Natural Product Synthesis

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Asymmetric Formal Synthesis of Azadirachtin

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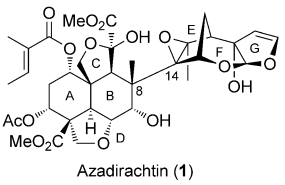
Abstract: *An asymmetric formal synthesis of azadirachtin, a potent insect antifeedant, was accomplished in 30 steps to Ley's synthetic intermediate (longest linear sequence). The synthesis features: 1) rapid access to the optically active right-hand segment starting from the known 5-hydroxymethyl-2-cyclopentenone scaffold; 2) construction of the B and E rings by a key intramolecular tandem radical cyclization; 3) formation of the hemiacetal moiety in the C ring through the α-oxidation of the six-membered lactone followed by methanolysis.*

Azadirachtin (**1**), which was isolated from the neem tree *Azadirachta indica* A. Juss (Meliaceae)[1] in 1968, exhibits potent antifeedant and growth inhibitory activities against insects (Figure 1).[2] Since the precise structure of **1** was



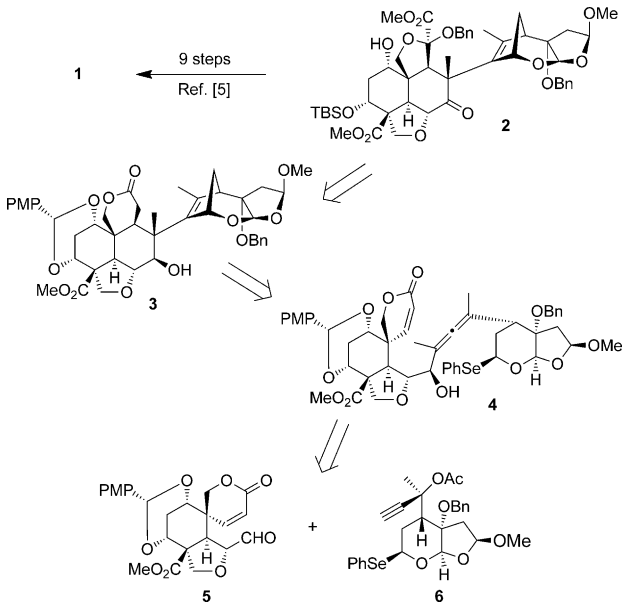
Azadirachtin (**1**)

Figure 1. Azadirachtin (**1**).

elucidated[3] in 1987, this complex molecule, possessing sixteen contiguous stereogenic centers, as well as various oxygen-containing functional groups, has reigned as a challenging target for synthetic chemists. The most difficult issue for the synthesis of **1** is considered to be the construction of the extremely hindered C8–C14 bond. Although some novel strategies to form the C8–C14 bond have been developed by the research groups of Ley,[4a,b] Murai,[4c] Nicolaou,[4d–g] and Tanino,[4h,i] to date, only the Ley group arrived at the completion of its synthesis.[5]

Our group embarked on studies toward the synthesis of **1** in 1989, during which a radical cyclization approach[6a] was found to be effective to construct the B ring with the C8–C14 bond in place. Subsequently, our continuous efforts led us to achieve a stereoselective synthesis of the fully functionalized left-hand segment, and an advanced tandem mode enabled the cyclization of the B and E rings at once.[6b] Herein, we describe an asymmetric formal synthesis of **1** along with a concise preparation of the optically active right-hand segment.

As depicted in Scheme 1, azadirachtin (**1**) could be accessed from Ley's intermediate **2** in nine steps,[5] and was



Scheme 1. Retrosynthetic analysis.

chosen as our synthetic goal. It was envisioned that a benzyl-protected hemiacetal moiety in **2** would be formed through the α-oxidation of the six-membered lactone in **3** and subsequent methanolysis. The complete carbon framework of **1** would be constructed by the key tandem radical cyclization of the allene **4**, which in turn arises through a coupling of both segments **5**[6b,7] and **6**, followed by S_N2' substitution with a methyl group.

Our synthesis of the optically active right-hand segment **6** commenced with the known (*R*)-**7**[8] (98% *ee*), which was reported by Nanda and co-workers (Scheme 2). Firstly, an aldol reaction of **7** with ethyl acetate gave **8** in 85% yield as a single diastereomer. Having faced the difficulties in introducing a benzyl group to the resulting tertiary alcohol, the TBDPS group was removed with TBAF/AcOH, and the diol **9** was treated with benzaldehyde dimethyl acetal, and PPTS to give the cyclic acetal **10** (1:2 inseparable mixture of α/

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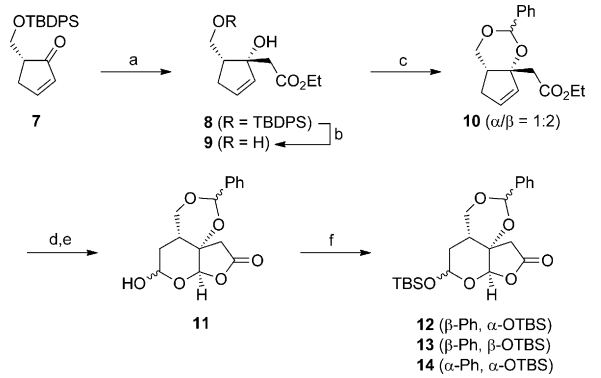
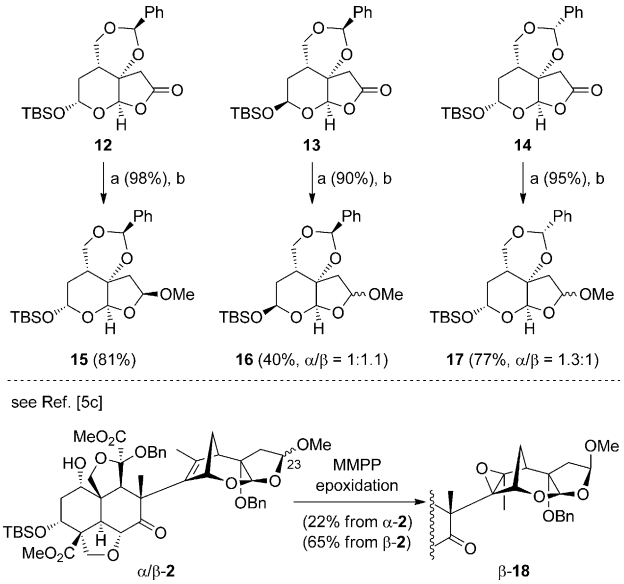


Scheme 2. Reagents and conditions: a) EtOAc, LiHMDS, THF, −78 °C, 85 %; b) TBAF, AcOH, THF, RT, 98 %; c) $PhCH(OMe)_2$, PPTS, CH_2Cl_2, RT, 95 %; d) LiOH, $MeOH/H_2O$ (3:1), RT; e) O_3, CH_2Cl_2; then Me_2S, −78 °C to RT; then PPTS, 54 % (2 steps); f) TBSOTf, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, RT, 30 % (**12**), 27 % (**13**) and 19 % (**14**). LiHMDS = lithium hexamethyldisilazide, PPTS = pyridinium toluene-*p*-sulfonate, TBAF = tetra-*n*-butylammonium fluoride, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

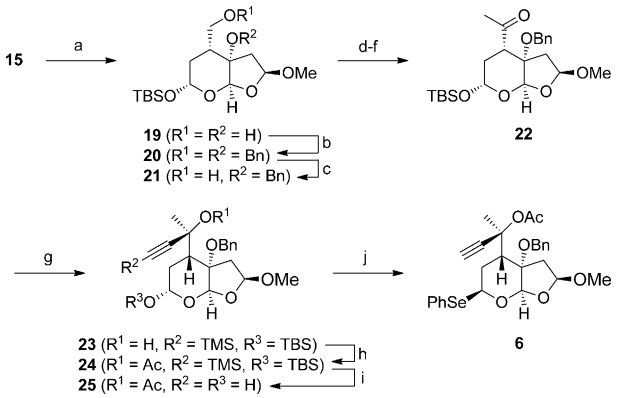


Scheme 3. Reagents and conditions: a) DIBALH, CH_2Cl_2, −78 °C; b) MeI, Ag_2O, CH_3CN, RT. DIBALH = diisobutylaluminum hydride, MMPP = magnesium monoperoxyphthalate hexahydrate.

β-isomers). The compound **10** was then converted into the tricyclic hemiacetal **11**, which comprises four inseparable diastereomers, through hydrolysis of ethyl ester followed by ozonolysis of the double bond and successive treatment with acid. TBS protection of **11** by using TBSOTf and 2,6-di-*tert*-butylpyridine gave the three products, **12**, **13**, and **14**,[9] which could be separated by silica gel column chromatography. The use of 2,6-di-*tert*-butylpyridine, a bulkier base, instead of Et_3N or 2,6-lutidine was crucial to providing the products in higher yield.[10]

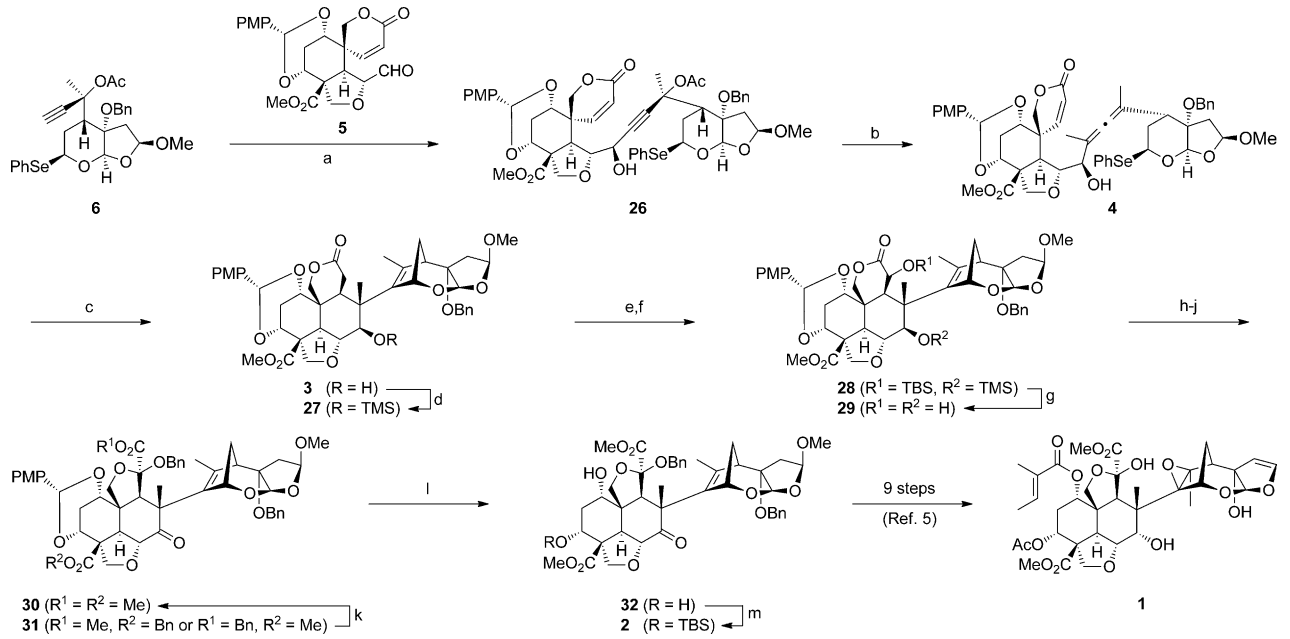
With the tricyclic lactones **12**–**14** in hand, we next investigated the transformation of the lactone moiety into the methyl acetal (Scheme 3). According to Ley's report,[5c] MMPP epoxidation of α-**2** as well as β-**2** afforded β-**18** with epimerization at C23, but the yield from the former was much lower (22 %) than that from the latter (65 %). This result suggested that the use of a β-acetal at C23 would be advantageous for the synthesis of the target molecule. Pleasingly, a reduction/methylation sequence of **12** afforded the desired **15** as a single β-isomer, which was selected as a substrate for the next reaction. In contrast, the compounds **13** and **14** afforded **16** and **17**, respectively, as diastereomeric mixtures.

The transformation of **15** into the primary alcohol **21** was then examined (Scheme 4). Since the direct conversion of **15** into **21** with DIBALH[11] was unsuccessful, **15** was transformed into **21** through a three-step sequence. Standard manipulations of **21** led to the methyl ketone **22** over three steps. The compound **22** was then treated with lithium trimethylsilylacetylide, and the major tertiary alcohol **23** was obtained in 45 % yield, together with 30 % of a diastereomer,[12] after separation by silica gel column chromatography. Acetylation of **23** followed by complete desilylation generated the hemiacetal **25**, whose hydroxy group was then replaced with a phenylseleno group via the mesylate to furnish the right-hand segment **6** in 18 steps from **7**.



Scheme 4. Reagents and conditions: a) H_2, $Pd(OH)_2/C$, MeOH, RT, 91 %; b) BnBr, NaH, DMF, 0 °C to RT, 86 %; c) H_2, Pd/C, MeOH, RT, 67 % (76 % brsm); d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 0 °C, 93 %; e) MeLi, THF, −78 °C; f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 0 °C, 85 % (2 steps); g) TMSC≡CH, *n*BuLi, THF, −78 °C, 45 % of **23** and 30 % of the diastereomer; h) Ac_2O, DMAP, toluene, reflux, 89 %; i) TBAF, AcOH, THF, 30 °C, 96 %; j) MsCl, Et_3N, CH_2Cl_2, 0 °C; then $(PhSe)_2$, $NaBH_4$, EtOH, 0 °C, 89 %. DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, DMAP = 4-dimethylaminopyridine, Ms = methanesulfonyl, TMS = trimethylsilyl.

Having achieved the asymmetric synthesis of **6**, we set out to undertake the coupling of both segments (Scheme 5). A lithium acetylide derived from **6** with LiHMDS reacted with the aldehyde **5** (98 % *ee*) to give **26** in 46 % yield without generation of the α-isomer. An S_N2' reaction of the propargyl acetate with a methylcopper reagent proceeded smoothly under Macdonald's conditions[13] to afford the allene **4**, a precursor for the radical cyclization, as a single diastereomer in 77 % yield. Although the configuration of the allene was not determined, it was supposed to be *S* from the reported



Scheme 5. Reagents and conditions: a) LiHMDS, THF, −78 °C, 46%; b) MeMgBr, CuI, LiBr, THF, 0 to 20 °C, 77%; c) nBu$_3$SnH, AIBN, DMF, 130 °C, 35%, d) TMSCl, imidazole, DMF, 0 °C, 87%, e) TBSOTf, Et$_3$N, CH$_2$Cl$_2$, 0 °C; f) 2-benzenesulfonyl-3-phenyloxaziridine, CH$_2$Cl$_2$, 0 °C to RT, 50% (2 steps); g) TBAF, AcOH, THF, 0 °C, 70%; h) DMP, CH$_2$Cl$_2$, RT; i) K$_2$CO$_3$, MeOH, RT; j) BnBr, Ag$_2$O, DMF, RT, 39% of **30** and 36% of **31** (3 steps); k) NaOMe, MeOH, 60 °C, 94%; l) PPTS, CH$_3$CN/H$_2$O, RT, 74%; m) TBSOTf, Et$_3$N, CH$_2$Cl$_2$, RT, 91%. AIBN = 2,2′-azobisisobutyronitrile, DMP = Dess–Martin periodinane, PMP = *p*-methoxyphenyl.

results of the similar *anti*-S$_N$2′ reaction.[14] A preliminary investigation showed that DMF was superior to other solvents we tested (benzene, toluene, dimethoxyethane, 1,4-dioxane, diglyme). Therefore, the key tandem radical cyclization was performed by heating **4** with reagents (nBu$_3$SnH, AIBN) in DMF at 130 °C,[15] and the product **3**, having the full carbon framework of azadirachtin, was obtained in a moderate yield.

The hydroxy group of **3** was protected as a TMS ether to give **27** in 87% yield (Scheme 5). Treatment of **27** with TBSOTf and Et$_3$N[16] formed the intermediate silyl ketene acetal, which was then oxidized with the Davis reagent[17] to afford the α-oxylactone **28**. It is worth noting that **3**, having a free hydroxy group, decomposed during the above oxidation step. The TBS and TMS groups of **28** were removed by TBAF/AcOH to give **29** in 70% yield. Oxidation of the diol **29** with Dess–Martin periodinane[18] followed by methanolysis of the resulting α-ketolactone gave rise to the formation of the five-membered cyclic hemiacetal present in the natural product. Subsequent protection of the hydroxy group with benzyl bromide and silver(I) oxide in DMF yielded the desired product **30** (39% in 3 steps) along with the unexpected benzyl ester **31** (36% in 3 steps), which could be converted into **30** by methanolysis. Finally, removal of the *p*-methoxybenzylidene acetal in **30** by treatment with PPTS in aqueous acetonitrile[19] followed by monosilylation of the diol provided **2**, from which azadirachtin (**1**) has been obtained in nine steps. Thus, we completed the formal synthesis of **1**. ^{1}H NMR and ^{13}C NMR spectra of our synthetic **2** were in good accordance with those of the sample of Ley.

In summary, we accomplished the asymmetric formal synthesis of azadirachtin (**1**) in 30 steps (longest linear sequence and 9 more steps are required to **1**). The key elements in the synthesis include: 1) rapid access to the optically active right-hand segment **6** starting from the known cyclopentenone derivative **7**; 2) construction of the B and E rings by the key intramolecular tandem radical cyclization (**4**→**3**); 3) formation of the hemiacetal moiety in the C ring through the α-oxidation of the six-membered lactone followed by methanolysis (**27**→**30**). This concise and efficient approach provides new aspects for the synthesis of complex natural products.

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