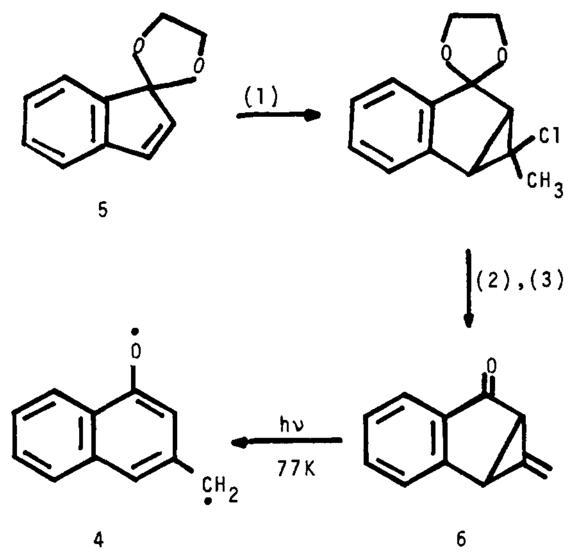
Scheme I[a]



[a] (1) CH_3CHCl_2, BuLi, −30 °C, Et_2O; (2) KO-*t*-Bu, Me_2SO, 60 °C; (3) THF, 5% H_2SO_4.

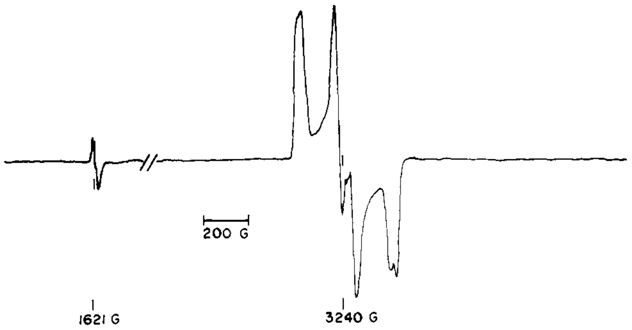


Figure 1. EPR spectrum of the triplet species **4** generated by irradiation of a 2-methyltetrahydrofuran matrix of enone **6** at 77 K. The small absorption near 3245 G is due to cavity background.

by hydrolysis of the corresponding ketal with $H_2{}^{17}O/HCl$.[17b] The details of the splitting cannot be seen in the randomly oriented sample, but increased line widths and altered line shapes, especially of the lowest- and highest-field $\Delta m_s = \pm 1$ transitions, are clearly discernible in the EPR spectrum of the labeled material (Figure 2). Similar perturbations of the extreme $\Delta m_s = \pm 1$ transitions of the monocyclic analogue **3** now also have been observed.[18]

In a polycrystalline matrix prepared by irradiation at 193 K of a frozen 0.1 M benzene solution of **6**, the EPR signal of **4** decays to about 5% of its original intensity with a rate that can be fitted to second-order kinetics. The remaining signal, which upon rescanning is seen to be identical in form with the starting spectrum, persists for a time equivalent to many additional half-lives of the second-order reaction. We tentatively interpret this behavior to mean that biradicals are generated in nonhomogeneous distribution in the matrix. Whether dimers corresponding to the second-order process can be observed on a preparative scale is not yet known.

A plot of the EPR signal intensity of **4** vs. reciprocal of absolute temperature is linear in the range 16–85 K. Below 16 K, the plot is convex, but at least part of this curvature is attributable to saturation associated with slow restoration of the Boltzmann spin distribution, as is clear from the nonlinear dependence of the signal intensity I upon the square root of the microwave power.[19] If we ignore the contribution of this effect and assume that the curvature in the experimental intensity I vs. $1/T$ plot is due solely to thermal population of a triplet state from a hypothetical singlet ground state, we may estimate an upper limit of the energy gap between these states by matching the experimental points to a curved plot calculated from eq 1 by using varying small values

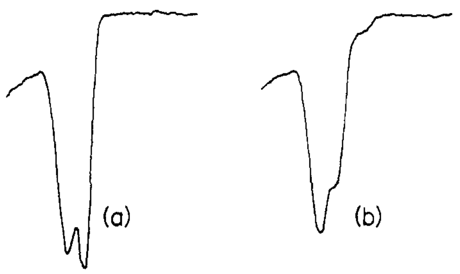


Figure 2. (a) Expanded view of the high-field z transition of **4**. (b) The high-field z transition of **4**-^{17}O, 40% isotopically enriched.

$$I = (a/T)(3[\exp(-\Delta E/RT)])/(1 + 3[\exp(-\Delta E/RT)]) \quad (1)$$

of ΔE. In eq 1, the constant a is determined empirically from the linear portion of the plot (>30 K). By this procedure, we conservatively estimate that the singlet cannot be lower in energy than the triplet by more than 0.01 kcal/mol. Accordingly, either the triplet and singlet are nearly degenerate or the triplet is the ground state.

Detailed theoretical treatment of the spin states of such systems would be valuable. In the meantime, the present and previous[8,9] empirical evidence suggests that heteroatomic analogues of non-Kekulé hydrocarbons potentially constitute a large class of molecules that have high-spin ground states, even when the heteroatom substitution lifts the degeneracy of the Hückel NBMOs.[20]

Acknowledgment. The support of this work by grants from the National Science Foundation (CHE-8011399) and the National Institutes of Health (GM-23375) is gratefully acknowledged. We also thank the National Science Foundation (CHE-7916210) for its support of the NSF Northeast Regional NMR Facility at Yale University. A. R. Matlin and D. A. Dougherty made helpful contributions to the early phases of this work.

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[17] (a) Analysis by mass spectrometry. (b) We thank Professor J. M. McBride for a gift of $H_2{}^{17}O$.

[18] We thank Mr. A. R. Matlin for this experiment.

[19] Wertz, J. E.; Bolton, J. R. "Electron Spin Resonance"; McGraw-Hill: New York, 1972; p 456.

[20] In some instances (e.g., the trisiminomethanes[21]), a highly symmetrical substitution pattern may preserve a Hückel degeneracy of the partially filled HOMOs. In a formal sense, Hund's rule applies to such molecules.

[21] Quast, H.; Bieber, L.; Danen, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1306.

Chirally Directed Synthesis of (−)-Methyl 5(*S*),6(*S*)-Oxido-7-hydroxyheptanoate (1), Key Intermediate for the Total Synthesis of Leukotrienes A, C, D, and E

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Received October 10, 1980

The levorotatory epoxy ester **1** has previously been synthesized in this laboratory and applied to the preparation of leukotriene A (**2**)[1] which is a synthetic[1,2] and biosynthetic[3] progenitor of the slow reacting substances (SRS's) leukotrienes C,[4] D,[5] and E.[6] In

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[1] Corey, E. J.; Clark, D. A.; Goto, G.; Marfat, A.; Mioskowski, C.; Samuelsson, B.; Hammarström, S. *J. Am. Chem. Soc.* **1980**, *102*, 1436, 3663.

[2] Corey, E. J.; Barton, A. E.; Clark, D. A. *J. Am. Chem. Soc.* **1980**, *102*, 4278.

[3] Rådmark, O.; Malmsten, C.; Samuelsson, B.; Clark, D. A.; Goto, G.; Marfat, A.; Corey, E. J. *Biochem. Biophys. Res. Commun.* **1980**, *92*, 954.

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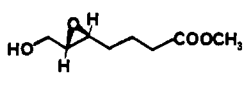

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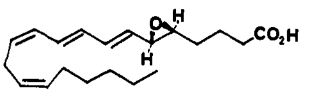

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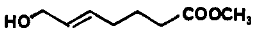
the earlier work the synthesis of 1 was effected expeditiously starting from D-(−)-ribose, a readily available chiral substance. In this paper we describe the synthesis of (−)-1 from achiral precursors by asymmetric induction using the felicitous discovery of Katsuki and Sharpless that a reagent produced from optically active diethyl tartrate, *tert*-butyl hydroperoxide, and titanium tetraisopropoxide effects epoxidation of allylic alcohols with high enantioselectivity.[7]

In fact, reaction of methyl *trans*-7-hydroxy-5-heptenoate (3) with the Katsuki-Sharpless reagent (from L-(+)-tartaric acid diethyl ester) in methylene chloride under the prescribed[7] conditions afforded at best only traces of the desired epoxide 1 (by thin-layer chromatographic (TLC) and spectroscopic analysis), although the starting material was consumed at the expected[7] rate (within ca. 4 h at −20 °C). Since the crude reaction product(s) did not seem to contain epoxide or $COOCH_3$ units (^{1}H NMR analysis), it was evident that if the epoxy ester were being formed, it was subject to very rapid Lewis acid catalyzed decomposition involving the neighboring methoxycarbonyl group. Therefore a different substrate, *trans*-8-methyl-2,7-nonadien-1-ol (4), was chosen for the synthesis.



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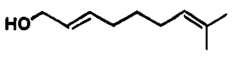

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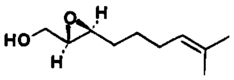

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Reaction of 1-bromo-3-methyl-2-butene[9] with *tert*-butyl lithioacetate[10] in tetrahydrofuran (THF)-hexamethylphosphoric triamide (HMPA) from −78 to −10 °C over 1 h gave (80%) *tert*-butyl 5-methyl-4-hexenoate, bp 90-92 °C (8 torr), and this upon reduction with lithium aluminum hydride in ether afforded 5-methyl-4-hexen-1-ol, bp 78-79 °C (13 torr), in 81% yield. Transformation of this alcohol into the corresponding tosylate (*p*-toluenesulfonyl chloride in pyridine at −10 °C for 1 h, 94% yield) and coupling with the lithio derivative of propargyl tetrahydropyranyl ether[11] in 4:1 THF-HMPA at 55 °C for 5 h provided the tetrahydropyranyl ether of 8-methyl-non-2-yn-7-en-1-ol, bp 109-111 °C (0.15 torr), in 71% yield.[12] Cleavage of the tetrahydropyranyl group (1.5% *p*-toluenesulfonic acid in methanol at 23 °C for 1.5 h, 96% yield) and reduction[13] of the propargylic alcohol thus obtained (lithium aluminum hydrride in ether at reflux for 20 h) gave 4 in 95% yield.

Oxidation[7] of 4 using 3 equiv of anhydrous *tert*-butyl hydroperoxide (4 M in $ClCH_2CH_2Cl$) in the presence of 1 equiv of L-(+)-diethyl tartrate and 1 equiv of titanium isopropoxide in CH_2Cl_2 at −23 °C for 2.5 h produced after extractive workup and chromatography on silica gel (deactivated with 1% of triethylamine) the 2,3-epoxide of 4 (5), $[\alpha]^{23}_{\mathrm{D}}$ −35.4° (*c* 2.1, $CHCl_3$), in 74% yield. Acetylation of 5 (Ac_2O-pyridine), ozonolysis of the acetate in ethyl acetate at −78 °C followed by oxidation of the resulting mixture with 2.5 equiv of Jones' reagent at −20 °C for 40 min, and esterification with diazomethane afforded (after column chromatography on silica gel) a 60% yield of the acetate of 1, $[\alpha]^{23}_{\mathrm{D}}$ −41.1° (*c* 2.38, $CHCl_3$). The optical purity of this product corresponds to 93% ee, since the rotation of optically pure acetate of 1[1] was found to be $[\alpha]^{23}_{\mathrm{D}}$ −44.3° (c 2.24, $CHCl_3$). Further, deacetylation of the $[\alpha]^{23}_{\mathrm{D}}$ −41.1° acetate of 1 using 1.5 equiv of potassium carbonate in methanol at 23 °C for 15 min gave the alcohol 1 (93%) of rotation $[\alpha]^{23}_{\mathrm{D}}$ −34.7° (c 2.16, $CHCl_3$), corresponding to 93% ee (the rotation of optically pure 1[1] is $[\alpha]^{23}_{\mathrm{D}}$ −37.4° (c 2.7, $CHCl_3$). The samples of 1 and its acetate prepared by the route outlined above were spectroscopically and chromatographically identical with authentic samples.[1] Clearly this synthesis is capable of providing leukotriene A of 93% optical purity. In addition, when L-amino acid derivatives for the further conversion of leukotrienes C, D, and E are used these substances can be obtained in pure form by reverse phase chromatography,[1] since the small amount (ca. 3.5%) of diastereomeric thiol conjugate is cleanly separable.[14,15]

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(15) This research was assisted financially by a grant from the National Science Foundation. We are grateful to Dr. Giichi Goto for reference samples.

Short, Stereospecific Total Syntheses of (±)-Modhephene and (±)-Epimodhephene

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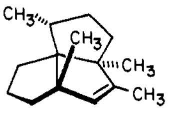
Received November 6, 1980

The toxic plant *Isocoma wrightii* (rayless goldenrod) has proven to be a rich source of structurally interesting sesquiterpenes.[1] In 1977, Zalkow and associates reported the isolation and characterization of isocomene (1), a novel tricyclo[6.3.0.0^{4,8}]undecane featuring a bridged spirane arrangement of three cyclopentane rings.[2] This unusual hydrocarbon immediately became a synthetic target for several research groups including our own,[3] and several imaginative routes to 1 have been completed at this time.[3-6]



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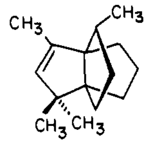

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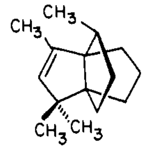

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