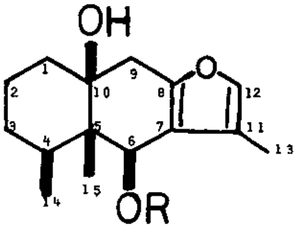
STEREOSELECTIVE SYNTHESIS OF (±)-10β-HYDROXYFURANOEREMOPHILANES[*,1]

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-hydroxyfuranoeremophilan-3,6-dione is described. The key step in this synthesis is the angular hydroxylation of 10-H-furanoeremophilan-6,9-dione using benzeneseleninic anhydride.

Tetradimodiol (**1a**)(6β,10β-dihydroxyfuranoeremophilane) and its 6β-esters(**1b**-**1g**) were isolated from Ligularia japonica,[2a] Othinna 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.



1a: R=H[2a] **1b**: $R=CH_3$[2a]
1c: R=angeloyl[2b] **1d**: R=tigloyl[2b]
1e: R=senecioyl[2c]
1f: R=2-methylbutanoyl[2a]
1g: R=isovaleroyl[2b]

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

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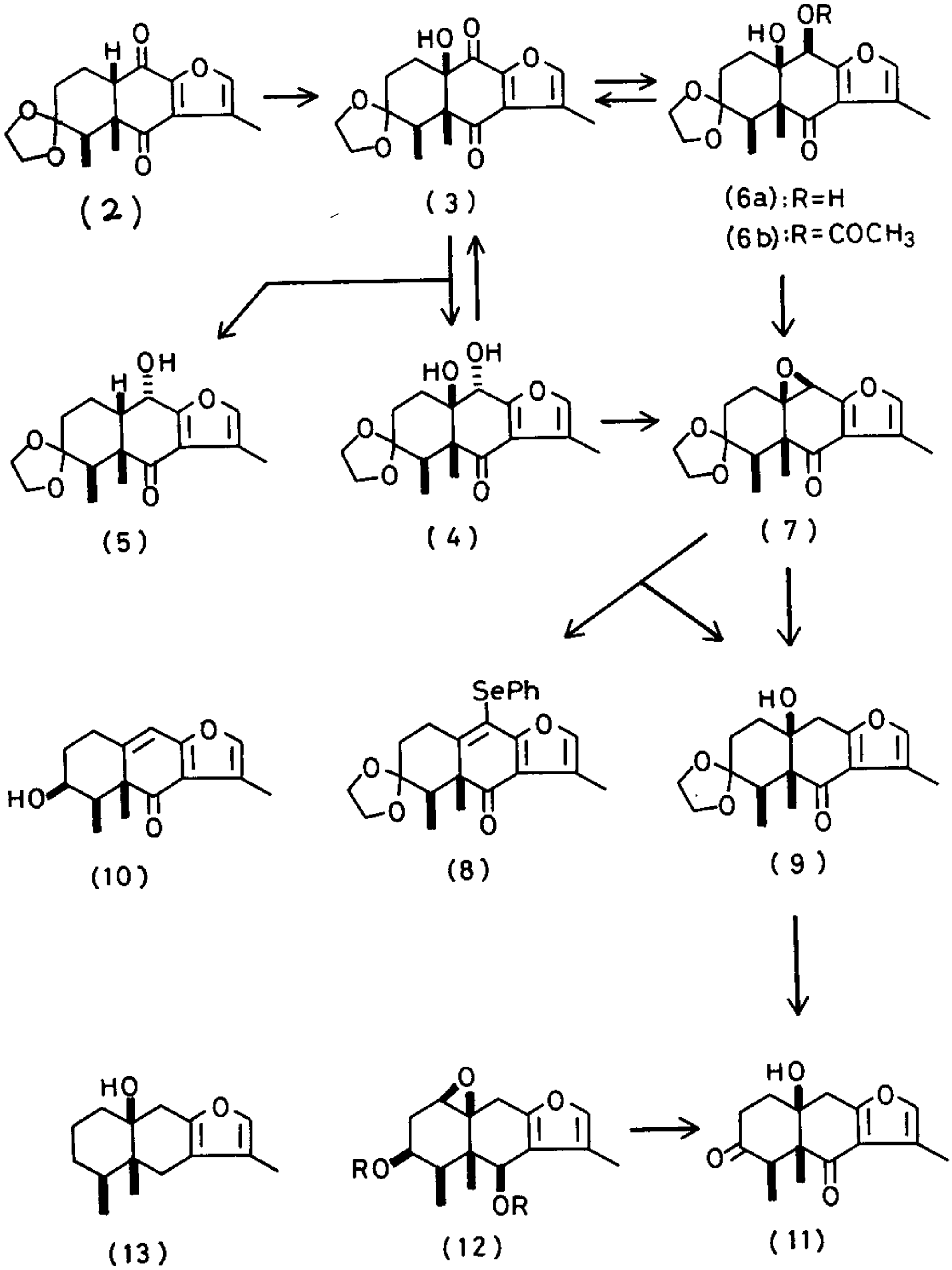
[*] Dedicated to Emeritus Professor K. Tsuda on the occasion of his 75th birthday.

copper sulfate in aq. ammonia. Reduction of 3 with zinc dust, according to the Wynberg'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}^{EtOH} 266 nm, which was consistent with the presence of the 6-oxofuranoeremophilane moiety,[5] therefore the structure of 4 should be 9β,10β-dihydroxy-6-oxofuranoeremophilane. 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 $NaBH_4$ gave a diol (6a), mp 240-243°, quantitatively. The structure of 6a was deduced to be 9α,10β-dihydroxy-6-oxofuranoeremophilane from their spectral data [MS m/z: 322, M^+; UV λ_{max}^{EtOH} 266 nm]. Oxidation of the both diols (4 and 6a) with activated MnO_2 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 $C_{15}H_{18}O_3$ in its mass spectrum. The epoxidation reaction of the diol (6a) proceeded faster than did the isomer (4). Since a nonsteroid conformation has already been discussed,[3] it is considered that the reduction of 3 with $NaBH_4$ would yield 9β(axial)-hydroxy compound (4), because $NaBH_4$ 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 $LiAlH_4$ 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 $NaBH_4$,[6] gave a phenylselenide (8)(88%) together with 10β-hydroxy compound (9)(12%). The UV spectrum of 8 showed λ_{max}^{EtOH} 330 nm, which was well consistent with that of the known 9,10-dehydro-6-oxo-3-hydroxyfuranoeremophilane (10).[7]


(2)
(3)
(6a):R=H
(6b):R=COCH3
(5)
(4)
(7)
SePh
(10)
(8)
(9)
(13)
(12)
(11)
HO
OH
OR
RO

The high-resolution In-Beem mass spectrum (IB-MS) of 8 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 ($C_{17}H_{23}O_5$); IR 3450 cm^{-1}]. When the epoxide (7) was treated with an excess amount of sodium phenylselenate, 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 λ_{max}^{EtOH} 269 nm (ε 2900); NMR δ 0.87 (3H, d, *J*=7 Hz, 4-CH_3), 1.12 (3H, s, 5-CH_3), 2.19 (3H, d, *J*=1.5 Hz, 11-CH_3), 2.66 (1H, q, *J*=7 Hz, 4-H), 3.05, 3.77 (each 1H, d, *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-hydroxyfuranoeremophilan-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

1. Studies on the Terpenoids and Related Alicyclic Compounds Part XXVII. Part XXVI. K. Yamakawa and T. Satoh, *Chem. Pharm. Bull. (Tokyo)*, in press.
2. a) M. Tada, Y. Moriyama, Y. Tanahashi, T. Takahashi, M. Fukuyama, and K. Sato, *Tetrahedron Lett.*, 1971, 4007; b) P.W. Jenning, J.C. Hurley, S.K. Reeder, A. Holian, P. Lee, C.N. Caughlan, R.D. Larson, *J. Org. Chem.*, 1976, **41**, 4078.
3. K. Yamakawa, T. Satoh, N. Ohba, and R. Sakaguchi, *Chem. Lett.*, 1979, 763. K. Yamakawa, T. Satoh, N. Ohba, R. Sakaguchi, S. Takita, and N. Tamura, *Tetrahedron*, 1981, **37**, 473.
4. H. Wynberg, J. de Wit, and H.J.M. Sinnige, *J. Org. Chem.*, 1970, **35**, 711.
5. L. Novotny, Ch. T-Wlotzka, V. Herout, and F. Sorm, *Coll. Czech. Chem. Commun.*, 1964, **29**, 1922.
6. K.B. Sharpless and R.F. Lauer, *J. Am. Chem. Soc.*, 1973, **95**, 2697.
7. K. Yamakawa and T. Satoh, *Chem. Pharm. Bull. (Tokyo)*, 1979, **27**, 1747.
8. L. Novotny, M. Krojidlo, Z. Samek, J. Kohoutova, and F. Sorm, *Coll. Czech. Chem. Commun.*, 1973, **38**, 739.

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