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SYNTHESIS OF THE A RING MOIETY OF TRIPTOLIDE

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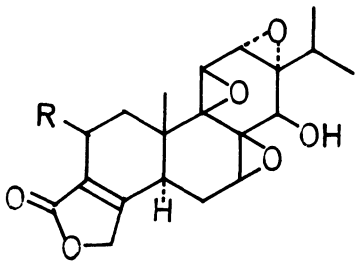
The synthesis of the A ring moiety of triptolide 1 has been achieved, starting from dehydroabietic acid 3.

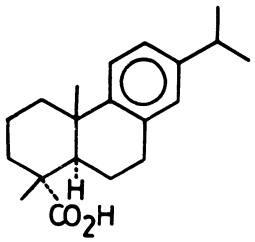
Triptolide 1 and tripdiolide 2 are highly active anti-leukemic compounds of plant origin.[1] We have recently reported on the stereospecific synthesis of the hydroxytri-epoxide system in the B/C ring moiety of 1 and 2.[2,3] In the continuation of our studies directed toward the total synthesis of triptolide 1, we investigated the construction of the 3,4-fused butenolide system in the A ring moiety of 1 on a model compound. The 18(4→3)-abeo-abietane skeleton is also found in the other closely related diterpenes.[1,4]



1 R = H
2 R = OH

Our starting material was dehydroabietic acid 3, which was converted to the methylenic compound 4 by the known procedure.[5] On treatment with selenium dioxide in aq. ethanol solution at refluxing temperature, 4 afforded the secondary allylic alcohol 5, IR(CCl_4): 3630, 1645, 910 cm^{-1}; PMR($CDCl_3$, δ): 4.45 (m, $W_{1/2}$ = 5 Hz, $-CH_2\underline{C}H(OH)-$), 4.83 (t, J = 2 Hz, $-\overset{|}{C}HC=C\underline{H}_2$), 5.16 (t, J = 2 Hz, $-\overset{|}{C}HC=C\underline{H}_2$), in 63% yield. After attempts to introduce a carboxyl function at C-3 by cyanide substitution reaction had frustrated, our attention was directed to the application of Claisen and the related rearrangement reactions. To this end the derivation of the primary allylic alcohol 6 from 5 by allylic rearrangement was investigated first.[6] A solution of 5 in aq. acetic acid (5:2 v/v) was heated at 100° to yield a mixture of the acetates 7 and 8 in approximately equal amounts. The exposure of 5 to thionyl chloride in ether solution at ambient temperature furnished the primary chloride 9, PMR($CDCl_3$): 4.24 (AB q, J = 11 Hz, $-CH_2Cl$), 5.64 (br s, $-CH_2\underline{C}H=\overset{|}{C}-$), in 71% yield with a small amount of the secondary chloride. The treatment of 9 with silver acetate in acetic acid gave a mixture (1:1) of the acetates 7 and 8, while the hydrolysis (NaOAc-H_2O-EtOH) afforded a mixture (6:7) of alcohols 5 and 6. After the failure to find an appropriate method for the conversion of 5 to 6, we investigated the [2,3]-sigmatropic rearrangements[7] of the ammonium or sulfonium ylid derivable from the primary chloride 9, taking advantage of its availability in good yield (vide ante). The reaction of 9 with N-cyanomethylpyrrolidine in dimethyl sulfoxide solution followed by treatment with potassium tert-butoxide[8] afforded only the product of elimination, 10, IR(CCl_4): 1640, 1605, 884 cm^{-1}; PMR($CDCl_3$): 5.02 (br s, $-\overset{|}{C}=CH_2$), 5.88 (m, $-CH_2\underline{C}H=CH-$), 6.32 (dd, J = 2 and 10 Hz, $-\underline{C}H=\underline{C}H\overset{|}{C}=CH_2$). On treatment with phenyl sulfide anion (PhSH-NaOEt), 9 furnished the substituted products 11 and 12

in a ratio of 88:12. This mixture was allowed to react with chloromethyl phenyl sulfide and potassium tert-butoxide in dimethoxyethane solution at -10°.[9] Work-up gave the rearranged product 13, PMR($CDCl_3$): 4.71 (d, J = 12 Hz, $-CH(SPh)_2$),[10] 4.83, 5.11 (each t, J = 2 Hz, $-\dot{C}=CH_2$), in 83% yield. Desulfurization of 13 to the aldehyde 14, IR($CHCl_3$): 1724 cm^{-1}; PMR($CDCl_3$): 3.25 (dd, J = 2 and 6 Hz, $-\dot{C}HCHO$), 5.09, 5.22 (each br s, $-\dot{C}=CH_2$), 9.76 (br s, -CHO), was effected by the treatment with N-chlorosuccinimide-silver nitrate in 80% aq. acetonitrile solution (60% yield from 11).[11] The configuration of the aldehyde group in 14 is assigned to be α on the basis of the coupling constants between C-3 methine proton and C-2 methylene protons.[12] When the desulfurization was carried out by the agency of mercuric chloride and calcium carbonate in aq. acetonitrile, the conjugated aldehyde 15 (17% yield), IR(CCl_4): 1665, 1621 cm^{-1}; PMR($CDCl_3$): 2.26 (br s, $CH_3\dot{C}=\dot{C}CHO$), 10.41 (s, $-\dot{C}=\dot{C}CHO$), was obtained together with 14 (36% yield). Oxidation of 14 with m-chloroperbenzoic acid yielded the Baeyer-Villiger product 16, IR(CCl_4): 1730, 1175, 1169 cm^{-1}; PMR($CDCl_3$): 4.97, 5.32 (each br s, $-\dot{C}=CH_2$), 5.63 (br s, $W_{1/2}$ = 4 Hz, $-CH_2CH(OCHO)\dot{C}=$), 8.13 (s, -OCHO), while on treatment with Jones' reagent 14 afforded smoothly the corresponding carboxylic acid 17, IR(CCl_4): 1710, 900 cm^{-1}; PMR($CDCl_3$): 3.46 (br s, $W_{1/2}$ = 8 Hz, $-CH_2CH(CO_2H)\dot{C}=$), 4.96, 5.12 (each br s, $-\dot{C}=CH_2$), 9.90 (s, $-CO_2H$). The conversion of 17 to $\Delta^{3,4}$-(18→19)-butenolide 18 was attained by several ways: 1. epoxydation with m-chloroperbenzoic acid followed by acid treatment in situ or TsOH in benzene or $HClO_4$-H_2O-acetone, 2. treatment with NBS-H_2O-DMSO and 3. oxidation with performic acid and subsequent acid hydrolysis. In the second procedure, which gave so far the best yield (∼50%), it is notable that concurrent lactonization and dehydration ensue the bromohydrin formation under the conditions described above. In contrast the treatment of 17 with NBS-H_2O in dioxane gave 19, the product of decarboxylative elimination, PMR ($CDCl_3$): 4.06, 4.22 (AB q, J = 10 Hz, $-CH_2Br$), 6.02 (m, $-CH_2CH=\dot{C}-$), as is also the case in the attempted iodolactonization (I_2-KI-$NaHCO_3$), which afforded 20, PMR ($CDCl_3$): 4.09 (s, $-CH_2I$), 6.09 (m, $-CH_2CH=\dot{C}-$). The difference would be ascribed to higher polarity and basicity of dimethyl sulfoxide as compared to dioxane, provided that the common bromohydrin 21 forms in both case via attack of bromine from the less hindered α-side followed by trans diaxial hydrolytic opening of the bromonium ion. Thus in dimethylsulfoxide solution the substitution as depicted by the arrows (⇒) and the subsequent β-elimination of the so-formed hydroxylactone would be favored. Without prior lactonization the decarboxylative elimination, which is stereoelectronically highly favorable, would occur as shown by the arrows (→). The spectroscopic data of the product obtained above fully substantiate its formulation as 18, MS: M^+ = 296.1778; IR(CCl_4):1785 cm^{-1};PMR($CDCl_3$):4.86 (br d J = 12 Hz, $-CO_2CH_\alpha H_\beta$), 5.02 (br dd, J = 2 and 12 Hz, $-CO_2CH_\alpha H_\beta$-); CMR($CDCl_3$): 123.4 (C-3), 138.7 (C-4), 177.3 (C-18), 69.0 (C-19). The PMR signals due to the methylene protons (C-19) of the lactone ring in 18 is to be mentioned with reference to those of triptolide 1 (multiplet at δ 4.78) and tripdiolide 2 (triplet with J = 1.5 Hz at δ 4.86). In the case of 18, C-19 methylene protons are nonequivalent and both protons show homoallylic couplings[13] with C-2 methylene protons, which resulted in the broadening of the signals. In addition 19α-proton couples with 5α-axial proton[14] and exhibits the signal shape indicated.



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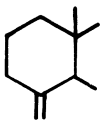

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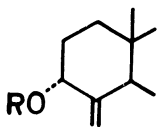
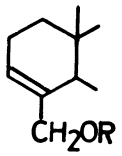
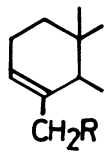


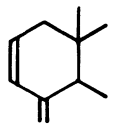
5 R=H
7 R=Ac
16 R=CHO



6 R=H
8 R=Ac



9 R=Cl
11 R=SPh
19 R=Br
20 R=I



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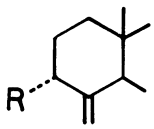
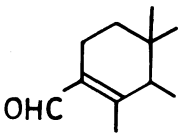


12 R=SPh
13 R=CH(SPh)$_2$
14 R=CHO
17 R=CO_2H



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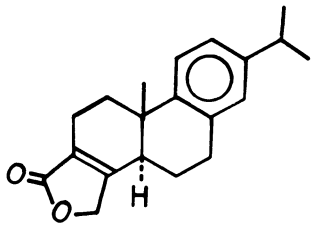

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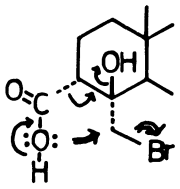

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Thus the exploitation of a method to construct the 3,4-fused $\Delta^{3,4}$-18,19-lactone on 18(4→3)-abeo-abietan skeleton from a resin acid is expected to serve the synthesis of triptolide 1 and the related diterpenoids.[15] The studies in this direction are now in progress.

References and Notes

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