

HETEROCYCLES, Vol. 70, 2006, pp. 177 - 180. © The Japan Institute of Heterocyclic Chemistry  
 Received, 30th September, 2006 Accepted, 30th October, 2006, Published online, 2nd November, 2006. COM-06-S(W)55

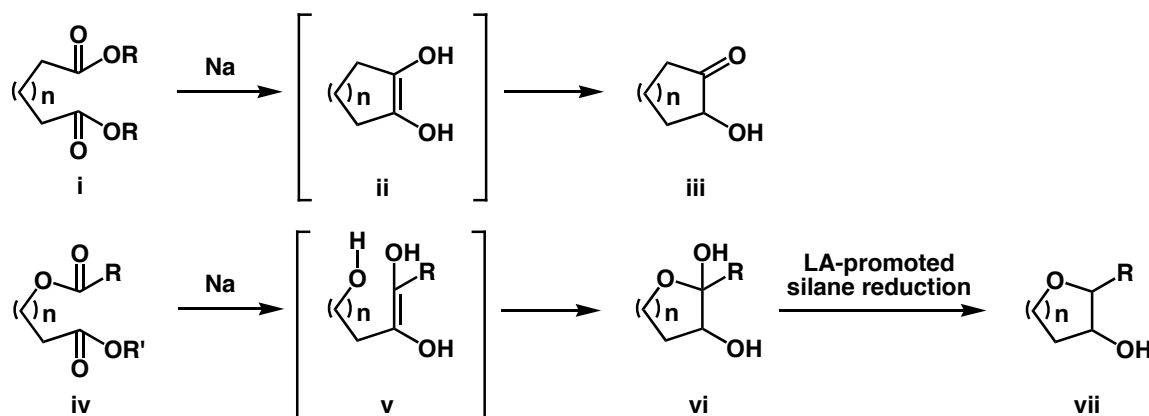
## SYNTHESIS OF CYCLIC ETHER VIA INTRAMOLECULAR ACYLOIN CONDENSATION

Tatsuo Saito, Atsushi Kimishima, and Tadashi Nakata\*

Department of Chemistry, Faculty of Science, Tokyo University of Science, 1-3  
 Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan

**Abstract** – Polycyclic ether was synthesized *via* intramolecular acyloin condensation and Lewis acid-promoted silane reduction.

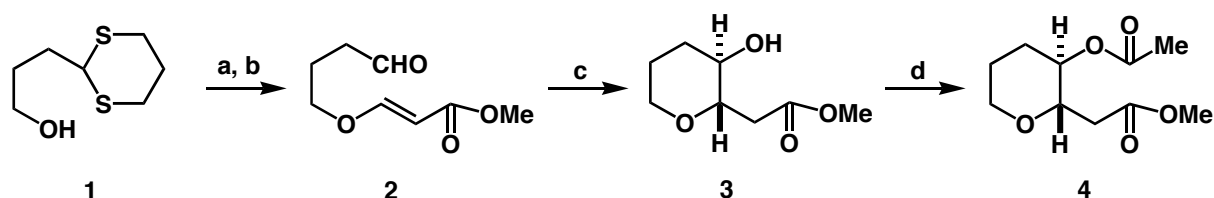
Many marine polycyclic ethers, exemplified by brevetoxin-B, ciguatoxin, and maitotoxin, have been isolated.<sup>1</sup> A structural feature of these natural products is the *trans*-fused polycyclic ether ring system. The synthetically challenging complex structures and potent bioactivities of these compounds have attracted the attention of numerous synthetic organic chemists. Thus, various methods for construction of the cyclic ether ring system have been extensively studied directed toward total synthesis of marine polycyclic ethers.<sup>2</sup> Inter- and intramolecular acyloin condensations have been widely used for the synthesis of many valuable compounds.<sup>3</sup> Intramolecular acyloin condensation of diester (**i**) efficiently took place to give  $\alpha$ -hydroxy cyclic ketones (**iii**) via enediol (**ii**) (Figure 1). Many applications using this type of reaction were successfully accomplished. On the other hand, intramolecular acyloin condensation of **iv** having the ester groups in the opposite direction has hardly been reported, to our knowledge. If this



**Figure 1.** Intramolecular acyloin condensation.

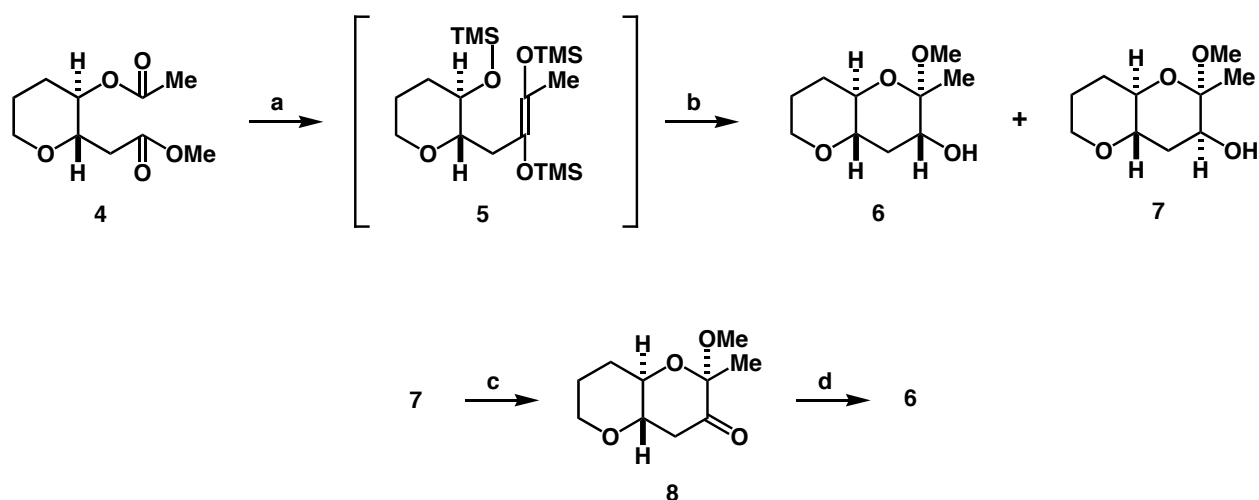
-----  
 This paper is dedicated to Prof. Steven M. Weinreb on occasion of his 65th birthday.

reaction proceeds,  $\alpha$ -hydroxy cyclic acetals (**vi**) could be produced via enetriol (**v**). Then, subsequent Lewis acid (LA)-promoted silane reduction of **vi** would provide cyclic ethers (**vii**). We now report the synthesis of cyclic ether by intramolecular acyloin condensation as a key step. Diester (**4**) as a substrate for the intramolecular acyloin condensation was efficiently synthesized based on our developed  $\text{SmI}_2$ -induced reductive cyclization<sup>4</sup> (Scheme 1). Hetero-Michael addition of hydroxy thioacetal (**1**),<sup>5</sup> prepared from dihydrofuran in two steps, with methyl propiolate in the presence of *N*-methylmorpholine in  $\text{CH}_2\text{Cl}_2$  afforded  $\beta$ -alkoxy acrylate,<sup>6</sup> which was hydrolyzed by MeI treatment<sup>7</sup> to give aldehyde (**2**). Treatment of **2** with  $\text{SmI}_2$ <sup>8</sup> in the presence of MeOH in THF effected reductive cyclization to give 2,3-*trans*-tetrahydropyran (**3**) in 90% yield. Acetylation of **3** afforded the requisite diester (**4**)<sup>9</sup> as the substrate.



**Scheme 1.** (a) methyl propiolate, *N*-methylmorpholine,  $\text{CH}_2\text{Cl}_2$ , rt, 77% (three steps from dihydrofuran); (b) MeI,  $\text{NaHCO}_3$ , aq. MeCN, rt, 91%; (c)  $\text{SmI}_2$ , MeOH, THF, 0 °C, 90%; (d)  $\text{Ac}_2\text{O}$ , pyridine, rt, 89%.

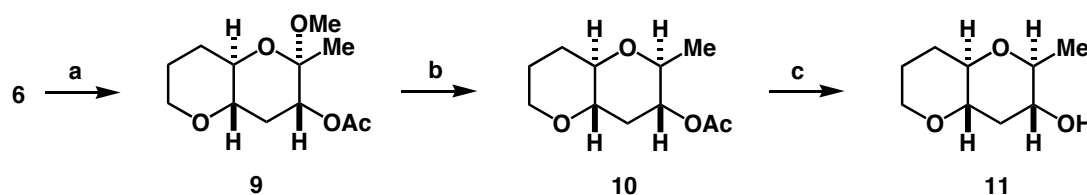
Acyloin condensation by treatment with Na is improved by addition of TMSCl to give bis-silyloxyalkenes, which are hydrolyzed to acyloins.<sup>10</sup> Thus, the substrate (**4**) was treated under these conditions. Upon treatment of diester (**4**) with Na in the presence of TMSCl in refluxing toluene, intramolecular acyloin condensation took place to give tri-TMS ether (**5**), which, due to its instability, was immediately treated with CSA in  $\text{CH}(\text{OMe})_3$ -MeOH to give a 4:1 mixture of  $\alpha$ - and  $\beta$ -hydroxy acetals (**6**<sup>11</sup> and **7**<sup>12</sup>) in 40% combined yield (two steps). The  $\beta$ -hydroxy acetal (**7**) was transformed to the desired  $\alpha$ -hydroxy acetal (**6**); oxidation of **7** with tetra-*n*-propylammonium perruthenate (TPAP) and *N*-



**Scheme 2.** (a) Na, TMSCl, toluene, reflux; (b) CSA,  $\text{CH}(\text{OMe})_3$ , MeOH, rt, 40% (two steps); (c) TPAP, NMO, MS 4A,  $\text{CH}_2\text{Cl}_2$ , rt; (d)  $\text{NaBH}_4$ , MeOH, 0 °C, 90% (two steps).

methylmorpholine *N*-oxide (NMO) in  $\text{CH}_2\text{Cl}_2$  afforded ketone (**8**), which was reduced with  $\text{NaBH}_4$  in MeOH at 0 °C to give  $\alpha$ -alcohol (**6**) in 90% yield (Scheme 2).

Then, conversion of acetal (**6**) to bicyclic ether (**11**) was carried out (Scheme 3). After acetylation of **6**, reduction of the resultant acetate (**9**) with  $\text{Et}_3\text{SiH}$  in the presence of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  in  $\text{CH}_2\text{Cl}_2$ <sup>13</sup> stereoselectively afforded the 2,6-*syn*-2,3-*trans*-tetrahydropyran ring to give bicyclic ether (**10**) in 96% yield. Methanolysis of acetate (**10**) with  $\text{K}_2\text{CO}_3$  furnished the known bicyclic ether (**11**)<sup>14,15</sup> in 95% yield.



**Scheme 3.** (a)  $\text{Ac}_2\text{O}$ , pyridine, rt, 96%; (b)  $\text{Et}_3\text{SiH}$ ,  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ ,  $\text{CH}_2\text{Cl}_2$ , -20 °C, 96%; (c)  $\text{K}_2\text{CO}_3$ , MeOH, rt, 95%.

In summary, a new method for construction of cyclic ethers have been developed based on intramolecular acyloin condensation of diester and Lewis acid-promoted  $\text{Et}_3\text{SiH}$  reduction.

## ACKNOWLEDGEMENTS

This work was financially supported by the Uehara Memorial Foundation and a Grant-in-Aid for Scientific Research (B 15390042 and on Priority Areas 17035080) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

## REFERENCES

- For reviews on polycyclic ether, see: (a) T. Yasumoto and M. Murata, *Chem. Rev.*, 1993, **93**, 1897; (b) Y. Shimizu, *Chem. Rev.*, 1993, **93**, 1685; (c) M. Murata and T. Yasumoto, *Nat. Prod. Rep.*, 2000, **17**, 293; (d) T. Yasumoto, *Chem. Rec.*, 2001, **1**, 228; (e) A. H. Deranas, M. Norte, and J. J. Fernández, *Toxicon*, 2001, **39**, 1101.
- For reviews on synthetic method and total synthesis, see: (a) E. Alvarez, M.-L. Cadenas, R. Pérez, J. Ravelo, and J. D. Martín, *Chem. Rev.*, 1995, **95**, 1953; (b) K. Fujiwara, N. Hayashi, T. Tokiwano, and A. Murai, *Heterocycles*, 1999, **50**, 561; (c) Y. Mori, *Chem. Eur. J.* 1997, **3**, 849; (d) F. P. Marmsäter and F. G. West, *Chem. Eur. J.*, 2002, **8**, 4347; (e) M. Inoue, *Org. Biomol. Chem.*, 2004, **2**, 1811; (f) K. Fujiwara and A. Murai, *Bull. Chem. Soc. Jpn.*, 2004, **77**, 2129; (g) M. Inoue, *Chem. Rev.*, 2005, **105**, 4379; (h) T. Nakata, *Chem. Rev.*, 2005, **105**, 4314.
- For reviews on acyloin condensation, see: (a) S. M. McElvain, *Org. React.*, 1948, **4**, pp. 256-268; (b)

- K. T. Finley, *Chem. Rev.* 1964, **64**, 573; (c) H. Kwart and K. King, 'Chem. Carboxylic Acids and Esters' ed. by S. Patai, Interscience-Publishers, London, New York, 1969, pp. 341-373; (d) J. J. Bloomfield, D. C. Owsley, and J. M. Nelke, *Org. React.*, 1976, **23**, pp. 259-403.
4. (a) N. Hori, H. Matsukura, G. Matsuo, and T. Nakata, *Tetrahedron Lett.*, 1999, **40**, 2811; (b) N. Hori, H. Matsukura, and T. Nakata, *Org. Lett.*, 1999, **1**, 1099; (c) G. Matsuo, N. Hori, and T. Nakata, *Tetrahedron Lett.*, 1999, **40**, 8859; (d) G. Matsuo, H. Kadohama, and T. Nakata, *Chem. Lett.*, 2002, 148; (d) N. Hori, H. Matsukura, G. Matsuo, and T. Nakata, *Tetrahedron*, 2002, **58**, 1853.
5. S. M. Kühnert and M. E. Maier, *Org. Lett.*, 2002, **4**, 643.
6. (a) E. Winterfeldt, *Chem. Ber.*, 1964, **97**, 1952; (b) E. Winterfeldt and H. Preuss, *Chem. Ber.*, 1966, **99**, 450.
7. S. Takano, S. Hatakeyama, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1977, 68.
8. (a) J. L. Namy, P. Girard, and H. B. Kagan, *Nouv. J. Chim.*, 1977, **1**, 5; (b) P. Girard, J. L. Namy, and H. B. Kagan, *J. Am. Chem. Soc.*, 1980, **102**, 2693; (c) B. H. Kagan, *New J. Chem.*, 1990, **14**, 453.
9. Other procedure for **3** and **4**; (a) E. Lee, J. S. Tae, Y. H. Chong, and Y. C. Park, *Tetrahedron Lett.*, 1994, **35**, 129; (b) B. W. Gung and M. B. Francis, *J. Org. Chem.*, 1993, **58**, 6177.
10. K. Ruehlmann, *Synthesis*, 1971, 236.
11. <sup>1</sup>H-NMR data for **6** (400 MHz, CDCl<sub>3</sub>); δ 3.92-3.88 (m, 1H), 3.52-3.45 (m, 1H), 3.39-3.33 (m, 1H), 3.26 (s, 3H), 3.26-3.19 (m, 3H), 2.97 (ddd, *J* = 11.5, 9.0, 4.1 Hz, 1H), 2.12 (dt, *J* = 11.3, 4.5 Hz, 1H), 2.06 (d, *J* = 11.3 Hz, 1H), 1.99-1.95 (m, 1H), 1.78-1.65 (m, 2H), 1.39 (s, 3H).
12. <sup>1</sup>H-NMR data for **7** (400 MHz, CDCl<sub>3</sub>); δ 3.95-3.39 (m, 1H), 3.73 (br, *W*<sub>1/2</sub> = 8.7 Hz, 1H), 3.45-3.28 (m, 3H), 3.27 (s, 3H), 2.09-1.94 (m, 3H), 1.83-1.47 (m, 3H), 1.36 (s, 3H).
13. M. D. Lewis, J. K. Cha, and Y. Kishi, *J. Am. Chem. Soc.*, 1982, **104**, 4976.
14. <sup>1</sup>H-NMR data for **11** (400 MHz, CDCl<sub>3</sub>); δ 3.93-3.88 (m, 1H), 3.41-3.32 (m, 2H), 3.23 (dq, *J* = 8.8, 6.0 Hz, 1H), 3.05-2.97 (m, 2H), 2.34 (dt, *J* = 11.5, 4.1 Hz, 1H), 2.08-2.04 (m, 1H), 1.76-1.68 (m, 2H), 1.51-1.37 (m, 2H), 1.30 (d, *J* = 6.0 Hz, 3H).
15. G. L. Simpson, T. P. Heffron, E. Merino, and T. F. Jamison, *J. Am. Chem. Soc.*, 2006, 128, 1056.