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Synthetic Studies on Azadirachtin (Part 3): Asymmetric Synthesis of the Tricyclic Dihydrofuran Moiety of Azadirachtin

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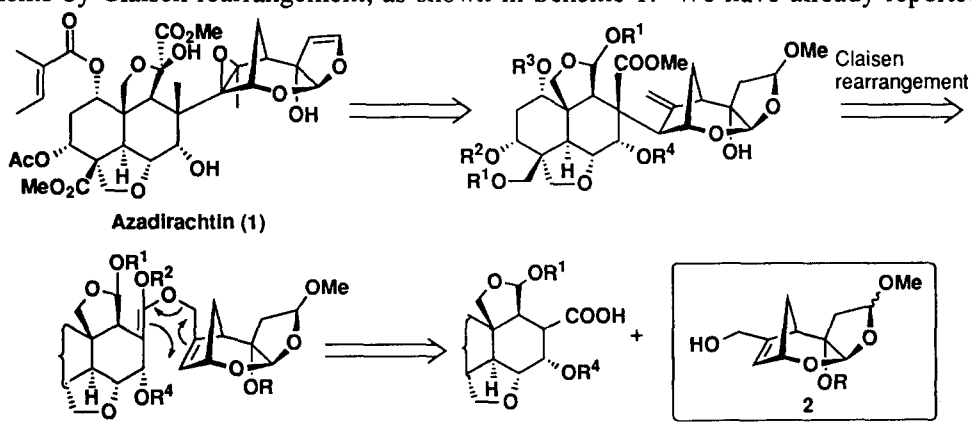
Abstract

An asymmetric synthesis of the tricyclic dihydrofuran moiety of azadirachtin is reported. The Diels-Alder adduct, which was catalyzed by Evans' chiral Cu-bisoxazoline complex, was easily converted to the tricyclic portion *via* SmI_2 reductive cleavage and selective functionalization.

Keywords: azadirachtin; dihydrofuran; asymmetric Diels-Alder reaction

The highly elaborated chemical defenses, which plants acquired against the attack of pathogens and insects, have gradually been elucidated by recent biochemistry.[1)] Various biologically active compounds were revealed in the course of the search for the secondary metabolites of plants. Azadirachtin (**1**) is a *C*-seco limonoid, which was isolated as an insect antifeedant from the seeds of *Azadirachta indica* A. Juss.[2)] The highly functionalized structure, along with its biological activities, urged us toward the total synthesis of this compound, which has not been reported yet. Our synthetic strategy involves the coupling of the right and the left fragments by Claisen rearrangement, as shown in Scheme 1. We have already reported the



Scheme 1.

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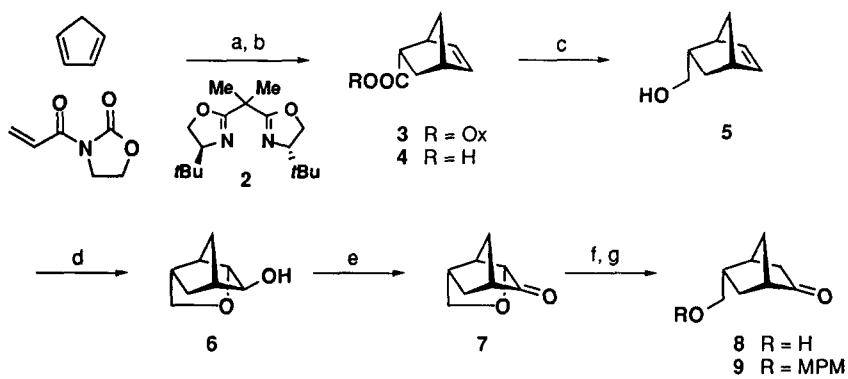
synthetic approach of the left fragment, the decalin portion of azadirachtin.[3] Herein, we disclose a synthesis of the tricyclic dihydrofuran moiety, **2**, in the naturally occurring form.[4]

Although an asymmetric Diels-Alder reaction is deemed feasible by the recent development of a chiral Lewis acid catalyst,[5] its application to the syntheses of natural products might be quite rare due to the limitation of substrates.[6] We selected the chiral Diels-Alder adduct **3**, prepared by Evans' method,[7] as the starting material of this synthesis. Indeed, compound **3** was readily obtained by the reaction of cyclopentadiene and an acryloyl derivative[8] in the presence of Cu(II) and chiral bisoxazoline in 99%ee with high *endo*-selectivity (Scheme 2). Hydrolysis of **3** afforded a carboxylic acid **4** by LiOOH,[9] followed by $LiAlH_4$ reduction to give alcohol **5** in 91% yield for 2 steps. When the alcohol was exposed to *m*CPBA, epoxidation and immediate cyclization occurred to furnish cyclic ether **6** in 91% yield, which was oxidized to ketone **7** in 99% yield. While Oppolzer reported that the ether cleavage of an analogous ketone with Al(Hg) in EtOH was successful,[10] similar treatment of **7** did not provide ketol **8** in constant yield (0-96%). Slight heating accelerated decomposition under the conditions. Finally, we found that the reduction of **7** was effective with SmI_2 in THF-MeOH (1:1) at -78 °C[11] to produce **8** in 98% yield. The primary alcohol was then protected by the MPM group to afford ketone **9** in 92% yield.

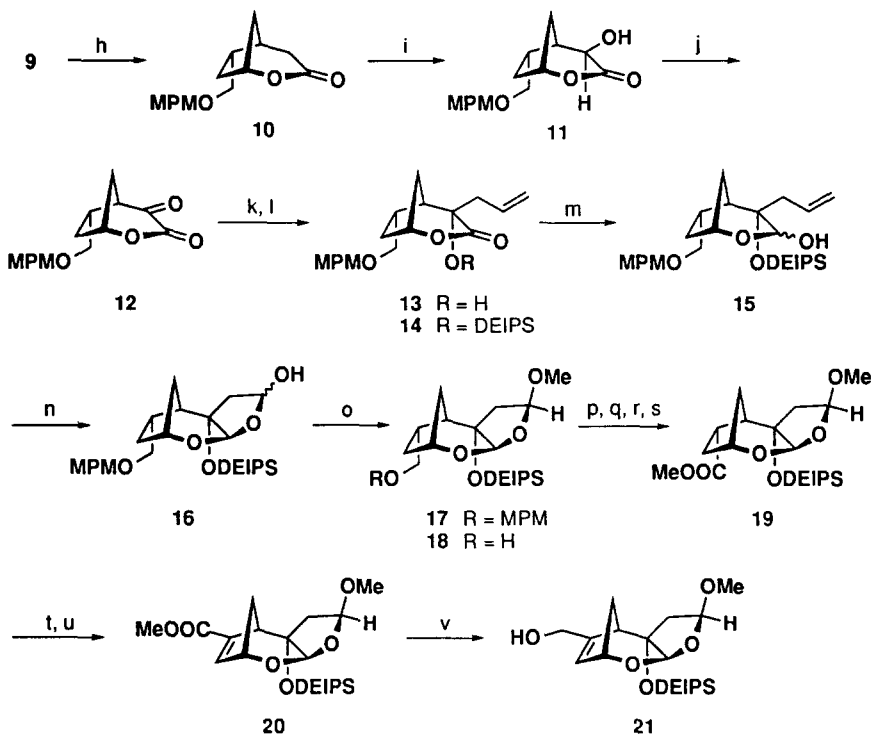


a) $Cu(OTf)_2$, **2**, -78°C, 23 h, 97% (99%ee); b) LiOH, H_2O_2, THF-H_2O, 0 °C, 40 min, 94%; c) $LiAlH_4$, Et_2O, 0 °C, 1.5 h, 97%; d) *m*CPBA, CH_2Cl_2, -10 °C → 23 °C, 1.5 h, 91%; e) Dess-Martin, CH_2Cl_2, 23 °C, 17 h, 99%; f) SmI_2, THF, MeOH, -78 °C, 40 min, 98%; g) MPMCl, NaH, TBAI, DMF, 23 °C, 2.5 h, 92%.

Scheme 2.

Baeyer-Villiger oxidation of **9** with MMPP smoothly gave lactone **10** in 95% yield (Scheme 3). When *m*CPBA was used, the reaction proceeded so slowly that extreme conditions were required such as refluxing in toluene. The α-oxygenation of **10** was carried out with KHMDS and MoOPD[12] in THF at -78 °C to afford hydroxylactone **11** as a single isomer in 86% yield, which was oxidized to ketone **12** in 100% yield. The selective allylation of **12** was successful with allyltributyltin in the presence of $LiClO_4$ in Et_2O[13] to give **13** in 98% yield exclusively. It seems that the nucleophiles approached from the β-side, avoiding the repulsion of the *pseudo*-axial MPM group. After the protection of the tertiary hydroxyl group with DEIPSOTf, the

reduction with DIBAL-H at -95 °C in the presence of TMSCl gave lactol **15** in 98% yield by Mori's procedure.[4d] The ^{1}H-NMR spectrum in $CDCl_3$ suggested a 5:2 mixture of one isomer of **15** and the corresponding aldehyde. Ozonolysis of **15** furnished tricyclic compound **16** in 91% yield as a 5:1 mixture of anomers. Based on the ^{1}H-NMR spectra, neither an aldehyde nor a dialdehyde would be found to exist in equilibrium of **16**. Subsequent methylation of the anomers was proved to be effective with NaH and MeI to give methyl acetal **17** as a single isomer in 96% yield. The stereochemistry of **17** was determined by ^{1}H- and ^{13}C-NMR spectra and DIFNOE.[14] The MPM group of **17** was detached with DDQ to compound **18**, which was easily converted to ester **19** in 75% yield for 4 steps. In the final stage, transformation of **19** to **20** was achieved by α-selenylation and subsequent *syn*-elimination in 94% yield. DIBAL-H reduction of the ester provided our desired allyl alcohol **21**. Thus, the tricyclic acetal **21** is obtainable on a large scale as an enantiomerically pure form from cyclopentadiene and acryloyl derivative in 21 steps in 25% overall yield. Further synthetic study is now under way in our laboratory.



h) MMPP, EtOH, H_2O, 23 °C, 2 h, 95%); i) KHMDS, THF, -78 °C, 1.5 h, then MoOPD, -78 °C, 6 h, 86%; j) Dess-Martin, CH_2Cl_2, 23 °C, 18 h, 100%; k) CH_2=$CHCH_2SnBu_3$, 2M $LiClO_4$, Et_2O, 23 °C, 22 h, 98%; l) DEIPSOTf, iPr_2NEt, CH_2Cl_2, 23 °C, 6.5 h, 89%; m) DIBAL-H, TMSCl, CH_2Cl_2, -95 °C, 0.5 h, 98%; n) O_3, CH_2Cl_2, -78 °C, 2 min, then Ph_3P, 86%; o) NaH, MeI, THF, 23 °C, 1.5 h, 96%; p) DDQ, CH_2Cl_2-H_2O, 23 °C, 4 h,100%; q) Dess-Martin, CH_2Cl_2, 23 °C, 16 h; r) $NaClO_2$, 2-methyl-2-butene, *t*-BuOH-H_2O, NaH_2PO_4, 23 °C, 16 h, 83% for 2 steps; s) CH_2N_2, Et_2O, 5 min, 90%; t) KHMDS, THF, -78 °C, 0.5 h, then PhSeCl, 5 min, 94%; u) H_2O_2, pyr., CH_2Cl_2, 0 °C, 15 min, 100%; v) DIBAL-H, Et_2O, -78 °C, 3 h, 86%.

Scheme 3.

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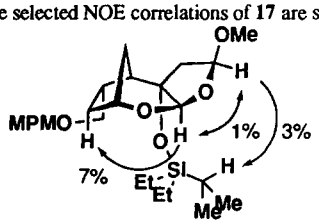
14) **17**: a colorless oil, $[\alpha]_D^{23}$ +88 (*c* 0.88, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$), δ 7.25 (2H, m), 6.87 (2H, m), 5.24 (1H, dd, *J* = 6.2, 4.4 Hz), 4.96 (1H, s), 4.48 (2H, s), 4.40 (1H, brd, *J* = 5.5 Hz), 3.84 (1H, dd, *J* = 9.5, 3.3 Hz), 3.80 (3H, s), 3.64 (1H, dd, *J* = 10.6, 9.5 Hz), 3.44 (3H, s), 2.46 (1H, brd, *J* = 4.8 Hz), 2.39 (1H, m), 2.36 (1H, dd, *J* = 15.0, 4.4 Hz), 2.21 (1H, m), 2.19 (1H, dd, *J* = 15.0, 6.2 Hz), 2.08 (1H, brd, *J* = 12.5 Hz), 1.70 (1H, ddd, *J* = 15.4, 7.0, 2.2 Hz), 1.42 (1H, ddd, *J* = 12.5, 4.8, 2.8 Hz), 0.98-0.92 (12H, m), 0.85 (1H, m), and 0.64-0.55 (4H, m); IR (neat), vmax 2944, 1614, 1515, 1467, 1371, 1347, 1305, 1248, 1194, 1125, 1065, 1038, 975, 942, 882,843, 822, 762, and 723 cm^{-1}.

The selected NOE correlations of **17** are shown as follows:



21: a colorless oil, $[\alpha]_D^{23}$ +85 (*c* 0.43, $CHCl_3$); ^{1}H-NMR (400 MHz, C_6D_6), δ 5.70 (1H, brs), 5.25 (1H, dd, *J* = 6.3, 2.9 Hz), 5.22 (1H, s), 4.52 (1H, brs), 4.32 (1H, d, *J* = 15.1 Hz), 4.13 (1H, d, *J* = 15.1 Hz), 3.38 (3H, s), 2.62 (1H, d, *J* = 4.9 Hz), 2.28 (1H, dd, *J* = 15.1, 2.9 Hz), 2.19 (1H, d, *J* = 11.2 Hz), 2.15 (1H, dd, *J* = 15.1, 6.3 Hz), 1.57 (1H, ddd, *J* = 11.2, 4.9, 2.9 Hz), 1.02-0.83 (13H, m), and 0.68-0.53 (4H, m); ^{13}C-NMR (100 MHz, C_6D_6), δ 156.4, 123.5, 108.8, 107.9, 85.2, 76.6, 62.3, 55.1, 48.9, 45.5, 41.0, 17.7, 17.6, 14.3, 7.5, 7.4, 5.2, and 5.1; IR (neat), vmax 3456, 2956, 2876, 1462, 1418, 1366, 1318, 1274, 1238, 1196, 1130, 1102, 1072, 1026, 962, 936, 912, 882, 844, 806, 762, 724, and 670 cm^{-1}.