ORGANIC LETTERS

2002
Vol. 4, No. 17
2877−2880

Studies Aimed at the Total Synthesis of Azadirachtin. A Modeled Connection of C-8 and C-14 in Azadirachtin

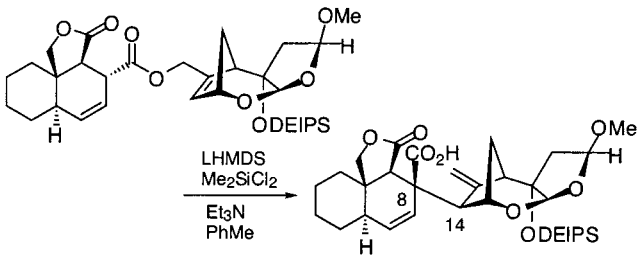
Takehiro Fukuzaki, Satoshi Kobayashi, Takamasa Hibi, Yohei Ikuma, Jun Ishihara,* Naoki Kanoh, and Akio Murai*,†

Division of Chemistry, Graduate School of Science, Hokkaido University, Sapporo 060-0810, Japan

amurai@rmail.plala.or.jp

Received May 30, 2002

ABSTRACT



Studies on the connection between the right and left segments of azadirachtin are described. The Ireland–Claisen rearrangement of Li-enolate of the modeled ester with dichlorodimethylsilane in toluene afforded the desired limonoid framework stereoselectively in good yield.

Azadirachtin (**1**) is a *C*-seco limonoid, isolated as an insect antifeedant from the seeds of Azadirachta indica A. Juss.[1,2] Its highly functionalized structure as well as biological activities urged us toward the total synthesis of this compound, which has not yet been reported.[3] In particular, the connection of the right and left segments remains unsolved due to the seriously hindered positions at C-8 and C-14. Our synthetic strategy involves coupling the right and left segments using Ireland−Claisen rearrangement,[4] as shown in Scheme 1. We have already reported the syntheses of the Decalin portion **2**[5,6] as the left segment and the tricyclic dihydrofuran moiety **3**[7] as the right segment. Claisen rearrangement is widely used as a key step in the syntheses of natural products, especially for the construction of a quaternary center, due to its high selectivity and ease of reaction.[8] Recently, Ley showed the utility of Claisen rearrangement of allyl vinyl ether in the formation between

† Current address: 6-14-4 Asabu-cho, Kita-ku, Sapporo 001-0045, Japan.

(1) (a) Culver, J. N.; Dawson, W. O. *Mol. Plant−Microbe. Interact.* **1991**, *4*, 458. (b) Van den Ackerveken, G. F. J. M.; Van Kan, J. A. L.; Dewit, P. J. G. M. M. *Plant J.* **1992**, *2*, 359. (c) Broughton, H. B.; Ley, S. V.; Slawin, A. M. Z.; Williams, D. J.; Morgan, E. D. *J. Chem. Soc., Chem. Commun.* **1986**, 46. (d) Kraus, W.; Bokel, M.; Klenk, A.; Pöhnl, H. *Tetrahedron Lett.* **1985**, *26*, 6435.

(2) For comprehensive reviews on azadirachtin, see: (a) Mordue (Luntz), A. J.; Blackwell, A. *J. Insect Physiol.* **1993**, *39*, 903. (b) Govindachari, T. R.; Gopalakrishnan, G. *J. Indian Chem. Soc.* **1998**, *75*, 655.

(3) (a) Ley, S. V.; Denholm, A. A.; Wood, A. *Nat. Prod. Rep.* **1993**, 109, and references therein. (b) Nishikimi, Y.; Iimori, T.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 3354. (c) Henry, K. J., Jr.; Fraser-Reid, B. *J. Org. Chem.* **1994**, *59*, 5128. (d) Watanabe, H.; Watanabe, T.; Mori, K. *Tetrahedron* **1996**, *52*, 13939. (e) Watanabe, H.; Watanabe, T.; Mori, K.; Kitahara, T. *Tetrahedron Lett.* **1997**, *37*, 4429, 2103−2106. (f) Nicolaou, K. C.; Follmann, M.; Roecker, A. J.; Hunt, K. W. *Angew. Chem., Int. Ed.* **2002**, *41*, 2103. (g) Nicolaou, K. C.; Roecker, A. J.; Follmann, M.; Baati R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2107.

(4) (a) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897. (b) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (c) Ireland, R. E.; Wipf, P.; Armstrong, J. D., III. *J. Org. Chem.* **1991**, *56*, 650.

(5) (a) Kanoh, N.; Ishihara, J.; Murai, A. *Synlett* **1995**, 895. (b) Kanoh, N.; Ishihara, J.; Murai, A. *Synlett* **1997**, 737. (c) Kanoh, N.; Ishihara, J.; Yamamoto, Y.; Murai, A. *Synthesis* **2000**, *13*, 1878.

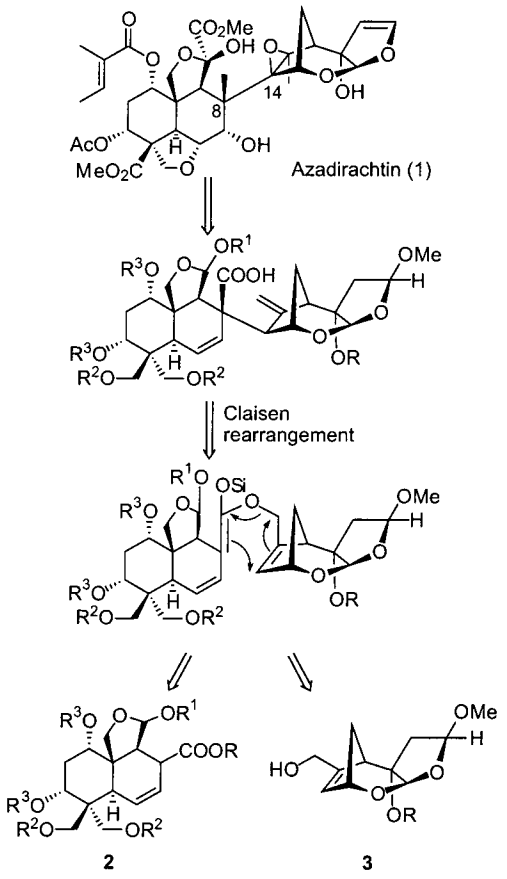
(6) (a) Ishihara, J.; Yamamoto, Y.; Kanoh, N.; Murai, A. *Tetrahedron Lett.* **1999**, *40*, 4387. (b) Yamamoto, Y.; Ishihara, J.; Kanoh, N.; Murai, A. *Synthesis* **2000**, *13*, 1894.

(7) Ishihara, J.; Fukuzaki, T.; Murai, A. *Tetrahedron Lett.* **1999**, *40*, 1907.

(8) (a) Ireland, R. E. *Aldrichmica Acta* **1988**, *21*, 59. (b) Gilbert, J. C.; Kelly, T. A. *Tetrahedron Lett.* **1989**, *32*, 4193. (c) Gilbert, J. C.; Selliah, R. D. *J. Org. Chem.* **1993**, *58*, 6255. (d) Chai, Y.; Hong S.-p.; Lindsay H. A.; McFarland, C.; McIntosh, M. C. *Tetrahedron* **2002**, *58*, 2905.

10.1021/ol026260y CCC: $22.00
Published on Web 07/31/2002

Scheme 1. Retrosynthetic Analysis of Azadirachtin (**1**)



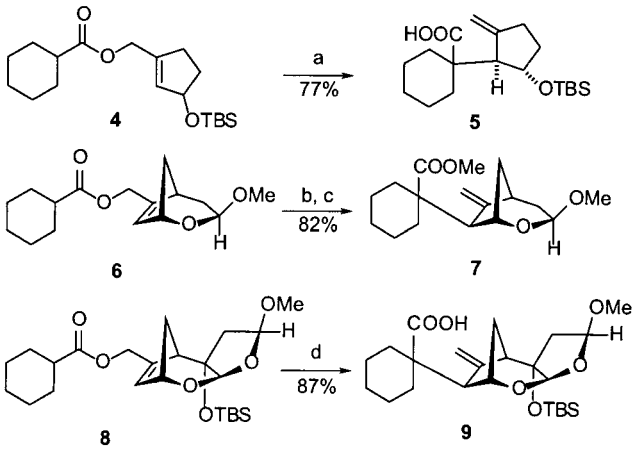
C-8 and C-14.[9] In this paper, we describe the connection of C-8 and C-14 in **1** by use of the model compounds leading to the desired limonoid framework via Ireland−Claisen rearrangement.

In the first stage, we performed Ireland−Claisen rearrangement of a simple cyclohexanecarboxylate **4** (Scheme 2). Treatment of **4** with LDA, TMSCl, and Et_3N in THF afforded a mixture of recovered **4** and byproducts without the desired compound **5**. Addition of HMPA was also fruitless. Results were improved dramatically through the use of a nonpolar solvent. When **4** was exposed to KHMDS, TMSCl, and Et_3N in PhMe at −110 °C and the mixture was warmed gradually to 70 °C, the rearrangement proceeded, affording **5** in 77% yield. The preceding reaction conditions for the rearrangement were applied to the more functionalized molecules. The rearrangement of oxabicyclo[3.2.1]-compound **6**, followed by methyl esterification, furnished compound **7** in 79% yield in two steps. The stereochemistry of **7** was determined by ^1H NMR, NOE, and X-ray crystallography. Ester **8** was also converted to the desired product **9** in 87% yield under similar conditions. These results suggested that the rearrangement was efficient for the bond formation between C-8 and C-14 of azadirachtin **1**.

We next examined the rearrangement of **12**, derived from chiral Decalin **10**[10] and **11** (Scheme 3, Table 1). Under the

(9) Ley, S. V.; Gutteridge, C. E.; Pape, A. R.; Spilling, C. D.; Zumbrunn, C. *Synlett* **1999**, *8*, 1295.

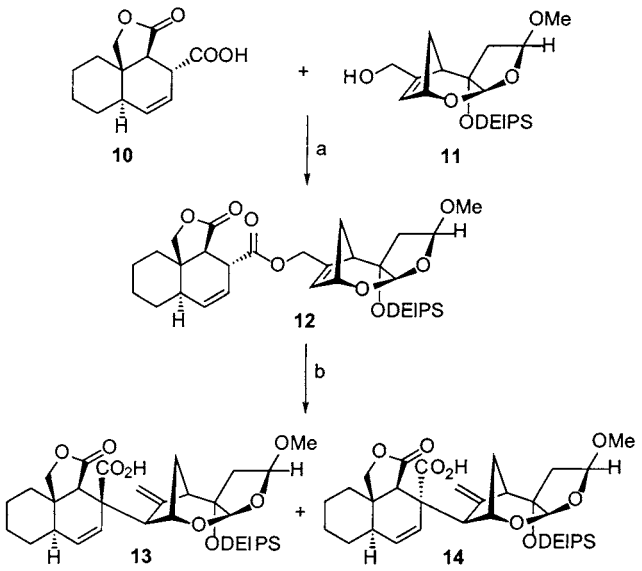
Scheme 2. Claisen Rearrangement of **4**, **6**, and **8**



[a] KHMDS, TMSCl, Et_3N, PhMe, from −110 to 70 °C, 6.5 h. [b] KHMDS, TMSCl, Et_3N, PhMe, from −85 to 70 °C, 6.5 h. [c] CH_2N_2, Et_2O, 0 °C, 1 h. [d] KHMDS, TMSCl, Et_3N, PhMe, from −78 to 70 °C, 15.5 h.

foregoing conditions, the reaction afforded the rearranged products as a 1:3 mixture of diastereomers **13** and **14** in 55% yield (Table 1, entry 1), which were separated by HPLC. The structures of these products were confirmed by NMR analyses of the corresponding methyl esters **15** and **16** (Figure 1). Unfortunately, it turned out that the minor product **13** had the desired configuration. The use of THF and THF−HMPA, however, furnished the products in moderate yields, the ratios of which were 1:1.6 and 1:1.4, respectively (entries 2 and 3). It should be noted that the ratio was slightly improved in polar solvents compared with the reaction in PhMe. Since solvent effects are generally responsible for the

Scheme 3. Claisen Rearrangement of **12**



[a] EDCI, DMAP, CH_2Cl_2, 23 °C, 2 h, 72%. [b] Summarized in Table 1.

Table 1. Claisen Rearrangement of **12**

entry	reagent	base	solvent	**13**:**14**	yield (%)
1	Me_3SiCl	KHMDS	PhMe	1:3.0	55
2	Me_3SiCl	KHMDS	THF	1:1.6	61
3	Me_3SiCl	KHMDS	THF−HMPA	1:1.4	56
4	Me_2SiCl_2	KHMDS	PhMe	1:1.6	41
5	Me_2SiCl_2	LHMDS	THF	1.7:1	81
6[a]	Me_2SiCl_2	LHMDS	THF	1.6:1	68
7	Me_2SiCl_2	LHMDS	PhMe	4.0:1	87
8	$MeSiCl_3$	LHMDS	PhMe	2.1:1	94
9	Me_3SiOTf	KHMDS	THF	dec	
10	$Me_2Si(OMe)_2$	KHMDS	THF	N.R.	

[a] To a mixture of **12**, Me_2SiCl_2, and Et_3N in PhMe was added LHMDS at −78 °C, and the mixture was warmed gradually to 70 °C. Except for entry 6, to a solution of **12** were added base, silyl reagent, and Et_3N at −78 °C, and the mixture was warmed gradually to 70 °C.

geometry of the silyl ketene acetal, it was suggested that the stereochemistry at C-8 in **13** and **14** would depend on the ratio of (*E*)- and (*Z*)-intermediates, respectively. On the basis of this assumption, the coordination of the silyl group to the lactone carbonyl, which was expected to have a significant effect on the geometry of the silyl ketene acetal, would be expected to have to occur selectively at C-8.

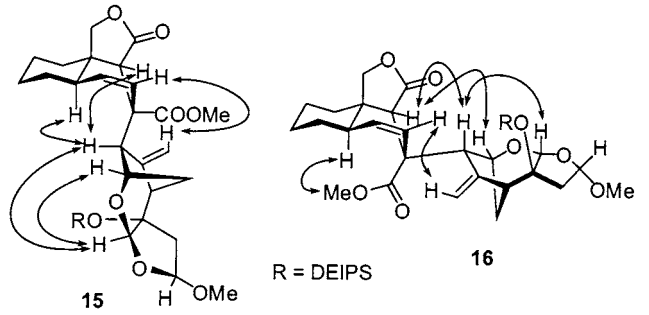


Figure 1. NOESY correlation of **15** and **16**.

Various silyl reagents were therefore examined for use in the next stage of the rearrangement. When **12** was exposed to KHMDS and dichlorodimethylsilane (Me_2SiCl_2) in PhMe, the undesired product **14** was obtained as the major product (entry 4). Further attempts with other solvents were also fruitless. Reaction with LHMDS, however, exhibited significantly different selectivity at C-8. Treatment of **12** with LHMDS and Me_2SiCl_2 in THF afforded the rearranged products as a 1.7:1 mixture of **13** and **14** in 81% yield (entry 5). In addition, the use of PhMe increased the selectivity to furnish the desired **13** as the major product (**13**:**14** = 4:1) in 87% combined yield (entry 7). Rearrangement with trichloromethylsilane, in contrast, resulted in lower selectivity (entry 8), and the reactions employing TMSOTf (entry 9) and dimethoxydimethylsilane (entry 10) were not successful.

In view of the stereochemistry of C-8 in products **13** and **14**, the transition states of the silyl ketene acetal intermediate could be predicted: the (*Z*)- and (*E*)-intermediates would be converted to **13** and **14**, respectively, via a chair transition state (TS-1 or TS-2), as shown in Figure 2. Under conditions

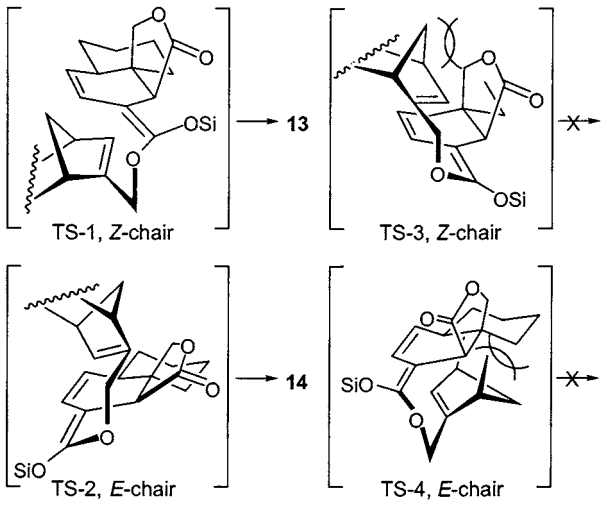


Figure 2. Predicted transition states of silyl ketene acetal intermediates.

employing TMSCl, the formation of (*E*)-silyl ketene acetal could be rationalized by the steric hindrance between TMS group and the carbonyl group of the five-membered lactone. The rearrangement would occur from the β-side of Decalin (TS-2) due to the strong interaction of the lactone and the tricyclo segment in TS-4. In contrast, in the case of Me_2SiCl_2, the (*Z*)-silyl ketene acetal would be favored due to the chelating effects of the silyl group on the carbonyl group in the lactone, and the reaction would take place on the less hindered α-side of Decalin (TS-1) rather than the β-side (TS-3). In addition, when LHMDS was added to a mixture of **12**, Me_2SiCl_2, and Et_3N in THF at −78 °C (entry 6), which would be regarded as kinetic conditions, the ratio of products was 1.6:1, similar to the results under thermodynamic conditions (entry 5). Consequently, the coordination of the chlorodimethylsilyl group could be attributed to the predominance of the (*Z*)-silyl ketene acetal. To confirm this assumption, we attempted to analyze the silyl ketene acetal intermediate through NMR spectra. Although direct NMR measurement of the silyl ketene acetal of **12** could not

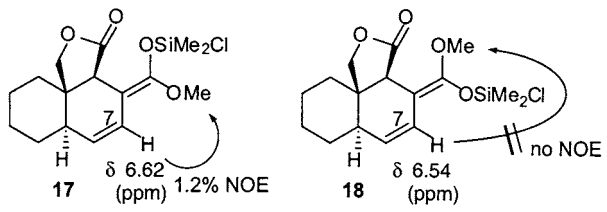


Figure 3. NOE experiments of **17** and **18**.

provide clear spectra due to its flexible conformation,[11] the structurally more simple intermediates **17** and **18** could be analyzed.

Compounds **17** and **18** were easily prepared from the methyl ester of **10**. When the methyl ester was treated with LHMDS, Me_2SiCl_2, and Et_3N in PhMe at −78 °C and the mixture was warmed gradually to 23 °C, **17** was produced as a major compound (**17**:**18** = 3:1). NOE enhancement between H-7 and the Me group in **17** was observed (1.2%), assigning the structure of **17** to the (*Z*)-silyl ketene acetal. The use of KHMDS and Me_2SiCl_2 in PhMe, however, afforded a mixture of silyl ketene acetals (**17**:**18** = 1:1.6) (Scheme 3). In the NOE experiment for **18**, significant NOE enhancement could not be detected.

In the present studies, the Ireland−Claisen rearrangement afforded the desired limonoid framework stereoselectively. This type of stereocontrolled Claisen rearrangement is unprecedented to the best of our knowledge. Application of this method to the total synthesis of azadirachtin is now under way in our laboratory.

Acknowledgment. This work was financially supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan (13680665 (J.I.) and 13010771 (T.F.)). We thank Dr. T. Oishi at Osaka University for his valuable suggestion regarding silyl reagents.

Supporting Information Available: Experimental procedures for compounds **4**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026260Y

(10) Preparation of the optically pure Decalin **10** is included in Supporting Information.

(11) The NMR measurement of a mixture of **12**, LHMDS, Me_2SiCl_2, and Et_3N in PhMe-d_8 was performed at −78, −30, and 0 °C and room temperature. The spectra exhibited a dependence on the temperature. At the ambient temperature, broad and multiple signals were detected, whereas at −78 °C, the peaks were significantly broad and low, showing that the product would have flexible conformations in equilibrium, even at low temperature.