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SYNTHESES OF THE A RING ANALOGS OF TRIPTOLIDE AND TRIPDIOLIDE[1)]

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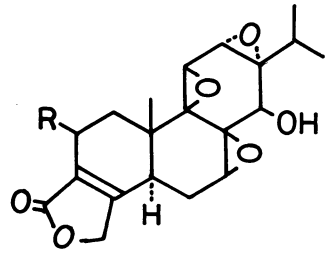
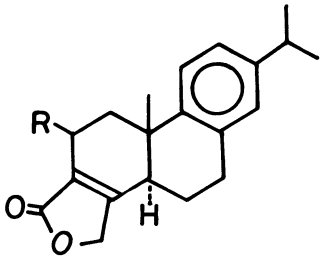
The synthesis of an A ring analog of tripdiolide as well as revised procedures for the synthesis of a triptolide analog (isodehydroabietenolide) from dehydroabietic acid via the previously reported intermediate is described.

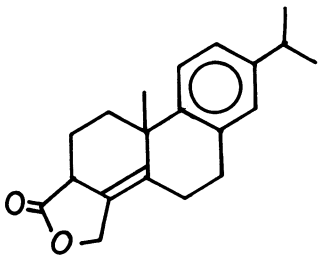
Triptolide 1 and tripdiolide 2 are potent antileukemic agents of plant origin,[2)] of which the latter is scheduled for preclinical pharmacology.[3)] In a study to synthesize an A ring model 3 of triptolide 1 from dehydroabietic acid,[4)] our synthetic product, later found to be 5, was erroneously assigned as 3.[5)] The model compound 3 was recently synthesized and designated as isodehydroabietenolide by van Tamelen.[6)] We would like to communicate here two independent corrected procedures for the derivation of 3 from the previously reported intermediate 7 and 9,[8)] and also the synthesis of an A ring analog 4 of tripdiolide 2.



1 R = H
2 R = OH



3 R = H
4 R = OH
22 R = α-OH



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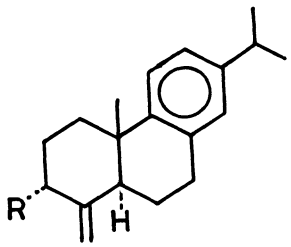
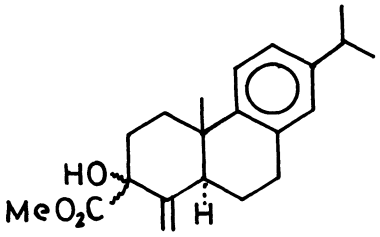
The first route for the synthesis of 3 started from lithium enolate derived from the methyl ester 9, which on oxidation with MoO_5·Py·HMPA complex afforded the α-hydroxylated product 11 (40% yield with 48% recovery of a mixture of 9 and the conjugated ester 10). The reaction of 11 with thionyl chloride in ether gave the

primary chloride 12 in 71% yield, which in turn was treated either by aq. NaOH-EtOH or by LiI-DMF under reflux to produce the desired lactone 3 in yields of 55 and 45% respectively. The identification of the product as 3 was performed by the comparison of the spectral data (IR, ^{1}H and ^{13}C NMR)[10] with those reported.[6] The reaction of the enolate of the ester 9 with dibenzoylperoxide furnished albeit in low yield (10%) a γ-benzoyloxylated product 13 which on hydrolysis with aq. NaOH-EtOH yielded the lactone 3. The second method was based on the application of photooxygenation to the enol dienes derived from the unsaturated aldehyde 7. The compound 7 was first converted to enol acetate 14[11] by successive treatment with t-BuOK and acetyl chloride. When a solution of 14 in a mixture of acetone and MeOH (1:4) containing Rose Bengal was irradiated by mercury fluorescent lamp under bubbling of oxygen, two products were obtained. The major product (41%) was the diene aldehyde 15, IR(CCl_4): 2830, 2700, 1700 cm^{-1}; ^{1}H NMR: 5.10, 6.07 (each 1H, m, 19-H), 6.59 (1H, m, 2-H), 9.47 (1H, s, 18-H), produced by an ene reaction and the other (18%) was endoperoxide 16, IR(CCl_4): 1752, 1220 cm^{-1}; ^{1}H NMR: 2.15 (3H, s, OAc), 4.24, 4.68 (each 1H, AB q, J = 17 Hz, 19-H), 6.19 (1H, s, 18-H). Treatment of 16 with Et_3N afforded the target lactone 3 quantitatively.[12] In an attempt to change the formation ratio of the ene product and the endoperoxide, the photooxygenation was investigated also on t-butyldimethylsilyl enol ether 17,[13] which was prepared from 7 by successive treatment with t-BuOK-THF and t-$BuMe_2SiCl$. The photooxygenation of 17 in the same way as above afforded the ene product 15 (52%) and an endoperoxide 18 (25%), the ratio of both products essentially remaining unchanged. Interestingly when the separation of the reaction mixture was performed carefully (silica gel TLC at 0°), a hydroperoxide 19, the precursor of 15, could be isolated as a mixture of epimers (crystals with mp 194-195°).[14] Treatment of 19 with Na_2SO_3-H_2O-THF at room temperature gave 15 quantitatively. Incidentally the transformations realized in the second method may have some implication for the biosynthesis of A ring functionality in triptolides.

Next the synthesis of tripdiolide analog 4 was investigated utilizing the diene aldehyde 15. Oxidation of 15 with hypobromite (NBS-H_2O-DMSO, r.t.) afforded 1,4-products 20 and 21 in a ratio of 3:1 (50 ∿ 60% yield). The stereochemistry of the hydroxyl groups in both compounds was assigned on the basis of the differences in the chemical shifts of angular methyl signals (δ 1.23 and 1.08 respectively) and the signal shape of the C-2 protons (triplet with J = 2 Hz versus multiplet with $W_{1/2}$ = 22 Hz) in the ^{1}H NMR spectra. When 20 was oxidized with sodium chlor-



6 R = H
7 R = CHO
8 R = CO_2H
9 R = CO_2Me
10 R = CO_2Me, $\Delta^{3:4}$



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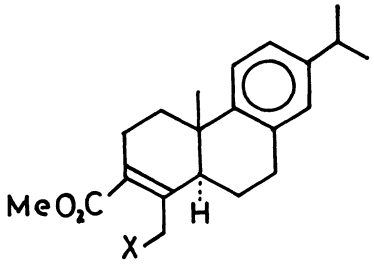
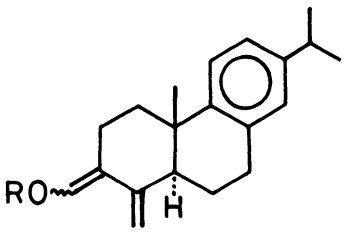
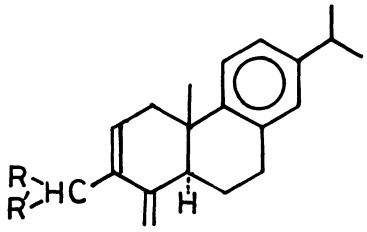


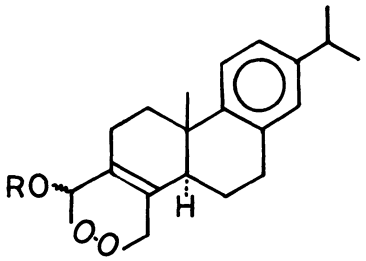
12 X = Cl
13 X = OCOPh



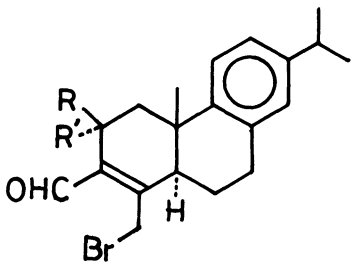
14 R = Ac
17 R = Si Me_2Bu_t



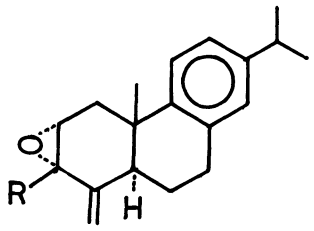
15 R = R′ = O
19 R = OSi Me_2Bu_t
R′ = OOH



16 R = Ac
18 R = $SiMe_2Bu_t$



20 R = OH, R′ = H
21 R = H, R′ = OH



23 R = CHO
24 R = CO_2Me

ite,[15] lactonization of the resulting bromo acid occurred spontaneously to give the desired tripdiolide analog 4, mp 194-196°, m/z 312; IR(CCl_4): 3450, 1760, 1675 cm^{-1}; ^1H NMR: 1.21 (3H, s, 20-H), 4.72 (1H, m, $W_{1/2}$ = 9 Hz, 2-H), 4.88 (2H, br s, 19-H); ^{13}C NMR: 60.5 (C-2), 70.8 (C-19), 126.9 (C-3), 165.3 (C-4), 173.8 (C-18). The oxidation of 21 in the same way furnished the epimeric lactone 22,[16] which was also obtained from 15 by a sequence of reactions: (1) epoxydation with 30% H_2O_2-NaOH-Et_2O-MeOH (1:1) giving α-epoxy aldehyde 23, (2) oxidation of 23 with Ag_2O-

NaOH-MeOH followed by methylation (CH_2N_2) giving methyl ester 24 and (3) treatment of 24 with trimethylsilyl triflate.

References

1) Part XVI of a series of publications titled 'Synthetic Studies on Terpenic Compounds.' Part XV: T. Tokoroyama, H. Koike, K. Hirotsu, and Y. Ezaki, Tetrahedron, 38, 2559 (1982).

2) S. M. Kupchan, W. A. Court, R. G. Dailey, jr., C. J. Gilmore, and R. F. Bryan, J. Am. Chem. Soc., 94, 7194 (1972).

3) J. M. Cassady and M. Suffness, "Anticancer Agents Based on Natural Product Models," ed by J. M. Cassady and J. D. Douros, Academic Press, New York (1980).

4) H. Koike and T. Tokoroyama, Chem. Lett., 1979, 333.

5) The ^{1}H NMR and IR spectra of our product were different from those[6] of 3 in the comparison made by Professor van Tamelen for which we are grateful. Scruting of the spectral data including ^{13}C NMR with reference to those of triptolides[2] and stemolide[7] indicated that the compound in question should be 5.

6) E. E. van Tamelen, E. G. Taylor, T. M. Leiden, and A. F. Kreft III, J. Am. Chem. Soc., 101, 7423 (1981).

7) P. S. Manchand and J. F. Blount, Tetrahedron Lett., 1976, 2489.

8) The compound 7 was synthesized[4] from the dehydroabietene 6[9] in 27% overall yield by five steps and its oxidation with Jones reagent provided 8, which on methylation gave 9.

9) J. W. Huffman and R. F. Stockel, J. Org. Chem., 28, 506 (1963).

10) IR(CCl_4): 1768, 1680 cm^{-1}; ^{1}H NMR: 1.05 (3H, s, 20-H), 1.24 (6H, d, J = 7 Hz, 16- and 17-H), 4.68 (2H, m, 19-H); ^{13}C NMR: 50.6 (C-19), 125.1 (C-3), 163.1 (C-4), 174.3 (C-18). The ^{1}H NMR spectrum conforms with that kindly sent from Professor van Tamelen.

11) The compound represents a single geometrical isomer as seen from its ^{1}H NMR spectrum.

12) The photooxygenation of 14 conducted in pyridine solution gave directly 3 in 20% yield along with the ene product 15 (46% yield).

13) The compound was obtained as an inseparable mixture of E- and Z-dienes in a ratio of 13:4 as seen from its ^{1}H NMR spectrum: 0.06, 0.17 (6H, s, $Me_2Si\lesssim$), 0.93, 0.97 (9H, s, t-BuSi$\lesssim$), 4.59, 5.02 (1H, m, 19-H), 4.90, 5.26 (1H, m, 19-H), 6.36, 6.13 (1H, m, 18-H).

14) ^{1}H NMR: 5.03 (1H, br s, 19-H), 5.30, 5.39 (1H, br s, 19-H), 5.75, 5.97 (1H, br s, 18-H), 6.23 (1H, m, 2-H), 8.25 (1H, s, OOH, shifted to higher field on warming).

15) B. O. Lindgren and T. Nilsson, Acta Chim. Scand., 27, 888 (1973).

16) IR(CCl_4): 3460, 1760, 1675, 1260 cm^{-1}; ^{1}H NMR: 1.08 (3H, s, 20-H), 4.83 (1H, m, $W_{1/2}$= ca 20 Hz), 4.83 (2H, br s, H-18); ^{13}C NMR: 62.5 (C-2), 70.5 (C-19), 126.6 (C-3), 164.7 (C-4), 173.4 (C-18).

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