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STEREOSELECTIVE SYNTHESIS OF (±)-OCCIDENTALOL

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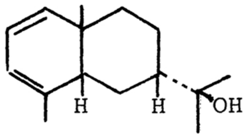
Stereoselective synthesis of the sesquiterpene alcohol, occidentalol starting from methyl c-4,c-9-dimethyl-6-methoxycarbonyl-2,7-dioxo-cis-decalyl-r-8-carboxylate was described.

There have been several reports[1] concerning the total synthesis of a sesquiterpene alcohol, occidentalol (1) characterised by cis-eudesmane skeleton. In connection with our work on the double Michael annelation for constructing cis-decalin derivatives[2], we report here a stereoselective synthesis of occidentalol.

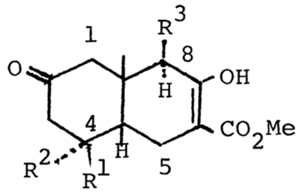
The X-ray crystallographic analysis of the stereoisomeric diketo-diesters (2) and (3) obtained by the double Michael annelation[2] (indicated as their enol-forms) revealed that the former (2) exists in a steroid form and the methoxycarbonyl group at C_8 is oriented in pseud-equatorial configuration, while the latter (3) does in a distorted non-steroid form and the methoxycarbonyl group at C_8 is oriented in pseud-axial configuration. Based on the above results, we expected that the methoxycarbonyl group at C_8 in (2) would be rather susceptible to the hydrolysis-decarboxylation reaction, preferring the diketo-diester (2) to the isomer (3) as the starting material. Treatment of the diketo-diester (2) with potassium t-butoxide in t-butanol under reflux overnight gave the diketo-ester (4) in 70% yield[3], the structure of which was incidentally disclosed by an attempt to reduce the ketone group of the β-ketoester functionality by Coates' procedure[4]. Thus, treatment of (4) with chloromethyl methyl ether in the presence of sodium hydride gave the methoxymethyl ether (5), which was subjected to a reduction with lithium in liquid ammonia to yield a diol (6) as only an isolable product in low yield. The n.m.r. spectrum of the diol showed a singlet at δ 4.72 assigned to an olefinic proton at C_8, confirming the structure of the parent diketo-ester (4).

Acetalisation of the diketo-ester (4) with ethylene glycol and boron trifluoride in tetrahydrofuran gave the mono-ketal (7) (m.p. 85-87°) in 80% yield. Reduction of (7) with sodium borohydride in aqueous tetrahydrofuran gave a mixture of stereoisomeric ketal-alcohols, from which the major isomer (8) was isolated as crystal (m.p. 96-97°) in 54% yield after column chromatography on silica gel in chloroform. Although the stereostructure of the ketal-alcohol (8) has not assuredly been elucidated, it was proposed tentatively to be (8) depicted in the Chart, since its n.m.r. spectrum exhibited a broad signal ($W_{1/2}$=8Hz.) assigned to an equatorial proton on the carbon bearing the hydroxyl group. Treatment of (8) with thionyl chloride in pyridine gave a mixture consisting of two products (revealed by t.l.c.), which was, without further purification, treated with 1,8-diazabicyclo[5.4.0]undecene-7 (DBU) in benzene to give the ketal-ester (9) (m.p. 74-76°), $\nu_{max.}$ 1700 (C=O) and 1640cm^{-1} (C=C); δ ($CDCl_3$) 0.91 (3H, d, J=5.5Hz.), 0.92 (3H,s), 3.73 (3H, s), 3.92 (4H, t) and 6.92 (1H, m), in 62% yield from (7). Attempt was made to hydrogenate the double bond of (9) using several catalysts, but the double bond was thwarted to the reduction. Then the ketal moiety was hydrolysed with acetic acid and hydrochloric acid to give the ketone (10), $\nu_{max.}$ 1695cm^{-1} (CO); δ, 1.03 (3H, d, J=5.3Hz.), 1.04 (3H, s), and 6.87 (1H, m). The ketone (10) was hydrogenated with Adams' catalyst in ethanol for 2 weeks to yield the hydroxy-ester (11) in 54% yield. The hydroxy-ester (11) would be confered a steroid conformation because the 1,3-diaxial steric repulsion of the two methyl groups at C_4 and C_9 might be serious, when it has a non-steroid conformation. The n.m.r. spectrum of the hydroxy-ester showed a signal at δ 4.12 as a quintet (J=3.0Hz.) assigned to an equatorial proton on the carbon bearing the hydroxyl group and the configuration of the methoxycarbonyl group was ultimately concluded by the fact that the diene-ester (14) synthesised from this hydroxy-ester (11) was spectroscopically identical with the authentic sample[1(b)].

Treatment of the ester-alcohol (11) with phosphorus oxychloride in pyridine gave the ester (12) as a sole product in 90% yield, which was transformed to the dibromide (13). The dibromide exhibited the nicely observal signal as a doublet (J=3.5Hz.) assigned to C_1proton, confirming, in turn, the structure of the ester (12). Treatment of the ester (12) with N-bromosuccinimide in carbon tetrachloride yielded a bromide, which was reasonably unstable. Then the bromide was, without purification, submitted to dehydrobromination with DBU in benzene to give the diene-ester (14) in 27% yield from (12). The i.r. and n.m.r. spectra of the



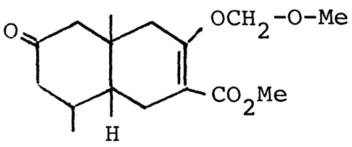
(1)



(2) R^1=Me; R^2=H; R^3=CO_2Me

(3) R^1=H; R^2=Me; R^3=CO_2Me

(4) R^1=Me; R^2=R^3=H



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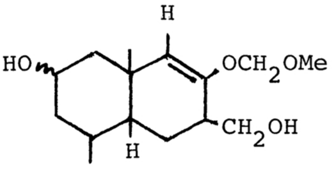
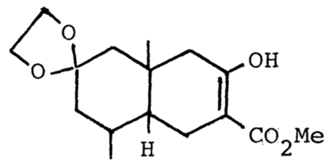
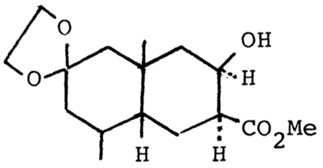


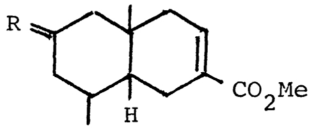
(6)



(7)

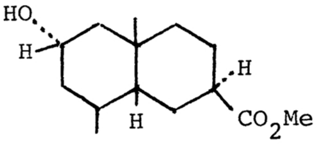


(8)

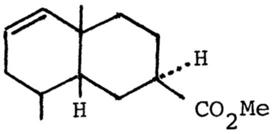


(9) R=-O-CH_2-CH_2-O-

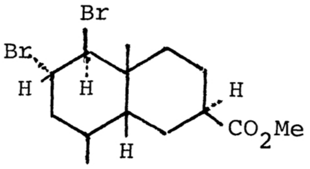
(10) R=O



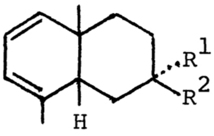
(11)



(12)



(13)



(14) R^1=H; R^2=CO_2Me

(15) R^1=CO_2Me; R^2=H

diene-ester were identical with those of the optically active one[1(b)]. Since the ester has been transformed into occidentalol, we traced the transformation reation of the diene-ester into occidentalol with a little modification. The diene-ester was smoothly converted to the epimeric ester (15) with sodium methoxide in methanol in a short period in much better yield (85%) than with potassium *t*-butoxide[1(a)]. The spectroscopic properties of the resulting ester (15) were also identical with those of the authentic sample[1(b)]. Reaction of the ester with methyl lithium gave (±)-occidentalol, m.p. 72-73°, the i.r. and n.m.r. spectra of which were identical with those of occidentalol, completing the stereoselective synthesis of this sesquiterpene alcohol.

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2) H. Irie, J. Katakawa, Y. Mizuno, S. Udaka, T. Taga, and K. Osaki, J. Chem. Soc., Chem. Commun., 1978, 717.

3) All the yields cited here are the isolated yields.

4) R.M. Coates and J.E. Shaw, J. Org. Chem., 35, 2597 (1970).

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