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Synthetic Studies on Azadirachtin: Construction of the Highly Functionalized Decalin Moiety of Azadirachtin

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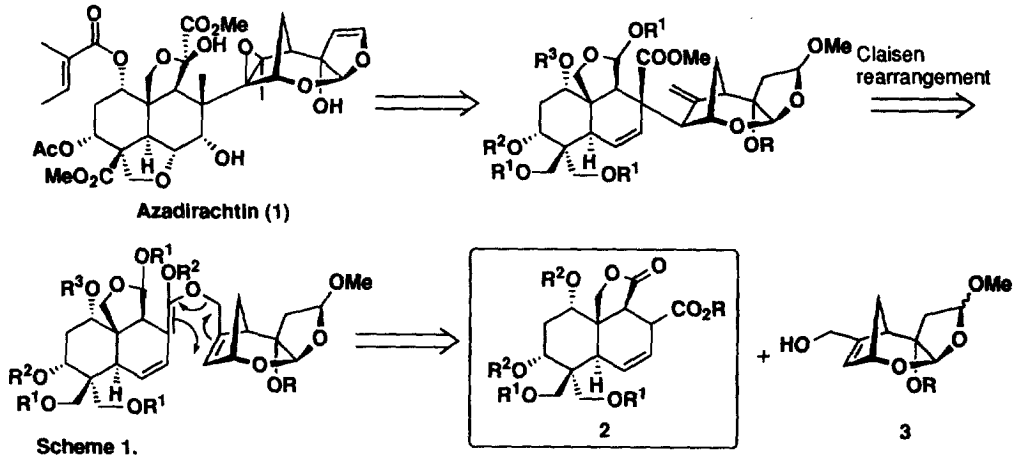
Abstract

Construction of the left segment of azadirachtin in naturally occurring enantiomer is described. The key reaction is an intramolecular Diels-Alder reaction, which was performed under thermal conditions to afford the highly functionalized decalin compounds selectively.

Keywords: azadirachtin; decalin; Diels-Alder reaction

In the course of the search for the secondary metabolites of plants, various biologically active compounds have been revealed, including limonoids. Azadirachtin **1** is a *C*-seco limonoid, which was isolated as an insect antifeedant from the seeds of *Azadirachta indica* A. Juss in 1968.[1] The highly functionalized structure of **1**, along with its biological activities, attracts many chemists;[2] however, the total synthesis has not been achieved yet. Our synthetic strategy involves the coupling of the two fragments **2** and **3** by Claisen rearrangement, as shown in Scheme 1. In connection with our synthetic studies of azadirachtin, we reported recently the synthesis of the tricyclic compound **3**[3] and the decalin compound **4**[4] (Fig. 1).

In the previous report, ketone **4** was prepared from ethyl malonate in 31 steps in a naturally



Scheme 1.

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occurring form.[4b] Unfortunately, reduction of **4** and its precursor **5** at C-1 afforded only the undesired β-alcohols, and it also failed to invert 1-OH of the alcohol **6**. Owing to the selective introduction of oxidative functionality at C-1, we were forced to reconsider our synthetic strategy. Herein, we disclose an alternative construction of the highly functionalized decalin moiety **2** of azadirachtin **1**.

Based on the plausible transition structures in the intramolecular Diels-Alder (IMDA) reaction, it was required that the functional groups at C-1 and 3 should be located at axial conformations, such as TS-1 (Fig. 2).[5] It was readily speculated that the reaction of a free 1,3-functionalized substrate would provide an undesired product *via* its flipped chair comformation, TS-2. Thus, the 1,3-diol could be fixed by some protective group.

The synthesis of the IMDA precursor was started with ethyl malonate (Scheme 2). Treatment with ethyl malonate and formalin in the presence of $KHCO_3$ afforded diol **7**.[6] Protection of the diol as an acetonide, followed by $LiAlH_4$ reduction, gave **9**. While the selective mono-protection of the diol was unsuccessful, **9** was converted to bis-MPM ether **10** in 86% for 4 steps. The subsequent treatment of **10** with DDQ provided compound **11** in 60% yield, along with acetal **12** in 20% yield, which could be transformed to **11** in 55% yield. Oxidation of the resulting alcohol with Dess-Martin periodinane furnished **13** in 96% yield. The asymmetric allylation of **13** was achieved by exposure to (+)-DIPCl and allylMgBr to give **14**,[7] the optical yield of which was evaluated to be 92%ee as its MTPA ester. After silylation of the alcohol with TMSCl and Et_3N in 94% yield, an aldehyde **16** was obtained in ~100% yield by dihydroxylation with OsO_4 and NMO, and the subsequent cleavage with $NaIO_4$. The coupling of **16** with lithiofuran, derived from **17**,[4a] proceeded smoothly in the presence of TMSCl to afford the furyl compounds. Removal of the silyl groups was effected with Bu_4NF and AcOH, leading to compound **18** as a 2:1 mixture in 87% yield for 2 steps.[8] The major product of the diol was **18**-*anti*, which could be converted to the desired **18**-*syn* compound by Mitsunobu inversion and hydrolysis. As a result, **16** was transformed readily to **18**-*syn* in 76% overall yield. The resulting diol was silylated to its bis-TES ether in 85% yield, and the MPM ether

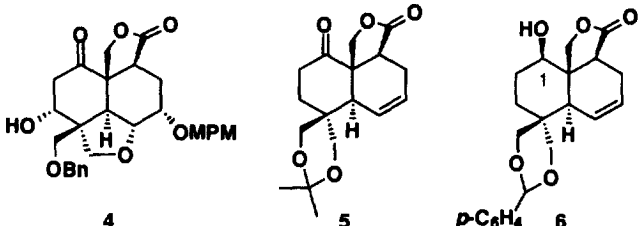


Fig. 1.

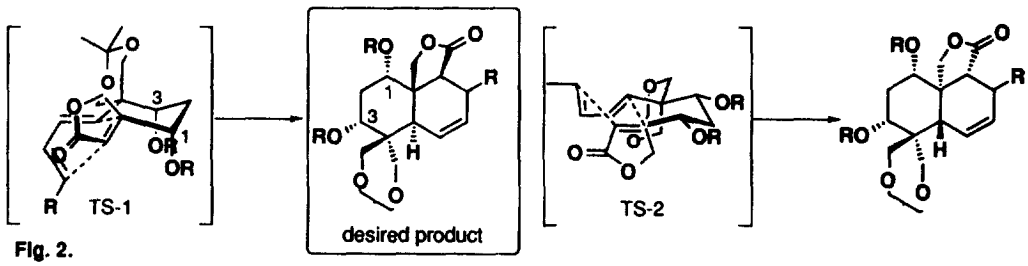
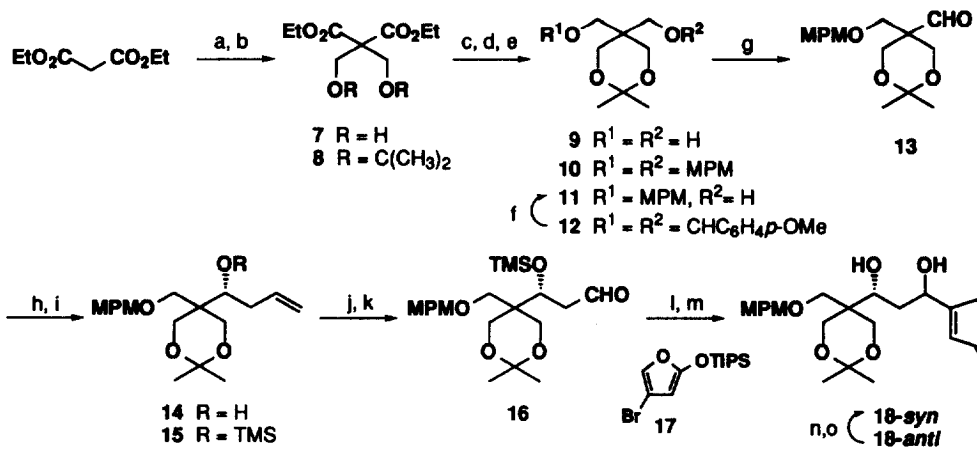
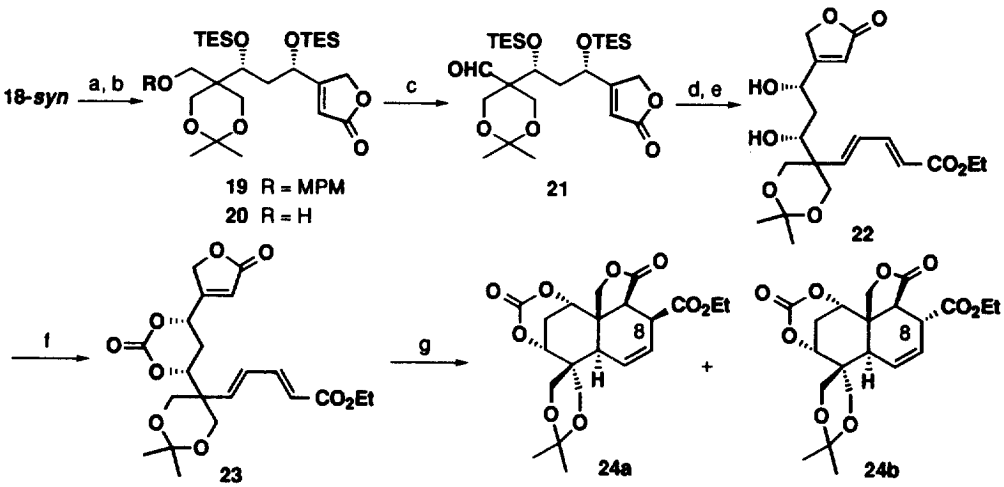


Fig. 2.



Scheme 2. a) 30% HCHO aq., $KHCO_3$, 25 °C, 1 h; b) $(CH_3O)_2C(CH_3)_2$, PTS, acetone, 25 °C, 1 h; c) $LiAlH_4$, Et_2O, 25 °C, 1 h; d) NaH, MPMCl, DMF, 25 °C, 1 h, 86% for 4 steps; e) DDQ, CH_2Cl_2-H_2O, 25 °C, 30 min, **11**: 60%, **12**: 20%, **10**: 15%; f) DIBAL-H, CH_2Cl_2, 25 °C, 55%; g) Dess-Martin, CH_2Cl_2, 25 °C, 6 h, 96%; h) (+)-DIPCl, allylMgBr, Et_2O, -78 °C,1 h, then **13**, -98 °C, 1 h, then 4N NaOH, 30% H_2O_2, THF, 25 °C, 2 h, 91% (92%ee); i) TMSCl, Et_3N, CH_2Cl_2, 25 °C, 30 min, 94%; j) OsO_4, NMO, THF-H_2O, 25 °C, 6 h; k) $NaIO_4$, MeOH-H_2O, 0 °C, 15 min, ~100%; l) **17**, BuLi, TMSCl, Et_2O, -78 °C, 2 h; m) Bu_4NF, AcOH, THF, 25 °C, 2 h, 87% for 2 steps; n) DEAD, Ph_3P, HCOOH, THF, 25 °C, 30 min; o) $NaHCO_3$, MeOH, H_2O, 25 °C, 1.5 h, 76% for 2 steps.

was removed with DDQ, furnishing primary alcohol **20** in ~100% yield (Scheme 3). Oxidation of **20** with TPAP and NMO allowed the generation of aldehyde **21** in 91% yield. The Horner-Emmons reaction of **21** with the ylide, derived from (E)-$(EtO)_2POCH_2CH{=}CHCO_2Et$ and LDA, followed by detachment of the silyl groups with Bu_4NF and AcOH, afforded diol **22** as a ~12:1 mixture in 60% yield for 2 steps. Finally, the cyclic carbonate formation of the diol with $(Cl_3CO)_2CO$ and pyridine provided **23** in 92% yield. Keeping the precursor **23** in hand, we explored the IMDA reaction. Heating compound **23** at 200 °C in a sealed tube, the IMDA



Scheme 3. a) TESCl, imidazole, DMF, 25 °C, 2 h, 85%; b) DDQ, CH_2Cl_2-H_2O, 25 °C, 30 min, ~100%; c) TPAP, NMO, MS-4A, CH_2Cl_2, 25 °C, 15 min, 91%; d) LDA, (E)-$(EtO)_2POCH_2CH{=}CHCO_2Et$, THF, 0 °C, 1.5 h; e) Bu_4NF, AcOH, THF, 24 °C, 4 h, 60% for 2 steps; f) $(Cl_3CO)_2CO$, pyr, CH_2Cl_2, 25 °C, 15 min, 92%; g) PhMe, 200 °C, 60 h, BHT, sealed tube.

Table 1.

Entry	Conditions	24a	24b	Recovery of 23
1	PhMe, 200 °C, 20 h, sealed tube	20%	trace	41%
2	PhMe, 200 °C, 40 h, sealed tube	10%	20%	35%
3	BHT, PhMe, 200 °C, 60 h, sealed tube	12%	31%	10%

reaction proceeded to give compounds **24a** and **24b**, along with recovery of **23** (Table 1). When the thermal treatment for 60 h in the presence of BHT was carried out, decalin compounds **24a** and **24b** were obtained in 12% and 31% yield, respectively (entry 3). Interestingly, no other tricyclic products could be detected in any cases. The structures of the two adducts were determined on the basis of ^{1}H-, ^{13}C-NMR, DQFCOSY, HSQC, HMBS, and NOESY spectra. **24b** was also identified by X-ray crystallography. Both products were found to be the desired *trans*-decalin compounds, and each was the diastereoisomer at C-8. It should be noted that the longer reaction time increased the yield of compound **24b**. It is plausible that compound **24b** would be produced by the isomerization of **24a**. In fact, the MM2 calculation indicated that the energy of **24b** was 1.5 kcal/mol lower than that of **24a**. Exclusive formation of the *trans*-decalin compounds in the IMDA of **23** would be attributed to the following steric effects: that is, i) the chair conformation would be preferential in the transition state in order to be fixed by the cyclic carbonate; ii) existence of a severe non-bonding interaction between the acetonide group and diene, and the $A^{1,3}$-strain of butenolide would be reponsible for the resultant facial selectivity. Both tricyclic products could be the versatile intermediates of the further coupling reaction with the right segment of **1**. The desired tricyclic intermediates of azadirachtin were thus prepared in 18 steps from ethyl malonate *via* a thermal intramolecular Diels-Alder reaction. Further synthetic study is now under way in our laboratory.

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References and Notes

1) a) Culver, J. N.; Dawson, W. O. *Molec. 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) a) Ley, S. V.; Denholm, A. A.; Wood, A. *Nat. Prod. Rep.* **1993**, 109, and references cited 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**, *38*, 4429.

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

4) a) Kanoh, N.; Ishihara, J.; Murai, A. *SYNLETT* **1995**, 895. b) Kanoh, N.; Ishihara, J.; Murai, A. *SYNLETT* **1997**, 737.

5) Recently, the IMDA reaction of a similar 1,2-functionalized substrate was reported: Murata, T.; Ishikawa, M.; Nishimaki, R.; Tadano, K. *SYNLETT* **1997**, 1291.

6) Block, Jr., P. *Org. Synth. Collect. Vol. 5*, **1973**, 381.

7) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401.

8) The addition of TMSCl was effective in this reaction. When a similar aldehyde was treated with lithiofuran without an additive, the yield of a furyl compound was low, accompanied with a β-elimination product.