

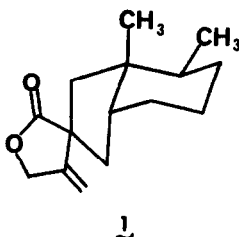
THE TOTAL SYNTHESIS OF (\pm)-BAKKENOLIDE-A

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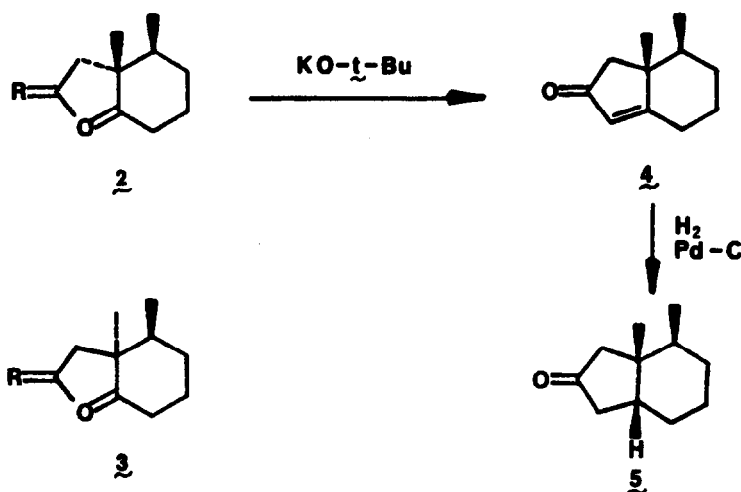
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Recently several examples of a new class of eremophilane sesquiterpenes have been isolated from *Petasites japonicus* of which bakkenolide-A (**1**) is a representative member.^{2,3} As a consequence of our interest in stereoselective [2,3] sigmatropic processes,⁴ we felt that the structurally interesting spiro- β -methylene- γ -lactone moiety contained in **1** could be readily constructed via such molecular rearrangements. Herein we wish to report the stereoselective synthesis of (\pm)-bakkenolide-A (**1**) employing a new lactone spiroannellation reaction sequence.



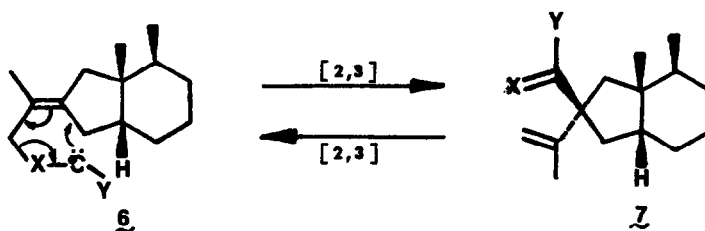
Starting from the epimeric mixture of olefinic ketones **2a**, **3a** (ratio ca. 4-5:1) previously synthesized by Piers from 2,3-dimethylcyclohexanone,⁵ the epimeric diketones **2b** and **3b** were prepared in 93% yield through a modified Lemieux-Johnson oxidation (OsO_4 , NaIO_4 , $t\text{-BuOH-H}_2\text{O}$) procedure.⁶ The desired liquid dione **2b**, conveniently purified at this stage by column chromatography on silica gel, exhibited the following spectral properties, nmr (CDCl_3 , TMS) δ : 2.13, s, 3H; 1.06, s, 3H; 0.91, d, $J = 7.0$ Hz.⁷ The observed benzene-induced solvent shift, Δ , ($\delta\text{CDCl}_3 - \delta\text{C}_6\text{H}_6$), of +16 Hz for the C-2 methyl group is consistent with the assigned stereochemistry of **2b**.⁸ Base-catalyzed cyclization ($\text{KO}-t\text{-Bu}$, $t\text{-BuOH-Et}_2\text{O}$) of **2b** afforded a 65% yield of the non-crystalline hydrindenone **4** which was stereospecifically hydrogenated (Pd-C , EtOH) to the *cis*-fused hydrindanone **5**,^{7,9} identical in all respects to a sample of **5** prepared by the degradation of fukinone.^{10,11}

Scheme I.



a. R = CH₂; b. R = O

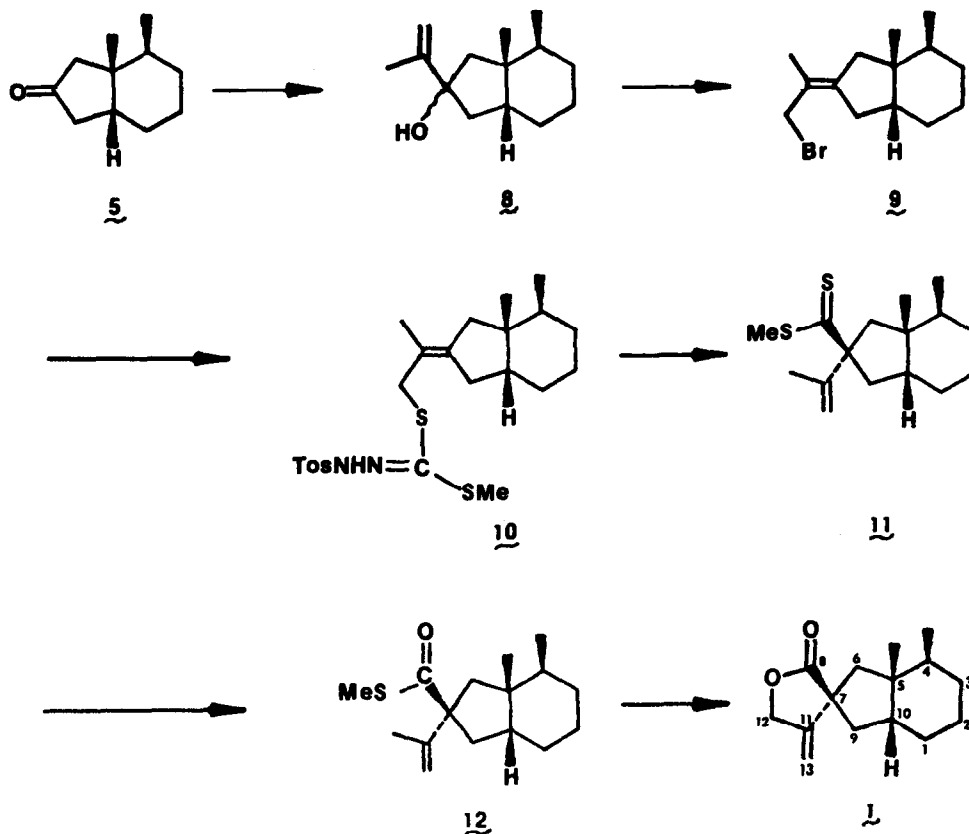
The spiro lactone annelation sequence of primary interest in this study evolved around the [2,3] sigmatropic rearrangement depicted in structures 6 and 7. As a consequence of our earlier work on the stereoselectivity of such bond reorganization processes,⁴ it was felt that the rearrangement of 6 would proceed across the less sterically biased convex face of the molecule establishing the required C-7 stereochemistry and functionality for elaboration to bakkenolide-A (1).



The transformation of the hydrindanone 5 to suitable real examples of 6 (X = S, Y = SMe)¹² is illustrated in Scheme II. Treatment of 5 with isopropenyllithium¹³ (Et₂O, 0°) afforded an epimeric mixture of allylic alcohols 8 in 68-70% yield. Transformation of 8 to the unstable allylic bromide 9 (as a mixture of double bond isomers) with PBr₃ (Et₂O, 0°) followed by immediate treatment with the sodium salt of *p*-toluenesulfonyl-S-methylcarbazate¹⁴ in acetonitrile (25°) afforded the hydrazone 10 isolated as an oil in 75% yield. It is presumed that both 9 and 10 are produced as a mixture of double bond isomers.

Treatment of 10 with one equivalent of sodium hydride in THF followed by heating the filtered solution for six hours at reflux afforded the dithioester 11 as an oil in 60% yield after chromatography on silica gel [nmr (CDCl₃) δ: 0.78, d, J = 6 Hz; 0.9, s; 1.67, s, 2.55, s; 4.9, 5.18, s, olefinic protons]. A very careful examination of the product mixture failed to reveal the C-7 diastereoisomer of ester 11. It thus appears that the anticipated [2,3] sigmatropic rearrangement went with a high degree of stereoselectivity to establish the required asymmetric center at the C-7 spiro lactone juncture in bakkenolide-A (1).¹⁵ It is presumed that this rearrangement proceeds *via* the sulfur-stabilized carbenoid 6 (X = S, Y = SMe),^{12,14} although it is mechanistically plausible for the rearrangement to occur prior to the loss of nitrogen.

Scheme II.



Construction of the lactone ring was accomplished by treatment of 11 with HgO (4 equiv) and HgCl₂ (1.5 equiv) in refluxing aqueous 70% acetone for 3 hours to give the thioester 12 (75%) which was lactonized to (±)-bakkenolide-A (1) with selenious acid in refluxing benzene (10 hr). The synthetic 1 was identical in all respects to an authentic sample of bakkenolide-A (1).^{16,17}

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REFERENCES

1. Camille and Henry Dreyfus Teacher-Scholar Recipient (1971-76); Alfred P. Sloan Fellow (1972-74).
2. a) N. Abe, R. Onoda, K. Shirahata, T. Kato, M. C. Woods, Y. Kitahara, Tetrahedron Lett., 369 (1968). b) K. Shirahata, T. Kato, Y. Kitahara, N. Abe, Tetrahedron, 25, 3179 (1969). c) Ibid., 4671 (1969).
3. K. Naya, M. Kobayashi, Bull. Chem. Soc. Japan, 44, 258 (1971), and references cited therein.
4. D. A. Evans, G. C. Andrews, Tetrahedron Lett., 5121 (1972).
5. E. Piers, R. W. Britton, W. de Waal, Can. J. Chem., 47, 831 (1969).
6. R. Pappo, D. S. Allen, Jr., R. U. Lemieux, W. S. Johnson, J. Org. Chem., 21, 478 (1956); the substitution of *t*-BuOH for dioxane decidedly improved the yields in this oxidation.
7. All compounds afforded satisfactory spectral properties and elemental analyses.
8. N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," S. F. Holdon-Day, Inc., San Francisco, 1966; and references cited therein.
9. For ample precedent for this hydrogenation step see: I. Giarrusso, R. E. Ireland, J. Org. Chem., 33, 3560 (1968); H. O. House, C. J. Blankley, ibid., 32, 1741 (1967); T. L. Jacobs, N. Takahashi, J. Amer. Chem. Soc., 80, 4865 (1958).
10. K. Naya, I. Takagi, Y. Kawaguchi, Y. Asada, Tetrahedron, 24, 5871 (1968). An authentic sample of **5** was kindly supplied to us by Professor Naya.
11. An independent synthesis of **5** by a similar route has been recently reported: S. Sarma, B. Sarkar, Indian J. Chem., 10, 950 (1972).
12. J. E. Baldwin, J. A. Walker, Chem. Commun., 354 (1972).
13. C. J. Timmons, J. Chem. Soc., 2000 (1950).
14. U. Schöllkopf, E. Wiskott, Annalen, 694, 44 (1966).
15. The proof of stereochemistry in **11** is dependent upon the correct stereochemical assignment for **1**.
16. A sample of bakkenolide-A was kindly provided by Professor Yoshio Kitahara.
17. Fukinone epoxide has recently been transformed to the methyl ester corresponding to **12**: K. Naya, M. Hayashi, I. Takagi, S. Nakamura, M. Kobayashi, Bull. Chem. Soc. Japan, 45, 3673 (1972). Professor Naya has informed us (private communication) that he has also carried out the lactonization step as well.