4-Diisopropylamino-2-butyne-1-ol

This aminoalcohol was prepared by the general method described above. Sufficient triethylamine was added to bring the pH to 8 and to aid in the solubilization of the insoluble bis-aminomethane. The reaction was heated at 80° for 72 h. A 1 mole run based on propargyl alcohol gave 147.5 g (87.5%) of the product, $n_D^{21.7}$ 1.4811, $d_4^{21.5}$ 0.931.

4-Pyrrolidino-2-butyne-1-ol

This compound was prepared by the general method described for the dimethyl analogue. A 1 mole run, based on propargyl alcohol, gave 117 g (84%) of the desired aminobutynol, b.p. 106–107° at 1.5 mm, $n_D^{21.7}$ 1.5039, $d_4^{26.5}$ 1.013 (reported (13) b.p. 101–102° at 0.4 mm, n_D^{22} 1.5092).

4-Piperidino-2-butyne-1-ol

This substance was prepared in 50% dioxane–water by the general method described above. A 1 mole run, based on propargyl alcohol, gave 122.4 g (80%) of the product, b.p. 112–113° at 1.5 mm, $n_D^{21.7}$ 1.5095, $d_4^{26.5}$ 1.030 (reported (13) b.p. 112–113° at 0.9 mm).

4-Morpholino-2-butyne-1-ol

This aminoalcohol was prepared by the general method. A 1 mole run, based on propargyl alcohol, gave 124 g (80%) of the desired product, b.p. 104–106° at 0.1 mm, $n_D^{21.7}$ 1.5095 (supercooled liquid), m.p. 51.5–52.5° (reported (14) b.p. 104–106° at 0.1 mm, n_D^{25} 1.5087).

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CONVERSION OF NEOABIETIC ACID INTO MANOOL

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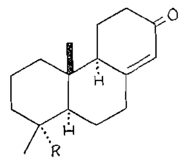
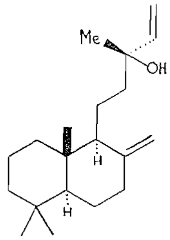
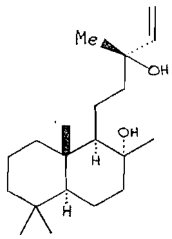
As a consequence of our recent total synthesis of abietoid resin acids (1), various intermediates became available for possible conversion into other diterpenic natural products. Thus, for example, the synthetic ketoester I*a* (2, 3), also a product of the ozonolysis of methyl neoabietate (2–4), appeared to be a likely candidate for transformation into manool (II) and sclareol (III), especially since the more readily accessible sclareol degradation product IV had already been converted into sclareol (5) and the latter had previously been transformed into manool (6). The present communication describes the transformation of I*a* into IV.



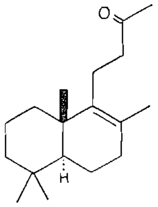
I*a*, R=CO$_2$Me
I*b*, R=Me



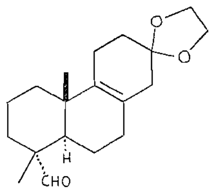
II



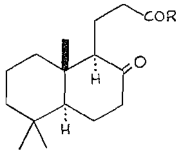
III



IV



V



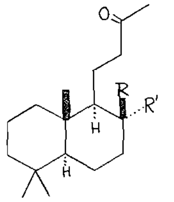
VI*a*, R=OH
VI*b*, R=Me

Ethylene glycol ketalation of I*a*, lithium aluminium hydride reduction of the ketal ester, and Sarett oxidation of the resultant ketal alcohol yielded the crystalline aldehyde V. The absence of any olefinic hydrogen signal in the proton magnetic resonance spectrum of the aldehyde indicated the tetra-substituted nature of its double bond. Wolff–Kishner reduction of the aldehyde, followed by acid-catalyzed deketalation, yielded the unsaturated ketone I*b*, a known product of the oxidative degradation of manool (II) (7–9). Although racemic I*b* has been converted into *d,l*-IV, only optically active ketone IV has been transformed into natural sclareol (III) (5), thus leaving the total synthesis of the natural product unfinished. As a consequence, the I*b*–IV transformation was repeated in the optically active series.

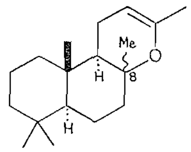
Ozonolysis of the ketone I*b* produced the ketoacid VI*a*, whose exposure to methyllithium yielded ketol VII*a* and enol ether VIII*a*. The latter was an 8-epimer of VIII*b* obtained by oxidation of sclareol (III) (*vide infra*) and dehydration of the intermediate ketol VII*b*. Acid-induced isomerization of either epimer VIII yielded a mixture of olefinic ketones IV and IX, only the former of which had been noted previously (5). This completed a formal total synthesis of sclareol (III), manool (II), and manoyl oxide (X) (10).

Both the present and related projects have depended on the availability of large quantities of tricyclic ketone I*b*. Although it has been prepared previously by oxidation of manool (II) (7, 8, 10–12), base treatment of the resultant diketone VI*b*, and acid-catalyzed dehydration of the intermediate ketol XI, the first step of the three-reaction sequence has been inefficient. As a consequence of a search for an improved procedure the oxidation of manool by osmium tetroxide – periodate (13) was investigated. Since initial experiments indicated the formation of mixtures of products, some of which could have arisen only from acid-induced chemical changes, a qualitative study of the pH dependence of the oxidation was undertaken.

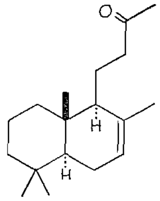
t-Butanolic solutions of manool were adjusted to various pH values while being exposed to periodic acid in the presence of a trace quantity of osmium tetroxide. At high alkalinity the product was exclusively the pentol XII. This may have been the consequence of low



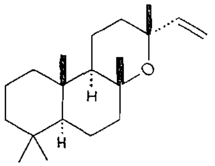
VIIa, R=OH, R'=Me
VIIb, R=Me, R'=OH



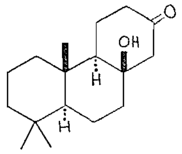
VIIIa, 8α-Me
VIIIb, 8β-Me



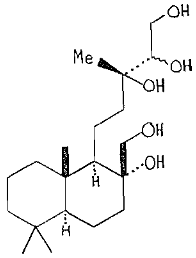
IX



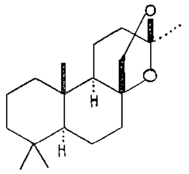
X



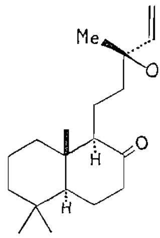
XI



XII



XIII



XIV

solubility of the product in the reaction medium. At pH 1 the oxidation yielded the diketone VI*b* along with the ketal XIII and a $C_{18}H_{30}O_4$ product whose structure was not investigated. In the pH range 6–8 the desired diketone VI*b* was the exclusive product. In a few experiments in which early nonhomogeneity of the reaction medium developed, hydroxyketone XIV appeared as a by-product. This product has not previously been obtained from oxidations of manool.

EXPERIMENTAL

All melting points are uncorrected. Unless otherwise stated, the optical rotations were carried out on chloroform solutions. A Beckman pH meter was used for the pH determinations.

Aldehyde V

A mixture of 1.26 g of the ketoester I*a*, 60 mg of *p*-toluenesulfonic acid, 5 ml of ethylene glycol, and 50 ml of benzene was refluxed for 18 h in the presence of a water separator. The mixture was cooled, washed with 10% sodium carbonate solution and with water, and evaporated. A solution of the residual (1.45 g), oily ketal ester in 30 ml of ether was added dropwise, with stirring, to a suspension of 0.5 g of lithium aluminium hydride in 20 ml of ether, and the mixture was refluxed for 3 h. After the usual work-up the mixture yielded 1.23 g of crude, gummy ketal alcohol. A solution of the latter in 13 ml of pyridine was added to a slurry of 1.2 g of chromic acid in 12 ml of pyridine, and the mixture was stirred at room temperature for 45 min. It then was extracted with ether and the extract washed successively with 10% sodium carbonate solution, water, 5% hydrochloric acid solution, and water once more. The extract was dried over sodium sulfate and evaporated to give 1.1 g of a pale-yellow, thick oil which became partly crystalline when allowed to stand. Several crystallizations from methanol yielded colorless needles of the ketal aldehyde V, m.p. 110–110.5°; $[\alpha]_D$ +90.0° (*c*, 1.5); μ (KBr) CH 3.67 (w), C═O 5.82 (s); δ C—CH_3 singlets at 1.02 and 1.04 p.p.m., ketal methylene broad singlet at 3.94 p.p.m., aldehyde CH singlet at 9.12 p.p.m.

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 75.10; H, 9.38.

Ketone Ib

A mixture of 0.74 g of crude ketal aldehyde, 8 ml of 95% hydrazine, and 32 ml of diethylene glycol was heated for 2 h at a bath temperature of 125–135°. After the addition of 4.0 g of potassium hydroxide pellets, heating (170–180°) was continued for 8 h. The usual work-up gave 0.64 g of a pale-yellow oil; chromatography of this oil on 10 g of alumina and elution with hexane yielded 0.38 g of an oil showing one spot on thin-layer chromatography. A solution of the product and 1.6 ml of sulfuric acid in 30 ml of methanol was refluxed for 30 min and then worked up in the usual manner. Chromatography of the resultant oil (0.29 g) on 8 g of alumina and elution with 20:1 hexane–ether yielded 205 mg of a solid. Several crystallizations from hexane yielded the enone *Ib*, m.p. and mixed m.p. 61.5–62.5°; its infrared spectrum was identical with that of an authentic sample.

Ketoacid VIa

An excess of ozone was bubbled for 20 min through a solution of 0.56 g of ketone *Ib* in 10 ml of glacial acetic acid and 15 ml of ethyl acetate cooled in an ice–salt bath. After the addition of 0.6 ml of 30% hydrogen peroxide and 5 ml of water, the mixture was left to stand at room temperature for 2 h and then heated at 60–70° for 5 min. Work-up gave 0.60 g of an acidic fraction and negligible amounts of neutral material. Chromatography of the former on silica gel and elution with 3:2 benzene–ether gave 0.48 g of a solid, m.p. 83–88°. Crystallization from hexane yielded ketoacid VI*a*, m.p. 90–92°; μ (KBr) OH 3.0–3.3 (m), 3.6–3.8 (m), $C{=}O$ 5.85 (s, broad).

Anal. Calcd. for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.10; H, 9.79.

Ketones IV and IX

An ethereal solution of methyllithium (from 0.5 g of lithium) was poured through a glass-wool plug into a solution of 0.25 g of crude acid VI*a* in 15 ml of ether, and the mixture was refluxed for 3.5 h. The cooled mixture was poured onto ice and worked up in the usual manner. A hexane solution of the neutral product (0.23 g of a pale-yellow, viscous liquid) was treated with charcoal and filtered through 1.5 g of alumina. The hexane filtrate contained 106 mg of a semisolid mixture, and a subsequent ether eluate was composed of 102 mg of VII*a* (μ (KBr) OH 2.84 (m), $C{=}O$ 5.87 (s)), m.p. 102–106° (softening at 95°). Despite crystallization from hexane and chromatographies over alumina the solid ketol could not be purified further. Chromatography of VII*a* and the earlier semisolid fraction (154 mg) on 5 g of alumina and elution with hexane yielded 86 mg of a colorless liquid which could be induced to crystallize. Unfortunately this substance, VIII*a*, m.p. 63–65° (μ (neat liquid) no OH, $C{=}C$ 5.91 (m)), was as sensitive as its ketol precursor and could not be purified further. A solution of 85 mg of the enol ether and 1 ml of 5 *N* hydrochloric acid in 5 ml of 95% alcohol was kept at 70° under nitrogen for 2 h. The usual work-up gave 75 mg of a ketone mixture. Its gas-phase chromatography (20% polyester LAC 446 on WAW column, 225–300°, F. and M. model 500 apparatus) yielded IV as the major component (retention time 18 min; μ (neat) $C{=}O$ 5.82 (s); δ $C{-}CH_3$ singlets at 0.83, 0.88, and 0.94 p.p.m., olefinic $C{-}CH_3$ singlet at 1.55 p.p.m., $COCH_3$ singlet at 2.13 p.p.m.) and IX as the minor component (retention time 22.8 min; μ (neat) $C{=}O$ 5.80 (s); δ $C{-}CH_3$ singlets at 0.78, 0.86, and 0.87 p.p.m., olefinic $C{-}CH_3$ broad singlet at 1.67 p.p.m., $COCH_3$ singlet at 2.13 p.p.m., olefinic CH multiplet at 5.43 p.p.m.).

A 1% solution (2 ml) of osmium tetroxide in *t*-butanol was added to a solution of 200 mg of sclareol (III) in 50 ml of *t*-butanol. After the addition of a 0.5 *M* aqueous solution of periodic acid (8 ml) and enough 0.5 *M* sodium hydroxide solution to bring the mixture to pH 8, it was stirred at room temperature for 10 h. Some sodium sulfite and water were added and the mixture was extracted with ether. The extract was washed with water, dried over sodium sulfate, and evaporated to give 161 mg of a grey liquid. Gas-phase chromatographic analysis (see above) indicated a single peak, retention time 10.7 min, μ (neat) no OH, $C{=}C$ 5.92 (m); hence it was VIII*b*. Acid-catalyzed isomerization of the latter in a manner identical with the isomerization of VIII*a* (see above) yielded also a mixture of IV and IX, identified and separated by gas-phase chromatography. As in the above case, IV was the major product, but much less so.

Osmium Tetroxide – Periodate Oxidations of Manool

A solution of osmium tetroxide (20 mg) in *t*-butanol (2 ml) was added to a solution of manool (200 mg) in *t*-butanol (50 ml). After the addition of a 0.5 *M* aqueous solution of periodic acid (15 ml) and a 0.5 *N* sodium hydroxide solution (100 ml) the mixture was stirred for 45 min. Within 5–10 min a fine precipitate appeared. The mixture was extracted with chloroform, and the extract was washed with saturated brine solution and dried over sodium sulfate. Evaporation of the solvent, chromatography of the residue (235 mg) on silica gel (8 g), and elution with chloroform–methanol (20:1) yielded a solid (196 mg) which, on crystallization from chloroform – ethyl acetate, gave pentol XII, m.p. 186–187° (lit. (10) m.p. 184–185°); $[\alpha]_D$ −9° (*c*, 0.80 in pyridine).

A solution of osmium tetroxide (50 mg) in *t*-butanol (5 ml) was added to a solution of manool (500 mg) in *t*-butanol (250 ml). After the addition of a 0.5 *M* aqueous solution of periodic acid (30 ml) and a 0.1 *N* solution (225 ml) of sulfuric acid the clear mixture was left to stand for 22 h. It then was extracted with ether and worked up as above. Chromatography of the residue (505 mg) on silica gel (15 g) and elution with pentane–ether (50:1) gave a solid (177 mg) which, on crystallization from hexane, gave ketal XIII, m.p. 119–121° (lit. (12) m.p. 115–116°); $[\alpha]_D$ +26° (*c*, 0.52) (lit. (12) $[\alpha]_D$ +31° (*c*, 1.08)); its infrared and proton magnetic resonance spectra were identical with those reported (12).

Anal. Calcd. for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.92; H, 10.80.

Elution with pentane–ether (9:1) gave the diketone VI*b* (195 mg) as an oil, $[\alpha]_D$ −10.3° (*c*, 2.08) (lit. (10) $[\alpha]_D$ +36° (*c*, 1.0)); μ (neat) C═O 5.85 (s); δ C—CH_3 singlets at 0.71, 0.84, and 0.97 p.p.m., $COCH_3$ singlet at 2.08 p.p.m.

Anal. Calcd. for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.37; H, 10.44.

Elution with pentane–ether (4:1) gave a solid (52 mg) whose crystallization from acetone–hexane yielded crystals, m.p. 173–175°; $[\alpha]_D$ +40.5° (*c*, 0.83); μ (KBr) OH 2.76 (w), 2.91 (m); δ C—CH_3 singlets at 0.77, 0.81, 1.02, and 1.24 p.p.m., hydroxymethine broad singlet at 5.01 p.p.m., molecular ion *m/e* 310.

Anal. Calcd. for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.61, 69.55; H, 9.65, 9.53.

A solution of osmium tetroxide (40 mg) in *t*-butanol (4 ml) was added to a solution of manool (400 mg) in *t*-butanol (320 ml). After the addition of a 0.5 *M* aqueous solution of periodic acid (40 ml), the mixture was brought to pH 6.0 by the addition of 0.5 *N* sodium hydroxide solution and kept at this pH by the addition of a phosphate buffer solution (500 ml composed of 357.5 ml of a 0.1 *M* potassium dihydrogen phosphate solution, 10 ml of a 0.5 *N* sodium hydroxide solution, and 132.5 ml of water). The clear mixture was left to stand for 8 h and then treated with a solution of sodium sulfite (2 g) in water (50 ml), stirred for 2 min, and extracted with ether. Isolation as above led to the diketone VI*b* (332 mg).[1]

Execution of the pH 6 experiment as above, except for the use of only 200 ml of *t*-butanol and 20 ml of periodic acid (the reaction mixture remaining a suspension throughout the experiment), yielded diketone VI*b* (272 mg) and an oil (XIV), eluted with pentane–ether (5:1), $[\alpha]_D$ +36.9° (*c*, 2.05); μ (neat) OH 2.85 (m), C═O 5.84 (s), CH═CH_2 10.08 (m), 10.90 (m); δ C—CH_3 singlets at 0.71, 0.84, 0.97, and 1.25 p.p.m., vinyl 12-line signal at 4.93, 4.97, 5.05, 5.08, 5.12, 5.15, 5.35, 5.38, 5.77, 5.93, 6.05, and 6.23 p.p.m.

Anal. Calcd. for $C_{19}H_{32}O_3$: C, 78.03; H, 11.03. Found: C, 77.74; H, 11.29.

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[1] *Experiments at pH 7.4 and 8.0 yielded similar results.*