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# STUDIES ON THE SYNTHESES OF SESQUITERPENE LACTONES V. TOTAL SYNTHESIS OF ARBORESCIN

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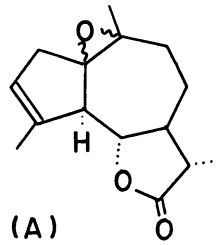
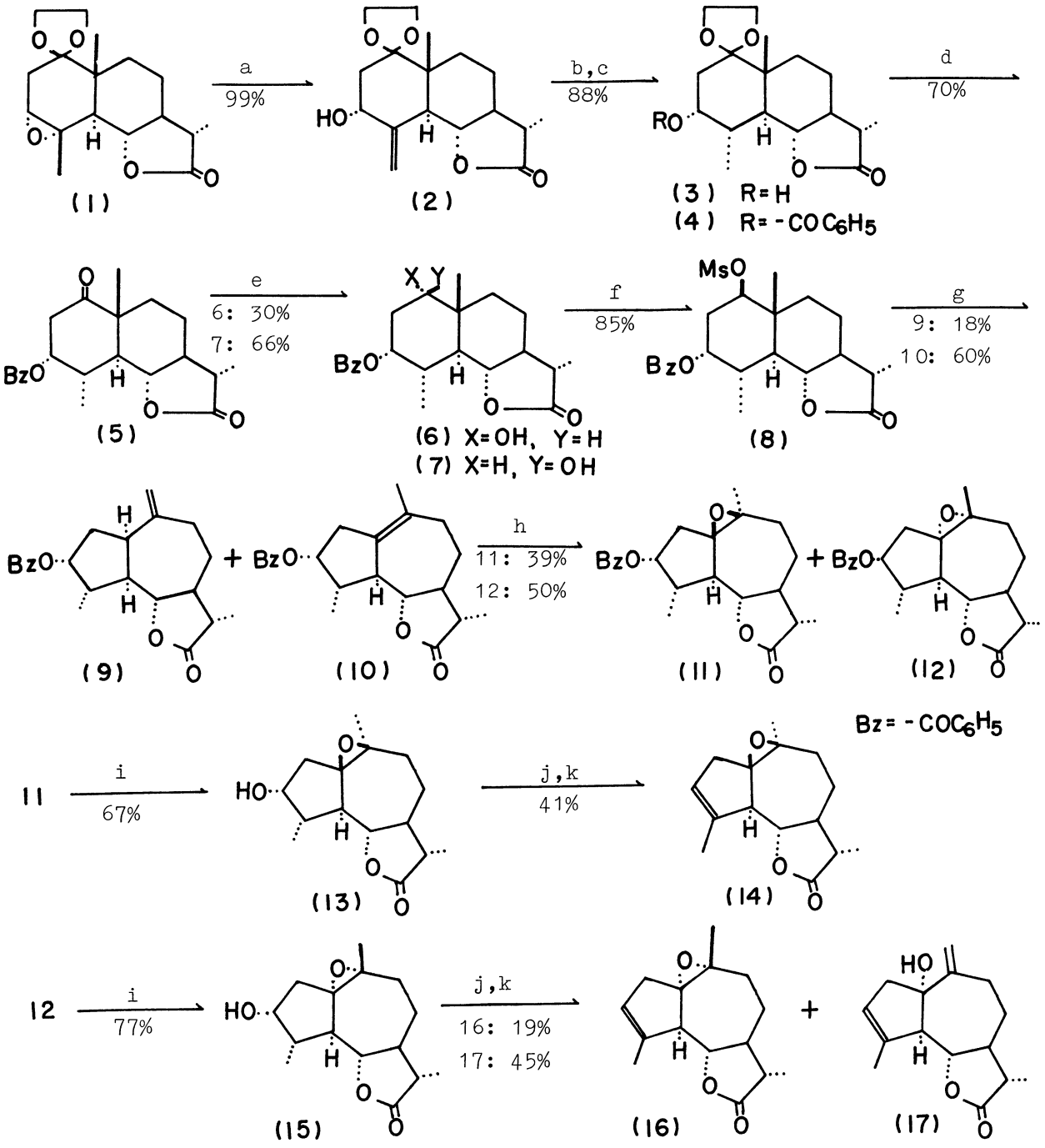
Arborescin has been synthesized in 11 steps from 3α,4α-epoxy-1,1-ethylenedioxy-5αH,6β,11βH-eudesman-6,13-olide. The key step involves solvolytic rearrangement of 3α-benzoyloxy-1β-mesyloxy-5αH,4β,6β,11βH-eudesman-6,13-olide. The stereochemistry of epoxide ring of arborescin has been determined to be β-orientation from this synthesis.

Arborescin was isolated by Meisels and Weizmann from Artemisia arboresces (Compositae), a plant used for contraceptive purpose by the ancient Greeks and Arabs.[1] The structure of this compound was proposed as shown in structure (A) by Herout et al. on the basis of its synthesis from isophotosantonic lactone acetate.[2] The stereochemistry of the epoxide ring at $C_{1(10)}$ was not clear from this chemical transformation. In this communication we want to report the total synthesis of arborescin by means of the solvolytic rearrangement of the appropriately functionalized eudesmanolide.

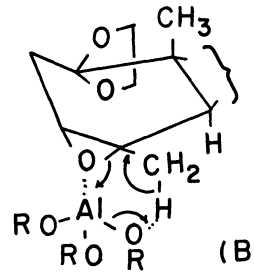


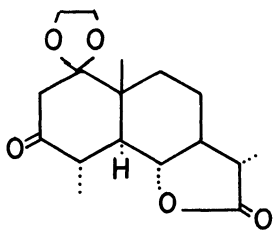
(A)

The starting material of our synthesis of arborescin is an epoxyacetal (1) which was prepared by the method reported in the previous paper.[3] Treatment of 1 with aluminium isopropoxide in boiling toluene gave an allyl alcohol (2), mp 235°C [IR (KBr): 3500 and 1657 $cm^{-1}$; NMR ($CDCl_3$+$D_2O$): δ 4.23 (1H, t, J=3.2 Hz, $C_3$-H), 5.05 (1H, dd, J=1.0 and 1.8 Hz, $C_{14}$-$H_a$), 5.21 (1H, m, $C_{14}$-$H_b$)] in 99% yield. The high regioselectivity of this reaction is presumed due to the preferred geometry of the possible intermediary complex (B). Catalytic hydrogenation of 2 in the presence of Pt/C in EtOAc gave an alcohol (3), mp 190°C, in 99% yield. Benzoylation of 3




a: $Al(i\text{-}PrO)_3$, toluene, ref; b: $H_2$, Pt/C, EtOAc; c: $C_6H_5COCl$, pyridine;
d: 50% aq AcOH, ref; e: $Zn(BH_4)_2$, DME; f: MsCl, pyridine;
g: 0.5M KOAc, AcOH, ref; h: $m\text{-}ClC_6H_4CO_3H$, $CH_2Cl_2$; i: 1M $K_2CO_3$, MeOH;
j: MsCl, pyridine; k: LiBr, $Li_2CO_3$, DMF, ref


(B)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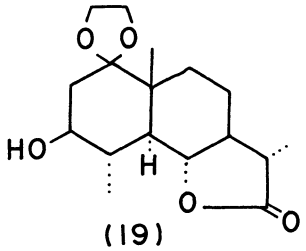

(19)

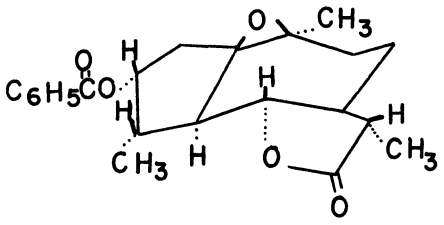
with benzoyl chloride in pyridine gave a benzoate (4) [IR ($CHCl_3$): 1710 $cm^{-1}$; NMR ($CDCl_3$): δ 5.14 (1H, q, J=3.0 Hz, $C_3$-H)] in 89% yield. Since the stereochemistry of $C_4$-Me in 3 and 4 could not be determined from their NMR spectra, 3 was converted to the corresponding ketone (18) by the Collins procedure. The down field shift [$\delta_{(CDCl_3)} - \delta_{(C_6H_6)} = -0.24$] of $C_4$-Me resonance in the NMR spectrum of 18 on passing from deuteriochloroform to benzene suggested the α-equatorial configuration of $C_4$-Me group in this compound. This was confirmed from the coupling constant of $C_3$-H in NMR spectrum ($CDCl_3$) [δ 3.33 (1H, ddd, J=6.0, 9.0 and 9.0 Hz, $C_3$-H)] of the 3β-alcohol (19) which was prepared by reduction of 18 with $Zn(BH_4)_2$ in DME.[4)]

Deacetalization of 4 by treatment with 50% AcOH aq gave a ketone (5), mp 167° C, in 70% yield. Reduction of 5 with $Zn(BH_4)_2$ in DME gave a 1α-alcohol (6), mp 259° C [IR (KBr): 3475 $cm^{-1}$; NMR ($CDCl_3$): δ 3.40 (1H, t, J=3.0 Hz, $C_1$-H)] in 30% yield and a 1β-alcohol (7) [IR ($CDCl_3$): 3475 $cm^{-1}$; NMR ($CDCl_3$): δ 3.70 (1H, dd, J=5.5 and 12.0 Hz, $C_1$-H)] in 66% yield. Attempted tosylation of 7 was unsuccessful under various conditions. Mesylation of 7 with mesyl chloride in pyridine at room temperature gave a mesylate (8) [NMR ($CDCl_3$): δ 2.96 (3H, s, $CH_3SO_2$-), 4.80 (1H, dd, J=5.5 and 11.5 Hz, $C_1$-H), 5.33 (1H, q, J=3.0 Hz, $C_3$-H)] in 85% yield.

Solvolytic rearrangement of 8 with 0.5M KOAc in boiling acetic acid gave 3α-benzoyloxy-1α,5αH,4β,6β,11βH-guai-10(15)-en-6,13-olide (9), mp 121° C [IR (KBr): 886 $cm^{-1}$; NMR ($CDCl_3$): δ 4.84 (1H, m, $C_{15}$-$H_a$), 4.94 (1H, m, $C_{15}$-$H_b$) and 5.49 (1H, q, J=2.2 Hz, $C_3$-H)] in 18% yield and 3α-benzoyloxy-5αH,4β,6β,11βH-guai-1(10)-en-6,13-olide (10), mp 81° C [NMR ($CDCl_3$): δ 1.72 (3H, d, J=1.8 Hz, $C_{10}$-Me), 5.38 (1H, q, J=3.2 Hz, $C_3$-H)] in 60% yield.

Epoxidation of 10 with m-chloroperbenzoic acid gave a 1β,10β-epoxide (11) [NMR ($CDCl_3$): δ 1.30 (3H, s, $C_{10}$-Me), 3.97 (1H, t, J=9.5 Hz, $C_6$-H), and 5.46 (1H, ddd, J=3.5, 5.1, and 5.1 Hz, $C_3$-H)] in 39% yield and 1α,10α-epoxide (12) [NMR

($CDCl_3$): δ 1.35 (3H, s, $C_{10}$-Me), 3.78 (1H, dd, J=9.5 and 11.5 Hz, $C_6$-H), and 5.48 (1H, ddd, J=2.5, 5.3, and 5.5 Hz, $C_3$-H)] in 50% yield. The cis relationship between $C_{1(10)}$-epoxide ring and $C_6$-H in 11 was clearly demonstrated in the NMR spectrum, in which the signal of $C_6$-H appeared at 0.19 ppm lower field than the corresponding signal of 12.[5,6]



(11)

Hydrolysis of 11 and 12 gave the corresponding alcohols (13) and (15) in 67% and 77% yields, respectively. Mesylation of 13 and successive treatment of the resulting mesylate with LiBr and $Li_2CO_3$ in boiling DMF gave arborescin in 41% yield, which was identical with the natural product in NMR ($CDCl_3$, 60 MHz).[7] On the other hand, the same treatment of 15 gave 1α,10α-epoxy-5αH,6β,11βH-guai-3-en-6,13-olide (16) [NMR ($CDCl_3$): δ 1.23 (3H, d, J=6.0 Hz, $C_{11}$-Me), 1.33 (3H, s, $C_{10}$-Me), 1.96 (3H, broad s, $C_4$-Me), 3.84 (1H, m, $C_6$-H), and 5.60 (1H, m, $C_3$-H)] in 19% yield and 1α-hydroxy-5αH,6β,11βH-guai-3,10(15)-dien-6,13-olide (17) [NMR ($CDCl_3$): δ 1.89 (3H, broad s, $C_4$-Me), 3.83 (1H, t, J=10.0 Hz, $C_6$-H), 5.03 (1H, broad s, $C_{15}$-$H_a$), 5.13 (1H, broad s, $C_{15}$-$H_b$), and 5.53 (1H, m, $C_3$-H)] in 45% yield.

References and Notes

1) A. Meisels and A. Weizmann, J. Am. Chem. Soc., 75, 3865 (1953).

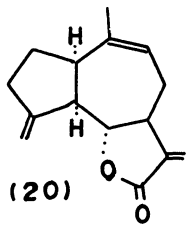
2) M. Suchý, V. Herout, and F. Šorm, Collect. Czech. Chem. Commun., 29, 1829 (1964).

3) M. Ando, A. Akahane, and K. Takase, Bull. Chem. Soc. Jpn., 51, 283 (1978).

4) Reduction of 18 with $Zn(BH_4)_2$ gave 19 and 3 in 58% and 42% yield, respectively.

5) The epoxide function deshields protons which are situated very close to the oxygen atom of the epoxide ring: N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day Inc., San Fransisco (1964), p 102.

6) It was reported that for a given pair of α- and β-oriented electronegative groups such as hydroxyl groups, epoxide rings, and halogens at $C_{10}$, only β-oriented isomer causes a marked down field shift for $C_6$-H in derivatives of eremanthin (20): L. A. Maçaira, M. Garcia, and J. A. Rabi, J. Org. Chem., 42, 4207 (1977), references and notes (6).



(20)

7) R. B. Bates, Z. Čekan, V. Procházka, and V. Herout, Tetrahedron Lett., 1963, 1127. The signal of $C_6$-H of arborescin appears at 0.18 ppm lower field than the corresponding signal of 16 in NMR ($CDCl_3$).

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