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Tandem ring expansion/aldol cyclization of bicyclo[5.4.0^{1,7}]undecanediones

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Abstract—Diazomethane ring expansion of **3** followed by deketalization, led to the formation of bicyclodione intermediates **6** and **8**. These intermediates underwent internal aldol cyclization to give the tricyclic adducts **7** and **9** in a 1:1 ratio, respectively.

In an attempt to apply our synthetic protocol in a recently reported synthesis of sativene,[1] we aimed toward the total synthesis of sesquiterpene natural product longifolene using *cis*-1-methyl-bicyclo[5.4.0^{1,7}]undecan-5,11-dione **8** as a synthetic precursor. Other examples of sesquiterpenes containing fused six- and seven-membered rings include himachalene,[2] and widdrol.[3]

Intramolecular aldol cyclizations where the equilibrium favors the internal aldol product have been previously observed with bicyclo[4.3.1]decalinediones,[4] and bicyclo[5.4.0]undecanedione.[5] In this paper we report new examples of intramolecular aldol reactions involving bicyclodiones **6** and **8**, leading to the more stable aldol products **7**, and **9**, respectively.

We had hoped to construct dione **8** by ring enlargement of Wieland–Miescher derived ketone **3**,[6] via treatment in situ with diazomethane, followed by deprotection of the product ketal **5** (Scheme 1). It is noteworthy that the ring expansion of **3**, in the presence of freshly distilled diazomethane in ether, did not occur even when the reaction was left stirring at rt overnight. It was discovered that diazomethane, produced by the action of diazald in the presence of KOH, could be used in situ with compound **3**.[7] However, instead of the expected diones **6** and **8**, this reaction sequence produced only two isomeric aldol products, 11-hydroxy-1-methyl-tricyclo[5.4.0.0^{5,11}]undecan-4-one **7**, and 11-hydroxy-1-methyl-tricyclo[5.4.0.0^{4,11}]undecan-5-one **9** in a 1:1 ratio, as evidenced from the ^{1}H NMR spectra. Separation of the mixture of **7** and **9** was poorly achieved by use of a chromatotron (10% ethyl acetate in hexane) giving rise to a combined yield of 43%. Recrystallization of the chromatographed product **7** in ether afforded the pure needles of **7** (mp 141–142°C), and that of product **9** in ether/hexane gave pure crystals of **9** (dec 236–240°C).[†] In the ^{1}H NMR spectrum of **7**, the methyl group at the ring junction appears as a singlet at 1.00 ppm, and in **9** it appears at 1.14 ppm. In the ^{13}C NMR spectrum of **7**, there are 12 distinct signals with a single carbonyl carbon at 215 ppm. Similarly, in the ^{13}C NMR spectrum of **9**, there are 12 distinct signals with the carbonyl carbon at 214.4 ppm. The IR spectrum of **7** shows the hydroxyl group at 3375 cm^{-1} and the carbonyl group at 1714 cm^{-1}. In **9** on the other hand, the hydroxyl group appears at 3484 cm^{-1}, and the carbonyl group appears at 1691 cm^{-1}. The GC/MS spectrum data for **7** indicated the molecular ion with m/z 194, and an ion with m/z 176 due to loss of water. The GC/MS spectrum data for **9** also indicated the molecular ion with m/z 194; however, the m/z 176 fragment is much less intense in this spectrum compared to **7**. The most intense ion (m/z 111) in both compounds **7** and **9**, appears to be due to the fragmentation of 2-methyl-2-cyclohexenone ion. This fragmentation pattern is similar to that observed for the aliphatic carbonyl compounds.[8] The mass spec-

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† Data for **7**: ^{1}H NMR ($CDCl_3$): δ 2.5 (m, 2H), 2.29 (m, 1H), 2.00 (m, 2H), 1.84–1.57 (m, 8H), 1.4 (m, 1H), 1.3 (m, 1H), 1.00 (s, 3H, methyl); ^{13}C NMR: δ 215, 82.4, 58.0, 43.9, 43.8, 35.2, 34.5, 33.8, 28.8, 27.1, 18.1, 17.2; GC/MS m/z 194, 176, 111; IR (KBr) 3375, 2919, 1714. Data for **9**: ^{1}H NMR ($CDCl_3$): δ 2.65 (dd, 1H, J=7.6 Hz), 2.55 (d, 1H, J=6.6 Hz), 2.22 (m, 1H), 2.03–1.30 (m, 12H), 1.14 (s, 3H, methyl); ^{13}C NMR: δ 214.4, 81.3, 63.2, 44.7, 41.9, 41.3, 35.8, 31.5, 27.6, 26.4, 18.9, 17.7; GC/MS m/z 194, 161, 111; IR (KBr) 3484, 2954, 2879, 1691.

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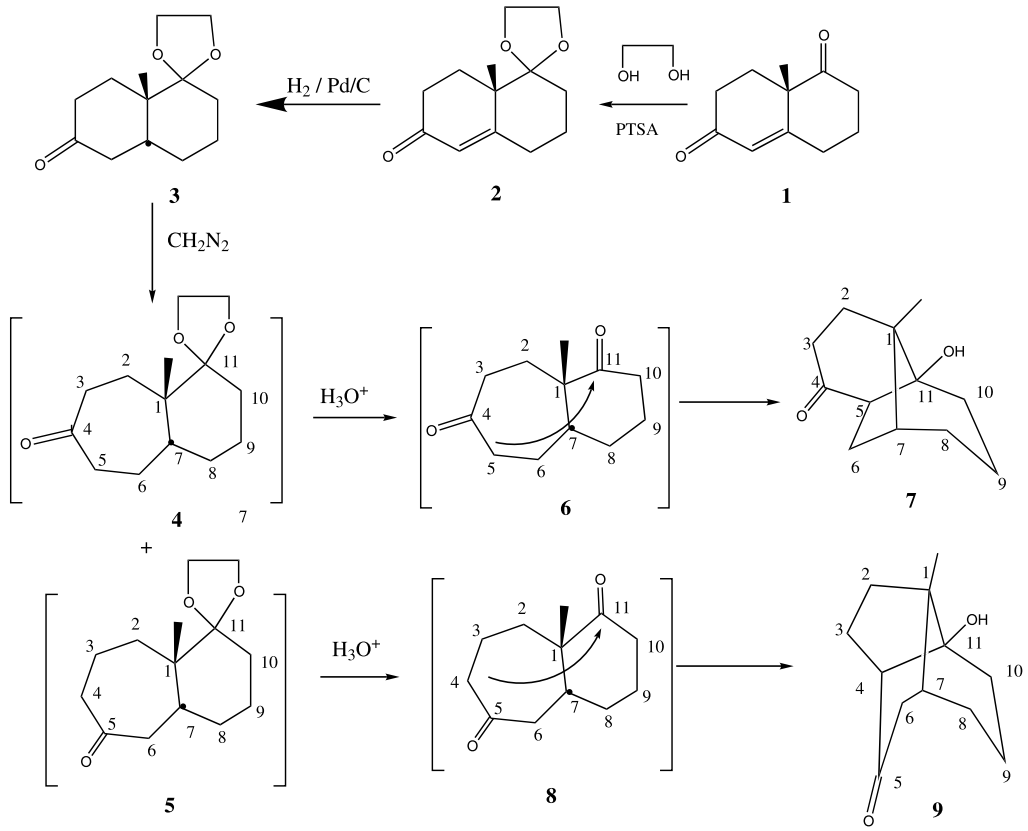

Scheme 1.

tra of compounds **7** and **9**, using atmospheric pressure chemical ionization (APCI), indicated the (M+H) at 195, and the (2 M+H) at 389. The structures of the two isomeric tricyclic alcohols **7** and **9** were unambiguously determined using X-ray crystallography[9] (Figs. 1 and 2).

A preliminary heat of formation calculation using PC Model,[10] Version 6, concurred with the experimental results. Calculations indicate that in both cases, ring closed aldol products **7** and **9** are more stable than their open form counterparts **6** and **8** as illustrated in Table 1. For example, heat of formation calculation for compounds **6** and **7** indicate that there is a difference of about 2.8 kcal/mol in favor of the aldol product **7**, and a difference of about 6 kcal/mol between **8** and **9** in favor of the aldol product **9**.

Diazomethane ring-expansion of **3** led to formation of *cis*-1-methyl-bicyclo[5.4.0^{1,7}]undecan-4,11-dione **6** and *cis*-1-methyl-bicyclo[5.4.0^{1,7}]undecan-5,11-dione **8** as intermediates. Subsequent aldol cyclization of **6** and **8**

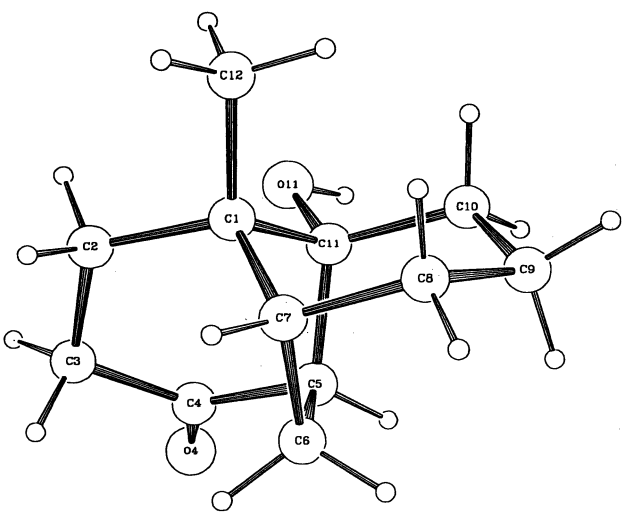

Figure 1. X-Ray structure of compound **7**.

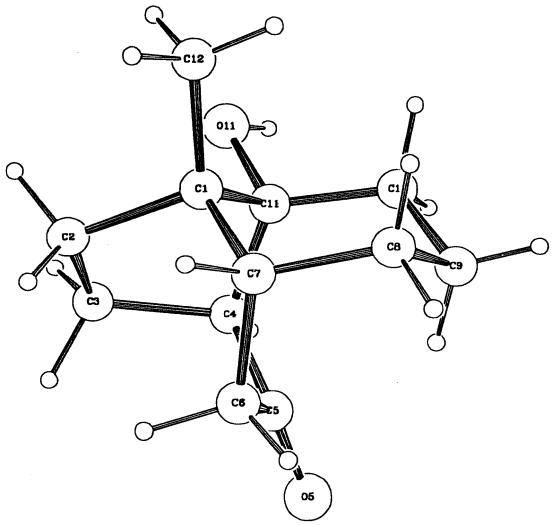

Figure 2. X-Ray structure of compound **9**.

Table 1.

Compound	**6**	**7**	**8**	**9**
Heat of formation (kcal/mol)	−93.74	−96.19	−94.0	−99.89

led to formation of tricyclic adducts **7** and **9**, respectively. Thus, aldolization of bicyclo[5.4.0^{1,7}]undecanedione into the tricyclo[5.4.0.0]undecanone ring systems can be added to the list of the tricyclo[5.4.0.0] skeletons where aldol adducts are the more stable products. Presently, we are considering an alternative path for ring enlargement into the longifolene skeleton.

Acknowledgements

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References

1. (a) Karimi, S. *J. Nat. Prod.* **2001**, *64*, 406–410; (b) Karimi, S.; Petersen, B.; Grohmann, K. G.; Barnett, M. D.; Todaro, L. *Tetrahedron Lett.* **1998**, *39*, 2689–2692.
2. (a) Tashiro, T.; Bando, M.; Mori, K. *Synthesis* **2000**, *13*, 1852; (b) Mori, K.; Tashiro, T.; Sano, S. *Tetrahedron Lett.* **2000**, *41*, 5243; (c) Sano, S.; Mori, K. *J. Org. Chem.* **1999**, *7*, 1679; (d) Challand, B. D.; Kornis, G.; Lange, G. L.; De Mayo, P. *Chem. Commun.* **1967**, 704; (e) Challand, B. D.; Hikino, H.; Kornis, G.; Lange, G. L.; De Mayo, P. *J. Org. Chem.* **1969**, *34*, 794.
3. (a) Sekizaki, H.; Ito, M.; Inoue, S. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 3663; (b) Enzell, C. *Tetrahedron Lett.* **1962**, *3*, 185.
4. (a) Momose, T.; Masuda, K.; Furusawa, S.; Muraoka, O.; Itooka, T. *Chem. Pharm. Bull.* **1990**, *38*, 1707; (b) Momose, T.; Muraoka, O.; Shimada, N.; Tsujimoto, C.; Minematsu, T. *Chem. Pharm. Bull.* **1989**, *37*, 1909; (c) Yordy, J. D.; Reusch, W. *J. Org. Chem.* **1975**, *40*, 14; (d) Momose, T.; Masuda, K.; Furusawa, S.; Muraoka, O.; Itooka, T. *Synth. Commun.* **1982**, *12*, 1039.
5. Seto, H.; Tsunoda, S.; Ikeda, H.; Fujimoto, Y.; Tatasuno, T.; Yoshioka, H. *Chem. Pharm. Bull.* **1985**, *33*, 2594.
6. McMurry, J. E. *J. Am. Chem. Soc.* **1968**, *90*, 6821.
7. De Boer, T. J.; Backer, H. J. *Org. Synth. Coll.*, 4, **1963**, 225.
   In a representative ring expansion reaction the following procedure was used: Compound **3** (1.42 g, 6.3 mmol) and diazald (3.00 g, 13 mmol) were dissolved in ethanol (8 mL, 95%) containing water (0.5 mL). The mixture was cooled to 0°C in an ice–salt bath before a solution of KOH (0.4 g) dissolved in ethanol (2.8 mL, 95%) was slowly added using an addition funnel with gentle stirring. The reaction was stirred at rt for 21 h. The light yellowish mixture was then cooled to 0°C, HCl (12 mL, 2 M) was added dropwise, and stirring was continued at rt for an additional 3 h. The mixture was then neutralized by addition of ice cold saturated aqueous $NaHCO_3$. The aqueous layer was extracted with diethyl ether (3×50 mL), and the combined organic layers were washed with 25 mL of saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo to give 3.00 g of a crude oily mixture. Purification by chromatography (chromatotron, 10% ethyl acetate in hexane) gave compound **7** (0.16 g), a mixture of **7** and **9** (0.24 g), and compound **9** (0.12 g) giving rise to a combined yield of 43% of pure aldol products.
8. Budzikiewicz, H.; Djerassi, C.; Williams, D. H. *Interpretation of mass spectra of organic compounds*; Holden-Day, 1964.
9. X-Ray crystallographic analysis was performed by Dr. Louis Todaro of Hunter College, CUNY.
10. Serena Software, Bloomington, IN. The calculations were performed by Professor W. F. Berkowitz of Queens College.