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HYDROXYLATION OF DAMMARANE TYPE TRITERPENES WITH m-CHLOROPERBENZOIC ACID[1)]

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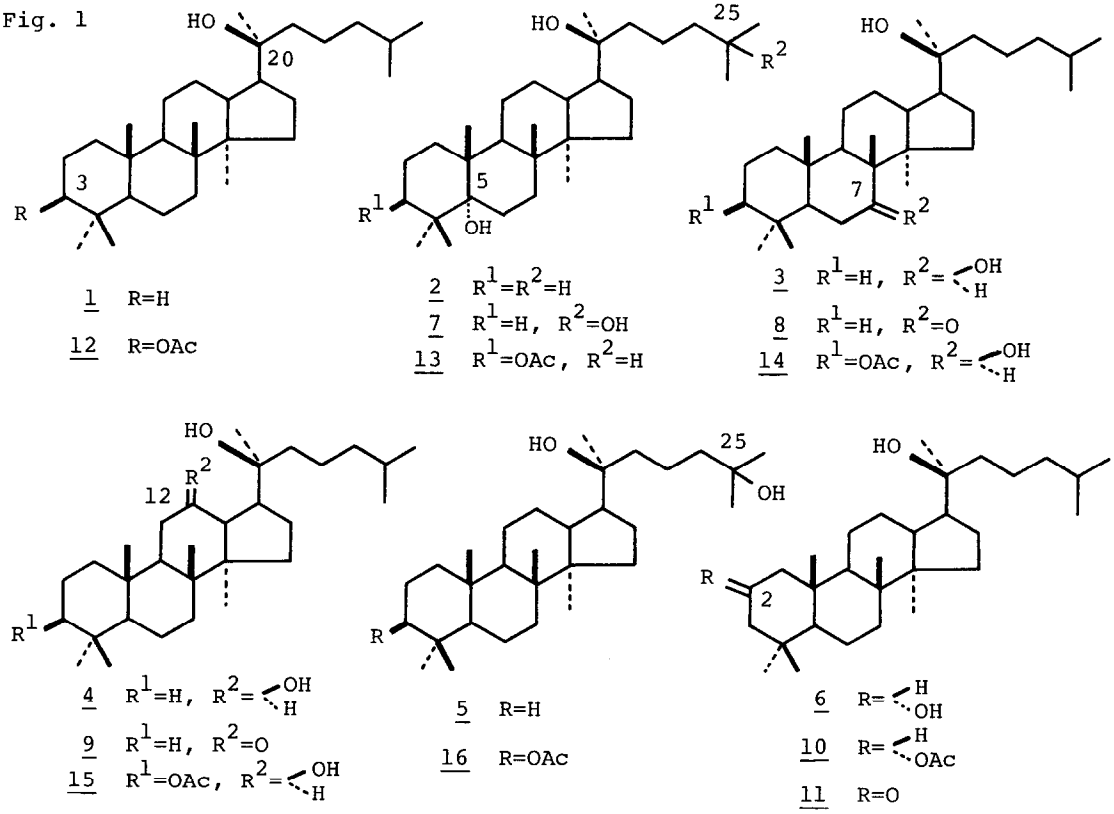
Dammaran-20(S)-ol and 20(S)-hydroxydammaran-3β-yl acetate were reacted with m-CPBA to give the corresponding 5α-ol, 7β-ol, 12β-ol, 25-ol, 2α-ol, and 5α,25-diol.

Oxidation reactions of natural products are very important from not only a synthetic but also a biological point of view. Much effort has been expended in simulating biological oxidations[2)] and in developing synthetic methodologies.[3)] Microbial oxidation,[4)] oxidation using mammals,[5)] dry ozonation,[6)] and remote oxidation[7)] have been given much attention and investigated extensively. None of these, however, is convenient as a synthetic method and ozonation can be dangerous.[6)] m-Chloroperbenzoic acid was first used as an oxidizing agent to introduce a hydroxyl group at a bridgehead position of a bicyclic compound.[8)] Since then, Takaishi et al.[9)] have reported the application of m-CPBA to hydroxylation at bridgehead positions in various polycyclic compounds. We report here a simple method for the introduction of hydroxyl groups into triterpene skeletons and the preparation of a Ginseng sapogenin by use of m-CPBA.

Dammaran-20(S)-ol (1) was treated with m-CPBA (1.2 equiv.) in chloroform under reflux for 6 h. The usual work up and column chromatography on silica gel gave the 5α-ol (2, 59 %),[10)] 7β-ol (3, 2.1 %),[10)] 12β-ol (4, 1.3 %),[10)] 25-ol (5, 28 %),[10)] 2α-ol (6, 4.2 %),[10)] and 5α,25-diol (7, 1.3 %)[10)] as well as the starting material (1) recovered in 77 % yield. The ^{1}H NMR spectrum of 2 showed no peak between 3 and 5 ppm and in the ^{13}C NMR spectrum thirty signals were observed, two of which were due to oxygen-bearing carbons [δ_C 77.3 (C-5) and 75.4 (C-20)].[11)] The mass spectrum showed a molecular ion peak at m/z 446 and a characteristic peak at m/z 362 (Fig. 2). These facts suggested that one hydroxyl group had been introduced at the C-5 position. From careful assignment of the ^{13}C NMR signals,[11,12)] it was concluded that 2 must be formulated as dammarane-5α,20(S)-diol (2).

In the ^{1}H NMR spectrum of 3, a double doublet centred at δ 3.80 (1H, J=11 and 5 Hz) was observed and the ^{13}C NMR spectrum indicated the presence of thirty carbons, two of which bore oxygen functions [δ_C 75.3 (C-7) and 75.4 (C-20)].[11)]

Fig. 1



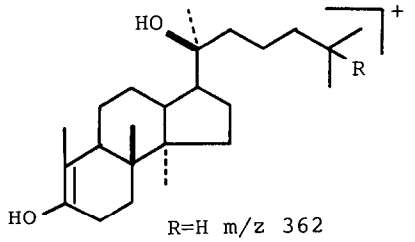
From the coupling pattern of the methine proton, the hydroxy group could be assigned to the 1β, 7β, or 15α position. Of the five quaternary carbon atoms [δ_C 75.4 (C-20), 49.7 (C-14), 46.2 (C-8), 37.3 (C-10), and 33.2 (C-4)][11] of 3, four of them had similar chemical shifts to those of dammaran-20(S)-ol (1) [δ_C 75.3 (C-20), 50.4 (C-14), 40.6 (C-8), 37.5 (C-10), and 33.4 (C-4)].[12] Namely the carbon signal at δ_C 40.6 assigned to C-8 has undergone a downfield shift of 5.6 ppm, indicating that 7β was the most probable position for the hydroxyl group. The secondary alcohol (3) was oxidized to the corresponding ketone (8)[10] by Jones' reagent. Methylene protons were observed at δ 2.50 (1H, t, J=15 Hz) and 2.20 (1H, dd, J=15 and 2.5 Hz) in the ^{1}H NMR spectrum of 8. From these results the secondary alcohol was determined to be dammarane-7β,20(S)-diol (3).

The third product (4) was a secondary alcohol from its ^{1}H NMR spectrum [δ 3.60 (1H, td, J=11 and 5 Hz)] and ^{13}C NMR spectrum [δ_C 74.4 (C-20) and 71.2 (C-12)].[11] The coupling pattern indicated that the position of the hydroxyl group was 6α, 11α, 12β, or 16β. Comparison of the ^{13}C chemical shifts with those of known dammarane triterpenes[12] implied a 12β-ol structure. Jones' oxidation of 4 gave ketone (9)[10] whose ^{1}H NMR spectrum showed a doublet at δ 2.85 (1H, J=10 Hz, H-13β), a doublet of doublets at δ 2.30 (1H, J=14 and 5 Hz, H-11α), and a triplet at δ 2.19 (1H, J=14 Hz, H-11β). From these facts the third product was concluded to be dammarane-12β,20(S)-diol (4).

The fourth product (5) was very easily assigned as dammarane-20(S),25-diol (5) from its mass spectrum [m/z 410 (M-H_2OX2), 191, 145, 127 (base), and 59]

and ^{1}H NMR spectrum (eight singlet methyls were observed at δ 1.23, 1.23, 1.14, 0.96, 0.88, 0.85, 0.84, and 0.81).

A triplet of triplets observed at δ 3.89 (1H, J=11 and 4.5 Hz) in the ^{1}H NMR spectrum of the penultimate product (6) indicated the presence of an equatorial secondary hydroxyl group with a methylene group on each side. The same pattern was observed in the ^{1}H NMR spectrum [δ 5.06 (1H, tt, J=10 and 6 Hz)] of its acetate (10).[10] The position of substitution is limited only to 2α (equatorial). The corresponding ketone (11)[10] obtained by Jones' oxidation showed four protons α to the carbonyl group [δ 2.39 (1H, dd, J=13 and 2 Hz), 2.28 (1H, d, J=13 Hz), 2.15 (1H, dd, J=13 and 2 Hz), and 1.98 (1H, d, J=13 Hz)]. These data were fully consistent with structure 6, dammarane-2α,20(S)-diol.



R=H m/z 362
R=OH m/z 378

Fig. 2

The most polar product (7) showed eight singlet methyls in its ^{1}H NMR spectrum and fragment peaks at m/z 444 (M-H_2O), 378 (Fig. 2), 127, and 59 in its mass spectrum, suggesting the presence of a 25-hydroxyl group. In the ^{13}C NMR spectrum thirty signals were detected, three of which corresponded to oxygenated carbons [δ_C 77.4 (C-5), 75.4 (C-20), and 71.1 (C-25)].[11] Comparison of the spectral data with those of 2 and 5 led directly to structure 7.

We next carried out a similar reaction of 20(S)-hydroxydammaran-3β-yl acetate (12) with m-CPBA in chloroform. Four products [13 (m/z 486, 426, 362, and 344; δ 5.12 (1H, dd, J=11 and 6 Hz) and 2.03 (3H, s); δ_C 170.9 (CO), 78.9 (C-5), 77.2 (C-3), and 75.4 (C-20)), 14 (m/z 486, 433, 419, 108, and 95; δ 4.48 (1H, dd, J=11 and 6 Hz), 3.79 (1H, dd, J=11 and 4 Hz), and 2.05 (3H, s); δ_C 171.0 (CO), 80.6 (C-3), 75.4 (C-20), and 75.1 (C-7)), 15 (m/z 468, 419, 341, and 108; δ 4.48 (1H, dd, J=11 and 6 Hz), 3.60 (1H, td, J=10 and 5 Hz), and 2.05 (3H, s); δ_C 171.0 (CO), 80.8 (C-3), 74.5 (C-20), and 70.9 (C-12)), and 16 (m/z 468, 189, 145, 136, 127, and 109; δ 4.48 (1H, dd, J=11 and 6 Hz) and 2.05 (3H, s); δ_C 171.0 (CO), 81.0 (C-3), 75.4 (C-20), and 71.0 (C-25))][10,11] were obtained in yields[10] of 16, 1.6, 1.6, and 40 %, respectively, after column chromatography on silica gel (12 was recovered in 91 % yield) and the structures were determined by comparing the spectral data with those of 2 - 7.

The spectral data of the third product (15) were completely identical with those of authentic 12β,20(S)-dihydroxydammaran-3β-yl acetate (15).[14] As this is an acetate of a typical sapogenin of Ginseng, this constitutes a one step synthesis of such types from a 12-deoxy compound. Tanaka and his group[15] reported the first successful application to compounds other than steroids of the remote oxidation initially explored by Breslow and his co-workers.[7] Photolysis of 20(S)-hydroxydammaran-3α-yl p-nitrophenylacetate in Bu^tOH gave dammarane-3α, 12α,20(S)-triol in 13 % yield after hydrolysis.[15] Although the yield of 15 was not so good as compared to that reported,[15] our method is quite simple and easy to carry out.

The hydroxylation reaction reported here can be explained as an attack on unactivated carbon atoms. Although the mechanism is unknown, this method is quite useful for introduction of a functional group at unactivated carbon atoms. Further applications to sesquiterpenes, diterpenes, and other classes of triterpenes are under way.

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References and Notes

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