1,3-Elimination Reactions of (3,4-Epoxybutyl)stannanes. Approach to the Synthesis of Hirsutene

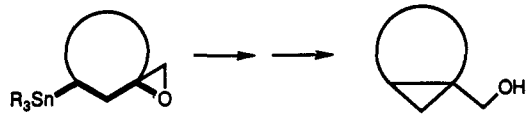
Louis Plamondon*[1,2] and James D. Wuest

Département de Chimie, Université de Montréal, Montréal, Québec, H3C 3J7 Canada

Received March 28, 1990

An advanced tricyclic precursor of hirsutene (3) was prepared by a 1,3-elimination reaction of spirocyclic epoxy stannane **7b**. Compound **7b** was synthesized efficiently from hydroxycyclohexenone **8b** by conjugate addition of $[(CH_3)_3Sn]_2CuLi$, Wittig methylenation, and $VO(acac)_2$-catalyzed epoxidation. Intermediate **8b** was prepared in five steps from the known enone **9** in 18% overall yield. An improved synthesis makes compound **9** available in four efficient steps from keto ester **12**.

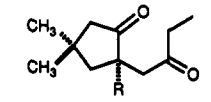
We have shown that treatment of typical spirocyclic epoxy stannanes 1 with $C_2H_5AlCl_2$ triggers 1,3-eliminations that lead reliably to bicyclic products 2 when tin, oxygen, and the three connecting atoms of carbon can assume a W orientation.[3] In this paper, we demonstrate that these 1,3-eliminations can be used to prepare advanced tricyclic precursors of hirsutene (3), a fungal metabolite.[4,5]



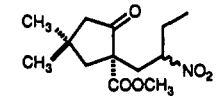
1 2

Previous work has shown that hirsutene can be made from tricyclic olefins similar to compound **5a** by conventional reactions.[6] In the retrosynthetic analysis summarized in Scheme I, we propose to make olefin **5a** by the thermal rearrangement of vinylcyclopropane **6a**.[7] The key step in Scheme I is formation of a precursor of compound **6a** by a 1,3-elimination reaction of epoxy stannane **7a**. We planned to make compound **7a** from cyclohexenone **8a** by normal conjugate addition of the trimethylstannyl group, methylenation, and epoxidation, and we expected to be able to produce compound **8a** from the known enone **9**.[8]

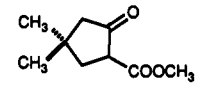
Previous syntheses of compound **9** are flawed by low yields in the final step, an intramolecular aldol condensation of diketone **10a**.[8] Since syntheses of similar bicyclic enones are typically more efficient when angular substituents are present, we decided to devise a modified synthesis of compound **9** in which aldol condensation of diketo ester **10b** is followed by decarboxylation.[9,10] When we were unable to prepare diketo ester **10b** from the known nitro compound **11**[8a] by various modifications of the Nef reaction, we turned to an approach developed by Paquette and co-workers.[9] Alkylation of the readily available keto ester **12**[8a] with the methanesulfonate of 2-methylene-1-butanol,[11] followed by heating, gave C-alkylated derivative **13** in 89%



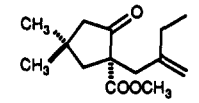
10a (R = H)
10b (R = $COOCH_3$)



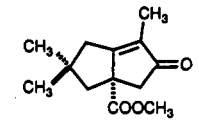
11



12



13



14

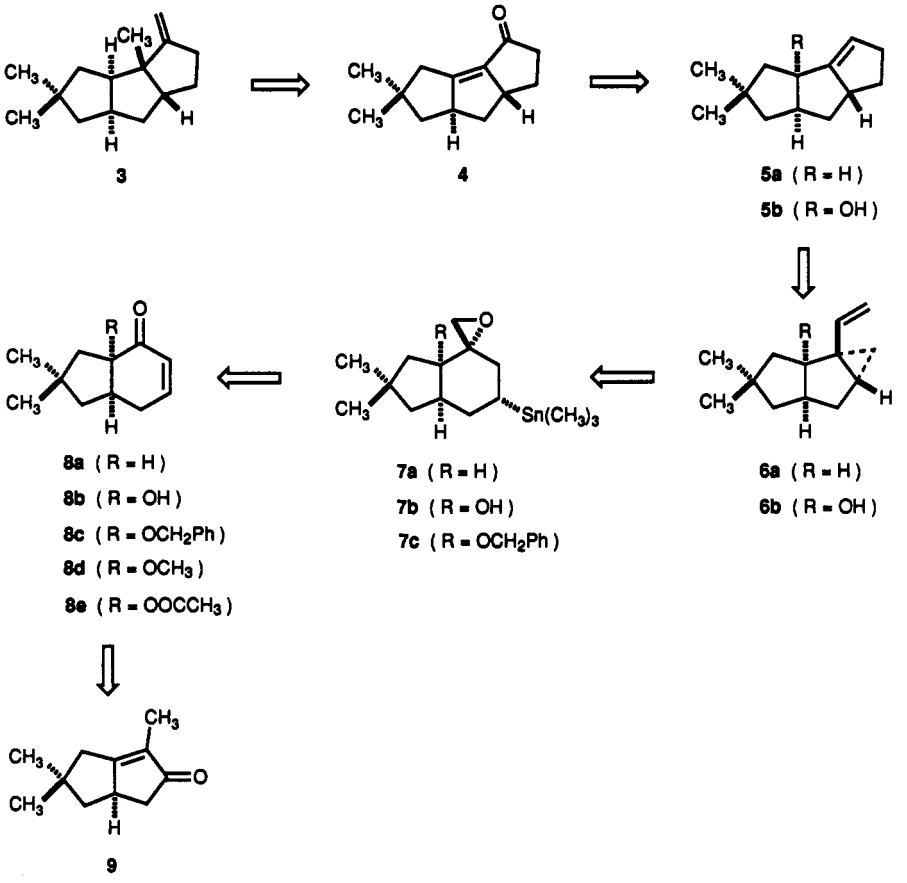
yield. Ozonolysis and a reductive workup with zinc and acetic acid then produced the required diketo ester **10b** in 100% yield. Aldol condensation[12] provided crude enone **14**, and subsequent decarbomethoxylation induced by lithium iodide gave target **9** in 48% overall yield. Our synthesis of enone **9** from keto ester **12** therefore requires four steps and proceeds in 42% yield.

We intended to prepare the next key intermediate, cyclohexenone **8a**, by an intramolecular aldol condensation of *cis*-keto aldehyde **15**, which was synthesized by the reactions shown in Scheme II. The enolate formed by reduction of enone **9** with lithium in ammonia was trapped with chlorotrimethylsilane,[13] and the resulting silyl enol ether **16** was converted directly into hydroxy ketone **17** in 57% overall yield from compound **9** by the procedure of Rubottom and co-workers.[14] The structure assigned to compound **17** is consistent with the expectation that oxygen should be delivered from the convex face of *cis*-bicyclo[3.3.0]octene **16**.[15] For similar reasons, reduction with $NaBH_4$ provided *trans*-diol **18**, which was isolated in 99% yield. Finally, cleavage of diol **18** with lead tetraacetate generated *cis*-keto aldehyde **15** in 89% yield.

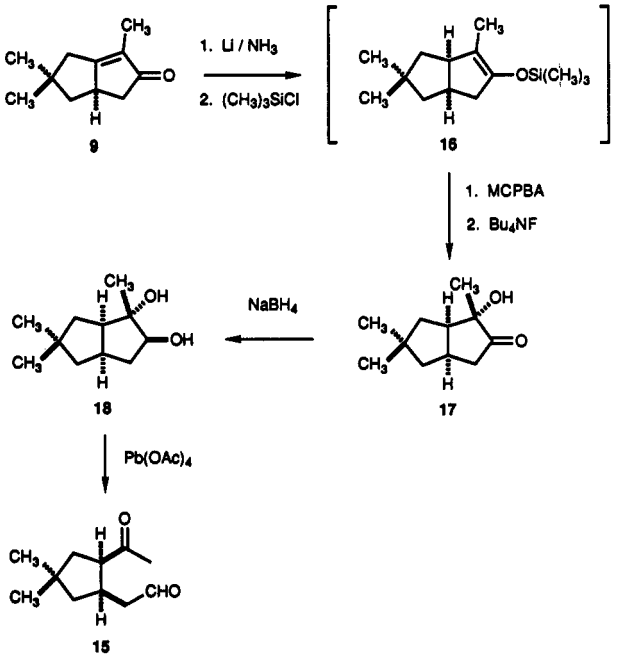
(1) Fellow of the Natural Sciences and Engineering Research Council of Canada, 1983-1987.
(2) Department of Chemistry, Harvard University, Cambridge, MA 02138.
(3) Plamondon, L.; Wuest, J. D. *J. Org. Chem.* **1991**, *56*, preceding paper in this issue.
(4) For references, see: Ayer, W. A.; Browne, L. M. *Tetrahedron* **1981**, *37*, 2199-2248.
(5) (a) For references to previous syntheses of hirsutene, see: Majetich, G.; Defauw, J. *Tetrahedron* **1988**, *44*, 3833-3849. Hua, D. H.; Venkataraman, S.; Ostrander, R. A.; Sinai, G.-Z.; McCann, P. J.; Coulter, M. J.; Xu, M. R. *J. Org. Chem.* **1988**, *53*, 507-515. Disanayaka, B. W.; Weedon, A. C. *Ibid.* **1987**, *52*, 2905-2910. (b) For a general discussion of polyquinane synthesis, see: Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1-160.
(6) Iyoda, M.; Kushida, T.; Kitami, S.; Oda, M. *J. Chem. Soc., Chem. Commun.* **1986**, 1049-1050. Little, R. D.; Muller, G. W. *J. Am. Chem. Soc.* **1981**, *103*, 2744-2749.
(7) For a review, see: Hudlický, T.; Kutchan, T. M.; Naqvi, S. M. *Org. React. (N.Y.)* **1985**, *33*, 247-335.
(8) (a) Froborg, J.; Magnusson, G. *J. Am. Chem. Soc.* **1978**, *100*, 6728-6733. (b) Kagawa, S.; Matsumoto, S.; Nishida, S.; Yu, S.; Morita, J.; Ichihara, A.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1969**, 3913-3916.
(9) Paquette, L. A.; Roberts, R. A.; Drtina, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 6690-6693.
(10) Klipa, D. K.; Hart, H. *J. Org. Chem.* **1981**, *46*, 2815-2816.
(11) Green, M. B.; Hickinbottom, W. J. *J. Chem. Soc.* **1957**, 3262-3270.
(12) Becker, D.; Brodsky, N. C.; Kalo, J. *J. Org. Chem.* **1978**, *43*, 2557-2562.
(13) Stork, G.; d'Angelo, J. *J. Am. Chem. Soc.* **1974**, *96*, 7114-7116. Stork, G.; Singh, J. *Ibid.* **1974**, *96*, 6181-6182.
(14) Spohn, R. F.; Grieco, P. A.; Nargund, R. P. *Tetrahedron Lett.* **1987**, *28*, 2491-2494. Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1978**, *43*, 1599-1602.
(15) Brown, H. C.; Vander Jagt, D. L.; Rothberg, I.; Hammar, W. J.; Kawakami, J. H. *J. Org. Chem.* **1985**, *50*, 2179-2188.

0022-3263/91/1956-2076$02.50/0

Scheme I

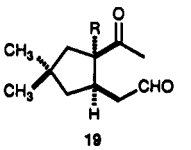


Scheme II



Unfortunately, persistent attempts to convert intermediate **15** into the key cyclohexenone **8a** by a wide variety of acid- and base-catalyzed aldol condensations were all unsuccessful.[16] Since ^{1}H NMR spectra of the products typically showed no vinylic hydrogens and since mass spectra contained peaks at twice the expected mass, we suspected at first that compound **8a** had been formed but dimerized by subsequent Michael additions. Similar hypotheses appear in the literature,[17] but they have not typically been confirmed by converting independently synthesized samples of the monomer into dimers under conditions of the aldol condensation. During later work described below, we were able to prepare cyclohexenone **8a** fortuitously by a completely different route. It survives the conditions we used to effect aldol condensations, so it cannot be generated in significant amounts from *cis*-keto aldehyde **15**. Further investigation showed that treatment of compound **15** with dilute aqueous acid establishes a cis–trans equilibrium favoring the trans isomer by a factor of 7:1. We propose that intermolecular aldol condensation of the predominant trans isomer produces dimers much more rapidly than intramolecular condensation of the minor cis isomer gives target **8a**.

This setback forced us to modify our plans in the following way. We reasoned that a substituted derivative **19** of *cis*-keto aldehyde **15** would be compelled to undergo a normal intramolecular aldol condensation. According to

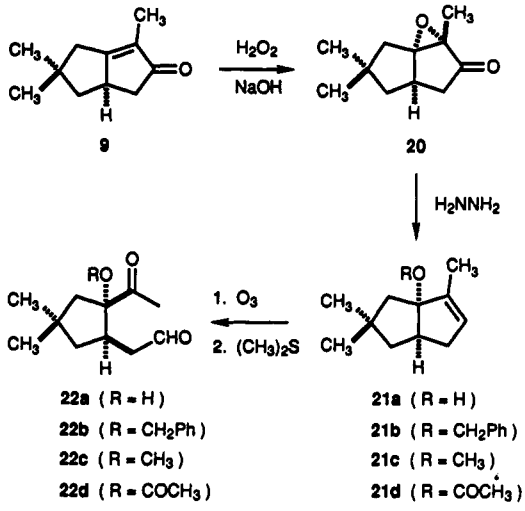


the retrosynthetic analysis outlined in Scheme I, the substituent R is destined to become hydrogen in hirsutene, so it must be easy to replace. We therefore decided to

(16) Curiously, condensation of an analogue of compound **15** without the geminal methyl groups has been reported to occur normally. Hacini, S.; Pardo, R.; Santelli, M. *Tetrahedron Lett.* **1979**, 4553–4556.

(17) Begley, M. J.; Cooper, K.; Pattenden, G. *Tetrahedron* **1981**, *37*, 4503–4508. Büchi, G.; Hansen, J. H.; Knutson, D.; Koller, E. *J. Am. Chem. Soc.* **1958**, *80*, 5517–5524.

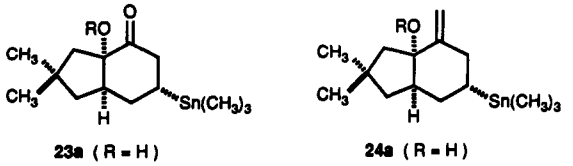
Scheme III



choose a hydroxyl group and to pursue the modified strategy summarized in Scheme I. In this approach, hirsutene (**3**) would be prepared by reductive methylation and methylenation of ketone **4**, which would be derived from alcohol **5b** by oxidative allylic transposition. We expected to be able to synthesize compound **5b** by thermal rearrangement of a derivative of vinylcyclopropane **6b**. Finally, we intended to make intermediate **6b** from the product of the 1,3-elimination reaction of epoxy stannane **7b**, which would be derived from cyclohexenone **8b** by simple reactions. This analysis shows that the hydroxyl group, added primarily to allow precursor **8b** to be made by an aldol condensation, can also be used advantageously in later stages of the synthesis of hirsutene.

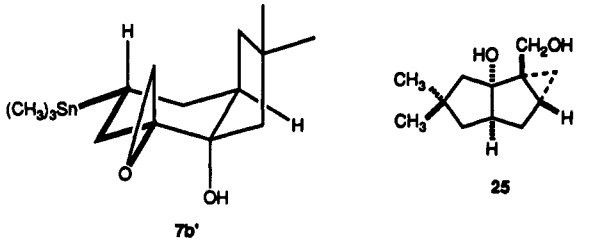
Protected derivatives of cyclohexenone **8b** could be prepared by the sequence of reactions summarized in Scheme III. Treatment of enone **9** with basic hydrogen peroxide provided epoxide **20** in 69% yield, and a subsequent Wharton fragmentation[18] produced alcohol **21a** in 41% yield. Conversion to the benzyl ether, followed by ozonolysis and a reductive workup, transformed compound **21a** into the sensitive keto aldehyde **22b**, which was immediately heated in benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid. As we had hoped, these conditions caused an aldol condensation that produced key intermediate **8c** in 71% overall yield from alcohol **21a**. Protection of the hydroxyl group of compound **21a** is fully justified, since attempted aldol condensations of alcohol **22a** gave only complex mixtures of products.

Conjugate addition of $[(CH_3)_3Sn]_2CuLi$[19] to cyclohexenone **8c** gave a 70% yield of a single stannane, assigned structure **23b** since we expected attack to occur primarily from the convex face.[15,20] Reaction of compound **23b** with the Lombardo reagent ($Zn/TiCl_4/CH_2Br_2$)[21] provided olefin **24b** in 81% yield, but all attempts to convert compound **24b** into the key epoxy stannane **7c** (Scheme I) were completely unsuccessful. We reasoned that both faces of the olefin were blocked and that a smaller protecting group should be used. We therefore returned to alcohol **21a** (Scheme III), prepared the methyl ether **21c** and acetate **21d**, and converted them into cyclohexenones **8d** and **8e** (Scheme I) by the normal sequence of ozonolysis, reductive workup, and acid-catalyzed aldol condensation. Although olefin **24c** could be prepared from methyl ether **8d** by conjugate addition of $[(CH_3)_3Sn]_2CuLi$ and Lombardo methylenation, epoxidation was again unsuccessful. The acetate sequence failed at an earlier stage, since the reaction of acetoxycyclohexenone **8e** with $[(CH_3)_3Sn]_2CuLi$ did not provide the expected stannane **23d**, but gave the previously inaccessible cyclohexenone **8a** (Scheme I) in 31% yield.



Since we were unable to effect epoxidations of protected derivatives of alcohol **24a**, we decided to take advantage of the ability of the free hydroxyl group to direct metal-catalyzed epoxidations.[22,23] Compound **24a** could be made from benzyl ether **8c** (Scheme I) in three steps. Deprotection of compound **8c** with DDQ[24] provided a 91% yield of hydroxycyclohexenone **8b**, which was converted into stannane **23a** in 83% yield by the conjugate addition of $[(CH_3)_3Sn]_2CuLi$.[25] Lombardo methylenation of compound **23a** was unsuccessful,[26] but Wittig methylenation provided olefin **24a** in 85% yield. As we had hoped, treatment of compound **24a** with t-BuOOH and a catalytic amount of $VO(acac)_2$[23] produced a single epoxy stannane, which could be isolated in 95% yield. The product can be assigned structure **7b** (Scheme I) with confidence, since the reliable diastereoselectivity of the epoxidation should be reinforced by the general preference for attack on the convex face.

Synthesis of epoxy stannane **7b** finally allowed us to test the key reaction of Scheme I. Compound **7b** should favor conformation **7b'**, in which tin, oxygen, and the three connecting atoms of carbon adopt the W orientation required for concerted 1,3-elimination with double inversion.[3] As expected, treatment of compound **7b** with $C_2H_5AlCl_2$ at −78 °C triggered a rearrangement that led uniquely to tricyclic diol **25**, which could be isolated in 75% yield.



(18) Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, *26*, 3615–3616. See also: Smith, A. B., III; Boschelli, D. *Ibid.* **1983**, *48*, 1217–1226.

(19) Piers, E.; Morton, H. E.; Chong, J. M. *Can. J. Chem.* **1987**, *65*, 78–87.

(20) However, stereoelectronic effects appear to favor anti conjugate additions to 5-alkoxy-2-cyclopentenones. Smith, A. B., III; Trumper, P. K. *Tetrahedron Lett.* **1988**, *29*, 443–446. Smith, A. B., III; Dunlap, N. K.; Sulikowski, G. A. *Ibid.* **1988**, *29*, 439–442.

(21) Lombardo, L. *Tetrahedron Lett.* **1982**, *23*, 4293–4296.

(22) For a similar strategy, see: Jackson, W. P.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1516–1519.

(23) Tanaka, S.; Yamamoto, H.; Nozaki, H.; Sharpless, K. B.; Michaelson, R. C.; Cutting, J. D. *J. Am. Chem. Soc.* **1974**, *96*, 5254–5255.

(24) Lee-Ruff, E.; Ablenas, F. J. *Can. J. Chem.* **1989**, *67*, 699–702. Horita, K.; Nagato, S.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron Lett.* **1987**, *28*, 3253–3256.

(25) Alcohols are typically less acidic than the conjugate acids of (trimethylstannyl)cuprates. Cox, S. D.; Wudl, F. *Organometallics* **1983**, *2*, 184–185. Piers, E.; Chong, J. M. *J. Chem. Soc., Chem. Commun.* **1983**, 934–935.

(26) In general, unprotected α-hydroxy ketones react inefficiently with the Lombardo reagent.[21]

The preparation of tricyclic diol **25** from keto ester **12** is interesting and efficient but relatively long, so we did not attempt to complete the synthesis of hirsutene according to the plan outlined in Scheme I. Our results are nevertheless significant because they show that 1,3-elimination reactions of suitably constructed epoxy stannanes can be used reliably in syntheses of complex polycyclic molecules.

Experimental Section

Our general experimental procedures have been described elsewhere.[3] Dichloromethane (CH_2Cl_2), dimethyl sulfide, triethylamine, toluene, *tert*-butyl alcohol, and chlorotrimethylsilane were dried by distillation from CaH_2, and benzene and tetrahydrofuran (THF) were dried by distillation from the sodium ketyl of benzophenone. Methanesulfonyl chloride (CH_3SO_2Cl) was distilled before use. All other reagents were commercial products of the highest purity available. Hexamethyldistannane was supplied by Organometallics, Inc. and a toluene solution of $C_2H_5AlCl_2$ was provided by Aldrich. In general, the purity of title compounds was assayed by ^1H NMR spectroscopy and capillary gas chromatography and was judged to be ≥95%.

2-Methylene-1-butanol Methanesulfonate. A stirred solution of 2-methylene-1-butanol (35.1 g, 0.408 mol)[11] and triethylamine (100 mL) in CH_2Cl_2 (800 mL) was treated dropwise at 0 °C with CH_3SO_2Cl (49 g, 0.43 mol). The mixture was kept at 0 °C for 25 min and then was diluted with CH_2Cl_2 and washed successively with cold 1 N hydrochloric acid, cold water, saturated aqueous $NaHCO_3$, and brine. Removal of volatiles from the dried organic phase by evaporation under reduced pressure left a residue of the methanesulfonate, a yellow liquid that was sufficiently pure to use directly in the following reaction (62.5 g, 0.381 mol, 93%): ^1H NMR (90 MHz, $CDCl_3$) δ 1.08 (t, ^3J = 7 Hz, 3 H), 2.14 (q, ^3J = 7 Hz, 2 H), 3.01 (s, 3 H), 4.66 (s, 2 H), 5.08 (bs, 1 H), 5.16 (m, 1 H).

Methyl 4,4-Dimethyl-1-(2-methylenebutyl)-2-oxocyclopentanecarboxylate (13). A dispersion of NaH in mineral oil (60%, 9.4 g, 0.24 mol) containing a trace of KH was washed thoroughly with toluene, and the purified hydride was stirred vigorously in toluene (400 mL) and treated dropwise at 25 °C under Ar with a solution of methyl 4,4-dimethyl-2-oxocyclopentanecarboxylate (40.1 g, 0.236 mol)[8a] in toluene (100 mL). The mixture was heated at reflux for 2 h, cooled to 25 °C, and treated with a solution of the above methanesulfonate (40.6 g, 0.247 mol) in toluene (150 mL). The mixture was heated at reflux for 16 h, cooled to 0 °C, and treated with 10% HCl. The aqueous phase was extracted with ether, and volatiles were removed from the combined organic phases by evaporation under reduced pressure. Distillation of the residue provided a pure sample of keto ester **13** as a colorless liquid (49.9 g, 0.209 mol, 89%): bp 100–106 °C (1.1 Torr); IR (liquid film) 1760, 1730, 1645 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.00 (t, ^3J = 7 Hz, 3 H), 1.12 (s, 6 H), 1.7–2.4 (m, 6 H), 2.71 (d, ^2J = 13 Hz, 1 H), 2.95 (d, ^2J = 13 Hz, 1 H), 3.71 (s, 3 H), 4.65 (m, 1 H), 4.83 (m, 1 H); MS (CI, isobutane) *m/e* 239.

Methyl 4,4-Dimethyl-2-oxo-1-(2-oxobutyl)cyclopentanecarboxylate (10b). At −78 °C, ozone was passed through a solution of keto ester **13** (49.7 g, 0.209 mol) in CH_2Cl_2 (750 mL) until a faint blue color persisted. The solution was then purged with a stream of N_2 and treated successively at 25 °C with 50% aqueous acetic acid (210 mL) and zinc powder (21.0 g, 0.321 mol). The mixture was stirred at 25 °C for 45 min, diluted with water, and filtered through Celite. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were washed successively with saturated aqueous $NaHCO_3$ and brine. Removal of volatiles from the dried organic phase by evaporation under reduced pressure left a residue of pure diketo ester **10b**, a colorless liquid (49.9 g, 0.208 mol, 100%): IR (liquid film) 1750 (broad) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.04 (t, ^3J = 7 Hz, 3 H), 1.12 (s, 3 H), 1.18 (s, 3 H), 1.6–2.1 (m, 2 H), 2.3–3.5 (m, 4 H), 2.38 (bs, 2 H), 3.69 (s, 3 H); MS (CI, isobutane) *m/e* 241.

4,5,6,6a-Tetrahydro-3,5,5-trimethyl-2(1*H*)-pentalenone (9). A dispersion of NaH in mineral oil (60%, 14 g, 0.35 mol) was washed thoroughly with toluene. More toluene (700 mL) was added to the purified hydride, and then the mixture was heated to reflux and treated dropwise under Ar with a solution of diketo ester **10b** (20.1 g, 83.6 mmol) in toluene (450 mL). The resulting mixture was stirred at reflux for 18 h, then was cooled to 0 °C and treated successively with water (100 mL) and 10% HCl (200 mL). The aqueous phase was extracted with ether, and the combined organic phases were washed with water and brine. Volatiles were removed from the dried organic phase by evaporation under reduced pressure, and the residue was purified by flash chromatography (silica, hexane (85%)/ethyl acetate (14%)/triethylamine (1%)).[27] A solution of the product and lithium iodide trihydrate (28 g, 0.15 mol) in dimethylformamide (1.2 L) was heated at reflux for 18 h. The mixture was then cooled, poured into water (1.2 L), and extracted with ether. The combined extracts were washed successively with water and brine, and volatiles were removed from the dried organic phase by evaporation under reduced pressure. Distillation of the residue provided a pure sample of the known bicyclic enone **9** as a colorless liquid (6.53 g, 39.8 mmol, 48%): bp 92–100 °C (1.7 Torr) (lit.[8] bp 69–71 °C (0.7 Torr)).

(1α,3aα,6aα)-Hexahydro-1-hydroxy-1,5,5-trimethyl-2(1*H*)-pentalenone (17). A boiling solution of lithium (0.126 g, 18.2 mmol) in freshly distilled liquid NH_3 (100 mL) was treated dropwise under Ar with a solution of bicyclic enone **9** (1.19 g, 7.25 mmol) and *tert*-butyl alcohol (0.49 g, 6.6 mmol) in THF (20 mL). The mixture was stirred for 10 min and then was treated with isoprene (0.5 mL). Volatiles were removed by evaporation at atmospheric pressure and then at reduced pressure, and the white solid residue was dried in vacuo for 1 h. The dried solid was dissolved in THF (80 mL), and the solution was cooled to −78 °C, stirred, and treated with part (10 mL) of the supernatant liquid produced when chlorotrimethylsilane (10 mL) was treated with triethylamine (10 mL). The resulting mixture was stirred at −78 °C for 5 min and at 25 °C for 12 h, and was then poured into a cold, vigorously stirred mixture of pentane and saturated aqueous $NaHCO_3$. The organic phase was washed successively with cold saturated aqueous $NaHCO_3$ and brine and was then dried (Na_2SO_4). The dried solution was filtered and passed rapidly through Florisil. Removal of volatiles from the eluent by evaporation under reduced pressure left a residue of silyl enol ether **16**, a yellow liquid pure enough to use directly in the following reaction.

A solution of this material in CH_2Cl_2 (50 mL) was treated with $NaHCO_3$ (2.4 g, 29 mmol), stirred, and cooled to −78 °C. Pure *m*-chloroperbenzoic acid (1.25 g, 7.24 mmol)[28] was then added, and the cold mixture was stirred for 3 h. After the addition of 10% aqueous sodium thiosulfate (15 mL), the mixture was stirred vigorously at 25 °C for 30 min and was then poured into ether. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine. Removal of volatiles by evaporation of the dried organic phase under reduced pressure left a yellow solid residue that was dissolved in CH_2Cl_2 (60 mL). The solution was cooled to 0 °C, stirred, and treated with tetrabutylammonium fluoride (8.0 mL, 1.1 M in THF, 8.8 mmol). The mixture was stirred at 0 °C for 5 min and at 25 °C for 14 h, diluted with CH_2Cl_2, and washed successively with saturated aqueous $NaHCO_3$, 5% HCl, and again with saturated aqueous $NaHCO_3$. Volatiles were removed from the dried organic phase by evaporation under reduced pressure, and the residue was purified by flash chromatography (silica, hexane (82%)/ethyl acetate (18%)).[27] This provided hydroxy ketone **17** as a yellow liquid (0.753 g, 4.13 mmol, 57%): IR (liquid film) 3430, 1750 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.99 (s, 3 H), 1.08 (s, 3 H), 1.21 (s, 3 H), 1.4–3.0 (m, 9 H); MS (CI, isobutane) *m/e* 183, 165, 137.

(1α,2β,3aα,6aα)-Octahydro-1,5,5-trimethylpentalene-1,2-diol (18). A solution of hydroxy ketone **17** (254 mg, 1.39 mmol) in ethanol (10 mL) was stirred at 0 °C and treated with $NaBH_4$ (130 mg, 3.4 mmol). The mixture was stirred at 0 °C for 2 h, diluted with water, and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried (K_2CO_3), and filtered through anhydrous $MgSO_4$. Removal of volatiles by evaporation under reduced pressure left a residue of pure diol **18**, a white solid

(27) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.
(28) Schwartz, N. N.; Blumbergs, J. H. *J. Org. Chem.* **1964**, *29*, 1976–1979.

(253 mg, 1.37 mmol, 99%): ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.89 (s, 3 H), 1.04 (s, 3 H), 1.26 (s, 3 H), 1.3–2.8 (m, 10 H), 3.93 (m, 1 H); MS (CI, isobutane) m/e 185, 167.

***cis*-2-Acetyl-4,4-dimethylcyclopentaneacetaldehyde (15).** Freshly recrystallized lead tetraacetate (585 mg, 1.32 mmol) was added in portions to a stirred suspension of diol **18** (237 mg, 1.29 mmol) in benzene (12 mL) at 6 °C. The resulting mixture was stirred at 6 °C for 15 min and was then diluted with ether and filtered through Celite and anhydrous Na_2SO_4. Volatiles were removed from the filtrate by evaporation under reduced pressure, and the residue was redissolved in ether and passed rapidly through Florisil. A second evaporation provided a pure sample of keto aldehyde **15**, a pale yellow liquid (209 mg, 1.15 mmol, 89%): IR (liquid film) 1725, 1710 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.01 (s, 3 H), 1.09 (s, 3 H), 1.2–1.8 (m, 4 H), 2.13 (s, 3 H), 2.4–2.9 (m, 3 H), 3.35 (m, 1 H), 9.71 (s, 1 H); MS (CI, isobutane) m/e 183, 165; HRMS (EI) calcd for $C_{11}H_{18}O_2$ 182.1302, found 182.1316.

(1aα,3aα,6aα)-Hexahydro-1,5,5-trimethyl-2-oxo-3*H*-pentalen[1,6a-*b*]oxirene (20). A stirred solution of bicyclic enone **9** (2.02 g, 12.3 mmol) in methanol (20 mL) at −23 °C was treated successively with 30% aqueous H_2O_2 (3.6 mL) and 4.0 N aqueous NaOH (1.2 mL). The mixture was stirred at 0 °C for 6 h, poured into water, and extracted with ether. The combined extracts were washed with brine, and volatiles were removed from the dried organic phase by evaporation under reduced pressure. The residue was pure epoxy ketone **20**, a colorless liquid (1.54 g, 8.54 mmol, 69%): IR (liquid film) 1725 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.09 (s, 3 H), 1.19 (s, 3 H), 1.33 (s, 3 H), 1.6–2.9 (m, 7 H); MS (CI, isobutane) m/e 181, 153.

(3aα,6aα)-1,3,6,6a-Tetrahydro-2,2,4-trimethyl-3a(2*H*)-pentalenol (21a). A solution of hydrazine monohydrate (3.9 g, 78 mmol) in methanol (6 mL) was stirred at 0 °C and treated dropwise with a solution of epoxy ketone **20** (864 mg, 4.79 mmol) in methanol (8 mL). The mixture was kept at 0 °C for 5 days, poured into water (25 mL), and extracted with ether. The combined organic phases were washed with brine, and volatiles were removed from the dried organic phase by evaporation under reduced pressure. Flash chromatography (silica, hexane (88%)/ethyl acetate (12%))[27] of the residue provided a pure sample of alcohol **21a** as a yellow liquid (325 mg, 1.95 mmol, 41%): ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.99 (s, 3 H), 1.14 (s, 3 H), 1.47 (bs, 1 H), 1.63 (bs, 2 H), 1.71 (bs, 3 H), 1.6–2.1 (m, 3 H), 2.4–2.7 (m, 2 H), 5.28 (bs, 1 H).

(3aα,6aα)-1,2,3,3a,6,6a-Hexahydro-2,2,4-trimethyl-3a-(phenylmethoxy)pentalene (21b). A suspension of KH (340 mg, 8.5 mmol) in THF (15 mL) was stirred at 25 °C under Ar and treated dropwise with benzyl bromide (960 mg, 5.6 mmol) and then with a solution of alcohol **21a** (589 mg, 3.54 mmol) in THF (9 mL). The mixture was stirred at 25 °C for 2 h, treated cautiously with saturated aqueous $NaHCO_3$, diluted with ether, and washed successively with saturated aqueous $NaHCO_3$ and brine. Volatiles were removed from the dried organic phase by evaporation under reduced pressure. Flash chromatography (silica, hexane (99%)/ethyl acetate (1%))[27] of the residue provided pure benzyl ether **21b** as a pale yellow liquid (898 mg, 3.50 mmol, 99%): ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.01 (s, 3 H), 1.14 (s, 3 H), 1.5–2.9 (m, 7 H), 1.68 (m, 3 H), 4.15 (m, 2 H), 5.48 (bs, 1 H), 7.30 (m, 5 H).

(1*R,2*S**)-2-Acetyl-4,4-dimethyl-2-(phenylmethoxy)-cyclopentanecarboxaldehyde (22b).** At −78 °C, ozone was passed through a solution of benzyl ether **21b** (0.898 g, 3.50 mmol) in a mixture of CH_2Cl_2 (20 mL) and methanol (20 mL) until a faint blue color persisted. The cold solution was then purged with a stream of O_2 and treated at −78 °C with dimethyl sulfide (20 mL). The mixture was stirred at 25 °C for 8 h, and then volatiles were removed by evaporation under reduced pressure. A solution of the residue in ether was washed successively with saturated aqueous $NaHCO_3$ and brine, and volatiles were removed from the organic phase by evaporation under reduced pressure. This provided a residue of unstable keto aldehyde **22b** that was used immediately in the next step. Further purification could be achieved by flash chromatography (silica, hexane (88%)/ethyl acetate (12%)),[27] which yielded a sample with the following spectroscopic properties: ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.14 (s, 3 H), 1.18 (s, 3 H), 1.7–2.0 (m, 4 H), 2.24 (s, 3 H), 2.3–2.6 (m, 3 H), 2.9 (m, 1 H), 4.35 (d, ^2J = 21.4 Hz, 1 H), 4.48 (d, ^2J = 21.4 Hz, 1 H), 7.35 (s, 5 H), 9.71 (t, ^3J = 1.8 Hz, 1 H); MS (CI, isobutane) m/e 289, 261, 245, 181, 91.

***cis*-1,2,3,3a,7,7a-Hexahydro-2,2-dimethyl-3a-(phenylmethoxy)-4*H*-inden-4-one (8c).** A solution of crude keto aldehyde **22b** in benzene (30 mL) was treated with the monohydrate of *p*-toluenesulfonic acid (24 mg, 0.13 mmol), and the mixture was heated at reflux for 31 h in a system equipped with a Dean–Stark trap. The mixture was then diluted with ether and washed successively with saturated aqueous $NaHCO_3$ and brine. Volatiles were removed from the dried organic phase by evaporation under reduced pressure, and the residue was purified by flash chromatography (silica, hexane (96%)/ethyl acetate (4%)).[27] This provided cyclohexenone **8c** as a yellow solid (668 mg, 2.47 mmol, 71% from benzyl ether **21b**): mp 53.5–54.5 °C; IR (melt) 1675 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (s, 3 H), 1.16 (s, 3 H), 1.41 (t, J = 13 Hz, 1 H), 1.58 (d, ^2J = 13.1 Hz, 1 H), 1.66 (dd, ^2J = 13.0 Hz, ^3J = 7.2 Hz, 1 H), 2.23 (dm, ^2J = 20.0 Hz, 1 H), 2.51 (d, ^2J = 13.1 Hz, 1 H), 2.73 (dm, ^2J = 20.0 Hz, 1 H), 2.87 (m, 1 H), 4.36 (dd, 2 H), 6.06 (dt, ^3J = 10.2 Hz, ^4J = 2 Hz, 1 H), 6.82 (dm, ^3J = 10.2 Hz, 1 H), 7.28 (m, 5 H); MS (CI, isobutane) m/e 271, 163, 107, 91; HRMS (EI) calcd for $C_{18}H_{22}O_2$ 270.1614, found 270.1641.

***cis*-1,2,3,3a,7,7a-Hexahydro-3a-hydroxy-2,2-dimethyl-4*H*-inden-4-one (8b).** A solution of enone **8c** (657 mg, 2.43 mmol) in CH_2Cl_2 (120 mL) was treated with water (6 mL) and 2,3-dichloro-5,6-dicyanobenzoquinone (5.53 g, 24.4 mmol). The mixture was stirred at 25 °C for 40 h and then filtered, and the orange solid was washed thoroughly with CH_2Cl_2. The combined filtrate and washings were extracted successively with 1 N aqueous NaOH, water, and brine. Volatiles were removed from the dried organic phase by evaporation under reduced pressure, and the residue was purified by flash chromatography (silica, hexane (86%)/ethyl acetate (14%)).[27] This provided hydroxy enone **8b** as a colorless liquid (396 mg, 2.20 mmol, 91%): IR (liquid film) 3500, 1680 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.19 (s, 3 H), 1.25 (s, 3 H), 1.3–2.7 (m, 8 H), 6.02 (bd, 1 H), 6.82 (dt, 1 H); MS (CI, isobutane) m/e 181, 163, 152, 135; HRMS (EI) calcd for $C_{11}H_{16}O_2$ 180.1146, found 180.1144.

(3aα,6aα,7aα)-Octahydro-3a-hydroxy-2,2-dimethyl-6-(trimethylstannyl)inden-4-one (23a). A stirred solution of hexamethyldistannane (4.7 g, 14 mmol) in THF (30 mL) was cooled to −23 °C under Ar and treated dropwise with a solution of methyllithium (9.0 mL, 1.5 M in ether, 14 mmol). The yellow solution was stirred at −23 °C for 15 min and at 0 °C for 25 min, cooled to −78 °C, and treated dropwise with a solution of a freshly recrystallized sample of the dimethyl sulfide complex of CuBr (1.40 g, 6.8 mmol)[29] in dimethyl sulfide (15 mL). The solution of cuprate was stirred at −78 °C for 20 min and then was treated dropwise with a solution of enone **8b** (392 mg, 2.17 mmol) in THF (8 mL). The mixture was stirred at −78 °C for 2.5 h, treated with cold methanol, warmed to 25 °C, treated with saturated aqueous NH_4Cl, and then diluted with ether. The resulting mixture was filtered and washed with saturated aqueous NH_4Cl. Volatiles were removed from the dried organic phase by evaporation under reduced pressure, and the residue was purified by flash chromatography (silica, hexane (93%)/ethyl acetate (7%)).[27] This provided stannane **23a** as a white solid (616 mg, 1.79 mmol, 83%): mp 61–65 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.07 (s, 9 H), 1.19 (s, 3 H), 1.22 (s, 3 H), 1.3–2.9 (m, 10 H), 3.79 (s, 1 H); MS (CI, isobutane) m/e 347, 329, 165; HRMS (EI) calcd for $C_{14}H_{26}O_2Sn$ 346.0947, found 346.0952.

(3aα,6aα,7aα)-Octahydro-2,2-dimethyl-4-methylene-6-(trimethylstannyl)-3a-indenol (24a). A suspension of methyltriphenylphosphonium bromide (3.6 g, 10 mmol) in THF (28 mL) was stirred at 0 °C under Ar and treated dropwise with butyllithium (6.2 mL, 1.5 M in hexane, 9.3 mmol). The resulting orange solution was stirred at 0 °C for 10 min and was then treated dropwise with a solution of stannane **23a** (448 mg, 1.30 mmol) in THF (4 mL). The mixture was stirred at 0 °C for 2.5 h and at 25 °C for 6 h, and then it was cooled again to 0 °C and treated with 20% aqueous NaH_2PO_4. Volatiles were removed by partial evaporation under reduced pressure, and the residue was diluted

(29) Wuts, P. G. M. *Synth. Commun.* **1981**, *11*, 139–140. House, H. O.; Chu, C.-Y.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460–1469.

with water and extracted with ether. The combined extracts were washed successively with water and brine, and volatiles were then removed from the dried organic phase by evaporation under reduced pressure. The residue was treated with pentane, and the resulting mixture was filtered through silica. Pentane was removed by evaporation under reduced pressure, and the residue was purified by flash chromatography (silica, hexane (95%)/ethyl acetate (4%)).[27] This yielded stannane **24a** as a colorless liquid (380 mg, 1.11 mmol, 85%): IR (liquid film) 3620, 3400, 1645 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.04 (s, 9 H), 1.11 (s, 3 H), 1.17 (s, 3 H), 1.2–2.6 (m, 11 H), 4.84 (m, 1 H), 5.03 (m, 1 H); MS (CI, isobutane) *m/e* 327, 311, 165; HRMS EI) calcd for $C_{15}H_{28}OSn$ 344.1154, found 344.1018.

(3aα,4aα,6α,7aα)-Octahydro-2,2-dimethyl-6-(trimethylstannyl)spiro[4*H*-indene-4,2′-oxiran]-3a-ol (7b). A green solution of stannane **24a** (27 mg, 79 μmol) and vanadyl acetylacetonate (1.4 mg, 5.3 μmol) in benzene (0.6 mL) was stirred at 25 °C and treated dropwise with a solution of 70% aqueous *tert*-butyl hydroperoxide (17 mg, 130 μmol) in benzene (0.6 mL). The red mixture was stirred at 25 °C for 2 h and was then diluted with ether and washed successively with 10% aqueous sodium thiosulfate and brine. Removal of volatiles from the dried organic phase by evaporation under reduced pressure left a residue of pure epoxy stannane **7b**, a colorless liquid (27 mg, 75 μmol, 95%): IR (liquid film) 3500; ^1H NMR (90 MHz, $CDCl_3$) δ 0.07 (s, 9 H), 1.13 (s, 3 H), 1.16 (s, 3 H), 1.2–2.2 (m, 11 H), 2.53 (d, ^2J = 4.7 Hz, 1 H), 2.98 (d, ^2J = 4.7 Hz, 1 H); MS (CI, isobutane) *m/e* 361, 343, 327, 195, 179; HRMS (EI) calcd for $C_{15}H_{28}O_2Sn$ 360.1103, found 360.1171.

(1aβ,1bα,4aα,5aα)-Octahydro-1b-hydroxy-3,3-dimethyl-1*H*-cyclopropa[*a*]-1a-pentalenemethanol (25). A solution of epoxy stannane **7b** (362 mg, 1.01 mmol) in CH_2Cl_2 (55 mL) was stirred at −78 °C under Ar and treated dropwise with a solution of $C_2H_5AlCl_2$ (1.2 mL, 1.8 M in toluene, 2.2 mmol). The mixture was stirred at −78 °C for 20 min, treated with methanol (5 mL), warmed to 25 °C, treated with 10% aqueous NH_4Cl, diluted with ether, and washed successively with 5% aqueous $NaHCO_3$ and brine. Volatiles were removed from the dried organic phase by evaporation under reduced pressure, and the residue was purified by flash chromatography (silica, hexane (50%)/ethyl acetate (50%)).[27] This provided diol **25** as a white solid (149 mg, 0.759 mmol, 75%): mp 106–107 °C; IR (KBr) 3280 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.51 (dd, ^3J = 8 Hz, ^2J = 5.0 Hz, 1 H), 0.80 (ddd, ^3J = 8 Hz, ^2J = 5.0 Hz, ^4J = 1.5 Hz, 1 H), 1.12 (s, 3 H), 1.20 (s, 3 H), 1.24–2.09 (m, 8 H), 1.87 (s, 2 H), 3.21 (d, ^2J = 11.4 Hz, 1 H), 4.25 (dd, ^2J = 11.4 Hz, ^4J = 1.5 Hz, 1 H); HRMS (EI) calcd for $C_{12}H_{20}O_2$ 196.1458, found 196.1461.

Acknowledgment. This work was financially supported by the Natural Sciences and Engineering Research Council of Canada and by the Ministère de l'Éducation du Québec. We thank Sylvie Bilodeau and Dr. M. T. Phan Viet of the Regional High-Field NMR Laboratory for recording our high-field ^1H NMR spectra. In addition, we are grateful to Michael Evans and Christine Johnson for recording our mass spectra.

Registry No. **3**, 59372-72-4; (±)-**7b**, 131863-74-6; (±)-**8b**, 131833-60-8; (±)-**8c**, 131833-48-2; (±)-**9**, 68691-09-8; (±)-**10b**, 131833-49-3; (±)-**12**, 68691-06-5; (±)-**13**, 131833-50-6; (±)-**15**, 131833-51-7; (±)-**17**, 131833-52-8; (±)-**18**, 131833-53-9; (±)-**20**, 131833-54-0; (±)-**21a**, 131833-55-1; (±)-**21b**, 131833-61-9; (±)-**22b**, 131833-56-2; (±)-**23a**, 131833-57-3; (±)-**24a**, 131833-58-4; (±)-**25**, 131833-59-5; $HOCH_2C(=CH_2)CH_2CH_3$, 4435-54-5; $CH_3SO_2OCH_2C(=CH_2)CH_2CH_3$, 131833-47-1.

Supplementary Material Available: ^1H NMR spectra of key compounds **7b**, **8b**, **8c**, **10b**, **21b**, **23a**, **24a**, and **25** (8 pages). Ordering information is given on any current masthead page.

Synthesis of Both Enantiomers of Nabilone from a Common Intermediate. Enantiodivergent Synthesis of Cannabinoids

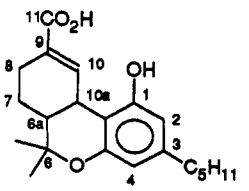
John W. Huffman,* H. Howard Joyner, Melissa D. Lee, Robert D. Jordan, and William T. Pennington[1]

Howard L. Hunter Chemistry Laboratory, Clemson University, Clemson, South Carolina 29634-1905

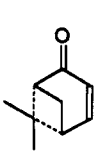
Received August 30, 1990

Both enantiomers of the synthetic cannabinoid nabilone (4) have been synthesized from a common intermediate, enone 7. Enone 7 was prepared by reaction of [2,6-dimethoxy-4-(1,1-dimethylheptyl)phenyl]lithium with (+)-apoverbenone (2), followed by PDC oxidation. Li/NH_3 reduction of 7 gave saturated ketone 9, which, after ether cleavage to 10, afforded (6a*S*,10a*R*)-hexahydrodibenzopyran 15 on reaction with $SnCl_4$. Isomerization to 6a*R*,10a*R* ketone 16 followed by ether cleavage gave the 6a*R*,10a*R* enantiomer of nabilone (4). The 6a*S*,10a*S* enantiomer of 4 (24) was prepared from 7 by ether cleavage to 18 and rearrangement to nonracemic tetrahydrodibenzopyran 20 using $AlCl_3$. Dissolving metal reduction of 20 followed by ether cleavage gave the 6a*S*,10a*S* enantiomer of nabilone (24). A model sequence employing (2,6-dimethoxyphenyl)lithium at the first step was carried out and the structure of one of the intermediates, ketone 12, was established by X-ray crystallography. A new preparation of apoverbenone (2) has been developed.

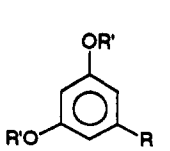
We have recently described a concise, efficient (seven steps, 14% yield) synthesis of (±)-11-nor-9-carboxy-Δ^9-THC (1) from (+)-apoverbenone (2) and the bis-MOM ether of olivetol (3).[2] This synthetic approach to cannabinoids employs as a key step the regioselective condensation of an aryllithium derived from 3 with enone 2, a process that precludes the formation of isocannabinoids in which the aromatic hydroxyl and alkyl substituents are exchanged. Although this synthesis is potentially applicable to the preparation of a variety of cannabinoids, it



1



2



3 R = C_5H_{11}, R' = CH_2OCH_3

8 R = C_6H_{19}, R' = CH_3

(1) To whom inquires regarding the crystallographic studies should be directed.

(2) Huffman, J. W.; Zhang, X.; Wu, M.-J.; Joyner, H. H.; Pennington, W. T. *J. Org. Chem.* In press.

0022-3263/91/1956-2081$02.50/0