TOTAL SYNTHESIS OF p-MENTHENOLIDES[1]

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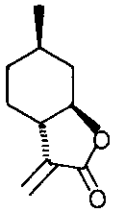
Abstract — A general approach to both cis- and trans-fused α-methylene γ-butyrolactones has been developed. This includes a new, mild method for the oxidation of α,β-unsaturated aldehydes. In addition, a new method to couple trans-α-methylene hydroxy acids into trans-lactones or, alternatively, cis-lactones has been developed. This strategy has been applied to the total synthesis of both cis- and trans-p-menthenolide, prepared in 35% (trans) and 21% (cis) overall yields from isopulegol.

Numerous naturally-occurring compounds contain α-methylene γ-butyrolactones.[2] Many of these natural products have antitumor activity[3] and this has caused much of the interest in developing new methods for the preparation of this functionality. Most of these procedures first form the lactone[4] and then introduce the α-methylene group;[5,6] however, a limited but growing number of methods have been devised for the direct conversion of an olefin into an α-methylene γ-butyrolactone.[7] Unfortunately, many of these approaches are useful for making either cis- or trans-fused products only, lack regiospecificity, involve exotic reagents or are very inefficient. We wish to report a new, general method for the preparation of both cis- and trans-fused α-methylene γ-butyrolactones from a single precursor.

The target molecules in the present study are trans-p-menthenolide (1) and cis-p-menthenolide (2). These lactones have been prepared in unspecified yield from isopulegol



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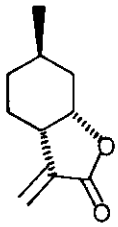

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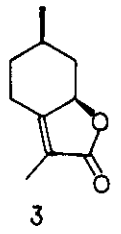
acetate[8] although a similar approach gave the isomeric lactone 3 among other products.[9] Our synthetic plan is outlined in equation 1. Isopulegol (4) will be converted first into the alcohol 5 and then the acid 6 as the key precursor for both of the desired products.



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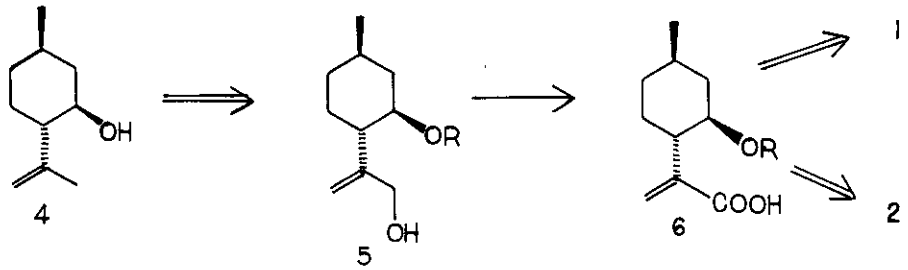
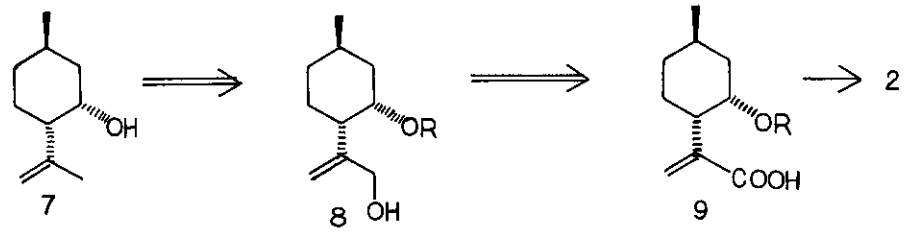


(1)

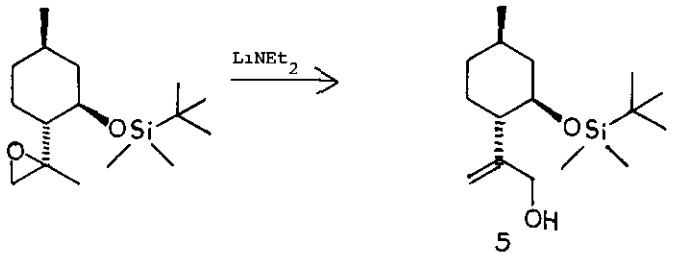
Alternatively, cis-p-menthenolide can be prepared from the epimer 7[10] of isopulegol via a parallel sequence of reactions involving the alcohol 8 and the acid 9 (eq 2). The use of optically active isopulegol as the starting material for these approaches will allow the



(2)

synthesis of optically active products and will establish the absolute configuration of the natural p-menthenolides.

The transformation of isopulegol into the unsaturated alcohol 5 necessitates initial protection of the hydroxyl group[12] followed by epoxidation with m-chloroperbenzoic acid (MCPBA)[13] and epoxide ring opening (for example, with lithium diethylamide[14]). A variety of different protecting groups has been explored[15] and the tert-butyldimethylsilyl ether[18] was found to be the best. This compound was prepared from isopulegol in 84% yield. Epoxidation as usual and ring opening with lithium diethylamide gave the allylic alcohol 5 (R=$SiMe_2$ (tert-butyl)) (eq 3). Oxidation of this alcohol with MnO_2 [19] gave the α,β-unsaturated aldehyde which can be deprotected with aqueous acid to give aldehyde 10.



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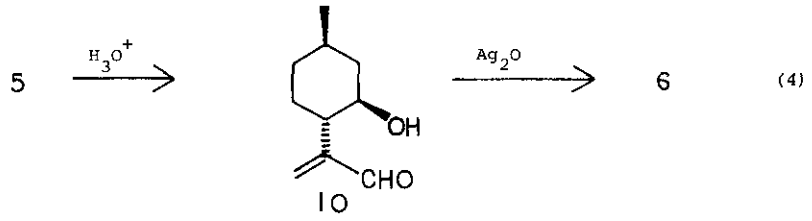
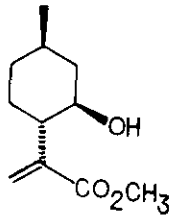
Oxidation to acid 6 (R=H) with silver oxide[7a] (eq 4) and cyclization to trans-p-menthenolide with dicyclohexylcarbodiimide (DCC)[7a] is accomplished in good yield.



(4)

Direct oxidation of the allylic alcohol 5 to acid 6 presents a significant problem apparently because of the sluggish oxidation of the α,β-unsaturated aldehyde.[20] Application of various reagents did not solve the problem. Jones reagent[16] cleanly gives the aldehyde after short reaction times even at low temperature but, eventually, deprotection and overoxidation results after the prolonged reaction times necessary to obtain the acid. Similar results are obtained from application of the Brown oxidation.[21] Application of Corey's oxidation method[22a] to the aldehyde derived from alcohol 5 (R = $SiMe_2$ (tert-butyl)) gave no reaction; however, the free hydroxyaldehyde 10 yielded the corresponding unsaturated ester 11 in addition to various other compounds including the β-cyanoaldehyde. Unfortunately, the maximum yield of the ester 11 was 20%. The use of Caro's acid[22b] on the aldehyde 10 gave the same product but this was contaminated with the cis-lactone 2. Fortunately, oxidation to acid 6 (R=$SiMe_2$ (tert-butyl)) can be carried out in 87% yield with sodium chlorite.[20] Consequently, the acid can be obtained without using the expensive silver oxide.



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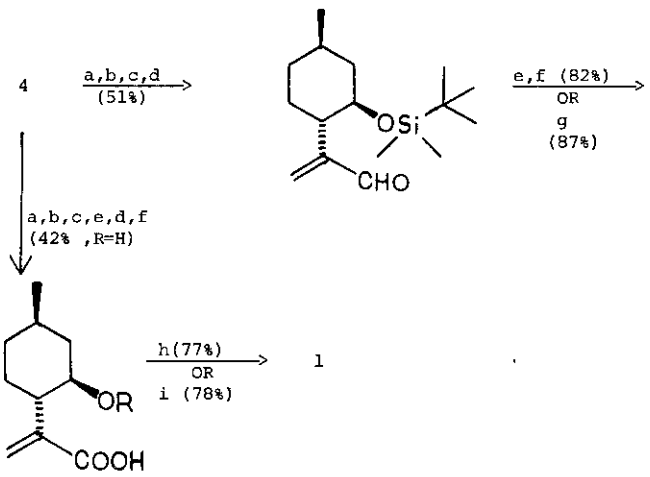
An alternative procedure for the coupling of trans-α-methylene hydroxy acid 6 (R=H) into the trans-lactone without the use of DCC has been developed. Either the free alcohol or the protected derivative (6, R=$C_6H_5CH_2$ or $SiMe_2$ (tert-butyl)) is simply allowed to react with TMSI[23] in refluxing chloroform.[24] The iodolactone 12 is obtained in good yield. Distillation of this compound causes loss of HI and gives trans-p-menthenolide in 78% yield from the acid 6 (R = $C_6H_5CH_2$ or $SiMe_2$ (tert-butyl)). The overall synthesis of lactone 1 is summarized in Scheme I.

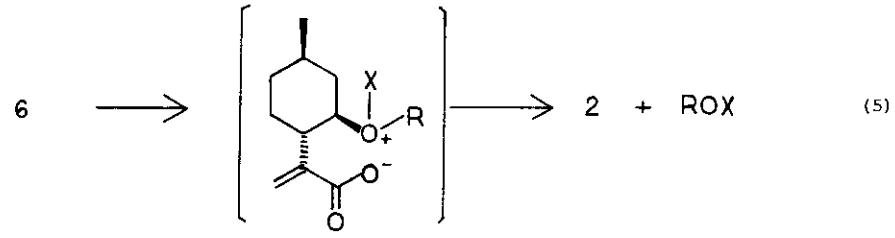
Scheme I. Synthesis of trans-p-Menthenolide



(a) $ClSiMe_2$ (tert-butyl), imidazole, DMF, RT
(b) MCPBA, $NaHCO_3$, 0°C
(c) $LiNEt_2$, -78°C
(d) MnO_2, C_6H_6, RT
(e) HCl, H_2O, MeOH, RT
(f) $AgNO_3$, NaOH, RT (R=H)
(g) $NaClO_2$, tert-BuOH (R=$SiMe_2$(tert-Bu))
(h) DCC, Pyr (R=H)
(i) TMSI, $CHCl_3$,Δ; Distill

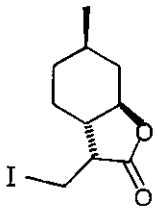
Preparation of cis-p-menthenolide can be accomplished essentially as outlined in equation 2. The epimer of isopulegol[10] is prepared in 84% yield from isopulegol. Protection as the tert-butyldimethylsilyl ether, epoxidation, lithium diethylamide treatment and deprotection with acid gives the diol 8 (R=H) in 40% overall yield. Oxidation with manganese dioxide yields cis-p-menthenolide (63%).[25] There is no need to prepare acid 9 as planned in equation 2.

Even though the overall yield of cis-p-menthenolide from isopulegol is 21%, a vast improvement in the aesthetics of the synthesis would result if the cumbersome epimerization of isopulegol could be avoided. In particular, if an intermediate in the approach to trans-p-menthenolide could be used, then an attractive, general method for preparing both cis- and trans-fused α-methylene lactones would be available. The compound of interest is the protected hydroxy acid 6 (eq 1).[26] The specific idea is to convert compound 6 into a derivative which would allow an intramolecular displacement by the carboxylate ion (eq 5).



(5)

Several possible reagents have been explored in an attempt to accomplish the conversion in equation 5. In fact, TMSI causes methoxy acids to form lactones with considerable inversion;[27] however, in the systems studied here, no inversion is observed. Instead, β-iodo-trans-lactones like compound 12 are formed. Another possibility involves the use of triphenyl-



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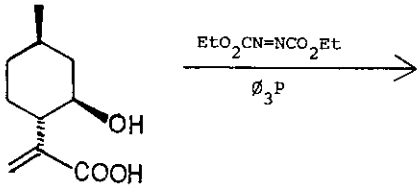
phosphine and diethylazodicarboxylate (DEAD).[28,29] Indeed, when the hydroxy acid 6 (R=H) is allowed to react with these reagents, cis-p-menthenolide is obtained in 43% yield (eq 6).[30]



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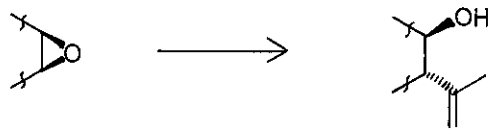
Consequently, both cis- and trans-α-methylene lactones are available from a single intermediate. This is especially significant when general application to other target molecules is considered. Preparation of trans-β-isopropenyl alcohols should be easy (eq 7)[31]



(7)

and this will allow entry into both cis and trans-α-methylene lactones by eventual application of TMSI or triphenylphosphine / DEAD. Thus, the cis system can be prepared without epimerization via oxidation and reduction. Furthermore, while reduction of isopulegone is stereospecific, other ketones may not reduce as cleanly so inversion via equation 6 eliminates this potential problem as well. The strategy presented here is being refined for application to more complex target molecules.[32]

EXPERIMENTAL SECTION

General

All reactions requiring anhydrous conditions were carried out under nitrogen in flamed-out apparatus. Proton NMR spectra were recorded on a Varian T-60 spectrometer while carbon NMR spectra were run on a JEOL PFT-100 instrument. All mass spectra were run on a Finnigan 4023 GC/MS. Infrared spectra were obtained on a Perkin-Elmer model 297 or 599B spectrophotometer. Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Tetrahydrofuran was freshly distilled from potassium and ether was distilled from calcium hydride. GC analyses were conducted using a Varian 90P instrument equipped with an SE-30 column.

tert-Butyldimethylsilyl ether of isopulegol

Isopulegol (7.71 g, 50.0 mmol)[33] was dissolved in 125 ml of DMF (freshly distilled from calcium hydride) and 6.8 g (100 mmol) of imidazole was added. tert-Butyldimethylsilyl chloride (8.29 g, 55.0 mmol) was added and the reaction mixture was stirred under nitrogen at room temperature overnight. The reaction mixture was quenched with 150 ml of cold water and then extracted with two 75 ml portions of ether. The combined organic layers were washed with 50 ml of brine, dried over anhydrous magnesium sulfate and concentrated to give 12.1 g (90%) of product (pure by GC and TLC) after distillation: BP 110-113°C (0.3 mm); ^{1}H NMR (CCl_4) δ 0.1 (s, 6H), 0.9 (s, 9H), 0.9-2.2 (m, 14H), 3.5 (td, 1H, J_t = 10 Hz, Jd = 4 Hz), 4.7 (s, 2H); IR (NaCl) cm^{-1} 3070, 2950, 2920, 2850, 1650, 1460, 1250, 1100, 1060, 870, 830, 770; ^{13}C NMR ($CDCl_3$) ppm - 3.840, -3.040, 18.105, 20.848, 25.847, 30.541, 31.699, 34.443, 45.172,

53.524, 73.276, 110.765, 147.464.

Epoxide of tert-butyldimethylsilyl ether of isopulegol

The silyl ether (12.1 g, 45 mmol) was dissolved in 150 ml of dichloromethane containing 0.5 g sodium bicarbonate and this was cooled to 0°C. Excess MCPBA (10.4 g of 80%, 60 mmol, Aldrich) was added and the reaction mixture was stirred for 36 hours, washed with 40 ml of saturated aqueous $NaHCO_3$ and 50 ml of water. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to give 11.9 g (93%) of the epoxide after distillation: BP 90-94°C (0.2 mm); NMR (CCl_4) δ 0.1 (s, 6H), 0.9 (s, 9H), 0.9-2.2 (m, 14H), 2.5 (m, 2H), 3.5 (m, 1H); IR (NaCl) cm^{-1} 2950, 2920, 2850, 1460, 1380, 1250, 1100, 1060, 870, 770; ^{13}C NMR ($CDCl_3$) ppm -4.755, -3.536, 16.337, 22.129, 25.725, 31.456, 33.711, 44.876, 52.610, 56.755, 57.608, 72.422.

Preparation of alcohol 5 (R=tert-butyldimethylsilyl)

Freshly distilled diethylamine (2.73 g, 34.7 mmol) was dissolved in 75 ml of dry ether under N_2 at 0°C. n-Butyllithium (14.8 ml of a 2.4 M solution in hexane, 35.5 mmol, Alfa) was added dropwise over 10 minutes and the resulting pale yellow solution was stirred 15 minutes more and then cooled to -78°C. The epoxide (4.83 g, 17.0 mmol) in 15 ml of ether was added dropwise over a 20-minute period. The brown reaction mixture was allowed to warm to RT and was stirred for 24 hours after which the reaction was quenched with 10 ml of saturated aqueous ammonium chloride (exothermic). The organic layer was washed with three 50 ml portions of water, dried ($MgSO_4$), concentrated and distilled to give 3.97 g (82%) of the desired product: BP 122-126°C (0.2 mm); ^1H NMR (CCl_4) δ 0.1 (s, 6H), 0.9 (s, 9H), 0.9-3.0 (m, 12H), 3.5 (td, 1H, J_t = 10 Hz, J_d = 4 Hz), 4.0 (s, 2H), 5.9 (d, 2H, J = 12 Hz); IR (NaCl) cm^{-1} 3400, 2950, 2920, 2850, 1650, 1460, 1360, 1250, 1100, 1060, 870, 830, 770.

Preparation of diol 5 (R=H)

The ether 5 (R = tert=butyldimethylsilyl, 2.84 g, 10.0 mmol) was dissolved in 50 ml of methanol and 10 ml of 15% aqueous HCl was added. This caused a slight exotherm. After 6 hours of stirring at room temperature, the reaction mixture was diluted with 50 ml of ether and this was washed three times with 50 ml portions of water. The combined aqueous layers were extracted with 50 ml of ether and the ether layers were combined, washed once with 50 ml of water, dried over $MgSO_4$ and concentrated to give a solid. This was triturated with hexane to leave 1.6 g (95%) of the white, crystalline diol: MP 87-90°C; ^1H NMR ($CDCl_3$) δ 0.8-2.3 (m, 11H), 3.2-3.9 (br s, 3H), 4.1 (br s, 2H), 5.1 (d, 2H, J = 8 Hz). This diol also can be prepared by workup of the lithium diethylamide reaction with aqueous HCl.

Preparation of aldehyde 10

The diol 5 (R=H, 1.5 g, 9.0 mmol) was dissolved in 60 ml of dry benzene and 6.0 g of activated manganese dioxide[19] was added. The reaction mixture was stirred overnight at

room temperature, filtered through celite and concentrated to give 1.25 g (83%) of the aldehyde (which decomposes upon distillation, BP 83-90°C (0.2 mm): ^{1}H NMR (CCl_4) δ 0.8-2.9 (m, 11H), 3.2-4.0 (m, 2H), 6.1 (d, 2H, J = 13 Hz), 9.3 (s, 1H); IR (NaCl) cm^{-1} 3400, 2920, 2860, 2700, 1690, 1450, 1220, 1090, 1045, 1020, 935, 890, 840.

Oxidation of compound 5 (R=tert-butyldimethylsilyl)

The alcohol 5 (R = tert-butyldimethylsilyl, 1.42 g, 5.00 mmol) was dissolved in 60 ml of dry benzene and 6.0 g of activated manganese dioxide[19] was added. After 7 hours of stirring at room temperature, the reaction mixture was filtered through celite and the filtrate was concentrated to give 1.2 g (80%) of the aldehyde: ^{1}H NMR (CCl_4) δ 0.1 (s, 6H), 0.9 (s, 9H), 0.9-2.8 (m, 11H), 3.9 (td, 1H, J_t = 10 Hz, J_d = 4 Hz), 6.2 (d, 2H, J = 14 Hz), 9.3 (s, 1H); IR (NaCl) cm^{-1} 2940, 2920, 2845, 2690, 1694, 1460, 1250, 1100, 1060, 870, 830, 770.

Oxidation of aldehyde 10

The aldehyde 11 (1.0 g, 6.0 mmol) was dissolved in 30 ml of a 1:1 mixture of ethanol and water containing 1.2 g of silver nitrate. To this was added dropwise a solution of 1.2 g of sodium hydroxide in 50 ml of water. The resulting black suspension of silver oxide was stirred for 4 hours at room temperature and the reaction mixture was filtered through celite. The filtrate was diluted with 50 ml of water and washed with 30 ml of ether. The aqueous phase was then acidified with cool 15% HCl and extracted with three 30 ml portions of benzene. The combined benzene layers were dried and concentrated to give an oil which solidified upon standing under hexane overnight. Trituration with hexane gave 0.95 g (83%) of colorless crystals of acid 6 (R=H): MP 82-86°C; IR (KBr) cm^{-1} 2300-3700, 3010, 2940, 2920, 1692, 1620, 1210, 750.

Preparation of trans-p-menthenolide (1) from the hydroxyacid 6 (R=H)

The acid 6 (R=H, 0.74 g, 4.0 mmol) was dissolved in 50 ml of dry pyridine and 0.76 g (3.7 mmol) of DCC was added. The reaction mixture was allowed to stir at room temperature for 36 hours and the pyridine was removed under vacuum without heat. The residue was washed with cold chloroform which was then concentrated and distilled to give 0.53 g (77%) of the α-methylene lactone: BP 120-123°C (0.2 mm); ^{1}H NMR (CCl_4) δ 1.0 (d, 3H, J = 4 Hz), 1.1-2.6 (m, 8H), 3.7 (td, 1H, J_t = 11 Hz, J_d = 4 Hz), 5.7 (dd, 2H, J_d = 36 Hz, J_d = 3 Hz); IR (NaCl) cm^{-1} 2920, 2860, 1775, 1450, 1240, 1220, 990, 780, 750; ^{13}C NMR ($CDCl_3$) ppm 21.885, 24.872, 31.273, 33.711, 38.466, 48.525, 82.479, 116.861, 139.236, 170.508; MS m/e 166 (P^+), 149, 138, 123, 109, 94, 81, 67, 53, 39.

Preparation of acid 6 (R = tert-butyldimethylsilyl)

The aldehyde (1.41 g, 5.00 mmol) was dissolved in 30 ml of tert-butyl alcohol and 7 ml (70 mmol) of tert-amylene (Shell Chemical Company). Sodium chlorite (0.8 g of 80%, Alfa)

and 0.8 g of sodium dihydrogenphosphate in 10 ml of water was added dropwise. The reaction mixture was stirred overnight at room temperature, dilute aqueous NaOH was added until the pH was 8-9 and the tert-butyl alcohol was removed under vacuum without heat. The residue was dissolved in 50 ml of water and this was washed with two 30 ml portions of hexane. The aqueous layer was acidified to pH 5 with dilute HCl and then was extracted three times with 50 ml portions of ether. The combined ether layers were washed with 50 ml of water, dried and concentrated to give 1.29 g (87%) of pure acid: ^{1}H NMR (CCl_4) δ 0.1 (s, 6H), 0.9 (s, 9H), 0.9-2.8 (m, 11H), 3.8 (td, 1H, J_t = 11 Hz, J_d = 4 Hz), 6.0 (d, 2H, J = 42 Hz), 11.1 (s, 1H); IR (NaCl) cm^{-1} 2300-3650, 1690, 1620, 1460, 1370, 1250, 1100, 1060, 865, 830, 770.

Preparation of trans-p-menthenolide from acid 6 (R=tert-butyldimethylsilyl)

The acid (0.3 g, 1.0 mmol) was dissolved in 35 ml of anhydrous chloroform and 0.40 g (2.0 mmol) of TMSI was added via syringe. This caused a slightly exothermic reaction with the formation of an iodine color. The reaction mixture was allowed to reflux for 8 hours and then cooled and washed twice with 15 ml portions of saturated aqueous sodium thiosulfate and once with 50 ml of cold water. The chloroform layer was dried and concentrated and bulb to bulb distillation of the residue gave 0.14 g (84%) of a colorless liquid: BP 123-128°C (0.4 mm). Spectra (^{1}H NMR and IR) were superimposable with the α-methylenelactone obtained from the hydroxyacid 6 (R=H). Prior to distillation, ^{1}H NMR and IR showed neither vinyl hydrogens nor the tert-butyldimethylsilyl group. A doublet at 3.4 δ is consistent with CH_2I and a saturated lactone C=O at 1780 cm^{-1} also was observed.

Preparation of epiisopulegol (7)[10,11]

Isopulegol (7.71 g, 50.0 mmol) was dissolved in 200 ml of acetone in a three-necked flask fitted with a mechanical stirrer. The reaction mixture was cooled to -15°C and Jones reagent was added dropwise until the characteristic orange color persisted for 20 minutes. The reaction mixture was filtered and the residue was washed thoroughly with ether. The combined organic layers were washed with three 80 ml portions of water, dried and concentrated to give 6.85 g (90%) of crude isopulegone: IR (NaCl) cm^{-1} 3070, 2950, 2920, 2860, 1710, 1650, 1450, 1370, 1190, 1120, 890.

This ketone (6.85 g, 45.0 mmol) was dissolved in 200 ml of dry THF at 0°C and lithium tri-sec-butylborohydride (50 ml of 1 M solution, Aldrich) was added via syringe. The reaction mixture was stirred for 9 hours and 15% aqueous NaOH was added at 0°C followed by 30% aqueous H_2O_2 and extracted with three 50 ml portions of ether. The combined organic layers were washed twice with 50 ml portions of brine, dried, concentrated and distilled to give 6.44 g (73%) epiisopulegol: BP 45-47°C (0.2 mm); ^{1}H NMR (CCl_4) δ 0.9 (d, 3H, J = 5 Hz), 1.0-2.2 (m, 15H), 3.9 (s, 1H), 4.8 (d, 2H, J = 8 Hz); IR (NaCl) cm^{-1} 2950, 3080, 2920, 1640, 1450, 1370, 1020, 950, 935, 890.

Protection of epiisopulegol as the tert-butyldimethylsilyl ether

Epiisopulegol (1.5 g, 10 mmol) was dissolved in 50 ml of freshly distilled DMF and 0.81 g (12 mmol) of imidazole was added followed by 1.65 g (11.0 mmol) of tert-butyldimethylchlorosilane. The reaction mixture was stirred for 12 hours at room temperature, diluted with 50 ml of water and extracted with three 50 ml portions of ether. The combined ether extracts were washed with 40 ml of cold brine, 40 ml of water, dried and concentrated. Distillation of the residue gave 1.9 g (70%) of the ether pure by GC: BP 110-113°C (3 mm); ^{1}H NMR (CCl_4) δ 0.1 (s, 6H), 0.9 (s, 9H), 0.9-2.2 (m, 14H), 4.0 (s, 1H), 4.7 (d, 2H, J = 6 Hz); IR (NaCl) cm^{-1} 3080, 2940, 2850, 1650, 1460, 1370, 1250, 1180, 1120, 1070, 1050, 980, 880, 830, 770; ^{13}C NMR ($CDCl_3$) ppm -4.938, -4.450, 18.166, 22.372, 24.323, 25.847, 35.113, 43.343, 49.074, 68.947, 110.218, 146.918.

Epoxidation of epiisopulegol tert-butyldimethylsilyl ether

The ether (1.9 g, 7.0 mmol) was dissolved in 100 ml of dry dichloromethane at 0°. Sodium bicarbonate (0.3 g) and 80% MCPBA (1.93 g, 8.9 mmol) were added and the reaction mixture was stirred for 24 hours. This was then washed three times with 50 ml portions of cold aqueous $NaHCO_3$ and once with 50 ml of cold water. The organic layer was dried, concentrated and distilled to give 1.5 g (79%) of the epoxide pure by GC: BP 85-95°C (0.2 mm); ^{1}H NMR (CCl_4) δ 0.1 (s, 6H),0.9 (s, 9H), 0.8-2.2 (m, 14H), 2.2-2.7 (m, 2H), 4.2 (m, 1H); IR (NaCl) cm^{-1} 2950, 2920, 2850, 1460, 1370, 1250, 1040, 975, 830, 770.

Preparation of alcohol 8 (R = tert-butyldimethylsilyl)

Diethylamine (0.88 g, 12.1 mmol) was dissolved in 30 ml of dry ether at 0°C and n-butyllithium (4.5 ml of a 2.4 M hexane solution, 11 mmol, Alfa) was added via syringe. After 10 minutes at 0°C, the reaction mixture was cooled to -78°C and 1.5 (5.5 mmol) of the epoxide from above dissolved in 10 ml of dry ether was added dropwise. The reaction mixture turned brown and was allowed to warm to room temperature overnight. This was then cooled to 0°C and 30 ml of saturated aqueous NH_4Cl was added dropwise (exothermic). Extraction with three 40 ml portions of ether, drying, concentration and distillation gave 1.2 g (73%) of the allylic alcohol: BP 140-150°C (0.2 mm); ^{1}H NMR (CCl_4) δ 0.1 (s, 6H), 0.9 (s, 9H), 0.9-2.8 (m, 12H), 4.0 (s, 2H), 4.9 (d, 2H, J = 14 Hz); IR (NaCl) cm^{-1} 3400, 2940, 2920, 2850, 1640, 1460, 1370, 1250, 1120, 1040, 980, 895, 830, 770.

Preparation of Diol 8 (R=H)

The ether 8 (R=tert-butyldimethylsilyl, 1.2 g, 4.0 mmol) was dissolved in 30 ml of methanol and 10 ml of 15% aqueous HCl was added. This was stirred for 4 1/2 hours at room temperature, diluted with 30 ml of water and extracted with four 40 ml portions of ether. The combined ether layers were washed twice with 30 ml of water, dried and

concentrated to give 0.65 (99%) of crystalline diol: MP 108-111°C; ^{1}H NMR ($CDCl_3$) δ 0.9 (d, 3H, J = 6 Hz), 1.0-2.3 (m, 11H), 2.5 (s, 2H), 4.1 (s, 2H), 5.1 (d, 2H, J = 10 Hz).

Preparation of cis-p-menthenolide (2) from diol 8 (R=H)

The diol 8 (R=H, 0.65 g, 4.0 mmol) was dissolved in 30 ml of dry benzene and 3.0 g of activated manganese dioxide[19] was added. The reaction mixture was stirred for 6 hours at room temperature, filtered through celite and the filtrate was concentrated. Distillation of the residue gave 0.40 g (63%) of the pure lactone 2: BP 112-116°C (0.3 mm); ^{1}H NMR (CCl_4) δ 0.9 (d, 3H, J = 6 Hz), 1.0-2.4 (m, 11H), 2.8 (m, 1H), 4.4 (m, 1H), 5.7 (d, 2H, J = 32 Hz); IR (NaCl) cm^{-1} 3080, 2940, 2910, 2860, 1765, 1675, 1450, 1400, 1260, 1190, 1125, 1035, 1000, 950, 880, 815; ^{13}C NMR ($CDCl_3$) ppm 21.702, 25.542, 28.347, 31.151, 35.662, 39.381, 76.994, 119.241, 141.978, 170.449; MS m/e 166 (P^+), 148, 138, 123, 109, 94, 81, 67, 53.

Preparation of cis-p-menthenolide (2) from acid 6 (R=H)

The acid 6 (R=H, 0.31 g, 0.75 mmol) was dissolved in 30 ml of benzene and 0.26 g (1.0 mmol) of triphenylphosphine and 0.17 g (1.0 mmol) of DEAD were added. The reaction mixture was allowed to stir for 36 hours at room temperature and was then washed once with 30 ml of water and once with 30 ml of 5% aqueous HCl. The benzene layer was concentrated and preparative TLC on silica gel gave 0.049 g (43%) of lactone 2 whose ^{1}H NMR and IR were superimposable with the material obtained from epiisopulegol.

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Received, 10th August, 1981