

# A Concise Total Synthesis of ( $\pm$ )-Bakkenolide A by Means of an Intramolecular Diels–Alder Reaction

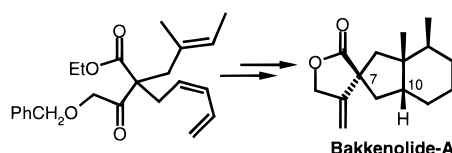
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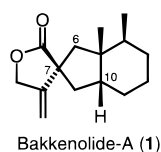
Received June 18, 1999

## ABSTRACT



( $\pm$ )-Bakkenolide A was prepared in five steps from ethyl 4-benzyloxycetoacetate by sequential alkylations with tiglyl bromide and *cis*-5-bromo-1,3-pentadiene, followed by an intramolecular Diels–Alder reaction as the key step. The known 7-epibakkenolide A and novel 10-epi- and 7,10-diepi-bakkenolide A stereoisomers were obtained as minor byproducts.

Bakkenolide A (**1**) is a sesquiterpene  $\beta$ -methylene spiro lactone that is structurally related to the eremophilanes.<sup>1</sup> It was first isolated from the wild butterbur *Petasites japonicus* by Kitahara et al.,<sup>2</sup> and independently by Naya et al.<sup>3</sup>



Bakkenolide-A (**1**)

Subsequent studies showed that **1** is cytotoxic toward several carcinoma cell lines<sup>4</sup> and that it acts as an effective insect antifeedant.<sup>5</sup> The reported biological activity and unusual structure of bakkenolide A have prompted several previous syntheses.<sup>6</sup> We recently attempted the preparation of **1** by

means of a radical cyclization/high-pressure intermolecular Diels–Alder approach.<sup>7</sup> Unfortunately, this resulted in poor stereoselectivity and afforded the corresponding 6-keto analogue that could not be reduced to the desired product. We now report a concise new synthesis of ( $\pm$ )-**1** based on an intramolecular Diels–Alder reaction.

The known  $\beta$ -keto ester **2**<sup>8</sup> was sequentially alkylated with tiglyl bromide (**3**)<sup>9</sup> and *cis*-5-bromo-1,3-pentadiene (**5**)<sup>10,11</sup> in yields of 85% and 92%, respectively, as shown in Scheme 1. The resulting pre-Diels–Alder triene **6** was then heated in toluene at 190 °C for 24 h in a sealed reaction vessel to effect the cycloaddition. Significantly improved yields were

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(1) For a review of bakkenolide A and other sesquiterpene lactones, see: Fischer, N. H.; Olivier, E. J.; Fischer, H. D. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Springer-Verlag: New York, 1979; Vol. 38, Chapter 2.

(2) Abe, N.; Onoda, R.; Shirahata, K.; Kato, T.; Woods, M. C.; Kitahara, Y. *Tetrahedron Lett.* **1968**, 369.

(3) Naya, K.; Takagi, I.; Hayashi, M.; Nakamura, S.; Kobayashi, M.; Katsumura, S. *Chem. Ind. (London)* **1968**, 318.

(4) (a) Jamieson, G. R.; Reid, E. H.; Turner, B. P.; Jamieson, A. T. *Phytochem.* **1976**, 15, 1713. (b) Kano, K.; Hayashi, K.; Mitsuhashi, H. *Chem. Pharm. Bull.* **1982**, 30, 1198.

(5) (a) Harmatha, J.; Nawrot, J. *Biochem. Syst. Ecol.* **1984**, 12, 95. (b) Nawrot, J.; Harmatha, J.; Novotný, L. *Biochem. Syst. Ecol.* **1984**, 12, 99. (c) Nawrot, J.; Bloszyk, E.; Harmatha, J.; Novotný, L.; Drozd, B. *Acta Entomol. Bohemoslov.* **1986**, 83, 327. (d) Isman, M. B.; Brard, N. L.; Nawrot, J.; Harmatha, J. *J. Appl. Entomol.* **1989**, 107, 524. (e) Nawrot, J.; Koul, O.; Isman, M. B.; Harmatha, J. *J. Appl. Entomol.* **1991**, 112, 194.

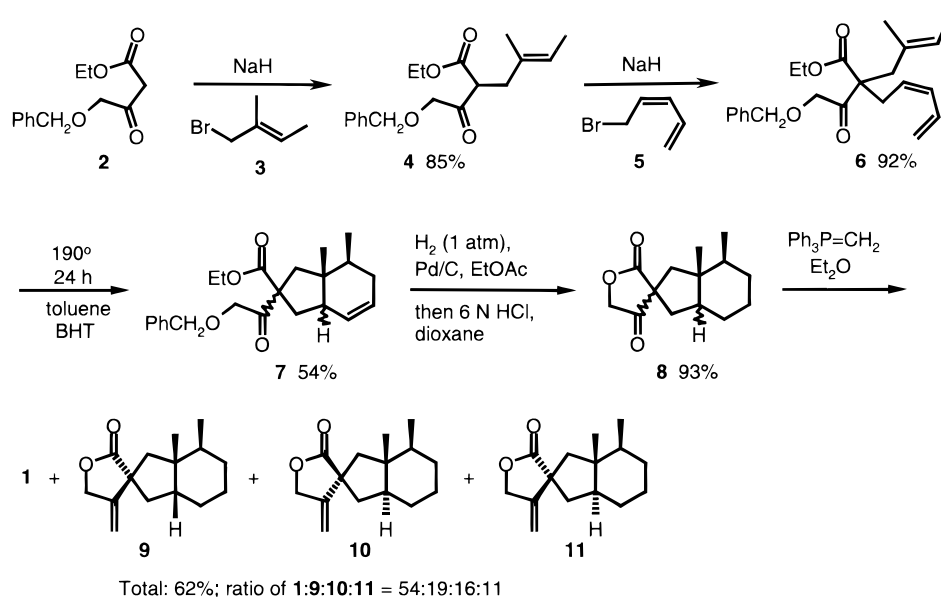
(6) (a) Hayashi, K.; Nakamura, H.; Matsushashi, H. *Chem. Pharm. Bull.* **1973**, 21, 2806. (b) Evans, D. A.; Sims, C. L.; Andrews, G. C. *J. Am. Chem. Soc.* **1977**, 99, 5453. (c) Greene, A. E.; Deprés, J.-P.; Coelho, F.; Brocksom, T. J. *J. Org. Chem.* **1985**, 50, 3943. (d) Greene, A. E.; Coelho, F.; Deprés, J.-P.; Brocksom, T. J. *Tetrahedron Lett.* **1988**, 29, 5661. (e) Srikrishna, A.; Reddy, T. J.; Nagaraju, S.; Sattigeri, J. A.; *Tetrahedron Lett.* **1994**, 35, 7841.

(7) Back, T. G.; Gladstone, P. L.; Parvez, M. *J. Org. Chem.* **1996**, 61, 3806.

(8) Meul, T.; Miller, R.; Tenud, L. *Chimia* **1987**, 41, 73.

(9) Katzenellenbogen, J. A.; Crumrine, A. L. *J. Am. Chem. Soc.* **1976**, 98, 4925.

Scheme 1



obtained when 10 mol % of the radical inhibitor 2,6-di-*tert*-butyl-4-methylphenol (butylated hydroxytoluene, BHT) was included in the reaction mixture to suppress polymerization, which was probably initiated by traces of peroxides in the absence of BHT. Extensive earlier investigations of intramolecular Diels–Alder reactions<sup>12</sup> have shown that transition state A is generally favored over C when a *cis*-diene is attached to the dienophile by a three-carbon tether (Scheme 2). This led to the expectation that the corresponding *cis*-fused cycloadducts would be formed preferentially.

The cycloadduct **7** was thus obtained in 54% yield as a mixture of stereoisomers that could not be easily separated at this stage. The unseparated mixture was therefore subjected to simultaneous hydrogenation and hydrogenolysis of the

benzyl group, followed by acid-catalyzed lactonization to afford 93% of **8**. Finally, the exocyclic methylene group was installed via a Wittig reaction. The resulting mixture of stereoisomers was obtained in 62% yield and contained **1**, 7-epibakkenolide A (**9**), 10-epibakkenolide A (**10**), and 7,10-diepi-bakkenolide A (**11**) in the ratio of 54:19:16:11. It was separated by reverse phase preparative HPLC,<sup>13</sup> and product **1** was identified by comparison to an authentic sample (GC-MS and <sup>1</sup>H and <sup>13</sup>C NMR), while **9** had spectroscopic

(10) Dienyl bromide **5** was obtained as a nearly pure geometric isomer (>95% *cis*) by treating *cis*-2,4-pentadien-1-ol with phosphorus tribromide. The precursor alcohol was in turn obtained by the following method: Margot, C.; Rizzolio, M.; Schlosser, M. *Tetrahedron* **1990**, *46*, 2411.

(11) Dienyl bromide **5** had been previously obtained as an *E,Z*-mixture: Davies, A. G.; Griller, D.; Ingold, K. U.; Lindsay, D. A.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1981**, 633.

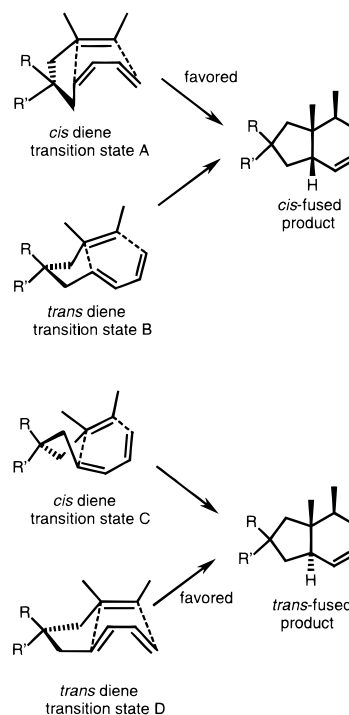
(12) For general reviews of the intramolecular Diels–Alder reaction, see: (a) Ciganek, E. *Org. React.* **1984**, *32*, 1. (b) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183. (c) Taber, D. F. *Intramolecular Diels–Alder and Alder Ene Reactions*; Springer-Verlag: Berlin, 1984. (d) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187. (e) Roush, W. R. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich CT, 1990; Vol. 2, p 91. (f) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1990; Chapter 3. (g) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, Chapter 4.4.

(13) The ratio of stereoisomers in the product mixture was determined by GC, and compounds **1**, **10**, and **11** were obtained in a high state of purity (>98%) by preparative HPLC. Compound **9** could not be completely separated from a small amount of **1**.

(14) Srikrishna, A.; Reddy, T. J. *Tetrahedron* **1998**, *54*, 11517.

(15) Compound **10**: <sup>1</sup>H NMR (400 MHz) δ 5.08 (m, 1 H), 4.97 (m, 1 H), 4.79 (m, 2 H), 2.17 (d, *J* = 13.2 Hz, 1 H), 2.06 (dd, *J* = 13.3, 12.2 Hz, 1 H), 1.80 (m, 2 H), 1.60–1.20 (m, 8 H), 0.91 (s, 3 H), 0.86 (d, *J* = 6.5 Hz, 3 H); <sup>13</sup>C NMR (100 MHz) δ 151.9, 104.9, 70.1, 51.8, 50.2, 49.1, 45.4, 43.8, 42.3, 30.0, 26.4, 24.5, 17.2, 11.9; mass spectrum, *m/z* (relative intensity, %) 234 (M<sup>+</sup>, 10%), 219 (7), 124 (67), 123 (100), 111 (80); exact mass calcd for C<sub>15</sub>H<sub>22</sub>O<sub>2</sub> 234.1620, found 234.1630.

Scheme 2



properties consistent with those reported in the literature.<sup>14</sup> Stereoisomers **10**<sup>15</sup> and **11**,<sup>16</sup> which differ in the relative configurations of their spiro centers, are new compounds that were fully characterized. It was possible to distinguish between them on the basis of an NOE that was observed between the angular methyl group and one of the exocyclic methylene protons in one epimer (assigned structure **11**), while the other epimer (assigned structure **10**) showed no such effect. When the alkylation of **4** was repeated with *trans*-5-bromo-1,3-pentadiene,<sup>17</sup> the corresponding *trans*-dienyl isomer of **6** was produced in 90% yield. Moreover, a

(16) Compound **11**: <sup>1</sup>H NMR (400 MHz)  $\delta$  5.17 (t,  $J$  = 2.0 Hz, 1 H), 5.03 (t,  $J$  = 2.0 Hz, 1 H), 4.77 (m, 2 H), 2.09 (dd,  $J$  = 12.2, 5.8 Hz, 1 H), 1.99 (d,  $J$  = 12.8 Hz, 1 H), 1.90–1.13 (m, 10 H), 0.85 (d,  $J$  = 6.7 Hz, 3 H), 0.80 (s, 3 H); double irradiation of the signal at  $\delta$  5.17 ppm resulted in an enhancement of 2% of the signal at  $\delta$  0.80 ppm; <sup>13</sup>C NMR (100 MHz)  $\delta$  149.9, 106.1, 70.5, 50.3, 49.3, 45.0, 43.1, 42.4, 30.0, 26.2, 24.5, 17.1, 13.1; mass spectrum,  $m/z$  (relative intensity, %) 234 ( $M^+$ , 5%), 219 (4), 124 (100), 123 (56), 109 (84), 111 (81); exact mass calcd for C<sub>15</sub>H<sub>22</sub>O<sub>2</sub> 234.1620, found 234.1627.

(17) Prévost, C.; Miginiac, P.; Miginiac-Groizeleau, L. *Bull. Soc. Chim. Fr.* **1964**, 2485.

higher yield of 95% was obtained in the subsequent cycloaddition step, but the ratio of products **1**, **9**, **10**, and **11** was 24:10:34:32. Thus, use of the *trans*-diene results in the preferential formation of the novel *trans*-fused diastereomers **10** and **11** via transition state D instead of B in Scheme 2.

Scheme 1 therefore provides a simple five-step synthetic approach from **2** to ( $\pm$ )-bakkenolide A (**1**), which is formed stereoselectively when the *cis*-diene **5** is employed in the alkylation of **4**. Since the opportunity exists to introduce further modifications to the diene and dienophile components before their incorporation into the  $\beta$ -keto ester **2**, this approach may also provide general access to other, more highly substituted members of the bakkenolide family.

**Acknowledgment.** We thank the Natural Sciences and Engineering Research Council of Canada (NSERC) for financial support. We also thank Dr. J. Harmatha for a generous gift of authentic bakkenolide A and for providing us with useful information about its biological properties.

OL990747Y

