STEREOSELECTIVE SYNTHESIS OF (±)-10β-HYDROXYFURANOEREMOPHILANE
t
Koji Yamakawa, * Tsuyoshi Satoh, and Satoshi Takita
Faculty of Pharmaceutical Sciences, Science University of Tokyo
Ichigaya–funagawara-machi, Shinjuku-ku, Tokyo 162, Japan

Abstract. The stereoselective total synthesis of (±)-10β-hydroxy-
furanoeremophilane-3,6-dione is described. The key step in this
synthesis is the angular hydroxylation of 10-H-furanoeremophilane-
6,9-dione using benzeneseleninic anhydride.

Tetradimodiol (1a)(68,10β-dihydroxyfuranoeremophilane) and its 6β-esters(1b-
~)
were isolated from Ligularia japonica, 2a Othinha amplexicaulis, 2b and Farfugium
japonicum. 2c Their structures possess the furanoeremophilane skeleton and 10β-
hydroxyl group as the common structural feature. It has attracted attention that
these compounds were shown to effect haptodysfunction.

The authors recently reported 3 an introduction of hydroxyl group to the angular
C-10 positions of furanoeremophilanes using benzeneseleninic anhydride. In this
communication, we wish to report an application of the hydroxylation to the total
syntheses of 10β-hydroxyfuranoeremophilane derivatives. Hydroxylation of the
6,9-dione (2) with benzeneseleninic anhydride gave 10β-hydroxy-6,9-dione (3) as the
major product, as reported previously. 3 Some attempts were made for reductive
decarbonylation of the C-9 carbonyl group of 3. Wynberg et al. 4 reported reduction
of aryl ketones into aryl methylene compounds with zinc dust in the presence of

* Dedicated to Emeritus Professor K. Tsuda on the occasion of his 75th birthday.
copper sulfate in aq. ammonia. Reduction of 3 with zinc dust, according to the Wyenberg's procedure, gave a diol (4), mp 223-225° (59%), together with a hydrogenolysis product (5) (20%). The UV spectrum of 4 showed λ_{max} \text{EtOH} 266 nm, which was consistent with the presence of the 6-oxofuranoremophilane moiety, therefore the structure of 4 should be 9α,10β-dihydroxy-6-oxofuranoremophilane. While, treatment of 4 with zinc dust under the same conditions did not give the ketol (5).

From these evidence, it was surmized that hydrogenolysis of 3 initially formed the diketone (2) as the intermediate, followed by reduction of 2 yielded the ketol (5). Reduction of 3 with NaBH₄ gave a diol (6a), mp 240-243°, quantitatively. The structure of 6a was deduced to be 9α,10β-dihydroxy-6-oxofuranoremophilane from their spectral data [MS m/z: 322, M⁺; UV λ_{max} \text{EtOH} 266 nm]. Oxidation of the both diols (4 and 6a) with activated MnO₂ gave the diketone (3).

The stereochemistries of the both diols (4 and 6a) were then investigated. Treatment of the diol (6a) with methanesulfonyl chloride in triethylamine at -20° for 3 hr gave a 9β,10β-epoxide (7), mp 123-124° (21%), and unchanged 6a (76%), whereas the diol (4) was recovered under the same conditions. When the diol (4), however, was treated with methanesulfonyl chloride at room temperature (22°C) for 20 hr, the epoxide (7) was obtained in 83% yield together with unchanged 4 (17%). The epoxide (7) showed the molecular ion (m/z, 304) corresponding to C₁₅H₁₈O₃ in its mass spectrum. The epoxidation reaction of the diol (6a) proceeded faster than did the isomer (4). Since a nonsteroidal conformation has already been discussed, it is considered that the reduction of 3 with NaBH₄ would yield 9β(axial)-hydroxy compound (4), because NaBH₄ should attack the 9-carobonyl group from the less hindered α-side due to the steric hindrance of the C-5 angular methyl group. While, the reduction of 3 with zinc dust affords a stable 9α(equatorial)-hydroxy compound (6a) under the thermodynamically controlled conditions. The stereoformulas of the diols (4 and 6a) were thus deduced to be cis-9β,10β-diol and trans-9α,10β-diol, respectively, from the above mentioned results.

Ring-opening reaction of the 9β,10β-epoxide of 7 with metal hydrides or some nucleophilic reagents was investigated. Treatment of the epoxide (7) with LiAlH₄ gave a complex mixture, in which no furan compound was detected. Treatment of the epoxide (7) with freshly prepared sodium phenylselenate, prepared from diphenyl diselenide and NaBH₄, gave a phenylselenide (8) (88%) together with 10β-hydroxy compound (9) (12%). The UV spectrum of 8 showed λ_{max} \text{EtOH} 330 nm, which was well consistent with that of the known 9,10-dehydro-6-oxo-3-hydroxyfuranoeremophilane (10).
The high-resolution In-Beem mass spectrum (IB-MS) of 9 showed the molecular ion at m/z 444.0809 corresponding to C_{23}H_{24}O_4Se. From these sepectral data, the structure of the phenylselenide was shown to be 8. The structure of the by-product (9) was deduced from spectroscopic data [high-resolution IB-MS m/z: M^+, 306.1432 (C_{17}H_{23}O_2); IR 3450 cm^{-1}]. When the epoxide (7) was treated with an excess amount of sodium phenylselenolate, the yield of 9 increased (87%). Therefore, NaBH_4 was regarded as the real reductant. Treatment of 7 with NaBH_4 indeed gave 9 (62%) together with unchanged 7 (37%).

Deketalization of 9 with aq. acetic acid gave a diketone (11), mp 188-188.5°, in 71% yield [high-resolution MS m/z: M^+, 262.1146. (C_{15}H_{18}O_4); IR (CHCl_3) 3600, 1710, 1670 cm^{-1}; UV \lambda_{max}^{	ext{EtOH}} 269 nm (ε 2900); NMR δ 0.87 (3H, d, \text{J}=7 Hz, 4-CH_3), 1.12 (3H, s, 5-CH_3), 2.19 (3H, d, \text{J}=1.5 Hz, 11-CH_3), 2.66 (1H, q, \text{J}=7 Hz, 4-H), 3.05, 3.77 (each 1H, d, \text{J}=18 Hz, 9-H), 7.12 (1H, bs, 12-H)]. The IR, UV, and NMR spectra of (11) were in good agreement with those of natural 10β-hydroxyfuranooeremophil-3,6-dione, which was derived from natural monensins (12) by Novotny et al. 8

The total synthesis of tetradimodiol (1a) and tetradimol (13) are now in progress.

REFERENCES


Received, 28th August, 1981