Total Synthesis of (+)-Elemol by Photoannelation

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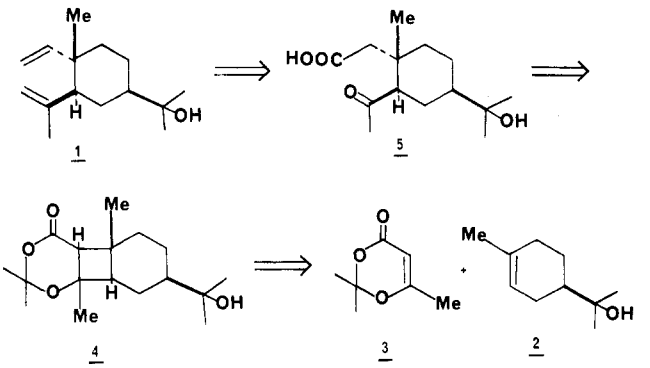
A total synthesis of the monocyclic sesquiterpene elemol has been accomplished in seven steps and 16.7% overall yield. The key new carbon–carbon bonds were formed by the [2 + 2] photochemical cycloaddition reaction between 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one and α-terpineol, a reaction that occurred with essentially complete regioselectivity (head/head) and good alkene face selectivity (3.35/1). The 35–38% enantiomeric purity of the starting (–)-α-terpineol was translated into optically active elemol predominating in the unnatural (+) enantiomer (ee = 31–40%).

The efficient formation of carbon–carbon bonds is a continuing challenge in organic synthesis. Of the many nontraditional approaches to this problem under investigation in different laboratories, photochemistry has received increasing attention, although it is still regarded in some circles as a last resort curiosity. Several years ago[2] we described the photochemical [2 + 2] cycloaddition reactions between 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**3**)[3] and several alkenes followed by the demonstration that the photoadducts could be readily transformed into useful synthetic intermediates. The photochemical reactions were characterized by considerable regiospecificity, with unsymmetrical alkenes showing a marked preference for the formation of head-to-head (HH) adducts.[4] For instance, 1-methylcyclohexene exhibited a HH/HT preference of 8/1. Since that time we have completed several synthetic investigations in which a photoaddition with **3** has played an essential role. Reported here is the efficient total synthesis of (+)-elemol that further underscores the value of this and related photocycloaddition reactions in synthesis.

The structure of elemol, a monocyclic sesquiterpene alcohol isolated from *Manila elemi* oil and *Java Citronella* oil[5] was revealed in 1926 as **1**,[6] with the absolute stereochemistry being determined nearly 40 years later.[7,8] Since then, elemol has been synthesized by several groups in both optically active[9] and racemic forms,[10] the most imaginative being that of Corey employing an intramolecular π-allyl nickel cyclization reaction.[10a]

Inspection of **1** suggests that its skeleton should be readily accessible by the photocycloaddition of **3** to an appropriate derivative of 1-methylcyclohexene. For instance, reaction between **3** and α-terpineol (**2**) would be expected to give either H/H photoadduct **4a** or **4b** as the major product, with the former predominating if reaction were to occur from the less hindered α-face of the alkene.



Hydrolysis of **4a**, accompanied by simultaneous retroaldol cyclobutane fragmentation and equilibration of the α-acetyl group to the more stable equatorial arrangement, would give **5**, the vicinal side chains being ideally suited for differential elaboration to the 1,5-diene of elemol. Because α-terpineol exists in both optical antipodes, either elemol stereoisomer is potentially available by this synthetic scheme although naturally occurring (–)-elemol would require (+)-α-terpineol as a starting material. In fact, the α-terpineol employed in this study showed an $[\alpha]_D$ = –37° corresponding to an enantiomeric excess of 35–38%.

Irradiation of a solution of **3** and α-terpineol (1/4 mole ratio) in either 10% acetone–acetonitrile or 10–40% ether–hexane with a Hanovia 450-W mercury lamp (corex filter) for 20 h followed by evaporative distillation afforded the mixture of photoproducts **4** in 88–94% yield. Although the ^{1}H NMR was rather complex, the region between δ 2 and 3 was informative. A singlet at δ 2.67 accompanied by a smaller adjacent singlet shoulder at δ 2.70 (combined integral ~1 H) strongly suggested that the major photoproducts were H/H stereoisomers such as **4a** and **4b** as anticipated from our earlier studies.[2] These absorptions were readily assigned to the isolated cyclobutane proton adjacent to the carbonyl. In the H/T adducts such as **4c** and **4d**, the corresponding proton adjacent to the carbonyl is generally seen as a doublet, vicinal coupling constants being approximately 8 Hz. Although no such doublets were apparent in the ^{1}H NMR of the product mixture, it was not possible to rule out the presence of small amounts (<10%) of H/T adducts at this time. It will be assumed in the subsequent discussion that the majority of the photoproduct mixture was comprised of H/H adducts **4a** and **4b**.

Several comments about the irradiation process are in order. Photoreactions with **3** are usually performed in the presence of excess alkene (3–6 equiv), although acceptable yields of photoproducts with 1/1 mixtures are possible in cases where the alkene is particularly valuable. In previous work hexane was employed as the reaction solvent.[2] It has since been found that the low solubility of some photo-

(1) (a) Part 16. Part 15: Baldwin, S. W.; Landmesser, N. G. *Tetrahedron Lett.* **1982**, *23*, 4443. (b) Partial financial support from the National Institutes of Health is gratefully acknowledged (Grant GM 26266). (c) Taken in part from the Ph.D. thesis of G.F.M. (Duke University, 1984). (d) Undergraduate research participant.

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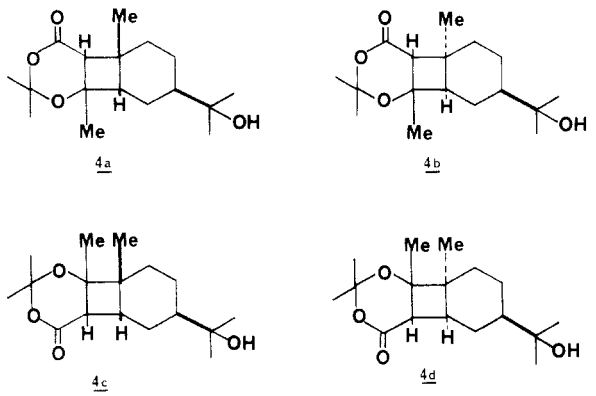
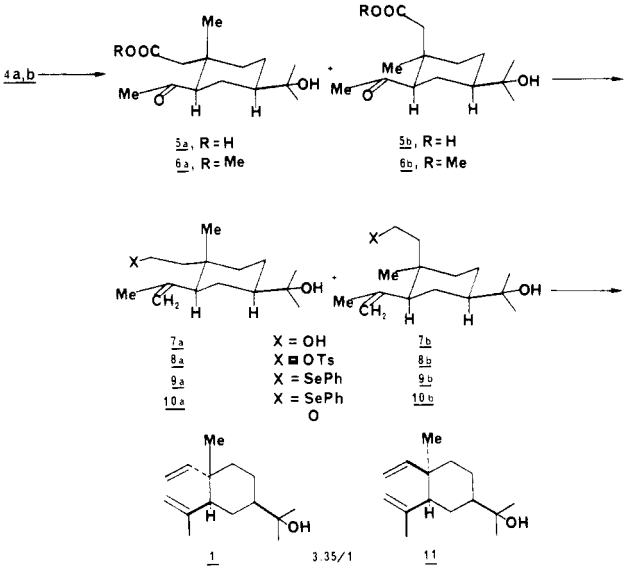


products in this solvent can lead to a serious loss of efficiency. More polar solvents such as ether, acetone, acetonitrile, or various mixtures of these have been valuable in avoiding this problem. Finally, the use of a corex filter in these reactions appears to be very important. We have found, verified independently by others,[11] that substituting other filter sleeves (vycor, Pyrex, uranium glass) or using unfiltered light is uniformally unacceptable, the yields of photoproducts becoming vanishingly low. We have not yet carried out a detailed wavelength study of this photoefficiency phenomenon.[12]

The stereochemical course of the photoreaction is of considerable interest in that four new chiral centers are created in one synthetic operation. The relative stereochemistry of these new centers as well as their relationship to the α-terpineol 2-propanol group is critical to the ultimate success of this project. However, since two of the four chiral centers will be lost in the next step (hydrolysis and retroaldolization), and because the derived acetyl group at C-2 will surely adopt the necessary equatorial (β) configuration on equilibration as in **5**, the stereochemical success or failure of the project is dependent only on alkene face selectivity in the photocycloaddition step. A general observation in bimolecular photoadditions of this type is that reaction occurs primarily from the less hindered face of the reacting photopartner.[4] It was not expected that a psuedoequatorial 2-propanol group two carbons removed from the reacting alkene would impart great steric bias to α-terpineol, although some selectivity was expected.

Basic hydrolysis of the photoproduct mixture, which was assumed to be two different H/H photoadducts by ^{1}H NMR analysis (vide supra), afforded a mixture of keto acids **5a** and **5b** in 99% yield. In fact it was possible to perform the photocycloaddition reaction and hydrolysis of the crude photoproduct in 95% yield for the two steps. ^{1}H NMR and GLC analysis of the derived methyl esters indicated the presence of two compounds in the approximate ratio of 3.5/1. Careful small-scale chromatographic separation of methyl esters **6a** and **6b** followed by equilibration and analysis of the separate isomers showed single compounds in each case, indicating that both compounds had adopted the more stable equatorial configuration of the acetyl group during the initial hydrolysis step as represented by structures **5a** and **5b**. As will be seen subsequently, the major keto acid isomer corresponds to **5a**, that structure necessary for the completion of elemol. In an attempt to alter the ratio of the photoproducts, the acetate and trimethylsilyl ether of α-terpineol were each added photochemically to **3** in good yield. Conversion of each photoproduct mixture to the keto esters **6** showed no change in the isomer ratio as compared to α-terpineol itself, and so the α-terpineol-derived photoproduct mixture was used in subsequent transformations.

Eventually it proved advantageous to separate the isomers at a later stage in the synthesis. Thus, exposure of the keto acid mixture **5** to 3 equiv of methylenetriphenylphosphorane[13] followed by reduction of the carboxylic acid with lithium aluminum hydride afforded alkene diols **7a** and **7b** that were readily separated by column chromatography (alumina) to give the major and minor isomers in 42.6% and 12.7% yields, respectively (3.35/1 ratio). Although the IR and ^{1}H NMR spectra of the separated isomers were very similar, it was possible to assign the major isomer as structure **7a** and the minor as **7b** on the basis of the ^{13}C NMR spectrum (INEPT pulse sequence[14]). Specifically, the absorption for the angular methyl carbon in the major isomer occurred 3.7 ppm upfield of the corresponding signal for the minor isomer (19.1 vs. 22.8 ppm), a shift consistent with predictions for an axial vs. equatorial methyl carbon due to the γ-shielding effect.



Conversion of major diol **7a** to elemol was accomplished in three steps by elimination of the selenoxide derived from the primary alcohol. Thus, displacement of the primary tosylate of **8a** with a preformed solution of phenylselenate anion[15] gave the phenyl selenide **9a** in 74% yield for the two steps. Finally, heating a THF solution of **9a** and *tert*-butyl hydroperoxide with suspended basic alumina according to the method of Krief,[16] followed by flash chromatography, afforded a 54% yield of elemol identical spectroscopically (IR; ^{1}H NMR, 80 and 250 MHz; ^{13}C NMR) to an authentic sample of naturally occurring material.[17] The specific rotation of the synthetic material, +1.4–1.8°, corresponds to an enantiomeric excess of 31–40%, consistent with that of the starting α-terpineol.

Similar treatment of the minor diol isomer **7b** afforded diene **11**, mp 70–72 °C, in 23% yield for the three steps.

(11) Professor W. D. Wulff, Department of Chemistry, University of Chicago, Chicago, IL 60637. Private communication.

(12) Corex filter sleeves are intermediate between Pyrex and vycor in wavelength transmission. Originally available from Ace Glass Co., Vineland, NJ, the corex filters have since been dropped from their product line.

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(17) The authors thank Professor O. Jeger, ETH, Zurich, Switzerland, for a generous sample of natural (−)-elemol.

The close similarlity of the coupling patterns for the vinyl and allylic methine protons in the ^1H NMR spectra (250 mHZ) of the two diene isomers lends further support to the suggestion that both elemol 1 and diene 11 were derived from H/H photoadducts, i.e., **4a** and **4b**, respectively. These regions in the spectrum of the alternate regioisomer would be significantly more complex because of the additional vicinal coupling between the allylic methine and vinyl protons.

In summary, (−)-α-terpineol has been converted to (+)-elemol in seven steps and 16.7% overall yield. The key photocycloaddition between dioxinone **3** and α-terpineol occurred with essentially complete H/H regioselectivity and reasonable stereochemical control (3.35/1 alkene face selectivity). The complimentarity of this photochemical method with other techniques as well as its overall efficiency is noteworthy.

Experimental[18] Section

Octahydro-7-(1-hydroxy-1-methylethyl)-2,2,4b,8b-4*H*-benzo[3,4]cyclobuta[1,2-*d*]-1,3-dioxin-4-one (4). Photocycloaddition between α-Terpineol (2) and 2,2,6-Trimethyl-4*H*-1,3-dioxin-4-one (3). In a flame-dried Pyrex phototwell equipped with a water-cooled jacketed quartz insert, argon bubbler, corex filter sleeve, and a 450-W Hanovia mercury lamp were placed 2.12 g (14.9 mmol) of dioxinone **3**,[3] 9.3 g (60 mmol) of α-terpineol **2** (Aldrich, $[\alpha]_D$ −37°), and 250 mL of 10% acetone–acetonitrile. The solution was degassed for 15 min and then irradiated with continuous argon bubbling for 20 h. Evaporation of the solvent and Kugelrohr distillation of the product (125–130 °C (0.05 mm)) afforded 4.44 g (93%) of cyclobutanes **4** as a viscous oil: ^1H NMR δ 1.16 (br s, 12 H, 4 CH_3), 1.4–2.1 (br d, 7 H, CH_2's and CH), 1.57 (s, 6 H, 2 CH_3), 2.67, 2.70 (sh s. 1 H, C(O)CH); IR (film) 1725 cm^{-1}. Anal. Calcd for $C_{17}H_{24}O_4$ (mixture of isomers): C, 69.12; H, 9.21. Found: C, 69.37; H, 9.43.

2-Acetyl-4-(1-hydroxy-1-methylethyl)-1-methylcyclohexaneacetic Acid (5a and 5b). A solution of 2.5 g (8.4 mmol) of cyclobutane photoproducts (**4**), 50 mL of 10% NaOH, and 50 mL of dioxane in a 250-mL flask was heated at reflux for 12 h whereupon the reaction mixture was cooled, acidified with 100 mL of 10% HCl, and extracted with ether (4 × 50 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried (Na_2SO_4), and concentrated to give 2.12 g (99%) of the crude keto acids **5a** and **5b**, which was used without further purification: ^1H NMR δ 1.13 (s, 3 H, CH_3), 1.17 (br s, 6 H, 2 CH_3), 1.2–1.8 (br d, 7 H, CH_2's and CH), 2.06, 2.19 (s, 3 H, C(O)CH_3), 2.15–2.36 (br d, 3 H, C(O)CH_2, C(O)CH), 5.05 (br s, 1 H, COOH); IR ($CDCl_3$) 1730, 1700 cm^{-1}.

(1*S*,3*R*,4*R*)- and (1*R*,3*S*,4*S*)-α,α,4-Trimethyl-3-(1-methylethenyl)-4-(2-hydroxyethyl)cyclohexanemethanol (7a) and (1*S*,3*R*,4*S*)- and (1*R*,3*S*,4*R*)-α,α,4-Trimethyl-3-(1-methylethenyl)-4-(2-hydroxylethyl)cyclohexanemethanol (7b). According to the general procedure of Corey,[13] to a dry 500-mL three-neck flask equipped with an addition funnel, N_2 inlet, magnetic stirrer, and condenser were added 2.75 g (57.2 mmol) of NaH (50% oil dispersion) and 20 mL of dry Me_2SO and then heated at 60 °C for 1 h. After cooling in an ice bath, a solution of 21 g (52 mmol) of dry methyltriphenylphosphonium bromide in 50 mL of Me_2SO was added dropwise and the resulting mixture stirred for an additional 30 min in an ice bath whereupon 4.51 g (1.73 mmol) of keto acid mixture **5a** and **5b** in 50 mL of dry THF was added dropwise. The reaction mixture was allowed to warm to room temperature and stirring continued for 18 h whereupon the solution was poured into 100 mL of 5% NaOH and extracted with ether (3 × 50 mL, discarded). The remaining aqueous material was acidified with 200 mL of 10% HCl and extracted with ether (3 × 50 mL). The combined ether extracts were washed with brine (2 × 50 mL), dried ($MgSO_4$), and concentrated to give a dark viscous oil that was used in the next step without further purification.

The above crude alkene acids were dissolved in 100 mL of dry ether and added dropwise to a suspension of 1.73 g (45.6 mmol) of $LiAlH_4$ in 200 mL of dry ether. After stirring overnight at room temperature, the reaction mixture was quenched by the sequential addition of 1.73 mL of H_2O, 1.73 mL of 10% NaOH, and 5.2 mL of H_2O. The resulting salts were removed by filtration and washed with 100 mL of ether, and the combined ethereal solutions were concentrated. Column chromatography (Woelm neutral alumina, activity III; ethyl acetate–hexane) afforded 1.80 g (42.6%) of major diol **7a** and 0.54 g (12.7%) of minor diol **7b**.

Major Diol 7a: ^1H NMR δ 0.90 (s, 3 H, CH_3), 1.16 (s, 6 H, 2 CH_3), 1.0–2.0 (br d, 10 H), 1.70 (s, 3 H, =CCH_3), 3.66 (t, J = 8 Hz, CH_2OH), 4.63 (s, 1 H, =CH), 4.83 (s, 3 H, =CH); ^{13}C NMR δ 19.1, 22.7, 23.5, 27.1, 28.6, 35.6, 39.2, 45.9, 49.2, 53.7, 59.3, 72.8, 113.0, 147.6; IR ($CDCl_3$) 3600 cm^{-1}. Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.94; H, 11.74. Found: C, 74.57; H, 11.54.

Minor Diol 7b: ^1H NMR δ 0.84 (s, 3 H, CH_3), 1.11 (s, 6 H, 2 CH_3), 1.0–2.0 (br d, 10 H), 1.69 (s, 3 H, =CCH_3), 3.56 (t, J = 8 Hz, CH_2OH), 4.56 (s, 1 H, =CH), 4.78 (s, 1 H, =CH); ^{13}C NMR δ 22.8, 24.6, 27.2, 28.2, 28.3, 34.1, 35.2, 37.7, 49.2, 55.7, 59.4, 72.8, 113.1, 147.2; IR ($CDCl_3$) 3600 cm^{-1}. Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.94; H, 11.74. Found: C, 74.67; H, 11.90.

(1*S*,3*S*,4*R*)- and (1*R*,3*R*,4*S*)-α,α,4-Trimethyl-3-(1-methylethenyl)-4-[2-(*p*-tolylsulfonoxy)ethyl]cyclohexanemethanol (8a). To a cooled solution (0 °C) of 630 mg (2.6 mmol) of diol **7a** in 10 mL of dry pyridine was added 820 mg (4.3 mmol) of TsCl and the mixture maintained at 0 °C for 32 h whereupon it was poured on to 20 g of ice and extracted with ether (3 × 25 mL). The combined ether extracts were washed with 10% HCl (30 mL), saturated $NaHCO_3$ (30 mL), and brine (30 mL), dried (Na_2SO_4), and concentrated to afford 952 mg (93%) of tosylate **8a**, which was used without further purification: ^1H NMR δ 0.86 (s, 3 H, CH_3), 1.18 (s, 6 H, 2 CH_3), 1.67 (s, 3 H, =CCH), 1.0–2,.0 (br d, 10 H), 2.44 (s, 3 H, ArCH_3), 4.11 (t, J = 6.6 Hz, 2 H, CH_2OTs), 4.58 (s, 1 H, =CH), 4.80 (s, 1 H, =CH), 7.58 (4 h, AB, J_{AB} = 8.8 Hz, Δν = 37.7 Hz, ArH).

(1*S*,3*S*,4*R*)- and (1*R*,3*R*,4*S*)-α,α,4-Trimethyl-3-(1-methylethenyl)-4-[2-(phenylselenyl)ethyl]cyclohexanemethanol In an adaptation of Sjoberg's procedure,[15] 1.08 g (3.46 mmol) of diphenyl diselenide in 25 mL of ethanol was treated with $NaBH_4$ until the solution became colorless. The reaction mixture was then cooled to 0 °C, and 0.952 g (2.42 mmol) of tosylate **8a** in 10 mL of THF was added dropwise whereupon it was warmed to room temperature and stirred for 16 h. After quenching with 10% $NaHCO_3$ (50 mL) and removal of the ethanol under vacuum, the resulting aqueous material was extracted with CH_2Cl_2 (2 × 50 mL) and the resulting organic layer dried (Na_2SO_4) and concentrated to give 0.803 g (79.2 %) of primary selenide **9a** after flash chromatography on silica gel, which was directly carried on to the next step: ^1H NMR δ 0.92 (s, 3 H, CH_3), 1.18 (s, 6 H, 2 CH_3), 1.66 (s, 3 H, =CCH_3), 1.0–2.0 (br d, 10 H), 2.86 (dd, J

(18) Melting poings were obtained on a Thomas-Hoover melting point apparatus and are uncorrected; boiling points are uncorrected. Infrared spectra (IR) were recorded on a Perkin-Elmer 297 infrared spectrophotometer either as thin films or as solutions in $CDCl_3$. Routine nuclear magnetic resonance (^1H NMR) spectra were recorded on an IBM NR/80 spectrometer (80 MHz) in $CDCl_3$. High-field ^1H NMR spectra were recorded on a Bruker WH 250 spectrometer (250 MHz) in $CDCl_3$. For clarity, certain proton absorptions are treated as first order by reporting apparent chemical shifts even though they may not be rigorously correct. Unless otherwise noted, all ^1H NMR spectra were obtained at 80 MHz. ^{13}C NMR spectra were recorded on a JEOL FX90Q spectrometer in $CDCl_3$. All resonances are reported in ppm (δ) downfield from an internal Me_4Si standard. Analytical thin-layer chromatography (TLC) was performed on 0.2-mm microscope size plates cut from 20 × 20 cm precoated with silica gel 60 F_{254} on aluminum backings with components visualized either by UV fluorescence or by the $Ce(NH_4)_2(NO_3)_6$ char technique. Flash chromatography[19] was performed with silica gel (230–400 mesh) with house air as a source of medium pressure. Anhydrous solvents were dried immediately prior to use. Tetrahydrofuran (THF) and diethyl ether (ether) were distilled from sodium and benzophenone. Dimethyl sulfoxide (Me_2SO) and pyridine were distilled from calcium hydride. Concentration refers to evaporation of solvent on a Buchi rotary evaporator at aspirator pressure followed by additional evacuation at high vacuum until constant weight was obtained. Kugelrohr distillation refers to the standard bulb to bulb process using a Buchi Kugelrohr apparatus with the listed temperature being that of the air bath. All reactions were conducted under a positive pressure of nitrogen or argon unless otherwise specified. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ 85018. All compounds reported in this work are an approximately 2/1 mixture of optical isomers, reflecting the enantiomeric composition of the starting α-terpineol.

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= 10, 11.1 Hz, CH_2Se), 4.61 (s, 1 H, =CH), 4.76 (s, 1 H, =CH), 7.20 (m, 3 H, ArH), 7.42 (m, 2 H, ArH).

(1*S*,3*S*,4*R*)- and (1*R*,3*R*,4*S*)-α,α,4-Trimethyl-3-(1-methylethenyl)-4-ethenylcyclohexanemethanol (1, Elemol). According to the method of Krief,[16] a mixture of 548 mg (1.31 mmol) of selenide **9a**, 1.01 g of basic alumina, and 0.6 mL of 90% *tert*-butyl hydroperoxide in 10 mL of THF was heated under nitrogen at 60 °C for 6.5 h. After gravity filtration, the solids were washed with ethyl acetate (50 mL) and the combined organic solutions concentrated to afford an oil that was purified by flash chromatography on silica gel to give 156 mg (53.7%) of a clear homogeneous oil. Analysis of this oil by TLC, GC, IR, and ^1H NMR (80 and 250 MHz) showed it to be identical spectroscopically to a sample of authentic elemol:[17] $[\alpha]_D$ ($CHCl_3$) 1.4–1.8°; ^1H NMR (250 MHz) δ 0.98 (s, 3 H, CH_3), 1.20 (s, 6 H, 2 CH_3), 1.2–1.7 (br d, 7 H), 1.71 (d, J = 0.7 Hz, 3 H, =CCH_3), 1.96 (dd, J = 8.5, 3.3 Hz, 1 H, =CCH), 4.58 (d, J = 0.7 Hz, 1 H, =CH), 4.82 (br s, 1 H, =CH), 4.87 (dd, J = 10.7, 1.6 Hz, 1 H, =CH), 4.88 (dd, J = 17.6, 1.6 Hz, 1 H, =CH), 5.80 (dd, J = 17.6, 10.7 Hz, 1 H, =CH); IR (film) 3085, 1638, 907, 890 cm^{-1}. Anal. Calcd for $C_{15}H_{26}O$: C, 81.08; H, 11.71. Found: C, 80.88; H, 11.49.

(1*S*,3*R*,4*S*)- and (1*R*,3*S*,4*R*)-α,α,4-Trimethyl-3-(1-methylethenyl)-4-[2-(*p*-tolylsulfonoxy)ethyl]cyclohexanemethanol (8b). To a cooled solution (0 °C) of 0.54 g (2.2 mmol) of minor diol **7b** in 10 mL of pyridine was added 0.88 g (4.6 mmol) of tosyl chloride. After 24 h at 0 °C the reaction mixture was pured onto 10 g of ice and the resulting material estracted with ether (3 × 20 mL). The organic layers were then washed with 10% HCl (3 × 50 mL), saturated $NaHCO_3$ (50 mL), and brine (50 mL), dried (Na_2SO_4), and concentrated to give 0.55 g (61.6%) tosylate **8b** which was used without further purification: ^1H NMR δ 1.16 (s, 6 H, 2 CH_3), 1.2–1.8 (br d, 9 H), 1.67 (s, 3 H, =CCH_3), 1.87 (m, 1 H, =CCH), 2.45 (s, 3 H, $ArCH_3$), 4.07 (t, J = 8 Hz, 2 H, CH_2OTs), 4.56 (br s, 1 H, =CH), 4.84 (br s, 1 H, =CH), 7.57 (AB, J_{AB} = 9 Hz, Δν = 37.2 Hz, 4 H, ArH).

(1*S*,3*R*,4*S*)- and (1*R*,3*S*,4*R*)-α,α,4-Trimethyl-3-(1-methylethenyl)-4-[2-(phenylselenyl)ethyl]cyclohexanemethanol (9b). In an adaptation of the procedure of Sjoberg,[15] 314 mg (1.00 mmol) of diphenyl diselenide in 15 mL of ethanol was treated with $NaBH_4$ until the solution became colorless. The reaction mixture was cooled to 0 °C, and 207 mg (0.53 mmol) tosylate **8b** in 10 mL of THF was added and the reaction mixture stirred at room temperature for 18 h whereupon it was quenced with 10% Na_2CO_3 (50 mL), the ethanol removed under vacuum, and the aqueous residue extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layer was washed with brime (50 mL), dried (Na_2SO_4), and concentrated to give an oil, which was purified by flash chromatography on silica gel to afford 131 mg (59%) of selenide **9b** used directly in the next reaction: ^1H NMR δ 0.90 (s, 3 H, CH_3), 1.12 (s, 6 H, 2 CH_3), 1.70 (s, 3 H, =CCH_3), 1.0–2.0 (br d, 10 H), 2.79 (m, 2 H, CH_2SeAr), 4.61 (br s, 1 H, =CH), 4.85 (br s, 1 H, =CH), 7.24 (m, 3 H, Ar*H*), 7.47 (m, 2 H, Ar*H*).

(1*S*,3*R*,4*S*)- and (1*R*,3*S*,4*R*)-α,α,4-Trimethyl-3-(1-methylethenyl)-4-ethenylcyclohexanemethanol (11, Isoelemol). According to the method of Krieg,[16] a mixture of 131 mg (0.31 mmol) of selenide **9b**, 1.3 mL of 90% *tert*-butyl hydroperoxide, and 247 mg of basic alumina in 5 mL of THF was heated at 60 °C for 4 h. The rection mixture was filtered, the solids were washed with ethyl acetate (20 mL), and the combined organics were concentrated to give an oil that was purified by flash chromatography on silica gel to give 47 mg (67.9%) of diene **11** as white crystals: mp 70–72 °C; ^1H NMr (250 MHz) δ 1.02 (s, 3 H, CH_3), 1.20 (s, 6 H, 2 CH_3), 1.69 (br s, 3 H, =CCH_3), 1.2–1.9 (br d, 7 H), 1.97 (dd, J = 11.0, 3.1 Hz, 1 H, =CCH), 4.64 (br s, 1 H, =CH), 4.77 (br s, 1 H, =CH), 4.96 (dd, J = 17.6, 1.5 Hz, 1 H, =CH), 5.01 (dd, J = 11.3, 1.5 Hz, 1 H, =CH), 6.26 (dd, J = 17.6, 11.1 Hz, 1 H, =CH); IR CCl_4) 3450 cm^{-1}. Anal. Calcd for $C_{15}H_{26}O$: C, 81.08; H, 11.71. Found: C, 80.95; H, 11.83.

Synthesis of 4-Hydroxy-*N*-[5-(hydroxymethyl)-3-isoxazolyl]-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide and [(5-Methyl-3-isoxazolyl)amino]oxoacetic Acid. Major Metabolites of Isoxicam

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4-Hydroxy-*N*-[5-(hydroxymethyl)-3-isoxazolyl]-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide (**2**), the major oxidative human metabolite of isoxicam (**1**), and [(5-methyl-3-isoxazolyl)amino]oxoacetic acid (**3**), the major rat metabolite of isoxicam (**1**), were synthesized. **2** was synthesized by condensation of the known benzothiazine ester **8** with the isoxazolamine **9b**. **9b** was synthesized via a nine-step sequence starting with 5-methyl-3-isoxazolecarboxylic acid (**14**). NBS bromination of **14** gave 5-(bromomethyl)-3-isoxazolecarboxylic acid, which was converted to the carbamate ester via a Curtius rearrangement of the acid azide. Displacement of bromine with silver acetate gave the acetoxy compound **21**. Hydrolysis of **21** gave the unstable 3-isoxazolamine derivative **9a**, which was converted to the $OSiMe_3$ derivative **9b**. The compound **3** was synthesized by reaction of ethyl oxalyl chloride with 5-methyl-3-isoxazolamine followed by base hydrolysis.

Isoxicam[1] (Maxicam, **1**) is a new nonsteroidal antiinflammatory agent which has been shown to be a clinically effective antiarthritic drug.[2] Pharmacokinetic[3,4] and metabolism studies in animals and man indicate **1** to have a long plasma half-life and to be metabolized via hy-

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