This assertion is supported by the fact that the 24-methylcholest-5,22-dien-3β-ol was found in a diatom (which forms the basis of the food chain in the marine environment) and also in a number of invertebrates.[16] Similarly the presence of peridinin, a carotenoid characteristic of dinoflagellates, in the sponge *Isis hippuris* has led to the suggestion that this carotenoid could have been derived from the food chain.[17] Recently it has been proposed that gorgosterol side chain (III) could have been derived from dinosterol (II) by a simple addition of a methylene group across the C-22,23 double bond.[18] The isolation of 4-methylgorgostanol (I) along with dinosterol and 24-demethyldinosterol from the dinoflagellate *G. foliaceum* supports the proposed mechanism[18] of the formation of gorgosterol side chain from dinosterol. Very recently Professor Djerassi's group has also isolated 4-methylgorgostanol from the dinoflagellate *Peridinium foliaceum*.[19]

We hope to resolve the biosynthetic scheme of 4-methylgorgostanol through studies currently in progress in our laboratory.

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Registry No. I, 71962-34-0; II, 58670-63-6; IV, 71912-00-0; cholesterol, 57-88-5; 24-demethyldinosterol, 71962-35-1; 3-oxo-4α-methyl-5α-gorgostane, 71912-00-0.

(16) I. Rubinstein and L. J. Goad, *Phytochemistry*, **13**, 485 (1974).
(17) P. T. Murphy, R. J. Wells, J. E. Johansen, and S. Liaaen-Jensen, *Biochem. Sys. Ecol.*, **6**, 85 (1978).
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(19) Professor C. Djerassi Personal communication.

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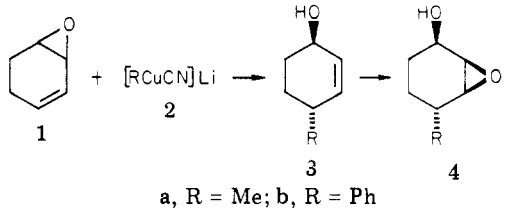
Stereospecific and Regiospecific Methodology for the Synthesis of Chiral Molecules

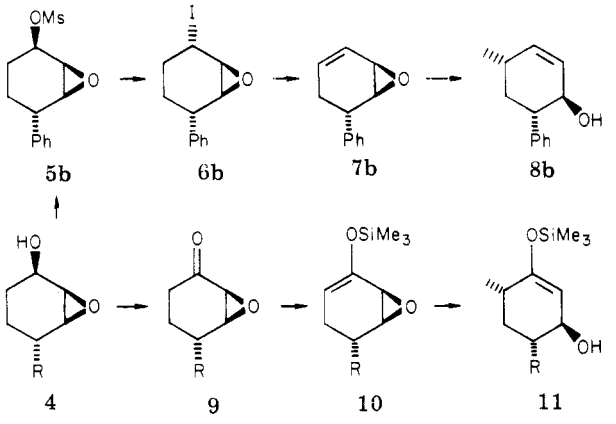
Summary: Sequential trans 1,4-openings of cyclohexene epoxides and hydroxyl directed epoxidations provide general methodology for the functionalization of five carbon atoms of a six carbon unit.

Sir: The formidable synthetic challenges associated with the total syntheses of macrolides and ionophores require efficient and general methods for the stereocontrolled introduction of substituents along a conformationally mobile backbone. Recent syntheses of the Prelog–Djerassi lactone by White[1] and Stork[2] as well as the macrolide total syntheses by Masamune[3] and Corey[4] have elegantly demonstrated the strategy of employing cyclic systems as precursors to chiral acyclic synthons. We wish to report the facile introduction of three chiral centers and the overall functionalization of five carbon atoms of a six-carbon unit. Our methodology is based on the stereospecific and regiospecific functionalization of the readily available 1,3-cyclohexadiene monoepoxide 1 and the subsequent oxidative cleavage of the final cyclohexene derivative. This approach relies on repetitive stereocontrolled 1,4 openings of cyclic epoxyalkenes[5] and hydroxyl-directed epoxidations.

Scheme I. Stereospecific Synthesis of Trans 4-Substituted *cis*-2,3-Epoxycyclohexanols



Scheme II. Stereospecific Synthesis of Trisubstituted Cyclohexenols



We have recently reported[5] a significant ligand effect in the reactions of mixed cyanoalkyl cuprates with 1,3-cycloheptadiene monoepoxide. Previous studies[6] of dimethylcopperlithium and epoxide 1 revealed that both 1,2 and 1,4 additions occurred as well as significant amounts of rearranged products. We have found that mixed cyanocuprates such as **2** add stereospecifically (100% trans) and regiospecifically (1,4 addition >95%) to epoxide 1 in ether at low temperatures (−78 to −40 °C) and in high yield (**3a**, R = Me, 95%; **3b**, R = Ph, 60%)[7] (Scheme I). Mixed cyanocuprates (**2**) are among the most stable organocopper reagents and can easily be prepared[8] on a large scale from

(1) White, J. D.; Fukuyama, Y. *J. Am. Chem. Soc.* **1979**, *101*, 226.
(2) Stork, G.; Nair, V. *J. Am. Chem. Soc.* **1979**, *101*, 1315.
(3) For a review on macrolide syntheses, see: Masamune, S. *Aldrichimica Acta* **1978**, *11*, 23; Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585.
(4) Corey, E. J.; Trybulski, E. J.; Melvin, L. S., Jr.; Nicolaou, K. C.; Secrist, J. A.; Lett, R.; Sheldrake, P. W.; Falck, J. R.; Brunelle, D. J.; Haslanger, M. F.; Kim, S.; Yoo, S. *J. Am. Chem. Soc.* **1978**, *100*, 4619.
(5) Marino, J. P.; Floyd, D. M. *Tetrahedron Lett.* **1979**, 675.
(6) Wieland, D. M.; Johnson, C. R. *J. Am. Chem. Soc.* **1971**, *93*, 3047. Staroscik, J.; Rickborn, B. *Ibid.* **1971**, *93*, 3046.
(7) All reported yields are materials isolated from flash distillation (compounds **3a**, **4a**, **9a**, **10a**) or column chromatography (compounds **3b**, **4b**, **5**, **6**, **7**, **8**, **9b**, **10b**). Reaction conditions have not been optimized for each step. All of the compounds cited above have analyzed satisfactorily (elemental and spectroscopically).

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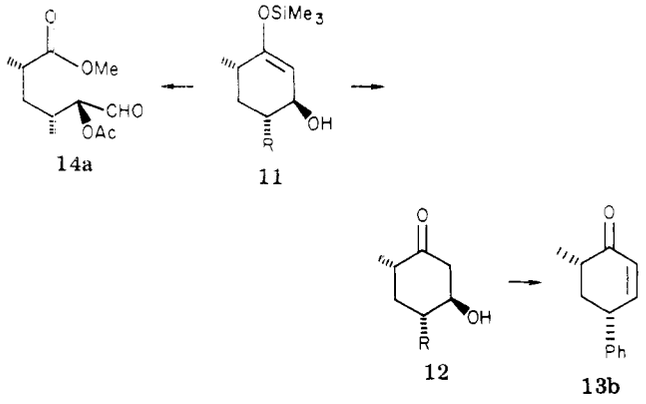
Scheme III. Transformations of Trans 4,6-Disubstituted 3-(Trimethylsiloxy)cyclohex-3-en-1-ols



14a 11 12 13b

commercially available organolithium reagents and cuprous cyanide. The *trans*-1,4-cyclohexenyl systems (**3**) produced are the pivotal intermediates for the methodology reported here and can be converted to numerous intermediates stereospecifically.

The stereospecific and hydroxyl-directed epoxidation of the *trans*-allylic alcohols **3** cannot be affected with a metal-catalyzed *tert*-butyl hydroperoxide oxidation. It has been shown by Teranishi[9] that a quasi-axial hydroxyl group is required for such hydroxyl-directed epoxidations. We have found that *m*-chloroperoxybenzoic acid (MCPA) does yield the epoxides **4** in good stereochemical purity (~95%) and in high yields (85–90%).

We have utilized the *cis*-epoxy alcohols **4** (R = Me, Ph) in two ways, as outlined in Scheme II, in order to introduce another carbon substituent in a stereocontrolled and regiospecific manner. In order to repeat the 1,4 addition to an epoxy alkene system, the equatorial hydroxyl group of **4b** was first converted to a mesylate (**5b**; 95%, MsCl, Et_3N, CH_2Cl_2, 0 °C). Since direct elimination of the equatorial mesylate was not possible under basic conditions, **5** was converted to its corresponding axial iodide (**6b**; 70%, NaI, refluxing methyl ethyl ketone), which was treated with DBN in refluxing THF for 12 h to obtain epoxycyclohexene **7b** (60%). This scheme constitutes a general and unique approach to this class of compounds. When epoxide **7b** was treated with 5 equiv of lithium methylcyanocuprate (**2a**) in ether (−78 to −40 °C, 3–4 h), cyclohexene **8b** (85%) was produced stereospecifically.

An alternative strategy for the introduction of a second carbon substituent via an epoxyalkene is shown in Scheme II. Epoxy alcohols **4** (R = Me, Ph) were easily oxidized to the corresponding epoxy ketones **9** (85%, CrO_3·Pyr_2, CH_2Cl_2), which are not accessible from 4-substituted cyclohexenones in a stereospecific manner by other methods. Epoxy ketone **9** was converted to its trimethylsilyl enol ether **10** (96%, LDA/THF, −78 °C; Me_3SiCl), which underwent the 1,4-addition reaction with lithium methylcyanocuprate at −78 °C (5 equiv, 4–5 h) to produce a new silyl enol ether, **11**, in essentially quantitative yield. Compound **11** could be characterized spectroscopically, but did not survive purification by chromatography.

As shown in Scheme III, the all equatorial β-hydroxy enol ether **11** was desilylated to the aldol **12** (60–70%) with 1.5 equiv of KF in anhydrous methanol (room temperature, 1 h). Aldol **12** was purified by column chromatography (silica, ethyl acetate) and subsequently dehydrated to *cis*-4-phenyl-6-methyl-2-cyclohexenone (**13b**; 10% HCl/THF, room temperature, overnight).

In order to demonstrate that our new methodology ultimately can lead to acyclic chiral molecules, we subjected the dimethyl compound **11a** (R = Me) to oxidative cleavage. The trimethylsilyl enol ether functionality allows for differentiation of the vinylic carbons in the acyclic products. While ozonolysis of silyl enol ethers[10] and allylic alcohol derivatives[11] is precedented, the ozonolysis of a molecule possessing both of these labile functionalities has not been clearly documented. The crude alcohol **11a** (R = Me) was first converted to its acetate (*n*-BuLi, Et_2O, −78 °C; AcCl), which was directly subjected to ozonolysis (Et_2O, −78 °C). The ozonolysis mixture was quenched at −78 °C with excess dimethyl sulfide and then washed successively with water and brine. The ether solution (dried over $MgSO_4$) was treated with diazomethane and concentrated to a clear oil. Column chromatography of the crude reaction mixture (silica, petroleum ether/ether 3:1) yielded the ester aldehyde **14a** (25% overall yield from **10**), in which three chiral centers are fixed and the extremities of the six-carbon unit are differentiated. The common occurrence of the *erythro*-1,3-dimethyl diastereomer in many macrolides and ionophores reinforces the need for simple and synthetically flexible routes to synthons such as **14**.

In summary, the methodology presented in this communication contains several new and unprecedented reaction sequences. In particular, the availability of trans 4-substituted cyclohexenols by the initial cuprate reaction allows for the stereospecific and regiospecific introduction of functionality α to the initially generated hydroxyl group. Other unique steps include (1) the use of a silyl enol ether double bond in the 1,4 addition to the epoxy alkene; (2) the subsequent transposition of the silyl enol ether group; and (3) ozonolysis of a β-oxysilyl enol ether system. Work is continuing in our laboratories on the synthetic applications of this methodology to chiral natural products.

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Registry No. 1, 6705-51-7; **2a**, 41753-78-0; **2b**, 41742-64-7; **3a**, 23713-60-2; **3b**, 71911-76-7; **4a**, 71911-77-8; **4b**, 71911-78-9; **5b**, 71911-79-0; **6b**, 71911-80-3; **7b**, 71962-33-9; **8b**, 71911-81-4; **9a**, 60965-96-0; **9b**, 71911-82-5; **10a**, 71911-83-6; **10b**, 71911-84-7; **11a**, 71911-85-8; **11a** acetate, 71948-49-7; **11b**, 71948-48-6; **12a**, 71911-86-9; **12b**, 71911-87-0; **13b**, 71911-88-1; **14a**, 71911-89-2.

(8) The alkyllithium reagent was added to an equivalent amount of reagent cuprous cyanide (Alfa) in anhydrous ether under a nitrogen atmosphere. The initially suspended cuprous cyanide went into solution (pale yellow) after 0.5 h at −40 °C.

(9) Itoh, T.; Jitsukawa, K.; Kaneda, K.; Teranishi, S. *J. Am. Chem. Soc.* **1979**, *101*, 159. These workers studied epoxidations of the conformationally fixed *cis*- and *trans*-5-*tert*-butylcyclohex-2-en-1-ols with MCPBA and VO $(acac)_2$/*t*-BuOOH. Our results on the epoxidations of the trans 4-substituted cyclohexenols (**4**) were consistent with their findings. Treatment of **4a** and **4b** with $VO(acac)_2$/*t*-BuOOH yielded the 4-substituted cyclohexenones as the major product (>80%).

(10) See ref 1 and 2 for recent examples.

(11) In order to avoid "anomalous" ozonolysis products, the acetate was used. See Bailey, P. S. "Ozonization in Organic Compounds"; Academic Press: New York, 1978; Vol. 1, Chapter 9, pp 147–183.

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