Intramolecular Addition of Hydroxy Group to a Diene System: Oxymercuration – Demercuration and Titanium Tetrachloride Catalyzed Synthesis of Manoyl Oxides

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The stereochemistry of the formation of tetrahydropyran ring of ent-manoyl oxides from ent-8a-hydroxylabda-13(16), 14-dienes has been studied in one and two-step oxymercuration-demercuration (OM–DM) processes as well as by a new titanium tetrachloride catalyzed cyclization which allows the preparation of this tetrahydropyran moiety of C-13 epimer manoyl oxides in high yield.

Some manoyl oxides, principally those isolated from the roots of Coleus forskohlii have been shown to be hypertensive agents with bronchopasmolytic, cardiotonic and inotropic activity. They activate adenylate cyclase and reduce intraocular pressure in man. These promising pharmacological properties have elicited the attention of synthetic chemists worldwide, including some interesting synthesis of manoyl oxides from bicyclic precursors, although in limited yields. Some of these processes involve microbial transformations of deoxy-forskolins to forskolin. We have obtained some 16-hydroxy derivatives of manoyl oxides from natural epi-8x-hydroxylabda-13(16),14-dienes via epoxidation. Now we report on the synthesis of manoyl oxides and 13-epi-manoyl oxides by means of a variety of oxymercuration-demercuration (OM–DM) processes and by a titanium tetrachloride catalyzed intramolecular addition of an hydroxy group to a diene system to obtain a tetrahydropyran ring.

ent-6x,18-Diacetoxy-8x-hydroxylabda-13(16),14-diene (6,18-diacetyl andalusol, I) was converted in an one-step OM–DM process with mercuric acetate and reduction with aqueous sodium borohydride in basic medium to give the product 2 (18%) with the same molecular formula (C_{28}H_{38}O_{3}) as the starting material. This product did not have the original hydroxy group (IR). Its 1H-NMR spectrum showed only three singlets for methyl groups (see experimental section). Although its 13C-NMR spectrum showed only two olefinic carbons (Table), the vinyl group was not an isolated ABX system (1H-NMR), showing furthermore a new oxygenated methine carbon (13C-NMR) whose proton showed an 1H-NMR signal at δ = 3.60 (1 H, m, W_{1/2} = 20 Hz). This signal was partially overlapped with one of the signals of the AB system due to the acetoxyethylene group of C-18. Thus, this product 2 was not a manoyl oxide as can be expected from a normal intramolecular OM–DM process. It has a tetrahydrofuran ring but the chain at C-13 was not a simple vinyl group having a three-carbon allyl moiety. To determine the configuration at C-13, several NOE-difference experiments on C-19 and specially on C-17 methyl group were performed. The irradiation of C-17 methyl group produced very clean NOE on H-6 and H-13. Thus we can conclude that product 2 has a 13S-configuration. This product 2 must be the result of the radical rearrangement as described for the OM–DM processes of diene systems.

On the other hand, if the demercuration process was performed with sodium amalgam, only the ent-manoyl oxides 3 (14%) and 4 (6%) were obtained. The configuration at C-13 of these products was determined after the consideration of 13C-NMR chemical shifts, principally of C-9 of both products 3 and 4. Thus, this procedure allowed the synthesis of both epimers at C-13 of ent-manoyl oxides, although in limited yield. A considerable quantity of starting material 1 was recovered unaltered (70%) and hence can be recycled.

In order to study the formation of rearranged product 2 and the manoyl oxides 3 and 4, we isolated the chloromercuric intermediates of the oxymercuration process. Treatment of 1 with mercuric acetate and sodium chloride gave products 5 (63%) and 6 (15%), whose configuration at C-13 was established on the consideration of 1H- (experimental) and 13C-NMR chemical shifts of C-9 (Table) as indicated above for manoyl oxides 3 and 4. Thus we can determine that in the first step of oxymercuration the chloromercuric compound 5, with 13-epi configuration was formed preferentially. We now checked the characteristics of demercuration process with 5 as the starting material. Reduction of 5 with basic sodium borohydride yielded the rearrangement product 2 (16%) and diene 1 (80%). As expected, the rearrangement occurred in the demercuration step to give the same configuration at C-13 as in the OM–DM procedure. When 5 was reduced with sodium amalgam, the ent-13-epi-manoyl oxide (3) (32%) and diene 1 (60%) were obtained. Thus, a radical rearrangement occurred in the demercuration process with basic borohydride, but only a product with a 13S-configuration was isolated. However, the OM–DM of product 1 with basic sodium borodeuteride gave only the
As can be seen, although the demercuration with basic sodium borohydride seems to occur via a free radical, only product 2 with 13S-configuration was isolated, and when this reduction was carried out with sodium borodeuteride the same configuration at C-13 was obtained with deuteration at C-13. Evidently, the stability of tetrahydropyran-2-yl radical is greater than the other radical structures of this process, because only its respective products of reduction were isolated when the demercuration was accomplished with basic borohydrides. Moreover, only one configuration at C-13 was detected in the processes of rearrangement. It is clear that, due to steric reasons the intermediate with the allyl chain equatorially disposed is more stable than the intermediate with an axial allyl chain, but the loss of stereochemistry during this type of reduction process is also known. Elsewhere the alkoxyalkyl radical intermediates are pyramidal and the non-bonded C-orbital prefers an orientation which allows conjugative delocalization. In this case, the p-type orbital on the oxygen atom produces a stereoelectronic preference of axial radical in the tetrahydropyran ring to some extent greater than expected in the corresponding cyclohexane, and with a conjugative delocalization and hyperconjugation which can not occur in the equatorial radical.

Thus, the ring oxygen atom adjacent to the radical center in tetrahydropyran system is apparently of critical importance as deduced from electron spin resonance (ERS) experiments and considerations of SOMO–LUMO interactions. Only axial products were found by attack on radical at C-2 of tetrahydropyrans in the $^4C_1$ conformation in both addition and abstraction reactions. On the other hand, the stereoelectronic control of reductive denitration of tertiary nitriles was studied, with the conclusion, after consideration of the stereochemistry of isolated products, that the axial configuration of the 2-aceoxyethyl-1-oxacycloalk-2-yl radical was practically alone responsible for the reaction, although an axial or equatorial benzyloxy group was situated at C-3. In our case, the π-system at C-2 of the 1-oxacycloalk-2-yl moiety of the molecule seems to exert a similar effect thus leading only to the H-axial at C-13 of the radically rearranged products in the one or two-step OM-DM
process with basic sodium borohydride, thus contributing to expected formation of axial 13-H (or D) derivatives as described.21

For the synthesis of 13-epi and 13-normal manoyl oxides, the OM–DM methods give only a limited yield. However, we have obtained ent-manoyl oxide (4, 57%) and ent-13-epi-manoyl oxide (3, 27%) through a new titanium tetrachloride catalyzed intramolecular addition of hydroxy group at C-8 of 1 to its 13(16)-double bond, in a similar form as described for the OM–DM procedures, but easily in high yield to give mainly the 13-normal configuration. To our knowledge, the intramolecular addition of an hydroxy group to a double bond catalyzed, by titanium tetrachloride is not described. Elsewhere the titanium-catalyzed addition of thiol groups to alkenes has been published.20 Possibly this reaction could be applied to tetrahydropyran compounds. In our case this method allows us to obtain, in high yield, ent-manoyl oxides which can be utilized for the synthesis of analogues of ent-forskolin.25–27

All reagents were of commercial quality from freshly opened containers. Melting points were taken using a Koller apparatus and are uncorrected. The optical rotations were measured at 20 °C on a Perkin-Elmer 240 polarimeter. Silica gel Merck 7729 (less than 0.08 mm) was used for column chromatography. CHCl₃ containing increasing amount of acetone or hexane containing increasing amount of Et₂O were used as eluents. Analytical TLC plates (silica gel 7774 Merck) were visualized by spraying with H₂SO₄/AcOH/H₂O (32: 160: 8) followed by heating at 120 °C for 5 min. IR spectra were obtained using Pye-Unicam-SP-1000 spectrophotometer. ¹H-NMR spectra were obtained using a Bruker WP 80 XY (80 MHz) and Bruker WM 360 (360 MHz) spectrometers. ¹³C-NMR spectra were obtained using a Bruker WP 80 XY (20 MHz) and Bruker WM 360 (90.6 MHz) spectrometers. Elemental analyses were made in Perkin-Elmer 240C analyzer.

Oxymercuration–Demercuration of 6,18-Diacetyl Andalusol (1) with Mercuric Acetate and Sodium Borohydride; (13S)-ent-6a,18-Diacetoxy-8(14-16)-aeeo-manoyl Oxide (2): 6,18-Diacetyl andalusol (1; 500 mg, 1.2 mmol), obtained from Sidaeiiis arborescens18 added to a stirred mixture of Hg(OAc)₂ (800 mg, 1.2 mmol), water (1.2 mL) and THF (1.2 mL). After stirring for 30 min at r.t. Et₂O (1.2 mL) is added. The mixture is cooled to 0°C with an ice-water bath and 3M NaOH in H₂O (1 mL) is added during 5 min. The reaction is completed by adding a freshly prepared solution of 0.5 M NaBH₄ in H₂O (1.2 mL) and stirring at 0°C. Finally, NaCl is added and the aqueous layer is extracted thoroughly with Et₂O. The organic layer is dried (MgSO₄) and concentrated under reduced pressure. The crude product is chromatographed on a silica gel column to give 2: yield: 90 mg (18%); syrup; [x]Dᵢ₀ = 33.8° (c = 1, CHCl₃).

C₆H₆O₃ calc. C 70.88 H 9.43

(406.3) found 70.70 9.52

IR (KBr): ν = 2935, 2117, 1736, 1640, 1459, 1437, 1381, 1240, 1033, 913, 756 cm⁻¹

¹H-NMR (CDCl₃): δ = 0.82 (s, 6H, CH₃-19,20), 1.30 (s, 3H, CH₃-17), 2.00, 2.10 (2s, 3H each, 2CH₃O), 2.62–4.05 (ABq, 2H, J = 12 Hz, H-18), 3.52 (m, 1H, W₁₋₂ = 20 Hz, H-13), 4.90–5.30 (m, 3H, W₁₋₂ = 26 Hz, H-6–H-16), 5.50–5.95 (m, 1H, W₁₋₂ = H-15).
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