CHEMISTRY LETTERS, pp. 617-620, 1978. Published by the Chemical Society of Japan

STUDIES ON THE SYNTHESES OF SESQUITERPENE LACTONES IV. TOTAL SYNTHESIS OF SAUSSUREA LACTONE

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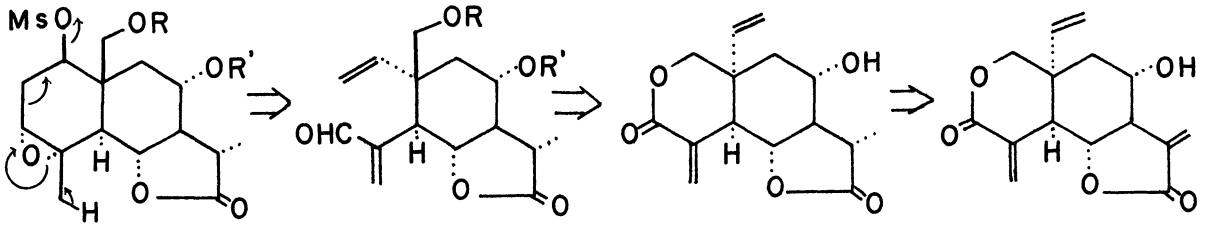
Saussurea lactone, a typical elemanolide, has been synthesized via a novel fragmentation reaction of 3α,4α-epoxy-1β-mesyloxy-5αH,6β,11βH-eudesman-6,13-olide with aluminium isopropoxide in toluene.

In connection with the total synthesis of vernolepin, we envisioned an approach which consisted of the fragmentation reaction of an appropriately functionalized epoxymesylate by base (A—B), oxidation and successive lactonization (B→C), and the conversion of α-methyl-γ-lactone group to α-methylene-γ-lactone group (C→vernolepin). In this approach the fragmentation reaction of the epoxymesylate (A) seemed to be a critical step. In this communication we want to report the total synthesis of saussurea lactone,[1] via a novel fragmentation reaction of an epoxymesylate (7) for the model study of applying this fragmentation reaction toward the total synthesis of vernolepin.



(A) (B) (C) vernolepin

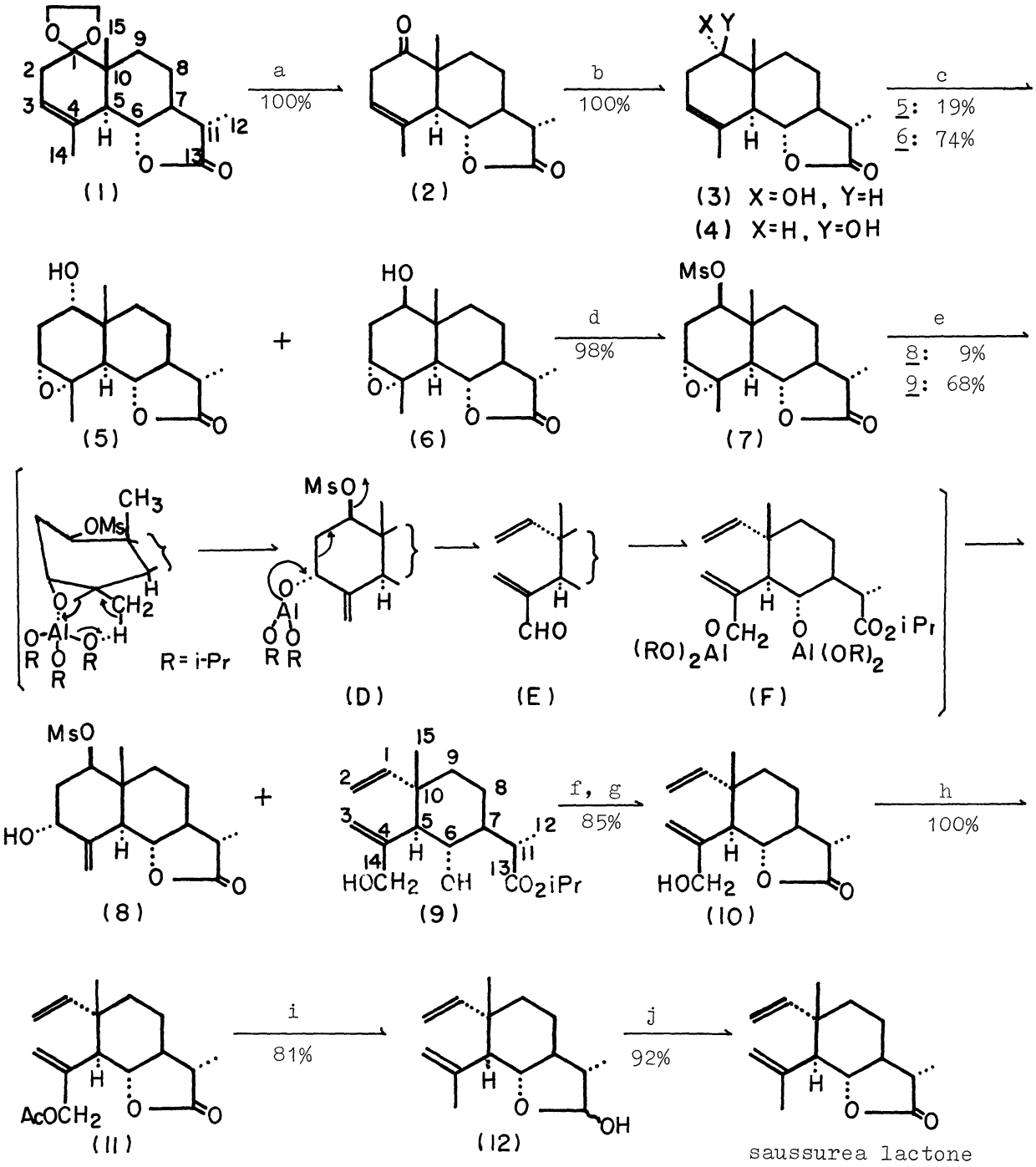
The starting material is an acetal (1) which was prepared by the method reported in the previous paper.[2] Deacetalization of 1 without isomerization of the double bond was established by treatment of 1 with boiling 50% acetic acid aq for 1.25 h, yielding a β,γ-unsaturated ketone (2)[3] in a quantitative yield,

mp 139°C [IR ($CHCl_3$): 1705 cm^{-1}; NMR ($CDCl_3$): δ 1.98 (3H, broad s, C_4-Me) and 5.57 (1H, m, $W_{h/2}$=9.0 Hz, C_3-H)]. Selective reduction of C_1-carbonyl group of 2 with $LiAl(t\text{-}BuO)_3H$ gave a 1:4 mixture of epimeric alcohols (3 and 4) in a quantitative yield. β-Equatorial configuration of the C_1-hydroxyl group in the major alcohol (4) was deduced from the NMR spectrum ($CDCl_3$) which showed a signal at δ 3.63 (1H, dd, J=7.0 and 10.0 Hz, C_1-H). Epoxidation of the mixture of 3 and 4 with m-chloroperoxybenzoic acid in dichloromethane gave the corresponding epoxides (5) and (6) in 19% and 74% yields, respectively. In agreement with the structure 6 the NMR spectrum ($CDCl_3$) showed peaks at δ 1.46 (3H, s, C_4-Me), 3.01 (1H, dd, J=0.8 and 3.3 Hz, C_3-H), and 3.43 (1H, ddd, J=4.6, 6.6 and 10.0 Hz, C_1-H). Mesylation of 6 with mesyl chloride and pyridine gave an epoxymesylate (7) in 98% yield, mp 120°C [NMR ($CDCl_3$): δ 1.47 (3H, s, C_4-Me), 2.99 (3H, s, CH_3-SO_2-), 3.05 (1H, d, J=5.0 Hz, C_3-H) and 4.49 (1H, dd, J=7.0 and 10.0 Hz, C_1-H)].

Treatment of 7 with aluminium isopropoxide[4] in boiling toluene under N_2 for 72 h gave a fragmentation product (9) in 68% yield as an oily substance [IR ($CHCl_3$): 3600, 3400, and 1713 cm^{-1}; NMR ($CDCl_3$): δ 1.23 (6H, d, J=6.2 Hz, $-CH(CH_3)_2$), 2.05 (1H, d, J=10.2 Hz, C_5-H), 3.62 (1H, dd, J=10.2 and 10.6 Hz, C_6-H), 3.93 (1H, d, J=13.5 Hz, C_{14}-H_a), 4.11 (1H, d, J=13.5 Hz, C_{14}-H_b), 4.75~5.05 (2H, m, AB part of ABX, C_2-H), 5.70 (1H, m, X part of ABX, C_1-H), 4.99 (1H, broad s, C_3-H_a), 5.38 (1H, broad s, C_3-H_b), and 5.01 (1H, sept, J=6.2 Hz, $-CH(CH_3)_2$)] and a mesylate (8) in 9% yield, mp 177-177.5°C [NMR ($CDCl_3$): δ 3.03 (3H, CH_3-SO_2-), 4.03 (1H, t, J=10.0 Hz, C_6-H), 4.43 (1H, m, C_3-H), 4.98 (1H, dd, J=5.0 and 11.0 Hz, C_1-H), 5.17 (1H, m, C_{14}-H_a) and 5.21 (1H, m, C_{14}-H_b)]. When this reaction was quenched in 12 h, the sole product was 8.

This fragmentation reaction seemed to be rationalized by the following explanation. The reaction was probably initiated by the coordination of aluminium isopropoxide to the oxygen atom of the epoxide ring for the strong affinity of aluminium atom to oxygen and simultaneous opening of the epoxide ring. Successive fragmentation of the resulting aluminium alkoxide (D) gave an aldehyde (E). Reduction of E under the Meerwein-Ponndorf reduction conditions and successive ring opening and esterification of the γ-lactone moiety gave an intermediate (F). Products (8 and 9) were formed by the hydrolysis of intermediates (D and F).

Hydrolysis of 9 with 1M KOH aq in ethanol at 50°C and successive



a: 50% AcOH aq ref; b: $LiAl(t\text{-}BuO)_3H$; c: $m\text{-}ClC_6H_4CO_3H$; d: MsCl, Py; e: $Al(i\text{-}PrO)_3$, toluene, ref; f: 1M KOH, EtOH, 50°C; g: p-TsOH, C_6H_6, ref; h: Ac_2O, Py; i: Li, NH_3; j: $CrO_3 \cdot 2Py$, CH_2Cl_2, 0°C → room temp.

lactonization of the resulting carboxylic acid with p-toluenesulfonic acid in boiling benzene gave a lactone (10) in 85% yield, mp 100-102°C [IR ($CHCl_3$): 3600 and 1770 cm^{-1}; NMR ($CDCl_3$); δ 2.36 (1H, d, J=11.6 Hz, C_5-H), 3.91 (1H, d, J=14.0 Hz, C_{14}-H_a), 4.14 (1H, d, J=14.0 Hz, C_{14}-H_b), 4.15 (1H, m, C_6-H), 4.75~5.18 (2H, m, AB part of ABX, C_2-H), 5.82 (1H, m, X part of ABX, C_1-H), 4.97 (1H, broad s, C_3-H_a), and 5.39 (1H, broad s, C_3-H_b)]. Acetylation of 10 with acetic anhydride and pyridine gave an acetate (11) in a quantitative yield [NMR ($CDCl_3$): δ 2.08 (3H, s, CH_3CO_2-)]. Reduction of 11 with lithium in liquid ammonia gave a hemiacetal (12) in 81% yield as a diastereomeric mixture of the C_{13}-hydroxyl group [NMR ($CDCl_3$) of the major component: δ 5.07 (1H, q, J=3.6 and 4.0 Hz, C_{13}-H)].

Oxidation of 12 by the Collins procedure gave saussurea lactone in 92% yield, mp 146-147°C (lit[1a] 146-147°C), which was identical with the natural product in IR (Nujol)[1a] and NMR ($CDCl_3$, 60 MHz).[5]

The transformation of saussurea lactone to dihydrocostunolide and costunolide has already been established by Grieco and Nishizawa by utilizing the Cope rearrangement.[1b]

References and Notes

1) a) Structure; A. S. Rao, A. P. Sadgopal, and S. C. Bhattacharyya, Tetrahedron, 13, 319 (1961). b) Synthesis; V. K. Honwad, E. Siscovic, and A. S. Rao, Tetrahedron, 23, 1273 (1967). P. A. Grieco and M. Nishizawa, J. Org. Chem., 42, 1717 (1977).

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

3) K. S. Rybalko and L. Dolejš, Collect. Czech. Chem. Commun., 26, 2909 (1961); T. A. Geissman and G. A. Ellestad, J. Org. Chem., 27, 1855 (1962).

4) The desired fragmentation product was not obtained by treatment of 7 with LDA, $LiNEt_2$, or t-BuOK.

5) H. Yoshioka, T. J. Mabry, and B. N. Timmermann, "Sesquiterpene Lactones", University of Tokyo Press, Tokyo (1973), p 412.

(Received April 21, 1978)