ce(NO_3)_6$ (0.1 equiv), CH_3CN/H_2O (7:3), Δ, 10 min followed by CrO_3 (2.4 equiv of a 2.5 M solution), acetone, 0 °C, 15 min then CH_2N_2 (excess), CH_2Cl_2, −78 °C; (f) KOH (2 equiv), CH_3OH/CH_2Cl_2 then CH_2N_2, CH_2Cl_2, −78 °C followed by $NaBH_4$, CH_3OH; (g) $LiAl(OtBu)_3H$ (1.5 equiv), THF, 0 °C, 30 min then CH_3OH (saturated with HCl(g))/CH_2Cl_2 (20:1), 25 °C, 3 h, followed by MsCl (3.6 equiv), Et_3N (4.8 equiv), CH_2Cl_2, 0 °C, 30 min; (h) KI (0.15 equiv), K_2CO_3 (3.6 equiv), DMF, 85 °C, 20 h.

Scheme II[a]



[a] Reagents: (a) $NaOCH_3$ (18 equiv), CH_3OH, Δ, 6 h; (b) $KN(TMS)_3$ (4 equiv), THF, −78 °C → 25 °C then LiI (1.2 equiv), collidine, 155 °C, 30 min; (c) LDA (1.1 equiv), THF, −78 °C, 20 min, followed by $Pd(OAc)_2$ (1.1 equiv), CH_3CN, 0 °C → 25 °C, 2 h; (d) **21**, HMPT (2 equiv), THF/Et_2O (1:1), −40 °C, 2 h; (e) $TsNHNH_2$ (1.3 equiv), $(CO_2H)_2$ (5 equiv), C_2H_5OH, 25 °C, 24 h; (f) $ZnCl_2$ (4 equiv), $NaCNBH_3$ (8 equiv), CH_3OH, 90 °C, 4 h.

created via a stereoelectronically controlled addition of the mixed cuprate **11** to **10**[11] and careful methanolysis of the resulting δ dienol lactone which provided the readily separable epimeric ketoesters **12** and **13** (6:1) in 65% yield.[17] The final ring junction stereocenter C_6 was established by Na/NH_3 reduction of keto ester **12**.

(16) The exclusive formation of the homoannular trienol lactone **10** was unfortunate and surprising in light of our model studies.[11] Stereoelectronically controlled axial addition of the cuprate to **10** is the expected result and creates the requisite trans relationship at the C_{10}–C_{11} ring junction in **1**.

(17) In principle, the δ dienol lactone precursor to **12** and **13** (of the appropriate absolute configuration) could have afforded access to either the ceroplastols or the ophiobolins; however, we have not as yet established cleavage conditions affording **13** as the major product. **13** is readily recycled to **12**.

The resulting mixture of alcohols (~8:1 (T/C) at the newly created ring junction) was directly subjected to successive oxidations, initially of the secondary hydroxyl group to the related ketone (with simultaneous removal of the ethoxyethyl group),[18] followed by exposure to excess Jones reagent[19] which resulted in oxidation to the derived keto aldehyde, concomitant aldol cyclization, and further oxidation to afford after esterification the tricyclic diketone **14** in 45% overall yield (chromatographically purified) from **12**. The structure and stereochemistry assigned to **12** was confirmed by single-crystal X-ray analysis of lactone **15** derived from **14** (Scheme I).[20] Creation of the eight-membered ring was then initiated by reduction of the more accessible carbonyl group in **14** to the required equatorial alcohol, deprotection of the remaining hydroxyl, and conversion to the bismesylate **16** (mp 122–124 °C) in standard fashion in 43% overall yield from **12** (Scheme I). Selective elimination of the primary mesylate provided the unsaturated mesylate **17** (58% yield, 76% conversion) possessing the requisite antiperiplanar geometry suitable for fragmentation.[21]

Exposure of **17** to excess $NaOCH_3$ in CH_3OH at reflux smoothly effected the desired cleavage to afford **18** in 73% yield (Scheme II). Closure of the final ring was then accomplished by Dieckman condensation, and immediate decarboxylation provided the crystalline ketone **19** (mp 55–57 °C) in 76% yield.

With the ring skeleton assembly complete, the final task was introduction of the eight carbon side chain of **1** which was initiated by conversion of ketone **19** via the intermediate lithium enolate, under Saegusa conditions, to the key tricyclic enone **20** in 55% yield (65% conversion).[22]

A variety of strategies were investigated to permit introduction of a suitably protected intact side chain with good stereocontrol over both sites of attachment (C_{14}) and the acyclic stereocenter (C_{15}).[20] However, high levels of stereocontrol have thus far been achieved only over C_{14}. Reaction of **20** with the mixed cuprate **21** derived from the suitably protected intact side chain gave an inseparable mixture of ketones **22** (~1:1) in 70% yield.[23] Fortunately, treatment of ketones **22** with $TsNHNH_2$ catalyzed by $(COOH)_2$ afforded a separable mixture (prep TLC) of the derived tosyl hydrazones **23** (more polar) and **24** in 86% yield.[24] Reduction of **23** with $ZnCl_2ONaCNBH_3$ in CH_3OH at 90 °C (sealed system) afforded (±)-ceroplastol I (**1**) (~50%) identical by spectroscopic (300 and 500 MHz NMR) and TLC (several solvent systems) comparison with the an authentic sample of natural (+)-**1**.[25,26] Subsequent conversion of (±)-**1** to the derived 3,5-dinitrobenzoate **25** and spectroscopic (300 and 500 MHz NMR), TLC, and HPLC comparison with a sample of (+)-**25** derived from natural material further confirmed their identity.

Further studies are currently underway whose goal is to devise a strategy which also will permit control over the acyclic C_{15} center. The foregoing sequence, which also constitutes formal total syntheses of ceroplastol II (**2**) and albolic acid (**3**), affords (±)-**1** in 22 steps (from **5**) and is readily adaptable to preparation of (+)-ceroplastol I.[12]

Acknowledgment. We are extremely grateful to the Institute of General Medical Sciences (NIGMS) of the National Institutes of Health for a grant (GM-29290) in support of these studies. We also thank Drs. S. D. Arthur and P. C. Naegely for their valuable contributions to the early stages of these studies.

Supplementary Material Available: Spectroscopic and selected analytical data for compounds **1**, **7**, **8**, **10**, **12**, **14–20**, **22**, and **23** (14 pages). Ordering information is given on any current masthead page.

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(23) The mixed cuprate **21** was readily prepared from (*E*)-1-hydroxy-2-methyl-2-hepten-6-one[27] by the following sequence: (a) TBSCl, imidazole, DMF, 25 °C, 10 h (79%); (b) $NaBH_4$, C_2H_5OH, 0 °C, 0.5 h (80%); (c) Ph_3P (2 equiv), CCl_4, Δ, 2 h (82%); (d) $Li^+(4\text{-}t\text{-}BuPh)_2^{\cdot-}$ (2 equiv), THF, −78 °C, 0.25 h, then added to $nC_3H_7C{\equiv}CCu$ (1 equiv) precomplexed with HMPT (2 equiv) at 25 °C, Et_2O, −23 °C, 3 min.[28]
(24) The stereochemistry at C_{14} and C_{15} in hydrazones **23** and **24** was assigned after reduction. Only **23** afforded (±)-**1**; however, the similarity of the NMR spectra of the diastereomer of ceroplastol I obtained from **24** strongly suggests that **23** and **24** are epimeric only at C_{15}.
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(26) We are grateful to Drs. Shuyen and Ian Harrison for supplying us with a generous sample of natural (+)-ceroplastol I 3,5-dinitrobenzoate for comparison with our synthetic materials. Natural (+)-ceroplastol I was obtained by cleavage of the 3,5-dinitrobenzoate.
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In Situ FTIR Spectroscopy at Elevated CO Pressure. Evidence for Single-Electron Transfer in the Catalytic Carbonylation of Nitroaromatics

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Much effort has been expended to develop alternative preparations of aryl isocyanates which avoid utilizing phosgene.[1] The focus of much work has been directed toward discovering a direct carbonylation of the nitro functionality to the isocyanate or carbamate[1-3] (eq 1). One of the most effective catalysts found

$$ArNO_2 + 3CO + CH_3OH \xrightarrow{cat.} ArNHC(O)OCH_3 + 2CO_2 \quad (1)$$

in eq 1 was Ru(dppe)$(CO)_3$ (dppe = 1,2-bis(diphenylphosphino)ethane).[3] We report here our studies on the deoxygenation steps in the mechanism of this reaction which suggest that activation of the nitro group occurs via a one-electron reduction by the Ru(0) complex.

The principal products under typical catalytic reaction conditions[4] using nitrotoluene were *p*-tolylmethylcarbamate and *p*-toluidine. Small amounts of formylidene-*p*-toluidine arising from the condensation of *p*-toluidine and formaldehyde were observed. Insight into the mechanism of the reaction was obtained by in situ examination of the working catalyst solutions using FTIR spectroscopy. The high-pressure CIR reactor has been described elsewhere[5,6] and is commercially available. Figure 1a shows that immediately after mixing all of the reagents with the catalyst the three absorptions at 2003, 1934, and 1912 cm^{-1} are attributable to the unchanged complex. After the solution was allowed to stand for 3 h under CO pressure, three new absorptions at 2058, 1982,

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(4) Typical conditions for the catalysis were 3 mM catalyst, 100 mM *p*-nitrotoluene, 40 mM methanol, a total volume of 15 mL, a temperature of 145 °C, and a pressure of CO of 83 atm. The composition of the starting solution differed in two aspects from the original reports.[3a,b,d] First, a solvent mixture of benzene and methanol (compared to neat methanol in the patent) was used to increase the solubility of the catalyst at lower temperatures. Second, the aryl amine was left out of the system.[3c]
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