The Geometrical Isomers of γ-Bisabolene

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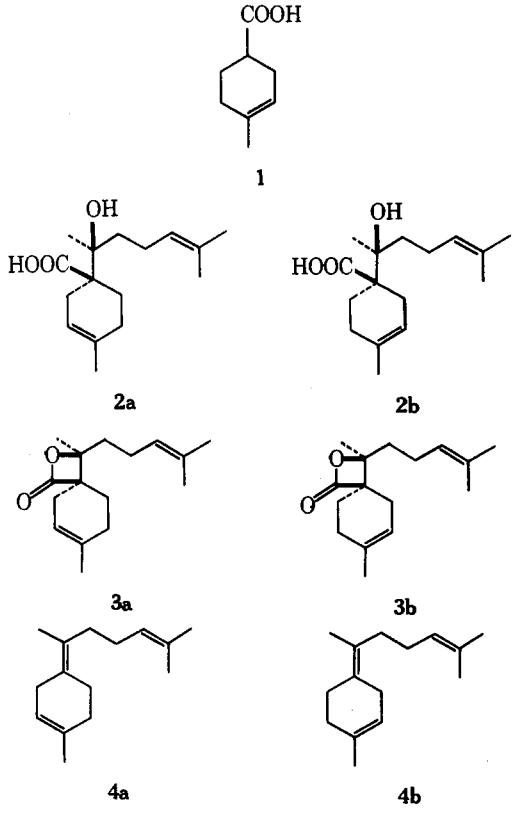
We have previously reported[2] a synthesis of γ-bisabolene which resulted in a mixture of two geometrical isomers about the tetrasubstituted olefinic bond. Although the isomers could be separated by GLC, we could find no way of determining the stereochemistry of the pure isomers from spectral data. We had determined that a red alga of the genus *Laurencia* contained only one isomer of γ-bisabolene, which must be identified before biosynthetic experiments can proceed. We wish to report a synthesis of γ-bisabolene which has allowed the separation and identification of the geometrical isomers.

There are relatively few methods available for the synthesis of tetrasubstituted olefinic bonds, and none of these could be used for a stereospecific synthesis of one isomer of γ-bisabolene. We chose to use the method of Krapcho and Jahngen,[3] since it offered the best opportunity for separating the two isomers at an intermediate stage.

The dilithium salt of 4-methyl-3-cyclohexenecarboxylic acid (1), which was obtained in 95% yield from the Diels–Alder reaction of isoprene with acrylic acid, was condensed with 6-methyl-5-hepten-2-one to prepare the diastereoisomeric β-hydroxy acids **2a,b**. The crude β-hydroxy acid mixture was obtained as a semisolid mass from which one diastereoisomer **2a** crystallized preferentially. Treatment of the crude β-hydroxy acids **2a,b** with *p*-toluenesulfonyl chloride in pyridine gave a mixture of two isomeric β-lactones **3a,b** (ir 1810 cm^{-1}), which was converted into a mixture of two isomeric γ-bisabolenes **4a,b** by decarboxylation at 140°C. The overall yield was 37% from the acid **1**.



1 **2a** **2b** **3a** **3b** **4a** **4b**

During this reaction sequence on the mixture of diastereoisomers, we noticed only one differentiating spectral feature. The NMR spectrum of the mixture of β-lactones **3a,b** contained two methyl signals at δ 1.43 and 1.47 ppm for the methyl groups on the β-lactone rings. We assumed that the methyl group in the *E* isomer **3a** was situated in the shielding cone of the olefinic bond[4] in the cyclohexene ring. The β-lactone, prepared from the crystalline β-hydroxy acid **2a**, has the methyl signal at 1.43 ppm and was therefore the precursor of isomerically pure (*E*)γ-bisabolene.

The rather insecure assignment of stereochemistry was confirmed by a single-crystal x-ray diffraction analysis of the *p*-bromophenacyl ester of the β-hydroxy acid **2a**.

Crystals of the *p*-bromophenacyl derivative of hydroxy acid **2a** are orthorhombic and centrosymmetric. Systematic extinctions uniquely identify the space group as *Pccn*. The unit cell dimensions are $a = 24.929$ (2), $b = 16.615$ (1), and $c = 11.148$ (1) Å. A calculated density of 1.33 g/cm^3 indicated one molecule of composition $C_{24}H_{31}BrO_4$ per asymmetric unit. A total of 3504 reflections were measured on a Syntex P_{2_1} four-circle automated diffractometer using Cu Kα (λ 1.5418 Å) radiation and an ω-scan technique, with a minimum scan speed of 2°/min. Of these, 1953 reflections were judged observed ($F_o \geq 3\sigma(F_o)$).

A Patterson synthesis[5] was used to determine the bromine position and all other nonhydrogen atoms were located in the subsequent bromine-phased electron density synthesis and refined anisotropically until convergence was reached. The final residual index was 0.087 for the observed reflections. No hydrogens have been included in the current model. Bond distances and angles agree well with generally accepted values.[6] Figure 1 is a computer-generated drawing of the final x-ray model.

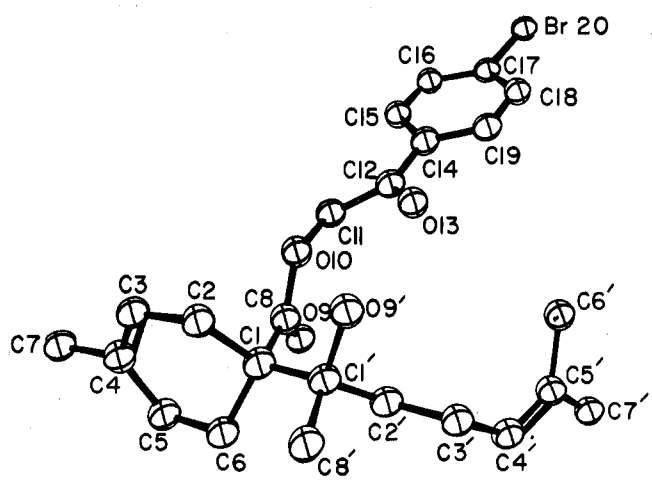


Figure 1. A computer-generated perspective drawing of the *p*-bromophenacyl derivative of hydroxy acid **2a**.

The GLC trace of a mixture of γ-bisabolene isomers

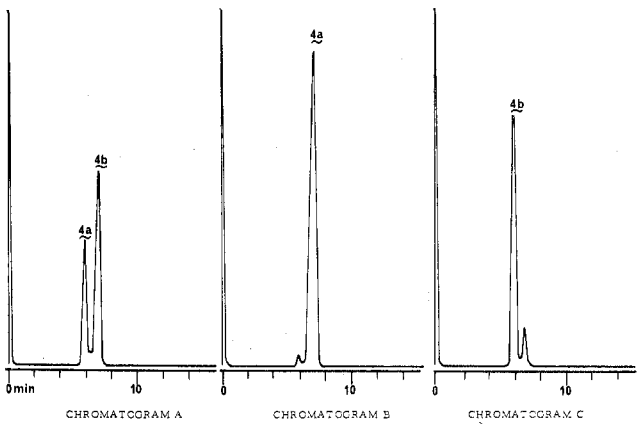


Figure 2. GLC traces of (a) a mixture of (*E*)- and (*Z*)-γ-bisabolene; (b) (*E*)-γ-bisabolene; (c) the purest sample of (*Z*)-γ-bisabolene obtained [2% Carbowax 20M on Chromosorb W (6 ft × 2 mm) at 100°C]. Retention time in minutes.

(Figure 2) contained two peaks at retention times of 5.8 and 6.5 min [2% Carbowax 20M on Chromosorb W (6 ft × 2 mm), 100°C]. On this and several other GLC systems,[7] the *Z* isomer always has the lower retention time. Thus we were able to determine that our previous synthetic route employing the Claisen rearrangement[2] gave a 60:40 ratio of (*E*)- and (Z)-γ-bisabolenes. We were able to determine that a species of *Laurencia* contained only the *E* isomer of γ-bisabolene and that a commercial sample of bisabolene[8] contained (*Z*)-γ-bisabolene as the major component. Commercial samples of Oil of Myrrh[8] and Oil of Lime[9] also contained only (*Z*)-γ-bisabolene.

Experimental Section

Commercially available chemicals were used without further purification unless otherwise stated. All solvents were either analar grade or redistilled prior to use. Melting points were measured on a Fisher-Johns apparatus and are uncorrected. NMR spectra were recorded on Varian HR-220 or EM-360 spectrometers; chemical shifts are expressed as values in parts per million relative to tetramethylsilane (0). Infrared spectra were recorded on a Perkin-Elmer 700 spectrometer. Gas chromatographic analyses were performed on a Hewlett-Packard 402 instrument. Mass spectra were recorded on a Hewlett-Packard 5930A mass spectrometer. High-resolution mass spectra were measured by Beth Irwin, Department of Chemistry, UCLA.

4-Methyl-3-cyclohexenecarboxylic Acid (1). Isoprene (27 g, 0.4 mol) and acrylic acid (28 g, 0.4 mol) were heated in a steel bomb at 100–110° for 24 h. After cooling, the 4-methyl-3-cyclohexenecarboxylic acid was obtained as a white solid: mp 94–96° (lit.[3] mp 99°); yield 54.0 g (96%); ir ($CHCl_3$) 3500–2900 (broad), 1700 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 1.68 (s, 3 H), 5.40 (broad, 1 H), 11.9 (s, 1 H).

1-(1′,5′-Dimethyl-1′-hydroxy-4′-hexene)-4-methyl-3-cyclohexenecarboxylic Acid (2a,b). A solution of lithium diisopropylamide was prepared by dissolving diisopropylamine (2.02 g, 20 mmol) in anhydrous tetrahydrofuran (50 ml) under an atmosphere of argon and adding *n*-butyllithium in hexane (Alpha) (10.9 ml, 20 mmol, 1.83 M) at −40°. The resulting solution was stirred for 20 min below 0° and then recooled to −40°. A solution of 4-methyl-3-cyclohexenecarboxylic acid (1.42 g, 10 mmol) in tetrahydrofuran (10 ml) was added dropwise with stirring. The temperature of reaction was maintained below −20° during the addition. The reaction mixture was heated to 50° for an additional 2 h. The resulting bright yellow solution was again cooled to −40°. 6-Methyl-5-hepten-2-one (1.26 g, 10 mmol) was added dropwise. The reaction mixture was stirred for 2 h at −40°, then poured over ice (100 g) and extracted with ethyl ether (4 × 50 ml). The aqueous phase was separated and acidified with 3 N hydrochloric acid (pH ≃ 3). The solution was again extracted with ethyl ether (4 × 50 ml). The organic layer was dried over anhydrous magnesium sulfate and solvent removed, to obtain (1-(1′,5′-dimethyl-1′-hydroxy-4′-hexene)-4-methyl-3-cyclohexenecarboxylic acid, a white solid, mp 129–133°, yield 2.10 g (80%). This solid was found to be a mixture of diastereoisomers. The mixture was separated by repeated fractional recrystallizations from chloroform. After four recrystallizations, white needles of one isomer were obtained, mp 149–150°. Data given were obtained for the pure isomer: ir ($CHCl_3$) 3500, 2950 (broad), 1240, 1690 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 1.23 (s, 3 H), 1.68 (s, 9 H), 5.18 (t, 1 H), 5.40 (broad, 2 H). Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.18; H, 9.59.

1-(1′,5′-Dimethyl-1′-hydroxy-4′-hexene)-4-methyl-3-cyclohexenecarboxylic Acid β-Lactone (3a). 1-(1′,5′-Dimethyl-1′-hydroxy-4′-hexene)-4-methyl-3-cyclohexenecarboxylic acid (0.534 g, 2 mmol) was dissolved in anhydrous pyridine (20 ml). The resulting solution was cooled to −5° using an ice–methanol bath, after which *p*-toluenesulfonyl chloride (1.07 g, 6 mmol) was added with stirring. The mixture was stirred at 0° for 18 h. The red solution was then poured over ice (100 g) and extracted with ethyl ether (4 × 50 ml). The organic extract was washed repeatedly with saturated copper sulfate solution (3 × 50 ml) to remove the pyridine. This was followed by several washes with sodium bicarbonate (4 × 50 ml). The ether extract was dried over anhydrous magnesium sulfate. Removal of solvent gave 1-(1′,5′-dimethyl-1′-hydroxy-4′-hexene)-4-methyl-3-cyclohexenecarboxylic acid β-lactone: yield 0.429 g (84%) of a clear oil; ir (film) 1810 cm^{-1}; NMR (220 MHz, CCl_4) δ 1.43 (s, 3 H), 1.60 (s, 3 H), 1.68 (s, 6 H), 5.15 (t, 1 H), 5.39 (broad, 1 H); high-resolution mass spectrum M^+ 248.1777 ($C_{16}H_{24}O_2$ requires 248.1776). No attempt was made to purify this material.

(*E*)-γ-Bisabolene (4a). 1-(1′,5′-Dimethyl-1′-hydroxy-4′-hexene)-4-methyl-3-cyclohexenecarboxylic acid β-lactone (537 mg, 2.6 mmol) was heated to 140° under argon for 2 h (evolution of CO_2 was observed), then cooled. The brown oil obtained was vacuum distilled using a Kugelrohr oven to yield pure (*E*)-γ-bisabolene, bp 90–110° (0.75 mm), yield 468 mg (94%). This material had properties identical with those of another sample of γ-bisabolene prepared by an alternate synthesis involving the Claisen rearrangement[2] as shown by NMR, mass spectrum, and GLC: NMR (220 MHz, CCl_4) δ 1.54 (s, 3 H), 1.63 (s, 9 H), 2.70 (s, 2 H), 5.12 (t, broad, 1 H), 5.38 (broad, 1 H); mass spectrum *m/e* (rel intensity) 204 (23), 107 (100), 193 (84), 135 (52). The GLC (2% Carbowax 20M on Chromosorb W, 6 ft × 2 mm, at 100°) showed a single component. Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.09; H, 11.78.

(*Z*)-γ-Bisabolene (4b). The residue (11.5 g, 0.04 mol) from the first recrystallization of the β-hydroxy acid **2a** was converted to the corresponding β-lactone **3b** with *p*-toluenesulfonyl chloride (24.7 g, 0.13 mol) in anhydrous pyridine (150 ml) at 0° for 18 h. This gave, after work-up, a light brown oil (4.9 g). The NMR (220 MHz, CCl_4), δ 1.47 (s, 3 H), 1.60 (s, 3 H), 1.68 (s, 6 H), 5.15 (5, 1 H), 5.39 (broad, 1 H), confirmed the structure of the β-lactone **3b.** Thermolysis at 150°, under argon, yielded the (*Z*)-γ-bisabolene. GLC analysis on 2% Carbowax 20M showed this material to be 90% of the desired *Z* isomer and 10% of the *E* isomer.

***p*-Bromophenacyl Derivative for X-Ray Analysis (5).** Purified β-hydroxy acid **2a** (266 mg, 1 mmol) was suspended in approximately 1–2 ml of distilled water containing a small amount of phenolphthalein indicator. A 10% sodium hydroxide solution was added dropwise until all the acid was dissolved and the solution was very slightly pink. Sufficient 5% hydrochloric acid was added to discharge the pink color. *p*-Bromophenacyl bromide (249 mg, 0.9 mmol) was dissolved in 100% ethanol (5 ml) and added to the acid mixture. A fluffy white precipitate began to form immediately. The mixture was refluxed for 2 hr, then cooled. The precipitate was filtered and suspended in 5% aqueous sodium carbonate solution and filtered again. This was followed by several cold water washes. The white precipitate was dissolved in hot ethanol and filtered. Hot distilled water was then added until crystallization began. Upon cooling, white crystals of **5** were obtained: mp 120–121° (recrystallized from chloroform); yield 400 mg (86%); ir ($CHCl_3$) 3550, 2950, 1738, 1705, 1595 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 1.23 (s, 3 H), 1.68 (s, 9 H), 3.45 (s, broad, 1 H), 5.20 (broad, 1 H), 5.40 (s, 1 H), 7.67 (s, 2 H), 7.72 (s, 2 H); mass spectrum *m/e* 444, 446 (1:1) (M − 18).

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Registry No.—**1,** 4342-60-3; **2a,** 57474-10-9; **2b,** 57474-11-0; **3a,** 57474-12-1; **4a,** 53585-13-0; **4b,** 13062-00-5; **5,** 57474-13-2; isoprene, 78-79-5; acrylic acid, 79-10-7; 6-methyl-5-hepten-2-one, 110-93-0.

Supplementary Material Available. A listing of fractional coordinates, bond distances, bond angles, and observed and calculated structure factors (12 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Camille and Henry Dreyfus Teacher-Scholar Grant Awardee, 1972–1977, and Fellow of the Alfred P. Sloan Foundation, 1973–1975.
(2) D. J. Faulkner and L. E. Wolinsky, *J. Org. Chem.*, **40**, 389 (1975).
(3) A. P. Krapcho and E. G. E. Jahngen, Jr., *J. Org. Chem.*, **39**, 1322 (1974).
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(5) The following library of crystallographic programs was used: C. R. Hubbard, C. O. Quicksall, and R. A. Jacobson, "The Fast Fourier Algorithm and the Programs ALFF, ALFFDP, ALFFT, and FRIEDEL", USAEC Report IS-2625, Iowa State University, Institute for Atomic Research, Ames, Iowa, 1971; W. R. Busing, K. O. Martin, and H. A. Levy, "A Fortran Crystallographic Least Squares Program", USAEC Report ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965; C. Johnson, "ORTEP, A Fortran Thermal-Ellipsoid Plot Program", U.S. Atomic Energy Commission Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965.
(6) See paragraph at end of paper regarding supplementary material.
(7) Two other GLC columns successfully used were 1% OV210 on Chromosorb G (6 ft × 2 mm), 100°C, and 2% SP2100 on Chromosorb W (6 ft × 2 mm), 150°C.
(8) We wish to thank Givaudan Corporation for generous gifts of bisabolene and Oil of Myrrh.
(9) We wish to thank Firtzsche, Dodge and Olcott for a generous gift of Oil of Lime.

A Short Synthesis of Camptothecin

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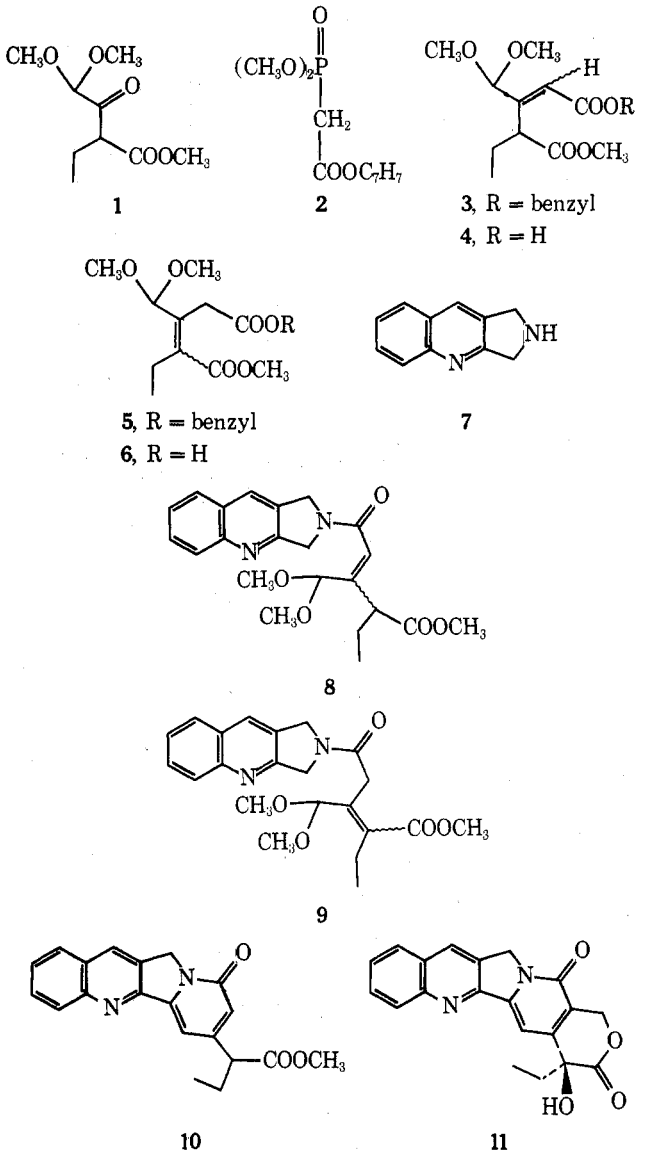
Camptothecin is an alkaloid first isolated from *Camptotheca acuminata*, a tree native to mainland China.[1] Structure **11** was established by x-ray crystallographic analysis of the iodoacetate.[2] Early clinical trials revealed promising antileukemic and antitumor properties causing many laboratories to commence work on total syntheses. Although subsequent testing uncovered the high toxicity of the compound, there is renewed interest in its inhibitory effect on macromolecular synthesis.[3] The first total synthesis of camptothecin (**11**) was completed in 1971[4] and since then a large number of successful approaches have been published.[5] All schemes thus far involve many steps and give low overall yields. In this note we describe another approach, although still not ideal, which does lead to intermediate **10** in five steps with an overall yield of 27%. This tetracyclic pyridone has previously been transformed to camptothecin (**11**) and the synthesis, owing to its convergent design, should be adaptable to the preparation of potentially more useful analogues.

The β-keto ester **1**,[6] readily available from methyl dimethoxyacetate and methyl butyrate, served as starting material. Wittig condensation with benzyl dimethylphosphonoacetate (**2**)[7] gave a mixture of *Z* and *E* benzyl esters **3** in 82% yield. Conversion to the carboxylic acids **4** was accomplished quantitatively and without disturbing the carbon–carbon double bond by hydrogenolysis over a 10% palladium on carbon catalyst in methanol. These sensitive acids were coupled without purification with the tricyclic amine **7**[8] by means of dicyclohexylcarbodiimide. The desired amides **8** were obtained in only 56% yield and we next explored the reactivity of the corresponding β,γ-unsaturated acids **6**. These were prepared by catalytic debenzylation of the tetrasubstituted unsaturated esters **5** available



in 96% yield by isomerization of the trisubstituted isomers **3** with potassium *tert*-butoxide in tetrahydrofuran. Dicyclohexylcarbodiimide promoted condensation of the diastereomeric mixture of these acids **6** with the tricyclic diamine **7** afforded the amides **9** (94%). Either isomers **8** or **9** could be converted to pyridone **10**[9] (41% yield) by treatment with boron trifluoride etherate followed by cyclization of the intermediate aldehydes in refluxing toluene containing a trace of trifluoroacetic acid. A sample of **10** recrystallized from ethyl acetate, mp 229–230°,[10] did not depress the melting point of authentic material, mp 228–230°, and infrared as well as ultraviolet spectra were superimposable. Nuclear magnetic resonance and mass spectra revealed a very minor but different impurity in each of the two samples of different derivation but otherwise confirmed identity. Furthermore, the compounds were indistinguishable by chromatographic techniques. Deoxycamptothecin accompanied by minor amounts of an isomer[11] has been prepared earlier in 35% yield by condensing the pyridone **10** with paraformaldehyde. The final conversion of deoxycamptothecin to *dl*-camptothecin (**11**) was accomplished in 55% yield by oxidation with hydrogen peroxide[9] or quantitatively by autoxidation in the presence of copper(II) species.[12]

Experimental Section

Microanalyses were performed by Midwest Microlab, Inc. Dry nitrogen was used in all reactions requiring an inert atmosphere.