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A TOTAL SYNTHESIS OF (±)-WIDDROL. SYNTHETIC APPLICATION OF THE FORMAL BRIDGEHEAD SUBSTITUTION OF 1-METHOXYBICYCLO[3.2.2]NON-6-EN-2-ONES WITH ALKYL GROUPS

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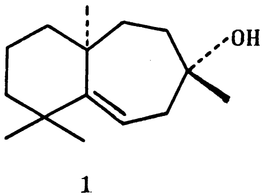
The [6-7] fused-ring sesquiterpene (±)-widdrol has been prepared stereospecifically utilizing the characteristic reactions of the bridged polycyclic compounds derived from 1-methoxy-5-methylbicyclo[3.2.2]non-6-en-2-one.

The sesquiterpene widdrol (1)1) possesses a carbon skeleton consisting of fused six- and seven-membered rings. This unique sesquiterpene has attracted widespread attention such as to the relation of its chemistry with that of thujopsene (2)2) and to the total synthesis which involves the stereospecific elaboration of the tertiary alcohol part.3)

In connection with our program to develop methods for stereoselective syntheses of [m-n] fused-ring terpenes from bridged bicyclic systems,4) we have examined pinacol-type rearrangement of 2-substituted 1-methoxybicyclo[3.2.2]non-6-en-2-ols (4) and established the formal displacement of the bridgehead methoxyl group of bicyclo[3.2.2]non-6-en-2-ones 3 with alkyl, alkenyl, and aryl groups to lead 1-substituted ketones 5.5)

This bridgehead-substitution method seems to promise facile formation of the tricyclic ketone 8 starting from the 1-methoxy ketone 6 *via* the diketone 7. The ketone 8 has a suitable functional group and carbon-carbon double bonds for the preparation of the *gem*-dimethyl derivative, with migration of one of the



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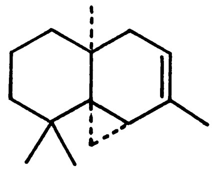

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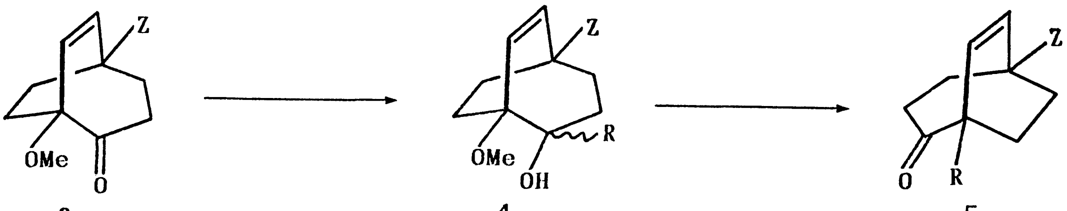


3 4 5

double bonds to the appropreate position, followed by conversion into the ketone 9. Baeyer-Villiger oxidation of this ketone should give the lactone 10, a crucial precursor of (±)-1. According to this plan, we have attempted a synthesis of (±)-widdrol.

Sonication of a solution of 6 and 3 equiv. of the Grignard reagent derived from 2-(2-bromoethyl)-2-ethyl-1,3-dioxolane$^{6)}$ in THF at 25 °C for 1.5 h gave a mixture of the isomeric tertiary alcohols (11 and 12).$^{7,8)}$ Without irradiation of ultrasound, this Grignard reaction proceeded slowly and gave a mixture of the alcohols in a yield of 61%.

Treatment of a mixture of 11 and 12 or each of them with 2 equivalents of p-toluenesulfonic acid (TsOH) in boiling benzene for 1 h gave a mixture of the desired ketone (8) and the isomer (14), in the ratio of 5 to 1, in more than 80% yield. A similar reaction of one of the alcohols, obtained in 49% yield, and 0.1 equiv. of TsOH for 1 h yielded bicyclic ketons 13 and 7 (in 47% and 24% yields, respectively) along with a mixture of 8 and 14 (26%). When 13 was treated with 2 equiv. of TsOH for 1 h, 8 and 14, in the ratio of 1 : 1.2, were obtained in 79% yield. Thus, formation of 14 seems to be inevitable under those tandem [pinacol-type rearrangement]-[aldol-type condensation] conditions.$^{9)}$ The desired ketone (8) was purified by recrystallization from hexane, however the presence of 14 did no harm to the following transformation (vide infra).

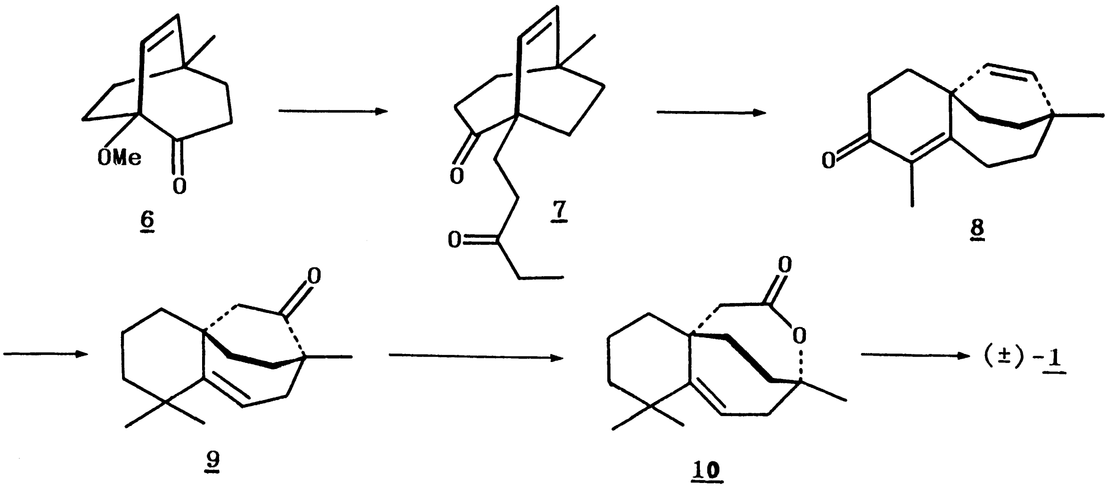
When a mixture of 8 and 14 was treated with potassium t-pentoxide and methyl iodide in THF, the gem-dimethyl derivative (15) was obtained in 88% yield and unreacted 14 was removed by silica-gel chromatography. Wolff-Kishner reduction of 15, using hydrazine hydrate (2 equiv.), potassium hydroxide (10 equiv.), and trimethyleneglycol at 200 °C under rigidly oxgen-free conditions, gave a hydrocarbon 16 in 81% yield.

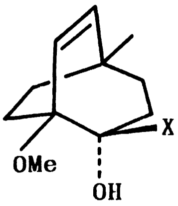
Hydroboration of the etheno bridge of 16 was performed by treating with thexylborane followed by alkaline hydrogen peroxide oxidation to give two kinds of alcohols (60% and 26%). Collins oxidation of the major alcohol formed the desired ketone (9) in 90% yield. The structure of 9 was estimated by comparing its NMR spectrum with that of the isomeric ketone (17) derived from that minor alcohol.

In order to derive the lactone 10 from 9, we adopted the oxidation with bis(trimethylsilyl)peroxide which is known as a useful Baeyer-Villiger oxidant even for substrates containing an isolated carbon-carbon double bond.$^{10)}$ When 9 was treated with bis(trimethylsilyl)peroxide and BF_3 etherate (5 equiv. each) in dichloromethane at -20 °C, 10 was obtained in 43% yield with the regioisomer (18, 5%).

Lithium tetrahydridoaluminate reduction of 10 gave the diol, whose primary alcohol was protected as t-butyldimethylsilyl ether. Acetylation of the tertiary alcohol gave 19 in 73% yield (from 10). The silyl ether of 19 was cleaved by acetic acid in aqueous THF.$^{11)}$ Collins oxidation of the resulting alcohol yielded the aldehyde 20 in 86% (from 19).

To remove one carbon from the two-carbon side chain, decarbonylation





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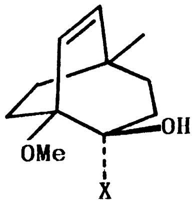

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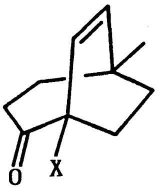
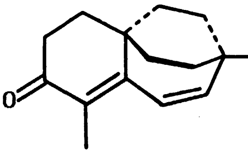
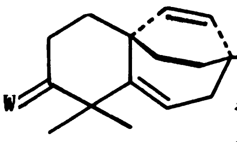


13

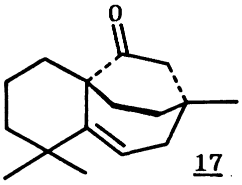
$X = (CH_2)_2C(OCH_2CH_2O)CH_2CH_3$



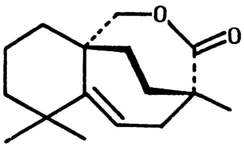
14



15 W=O
16 $W=H_2$



17



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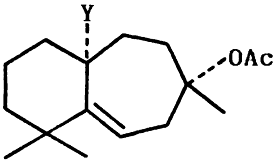

19 $Y=CH_2CH_2OSi(Me)_2Bu^t$
20 $Y=CH_2CHO$
21 Y=Me

reaction was carried out using chlorotris(triphenylphosphine)rhodium.[12] With just one equivalent of Wilkinson's complex, heating of a benzonitrile solution of 20 at 145 °C gave the decarbonylation product (21) in 79% yield.

Reduction of 21 with lithium tetrahydridoaluminate gave the tertiary alcohol, in 96% yield, whose spectroscophic properties are identical with those of natural widdrol (1).

Thus, we have demonstrated that the [6-7] fused-ring sesquiterpene is derived from the bicyclo[3.2.2]nonenone system and the formal bridgehead-substitution method, based on the pinacol-type rearrangement, is incorporated into the synthetic route of the natural product.

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7) These alcohols were isolated in 49% and 44% yields. Their stereostructures have not yet been assigned.
8) All new compounds reported here exhibit satisfactory spectral (IR and NMR) and analytical and/or mass spectral characteristics.
Representative physical properties: 8: Mp 35.5-36.5 °C; IR (CCl_4) 1668 cm^{-1}; NMR δ=5.94 (1H, d, J=9.3 Hz), 5.83 (1H, d, J=9.3 Hz), 1.68 (3H, s), and 1.08 (3H, s). 14: IR (CCl_4) 1662 cm^{-1}; NMR δ=6.34 (1H, d, J=10.8 Hz), 5.95 (1H, d, J=10.8 Hz), 1.76 (3H, s), and 1.11 (3H, s). 15: Mp 48.5-49.5 °C; IR (CCl_4) 1717 cm^{-1}; NMR δ=5.92 (1H, d, J=9.0 Hz), 5.68 (1H, d, J=9.0 Hz), 5.23 (1H, t, J=4.0 Hz), 1.21 (3H, s), 1.16 (3H, s), and 1.04 (3H, s). 9: IR (CCl_4) 1720 cm^{-1}; NMR δ=5.43 (1H, t, J=4.5 Hz), 1.10 (6H, s), and 0.96 (3H, s). 17: IR (CCl_4) 1715 cm^{-1}; NMR δ=5.56 (1H, dd, J=5.1 and 4.0 Hz), 1.10 (3H, s), and 0.97 (6H, s). 10: Mp 106-107 °C; IR (CCl_4) 1725 cm^{-1}; NMR (CCl_4) δ=5.50 (1H, dd, J=5.7 and 4.1 Hz), 2.98 (1H, bd, J=16.2 Hz), 2.49 (1H, d, J=16.2 Hz), 1.32 (3H, s), 1.11 (3H, s), and 1.09 (3H, s). (±)-1: Mp 82-83 °C (lit.[3)] 83-84 °C).
9) Formation mechanism of 14 from 13 and the related acid-catalyzed rearrangements will be reported in due course.
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