The optimized molecule is symmetrical about a plane bisecting the top and bottom portions of the molecule and contains two opposed cyclopropano groups connected by a strong double bond. One of the hexagonal rings in the molecule is best described as a cyclohexatriene moiety frozen in one of the Kékulé structures of benzene. This cyclohexatriene moiety contains abnormally long bonds which are calculated to exhibit multiple-bond character.

Acknowledgment. We thank the Northern Arizona University Computer Services for their generous donation of computer time and resources and the Office of Grant and Contract Services and the Organized Research Committee of Northern Arizona University for their support. We gratefully acknowledge the Department of Computer Science and Engineering of the College of Engineering and Technology, Lanny J. Mullens, Chair, for allowing our use of the Apollo/Hewlett-Packard 4600 computers. This is also a contribution from the Apollo/Hewlett-Packard Undergraduate Computer Project in Computer-Aided Molecular Design and Computational Chemistry, Earle B. Hoyt, Jr., director.

Supplementary Material Available: Tables of final atomic coordinates, molecular orbital energies, and calculated vibrational frequencies for *cyclo*-anthracene (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Elucidation of the Relative and Absolute Stereochemistry of Lobatriene, a Marine Diterpene, by a Modified Mosher Method

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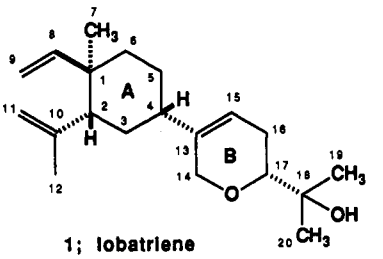
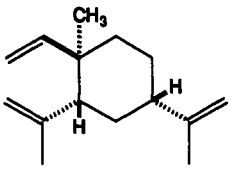
We have recently demonstrated the versatility of a modified Mosher method to elucidate the absolute configuration of organic compounds possessing a secondary alcohol moiety.[1] This method has been further extended to the absolute configurations of primary amines such as amino acids.[2] This method seems to be superior to other chemical methods in that it utilizes the chemical shift differences of many protons, and it as well has a self-examining function.[1] Although application of the method is limited to the compounds possessing a hydroxyl (or an amino) group, it should be employed for non-hydroxyl compounds that have the functional group that can be converted to a secondary alcohol. In this report we describe another application of the method used to determine the stereochemistry of a marine diterpene.

In the course of our searches for pharmaceutically active components from the Okinawan soft coral of the genus *Sinularia flexibilis*,[3] we isolated lobatriene (1) as a moderately cytotoxic substance together with (+)-β-elemene (2). Lobatriene has been obtained from the Great Barrier Reef soft coral of the *Lobophytum* species, and its structure has been deduced by comparison of its NMR properties with those of its analogues and 2.[4]

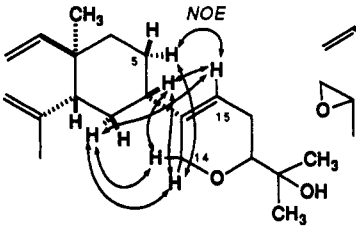
We at first confirmed the validity of the proposed relative stereochemistry of the substituents on ring A by extensive analysis of the NMR (500 MHz) data including COSY, H–C COSY, and NOESY spectra. We next turned our attention on the stereochemistry of the dimethylhydroxymethyl group at C-17 of ring B relative to the asymmetric centers of ring A. The dimethylhydroxymethyl group was deduced to exist in an equatorial position because H-17 (δ 3.25) appears as a doublet of doublets (J = 4 and 11 Hz). If ring B has a particular conformation with respect to ring A, NMR spectroscopy should be advantageous to deduce the stereochemical relationship between the substituents on rings A and B.[5] The NOEs (see **1a**) observed in the phase-sensitive NOESY spectrum are, however, quite confusing: Several unusual NOE cross peaks (e.g. $H_5 \rightleftarrows H_{15}$ and also $H_5 \rightleftarrows H_{14}$) appear from the protons on ring A to those on ring B. This anomaly must be owing to the rapid (on an NMR time scale) rotation of the rings around single bond C_4–C_{13}. The rotation seemed not to retard even at −40 °C, because most of the NOEs shown in **1a** were still observed at this temperature. Epoxidation of the double bond C_{13}=C_{15} (to afford diepoxide **3**), which was done to increase the sterical bulkiness around C_{13}–C_{15}, was ineffective in slowing down the rotation. We therefore performed some chemical reactions to determine separately the absolute configurations of the substituents of rings A and B.



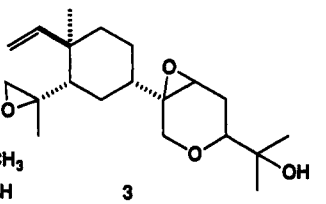
1; lobatriene



2



1a



3

Lobatriene (1) was treated with lithium in liquid ammonia,[6] which resulted in the unusual product **4**. On the contrary, reduction of **1** with lithium in ethylamine[7] gave diol **5**, in which the vinyl and isopropenyl groups on ring A were also saturated. The CD spectrum of **5** measured in the presence of a lanthanide shift reagent[8] exhibited the first negative Cotton effect [λ 307 ($\Delta\epsilon$ −9), 294 (0), 283 ($\Delta\epsilon$ +8) nm] to indicate the R configuration at C-17. This finding was verifed by the modified Mosher's method: The (R)- and (S)-MTPA (methoxy(trifluoromethyl)phenylacetic acid) esters of the diol (**5**; 1 mg in each reaction) were

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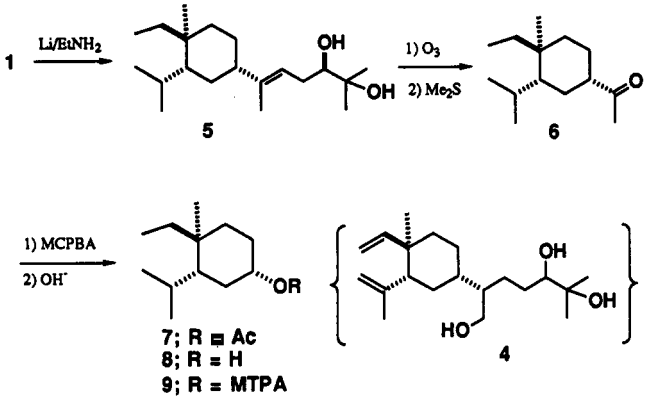
prepared, and the proton signals of the respective derivatives were assigned by use of the COSY spectrum. The $\Delta\delta$ ($\delta_S - \delta_R$) (ppm) values obtained for the respective protons are shown in **5a**. The systematic arrangement of positive and negative $\Delta\delta$'s confirmed the *R* configuration at C-17. Noteworthy is the fact that the protons of the alkyl substituents on ring A show all negative $\Delta\delta$ values. This may be interpreted that the molecule exists in an folded conformation and the substituents are actually on the left side of the MTPA plane. The same tendency was observed for the MTPA derivatives of sipholenol A.[9]

Our attention was next focused on the absolute configurations of three asymmetric centers of ring A. As mentioned above the relative stereochemistry of the substituents of ring A has been already established.

Ozonization[10] of the double bond of **5** produced the ketone **6**. The equatorial orientation of the acetyl group was confirmed from the coupling pattern of H-4 (tt, J = 4, 12 Hz). The ketone **6** was treated with M-CPBA to give the single acetate **7** in a good yield. Retention of the



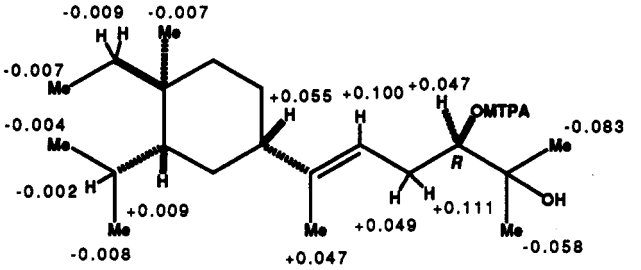
configuration in the Baeyer–Villiger reactions are well documented.[11] Actually, the newly formed acetoxymethine proton (δ 4.64) appears as a triplet of triplets (J = 5, 11 Hz), indicating that no inversion occurred during the reaction course. The acetate **7** was saponified (NaOH/MeOH), and the resulting alcohol **8** was transformed to (*R*)- and (*S*)-MTPA esters **9**. The $\Delta\delta$ values obtained from these MTPA derivatives are shown in **9a**. The systematic arrangement of the values clearly show the *S* configuration at C-4. Thus, *S*, *R*, and *S* configurations are assignable to C-1, 2, and 4, respectively, for the alcohol **8**. This spontaneously led to the assignment of all the asymmetric centers of lobatriene (**1**) as shown in its structure.

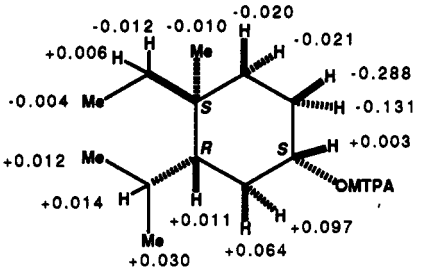
Interestingly, the absolute stereochemical features of ring A of lobatriene (**1**) (diterpene) are exactly the same as those of (+)-β-elemene (**2**) (sesquiterpene). Coexistence of these compounds in the present soft coral suggests that **2** can be a biogenetic precursor of **1**, or they can be biosynthesized by the same or very similar enzyme.

Experimental Section

Materials. The soft coral of the *Sinularia flexibilis* (2 kg) was collected in April 1988 at the Henoko beach in Okinawa Island. A voucher specimen is preserved at the Natural Product Laboratory of the University of Tsukuba.

Chromatography. Vacuum, flash, and open chromatographies were performed by using Kieselgel 60H, Wakogel C300, and Kieselgel 60, respectively. Preparative TLC was done with Kieselgel F254. Short column chromatography was on a 10 mm × 50 mm silica gel layer (Kieselgel 60).





Isolation of Lobatriene (1). The freshly collected soft coral was soaked in acetone (20 L) in a polyvinyl chloride tank. The acetone was decanted from the tank and concentrated on a rotary evaporator (40 °C). The brown residue (ca. 200 g) was partitioned into hexane (97 g), CH_2Cl_2 (5.4 g), and EtOAc-soluble (0.4 g) fractions. The hexane-soluble fraction (21 g) was separated by vacuum chromatography (hexane–EtOAc), affording nine fractions. Half of the third fraction (2.2 g) eluted with hexane–EtOAc (4:1) was further separated by flash chromatography to yield 12 fractions. Half of the tenth fraction (520 mg) eluted with EtOAc was further separated by flash chromatography on 10% $AgNO_3$–SiO_2 (hexane–EtOAc) to yield 10 fractions. Fractions 3, 4, 5, and 6 were combined (350 mg), and the mixture was further separated by flash chromatography (10% $AgNO_3$–SiO_2; hexane–EtOAc) to give five fractions. The second fraction (116 mg) was pure lobatriene (**1**). The ^1H and ^{13}C NMR spectra of the material were identical with those reported: IR (film) 3400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.80 (dd, 1 H, J = 11, 18 Hz, H-8), 5.56 (td, 1 H, J = 2, 7 Hz, H-15), 4.89 (d, 1 H, J = 18 Hz, H-9), 4.88 (d, 1 H, J = 11 Hz, H-9), 4.81 (br t, 1 H, J = 2 Hz, H-11), 4.56 (br d, 1 H, J = 2 Hz, H-11), 4.18 (br s, 2 H, H-14), 3.25 (dd, 1 H, J = 4, 11 Hz, H-17), 2.14 (br t, 1 H, J = 11 Hz, H-16), 1.98 (m, 1 H, H-2), 1.93 (m, 1 H, H-16), 1.69 (s, 3 H, H-12), 1.21 (s, 3 H, H-20), 1.16 (s, 3 H, H-19), 1.00 (s, 3 H, H-7); ^{13}C NMR ($CDCl_3$) δ 150.2 (d, C-8), 147.5 (s, C-10), 141.2 (s, C-13), 116.4 (d, C-15), 112.3 (t, C-11), 110.0 (t, C-9), 80.4 (d, C-17), 71.8 (s, C-18), 68.2 (t, C-14), 52.8 (d, C-2), 41.7 (d, C-4), 39.9 (t, C-6), 39.8 (s, C-1), 32.7 (t, C-3), 27.1 (t, C-5), 26.2 (q, C-20), 25.4 (t, C-16), 24.8 (q, C-12), 23.8 (q, C-19), 16.6 (q, C-7); $[\alpha]^{25}_D$ +86.7° (*c* 0.19, $CHCl_3$); HREIMS calcd for $C_{20}H_{32}O_2$ 304.2402, found 304.2409.

Epoxidation of 1. To a solution of **1** (19 mg, 63 μmol) in CH_2Cl_2 (5 mL) was added *m*-CPBA (30 mg, 174 μmol), and the mixture was stirred at 0 °C for 16 h. The mixture was washed successively with a 20% sodium bisulfite and a 10% sodium bicarbonate solutions and brine. The crude product was separated by preparative TLC [hexane–EtOAc (1:1)] to give the diepoxide **3** (4 mg) as a colorless oil: ^1H NMR ($CDCl_3$) δ 5.72 (dd, 1 H, J = 11, 18 Hz, H-8), 4.99 (d, 1 H, J = 18 Hz, H-9), 4.95 (d, 1 H, J = 11 Hz, H-9), 4.18 (d, 1 H, J = 15 Hz, H-14), 3.79 (d, 1 H, J = 15 Hz, H-14), 3.24 (d, 1 H, J = 7 Hz, H-15), 3.00 (dd, 1 H, J = 4, 12 Hz, H-17), 2.64 (d, 1 H, J = 7 Hz, H-11), 2.60 (d, 1 H, J = 7 Hz, H-11), 1.94 (dd, 1 H, J = 12, 15 Hz, H-16), 1.84 (m, 1 H, H-16), 1.20 (s, 3 H, H-12), 1.17 (s, 3 H, H-20), 1.11 (s, 3 H, H-19), 1.09 (s, 3 H, H-7).

Reduction of 1 with Lithium in Liquid Ammonia. A solution of **1** (25 mg, 82 μmol) in dry THF (1 mL), was added to liquid ammonia (10 mL), which was dried with Na and distilled, and ethanol (0.1 mL). Lithium (22 mg, 3.2 mmol) was added, and

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the blue solution was stirred for 20 min, during which time the blue color disappeared. The ammonia was evaporated, and brine was added to destroy the excess lithium. The product was taken up in ether (100 mL). Evaporation of the solvent gave a colorless oil (37 mg), which was separated by column chromatography [hexane–EtOAc (1:4)], yielding the triol 4 (8 mg): ^{1}H NMR ($CDCl_3$) δ 5.80 (dd, 1 H, J = 11, 17 Hz), 4.90 (d, 1 H, J = 17 Hz), 4.89 (d, 1 H, J = 11 Hz), 4.81 (d, 1 H, J = 1 Hz), 4.57 (br s, 1 H), 3.66 (dd, 2 H, J = 6, 11 Hz), 3.37 (d, 1 H, J = 10 Hz), 1.95 (m, 1 H), 1.69 (s, 3 H), 1.55 (m), 1.20 (s, 3 H), 1.16 (s, 3 H), 0.99 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 150.3 (d), 148.0 (s), 112.0 (t), 109.9 (t), 79.1 (d), 73.2 (s), 63.5 (t), 52.9 (d), 46.0 (d), 40.0 (s), 40.0 (t), 39.5 (d), 31.7 (t), 29.7 (t), 25.6–24.9 (4 peaks), 23.4 (q), 16.7 (q); MS m/z 322 (M^+). The same product was not obtained when the reaction was carried out in the nitrogen atmosphere.

Reduction of 1 with Lithium in Ethylamine. Ethylamine (ca. 10 mL) was dried with Na, and the dry ethylamine was introduced into a two-necked flask connected with a dry ice trap. Lithium (18 mg, 2.6 mmol) was dissolved, and a solution of 1 (49 mg, 161 μmol) in dry THF (0.5 mL) was added to the blue solution. The reaction mixture was stirred for 1.5 h, and ethylamine was evaporated on a water bath (25 °C). The residue was treated with brine, and the product was extracted with ether (100 mL). Evaporation of the ether gave a crude material (49 mg), which was purified by a short silica gel column [hexane–EtOAc (5:1)] to produce the pure diol 5 (45 mg, 91.3%) as a colorless oil: IR (film) 3400, 1465, 1380 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.24 (t, 1 H, J = 7 Hz, H-15), 3.41 (m, 1 H, H-17), 2.20 (m, 2 H, H-16), 1.90 (sept, 1 H, J = 7 Hz, H-10), 1.83 (tt, 1 H, J = 4, 12 Hz, H-4), 1.65 (s, 3 H, H-14), 1.47 (m, H-5), 1.39 (m, H-3), 1.28 (m, H-6), 1.24 (s, 3 H, H-20), 1.18 (s, 3 H, H-19), 1.14 (dd, 1 H, J = 3, 12 Hz, H-2), 0.89 (d, 3 H, J = 7 Hz, H-11), 0.82 (s, 3 H, H-7), 0.79 (t, 3 H, J = 7 Hz, H-9), 0.75 (d, 3 H, J = 7 Hz, H-12); ^{13}C NMR ($CDCl_3$) δ 145.0 (s), 118.4 (d), 77.8 (d), 72.7 (s), 48.2 (d), 38.3 (t), 36.4 (s), 34.6 (t), 30.4 (t), 27.6 (t), 27.2 (t), 26.7 (d), 25.3 (q), 24.6 (q), 23.8 (q), 20.2 (q), 18.6 (q), 15.0 (q), 7.7 (q); $[\alpha]^{26}_D$ +25.7° (c 0.04, $CHCl_3$); CIMS m/z 309 (M^+ – 1); HREIMS calcd for $C_{20}H_{34}O$ ($M - H_2O$) 290.2610, found 290.2610.

Ozonization of the Diol 5. Ozone was introduced into a solution of 5 (41.3 mg, 134 μmol) in methanol (10 mL) at –78 °C for 15 min. The excess ozone was removed by applying nitrogen stream, and dimethyl sulfite (0.4 mL) was added. The mixture was allowed to stand at room temperature, and methanol was evaporated on a rotary evaporator. After brine was added onto the residue, the product was taken up into hexane–ether (1:1). The crude material (45.0 mg) was purified by short column chromatography (hexane–EtOAc) to yield pure ketone 6 (24.1 mg, 85.8%): $[\alpha]^{25}_D$ + 27° (c 0.06, $CHCl_3$); IR (film) 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.25 (tt, 1 H, J = 4, 12 Hz, H-4), 2.14 (s, 3 H, H-14), 1.94 (sept, 1 H, J = 7 Hz, H-10), 1.70 (m, 1 H, H-3), 1.61 (qd, 1 H, J = 4, 13 Hz, H-5), 1.14 (dd, 1 H, J = 3, 12 Hz, H-2), 0.90 (d, 3 H, J = 7 Hz, H-12), 0.83 (s, 3 H, H-7), 0.79 (t, 3 H, J = 8 Hz, H-9), 0.78 (d, 3 H, J = 7 Hz, H-12); ^{13}C NMR ($CDCl_3$) δ 212.4 (s), 52.5 (d), 47.8 (d), 37.6 (t), 36.3 (s), 34.5 (t), 28.1 (d), 25.3 (q), 24.6 (t), 24.6 (q), 24.0 (t), 19.9 (q), 18.4 (q), 7.6 (q); MS m/z 210 (M^+), 181 (M – 29), 167 (M – 43); HREIMS calcd for $C_{14}H_{26}O$ 210.1984, found 210.2000.

Baeyer–Villiger Reaction of the Ketone 6. m-Chloroperbenzoic acid (25 mg, 0.15 mmol) was added to a solution of the ketone 6 (18.1 mg, 86 μmol) in dry chloroform (1 mL), and the mixture was stirred at 50 °C for 16 h. The residue obtained on evaporation of the solvent was purified by short column chromatography [hexane–EtOAc (95:5)] to give the acetate 7 (18.3 mg, 94.3%): IR (film) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.64 (tt, 1 H, J = 5, 11 Hz, H-4), 2.04 (s, 3 H, H-14), 1.89 (sept, 1 H, J = 7 Hz, H-10), 1.79 (m, 1 H, H-3), 1.70 (tdd, 1 H, J = 2, 5, 11 Hz, H-5), 1.45 (dq, 1 H, J = 5, 11 Hz, H-5), 1.20 (dd, 1 H, J = 3, 12 Hz, H-2), 0.90 (d, 3 H, J = 7 Hz, H-11), 0.83 (s, 3 H, H-7), 0.79 (t, 3 H, J = 8 Hz, H-9), 0.78 (d, 3 H, J = 7 Hz, H-12); ^{13}C NMR ($CDCl_3$) δ 170.7 (s), 74.7 (d), 46.4 (d), 36.0 (t), 34.1 (t), 27.9 (t), 27.6 (t), 25.3 (d), 24.4 (q), 21.5 (q), 21.5 (q), 19.8 (q), 18.4 (q), 7.7 (q); CIMS m/z 227 (M^+ + 1); MS m/z 166 (M – 60), 151 (166 – Me), 137 (166 – Et), 123 (166 – Ac); HREIMS calcd for $C_{12}H_{22}$ (M – AcOH) 166.1721, found 166.1723.

Hydrolysis of the Acetate 7. A solution of 7 (9.0 mg, 40 μmol) in MeOH (1 mL) was treated with 5 drops of a 1 M aqueous NaOH solution, and the mixture was allowed to stand for 2 h. The mixture was neutralized, the methanol was evaporated, and the residue was extracted with ether (100 mL). The crude product was purified by short column chromatography (hexane–EtOAc) to afford pure 8 (7.3 mg, 99.2%): IR (film) 3330 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.52 (tt, 1 H, J = 5, 11 Hz, H-4), 1.89 (sept, 1 H, J = 7 Hz, H-10), 1.77 (m, 1 H, H-3), 1.70 (tdd, J = 3, 5, 12 Hz, H-5), 1.56 (m, 1 H, OH), 1.13 (dd, 1 H, J = 3, 13 Hz, H-2), 0.89 (d, 3 H, J = 7 Hz, H-11), 0.84 (s, 3 H, H-7), 0.78 (t, 3 H, J = 8 Hz, H-9), 0.78 (d, 3 H, J = 7 Hz, H-12); ^{13}C NMR ($CDCl_3$) δ 72.2 (d), 46.6 (d), 36.3 (t), 35.9 (s), 34.2 (t), 31.7 (t), 31.6 (t), 25.2 (d), 24.5 (q), 19.9 (q), 18.5 (q), 7.7 (q); MS m/z 184 (M^+), 155 (M – 29), 137 (M – 47); HREIMS calcd for $C_{12}H_{22}$ ($M - H_2O$) 166.1721, found 166.1720.

Synthesis of the (*R*)-MTPA Ester of the Alcohol 8. A solution of 8 (1.0 mg, 5.4 μmol) in dry pyridine (20 μL) was treated with (+)-MTPA chloride (2.5 μL, 13 μmol), and the solution was allowed to stand for 16 h. *N,N*-Dimethyl-1,3-propanediamine (2.5 μL) was added to quench the excess chloride, and after 30 min, the pyridine was evaporated by applying nitrogen stream. The residue was subjected to preparative TLC [hexane–EtOAc (9:1)] to give the MTPA ester 9 (0.8 mg, 50%). The (*S*)-MTPA ester was obtained in the same manner. The ^{1}H NMR data of the (*R*)- and (*S*)-MTPA esters are summarized in Table II.[12]

Synthesis of the (*R*)-MTPA Ester of the Diol 5. The diol 5 (1 mg, 3.2 μmol) was dissolved in dry pyridine (20 μL), and (+)-MTPA chloride (1.2 μL, 6.3 μmol) was added. After 15 h, *N,N*-dimethyl-1,3-propanediamine (2.5 μL) was added, and the mixture was allowed to stand for 30 min. The solvent was evaporated and the residue was subjected to preparative TLC [hexane–EtOAc (8:2)] to give the MTPA ester 5a (0.5 mg, 30%). The (*S*)-MTPA ester was obtained in the same manner. The ^{1}H NMR data of the (*R*)- and (*S*)-MTPA esters are summarized in Table I.[12]

Supplementary Material Available: ^{1}H NMR data for the (*R*)- and (*S*)-MTPA esters of diol 5 and 9 and NMR spectra of 1, 3, 4, 5, 6, 7, 8, (*R*)- and (*S*)-MTPA ester of 5, and (*R*)- and (*S*)-9 (18 pages). Ordering information is given on any current masthead pages.

(12) Available as supplementary material.

Reaction of $Na_2Fe(CO)_4$ with an Unsaturated Aziridinium Ion. Unprecedented Rearrangement of an Alkyltetracarbonylferrate Intermediate

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As a potential approach for forging the sixth ring of the complex oxindole alkaloid gelsemine (6),[1] we recently considered the sequence outlined in Scheme I. A key step in this plan would be carbonylation of the unsaturated aziridinium ion 2 with an anionic metal complex to form the cyclopentanone ring of the hexacyclic ketone 4. Baeyer–Villiger oxidation of this latter intermediate could plausibly allow development of the final hydropyran ring of the target alkaloid (4 → 5 → 6). Earlier studies in our laboratories had led to an expeditious sequence for preparing the hexacyclic aziridine 1.[2–5] Moreover, these in-

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