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SYNTHESIS OF BISABOL-10-ENE-3,7-OXIDE

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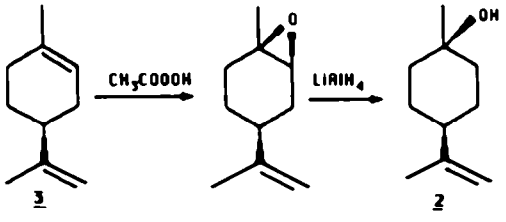
ABSTRACT: The synthesis of bisabol-10-ene-3,7-oxide was accomplished using as the key intermediate a radical obtained in the reduction of an organomercuric compound, and starting either from limonene or β-terpineol.

Introduction: Bisabolenes (1) are sesquiterpenes frequently found in plants as secondary (2) metabolites. Many of them present pharmacologic activity, they can be antiinflamatory, spasmolytic, antiphlogistic and cosmetic or they could be useful in other ways, such as hernandulcine, a thousand times sweeter than sucrose (3). We, and others (4) have isolated a new bisabolene whose spectroscopic properties suggest that it is bisabol-10-ene-3,7-oxide 1. However, only spectroscopics evidence supports this structure, and no X-ray analysis can be carried out because it an oily substance . These facts encouraged us to work out the synthesis of this novel compound.

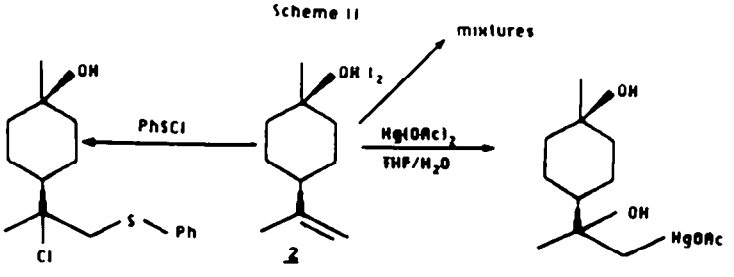
Our first strategy started from β-terpineol 2. We hoped that treatment of the terminal double bond of this compound with the right electrophiles (5) such as I_2, PhSCl or $Hg(OAc)_2$ could induce the intramolecular attack of the oxygen atom yielding the necessary oxide bridge. β-terpineol was obtained using the procedure by Mestres (6) epoxydizing limonene 3 with peracetic acid (scheme I). The axial alcohol obtained in the reduction with $LiAlH_4$ shows the necessary cis relationship with the propyl substituent carrying the double bond. However, after treatment of β-terpineol with the afore mentioned electrophiles, in no case could an oxygen intramolecular attack be obtained. When iodine was used, the result was complex mixtures; in no case did we achieve either the opening of the π-complex by other nucleophiles or the desired oxygen bridge (scheme II).

Scheme I



3 2

Scheme II



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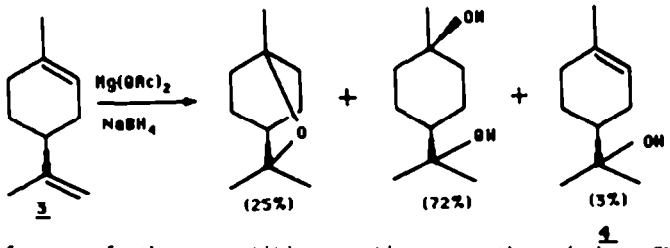
We found this behavior surprising, because limonene 3 itself can undergo intramolecular oxygen bridging easily when treated with $Hg(OAc)_2$, followed by reduction with $NaBH_4$, as was already known (7). The explanation must be that an α-terpineol 4, intermediate is what produces the intramolecular bridge (scheme III).

Scheme III

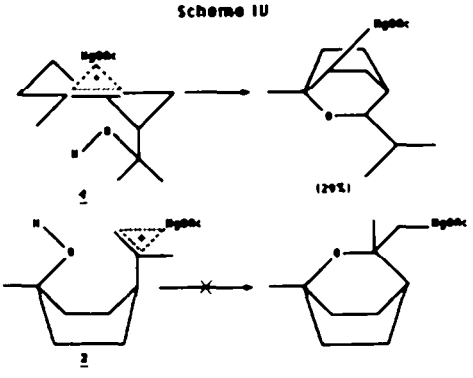


The conformational flexibility of the cyclohexene ring in the α-terpineol molecule probably facilitates the approach of oxygen and the π-complex, whereas the β-terpineol 2 molecule only allows the reaction in a much more energetic boat conformation. This handicap leads to a preference of other competitive reactions over these (scheme IV).

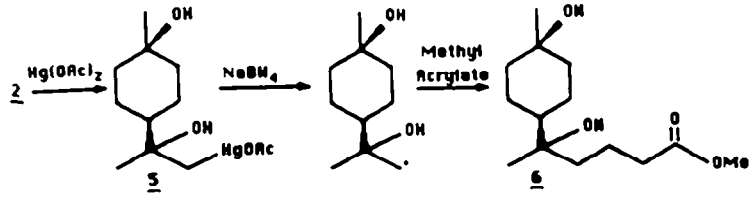
This led us to change the synthetic strategy to obtain an α-terpineol intermediate, from which the oxide bridge should be easy to achieve.

The first approach started again from β-terpineol. Oxymercuration of the terminal double bond yielded an organomercuric compound 5. Its reduction with $NaBH_4$ in the presence of methyl acrylate allowed the primary radical to be trapped to afford the dihydroxy methyl ester 6 (scheme V).

Scheme IV



Scheme V



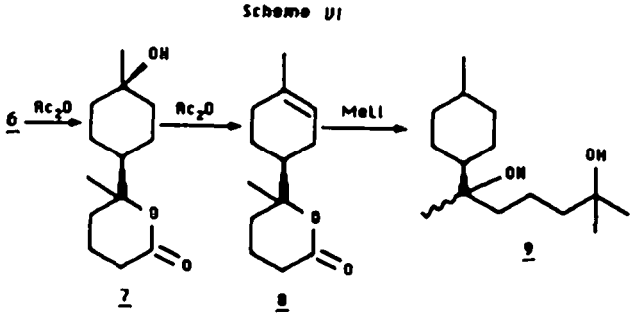
Hydrolysis and treatment with AcO_2 permitted protection of one of the tertiary hydroxy groups such as the δ-lactone derivative 7. If further heating of the reaction mixture takes place the free hydroxy group undergoes elimination to yield the unsaturated lactone as an epimeric mixture 8 (scheme VI).

When the lactone reacts with MeLi, ring opening takes place and the two carbon atoms necessary to finish the carbon skeleton are introduced 9.

The yield of this reaction is however somewhat low, probably because of extensive enolization of the lactone.

The preceding reactions also showed disappointing yields. This and the fact that β-terpineol is not very easily available led us to decide to obtain this diol by using limonene as the starting material. Limonene has two double bonds which can compete in the oxymercuriation step. Furthermore the trisubstituted double bond should be more electrophilic than the terminal one. This is the case when the epoxydation takes place, only the more substituted olefin undergoes oxidation. However, when the very bulky mercury atom is used as the reactant, the terminal double bond seems to react faster (7). So we carried out the reaction of an excess of limonene with $Hg(OAc)_2$ in THF. Reduction in the presence of methyl acrylate led us to a complex mixture from which chromatography yielded the desired hydroxymethyl ester 10. Despite the low yield (10%), the ready availability of the starting materials makes us prefer this second way. As expected, the reaction also afforded α-

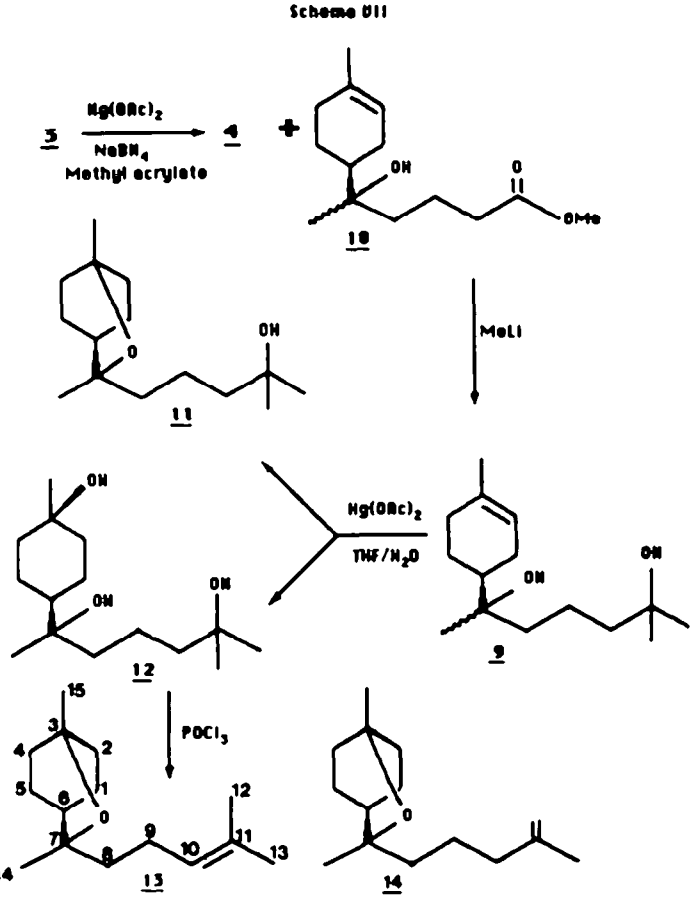
Scheme VI



terpineol 4 due to competitive reduction of the primary radical against trapping with methyl acrylate. MeLi transformed the methyl ester into the foregoing unsaturated diol 9 (scheme VII). Now this β-terpineol derivative should cyclize easily in the presence of $Hg(OAc)_2$, as is in fact, the case. Formation of the oxide ring 11 competes however with the obtention of the triol 12.

We have not been able to increase the yield of the oxide-bridged product by reducing the amount of water in the reaction mixture. If the amount of water is too low no reaction takes place and the starting olefin is recovered unchanged. Finally phosphorus oxychloride effected dehydration to give the two possible double bonds 13 and 14. $AgNO_3/SiO_2$ chromatography allowed us to easily separate both olefins. The one with the trisubstituted double bond showed all the expected properties of the natural compound isolated from Anthemis alpestris, which confirms the proposed structure.

Scheme VII



EXPERIMENTAL

I.R. spectra were run as liquid films. ^{1}H-NMR spectra were recorded at 200 MHz, $CDCl_3$, TMS as int. standard. ^{13}CNMR were recorded at 50.3 MHz. MS were operated at 70 eV.. Analytical TLC was performed on Si-gel G (Merck 7731), and CC on Si-gel 60 (Merck 7734).

Synthesis of 6 from β-terpineol: Methyl acrylate (10 ml.) was added to a soln of β-terpineol (1.5 g.) in THF (10 ml.), H_2O (2ml.) and $Hg(OAc)_2$ (4 g.). The mixture was spilled on methyl acrylate (10 ml.) with $NaBH_4$ (1 g.) and cooled to 0°C. This material was treated with Et_2O-H_2O and the organic layer (2.05 g.) was chromatograhed (si-gel) to afford 6 (900 mg.). IR ν_{max} cm^{-1}: 3400 (O-H), 1735 (C=O). ^{1}HNMR (δ ppm.): 3.50 (3H, s, OCH_3), 2.1 (2H, t, J=6Hz, CH_2-CO), 1.1 (3H, s, Me). Synthesis of 8 from 6: Compound 6 was hydrolyzed for 2 hr. with 2.5M NaOH/MeOH and the product was treated with NaAcO (200 ml.) and Ac_2O (5 ml.), the soln was treated at reflux for 17 hr.. The evaporation of Ac_2O and the chromatography of the reaction product gave the epimeric mixture 8 (350 mg.). ^{1}HNMR (δ ppm.): 5.3 (2H, m, CH=C), 1.5 (6H, s, 2Me), 1.23 (3H, s, Me), 1.22 (3H, s, Me). ^{13}CNMR in table 1.

Synthesis of 10 from limonene: $Hg(OAc)_2$ (23 g.) was added to a soln of limonene (20 gr.) in THF (190 ml.) and H_2O (20 ml.), and the mixture was stirred for 1 hr.. Following this, methyl acrylate (45 ml.) was added and when the mixture was cooled to -80°C, $NaBH_4$ (2.5 g.) was added. When the reaction had finished, the mixture was treated with Et_2O-HCl(aq.). From the organic layer were removed Et_2O and the excess of limonene, diazomethane was added to give a reaction product (11.3 g.), which was chromatographed over a Si-gel column using hexane with gradually increasing proportions of Et_2O as eluent. With hexane-Et_2O 14:1 α-terpineol (2.2 g.) was eluted and with hexane-Et_2O 8:2, an epimeric mixture of 10 (1.5 g.). IR ν_{max} cm^{-1}: 3450 (O-H), 1745 (C=O), 3030, 1650 and 810 (C=C). ^{1}HNMR (δ ppm.): 5.3 (2H, m, CH=C), 3.6 (6H, s, 2OMe), 1.6 (6H, s, 2Me), 1.1 (3H, s,

Me), 1.0 (3H, s, Me). ^{13}CNMR in table 1. MS (m/e, %): 240 (M^+, 0.4); 222 (M^+-H_2O, 32); 209 (M^+-OMe, 50); 145 (20); 123 (100); 95 (96); 69 (30).

Synthesis of 9 from 10: 10 (1.5 g.) in THF (10 ml.) was slowly added to a soln, cooled to -5°C, 1M (10 ml) of MeLi in Et_2O, and the mixture was maintained under N_2 with stirring until no more CH_4 was evolved. The reaction product, after treatment with Et_2O-H_2O, was chromatographed to afford an epimeric mixture of compound 9 (1.14 g.). M.p.: 96°C. IR (KBr) ν_{max} cm^{-1}: 3400 (O-H), 3010, 1650 and 805 (C=C). ^{1}HNMR (ppm.): 5.3 (2H, m, CH=C), 1.6 (6H, s, 2Me), 1.2 (12H, s, 4Me), 1.1 (3H, s, Me), 1.0 (3H, s, Me). MS (m/e, %): 240 (M^+, 0.6); 222 (M^+-H_2O, 10); 204 (M^+-$2H_2O$, 33); 109 (75); 95 (34); 69 (40).

Synthesis of 11 from 9: A soln of $Hg(OAc)_2$ (2 g.; 6.3 meq.) in H_2O (10 ml.) was added to 9 (1.05 g.; 4.4 meq.) in THF (30 ml.) and the mixture was stirred for 72 hr.. Following this, $NaBH_4$ (0.25 g.) was added and the reaction product was separated by filtration and finally treated with Et_2O-H_2O. Evaporation of Et_2O gave 720 mg. of the reaction product, which by CC afforded 11 (300 mg.) and 12 (200 mg.).

Bisabol-11-hydroxy-3,7-oxide (11). IR ν_{max} cm^{-1}: 3400 (O-H), 1160, 1050 and 1020 (C-O). ^{1}HNMR (δ ppm.): 1.2 (3H, s, Me), 1.18 (6H, s, 2Me), 1.0 (3H, s, Me). ^{13}CNMR in table 1.

Bisabol-3,7,11-trihydroxy (12). IR ν_{max} cm^{-1}: 3340 and 1150 (O-H). ^{1}HNMR (δ ppm.): 1.3 (3H, s, Me), 1.1 (6H, s, 2Me), 1.0 (3H, s, Me).

Synthesis of 13 from 11: 0.5 ml. of $POCl_3$ were added to a soln of 11 (88 mg.) in pyr. to -5°C and the mixture was stirred under N_2 for 4 hr.. The reaction product was extracted with Et_2O and the ethereal fraction washed with 2N HCl and Na_2CO_3. Evaporation of solvent and the chromatography of the reaction product over a silicagel-$AgNO_3$(20%) column using 14:1 hexane-Et_2O as eluent gave 13 (38 mg.) and 14 (23 mg.).

Bisabol-10-ene-3,7-oxide (13). IR ν_{max} cm^{-1}: 3020, 1660 and 850 (C=C), 1160, 1050 and 1020 (C-O). ^{1}HNMR (δ ppm.): 5.2 (1H, m, CH=C), 1.6 (3H, s, Me), 1.5 (3H, s, Me), 1.2 (3H, s, Me), 1.0 (3H, s, Me). ^{13}CNMR, in table 1. MS (m/e, %): 222 (M^+, 15); 204 (M^+-H_2O, 30); 139 (100); 109 (40); 95 (70); 69 (45).

Bisabol-11-ene-3,7-oxide (14). IR ν_{max} cm^{-1}: 3060, 1640 and 885 (CH_2=C), 1160, 1050 and 1020 (C-O). ^{1}HNMR (δ ppm.): 4.8 (2H, m, CH_2=C), 1.7 (3H, s, Me), 1.2 (3H, s, Me), 1.0 (3H, s, Me). MS (m/e, %): 222 (M^+, 9); 204 (M^+-H_2O, 13); 139 (100); 109 (20); 95 (50); 69 (27).

Table 1. ^{13}CNMR spectral data of compounds 8, 10, 11 and 13 (50.3 MHz, $CDCl_3$, chem. shifts are in δ-values from TMS).

C	8		10		11	13
1	26.5	26.1	26.4	25.8	22.7	22.7
2	120.1	119.6	120.5	120.3	31.9	31.9
3	133.8	134.3	133.4	133.1	75.8	75.6
4	30.7	30.5	30.7		31.9	31.9
5	23.4	23.3	23.6	23.0	22.7	22.7
6	44.3	44.0	43.0	42.8	30.5	30.5
7	86.6	86.4	73.3		69.6	69.5
8	29.6	29.5	39.2	38.5	42.5	41.9
9	16.6	16.5	18.7	18.5	19.5	23.5
10	34.5		34.0		44.7	124.9
11	171.4		173.6		71.0	131.1
12					29.4	17.6
13					29.4	25.7
14	23.3	23.2	22.8	22.7	27.6	27.6
15	23.9	23.8	23.8		25.9	25.7
OMe			50.8			

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