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Synthetic Study on Azadirachtin (Part 2). Construction of the Decalin Moiety with Full Functionality on B-ring.

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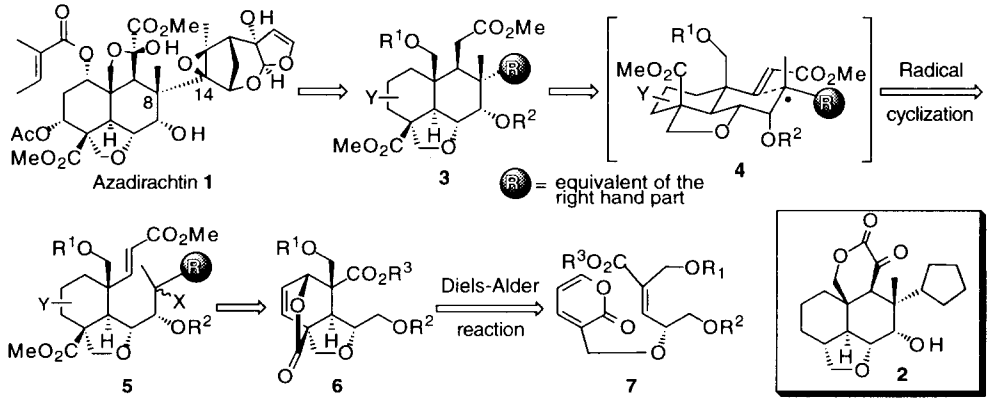
Abstract: As a synthetic study towards a potent insect antifeedant azadirachtin (**1**), a stereoselective synthesis of a highly functionalized model compound (**2**) is described. Intramolecular Diels-Alder reaction and radical cyclization were employed as key reactions for the construction of the decalin skeleton. © 1997 Elsevier Science Ltd.

Azadirachtin (**1**) is a C-*seco*-limonoid isolated from the neem tree *Azadirachta indica* A. Juss (Meliaceae)[1] and possesses potent antifeedant and growth inhibitory activities.[2] Its complicated structure as well as its activities fascinate synthetic chemists, and up to the present time, syntheses of both highly oxygenated decalin skeletons and the tricyclic dihydrofuran portions towards the total synthesis of **1** were achieved,[3] but the formation of the C8-C14 bond linking the right and the left hand parts has not been reported yet. After completing the preparation of the right hand part,[3c] we moved our attention to the construction of the decalin part and the connection of both parts. Herein, we would like to report a stereoselective synthesis of a model compound (**2**) whose B-ring is fully functionalized, including the C-C bond corresponding to the C8-C14 bond of azadirachtin (**1**).

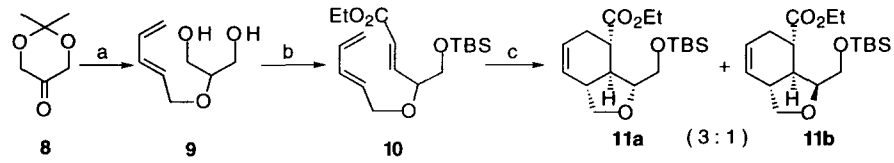
Our synthetic strategy focused on the decalin formation is summarized in Scheme 1. The C8-C14 bond of azadirachtin (**1**) is so hindered that it seems very difficult to couple the right and the left fragments at the final stage in the total synthesis. So we envisaged coupling of the both parts (**6**→**5**) before constructing the B-ring



Scheme 1

employing radical cyclization from **5** to **3** as a key reaction. During the cyclization, two new chiral centers were expected to be introduced in correct stereochemistry via the most stable transition state (**4**). The A-ring and the bridged ether were thought to be constructed by an intramolecular Diels-Alder reaction of **7**. To know the feasibility of our Diels-Alder and radical cyclization strategy, we synthesized the simpler model compound (**2**), as described below.

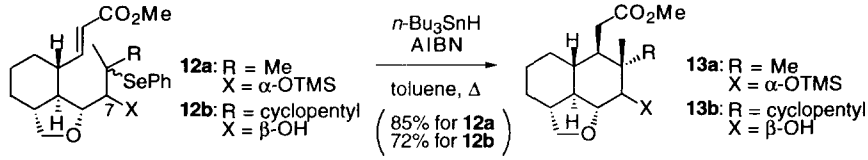
At first, we examined the intramolecular Diels-Alder reaction of **10**. Starting from the known ketone **8**[4], reduction with lithium aluminum hydride, alkylation with (*E*)-5-bromo-1,3-pentadiene[5] and deacetalization gave **9** (Scheme 2). Monosilylation of the diol and Swern oxidation[6] gave the intermediate aldehyde which was converted into the triene (**10**) by Horner-Emmons reaction. Intramolecular Diels-Alder reaction gave only *endo* adducts in the presence of ethylaluminum dichloride and the desired compound (**11a**) was obtained as a major product (**11a/11b**=3:1). On the other hand, in the absence of Lewis acid (refluxing in toluene, 7 h), this reaction showed a 2:1 *endo*:*exo* selectivity.



Scheme 2

a) i) LAH, 91%; ii) KH; (*E*)-5-bromo-1,3-pentadiene, 88%. iii) TsOH, MeOH, 90%. b) i) *n*-BuLi; TBSCl, 79%; ii) $(COCl)_2$, DMSO; Et_3N; iii) triethyl phosphonoacetate, NaH, 93% (2 steps). c) $EtAlCl_2$ / CH_2Cl_2, -78℃~0℃, 67%.

We then attempted radical cyclizations of simpler models (**12a** and **12b**) which could readily be prepared from **11a**, and the desired decalins (**13a** and **13b**) were obtained with complete stereoselectivity in good yields (Scheme 3). It should be noted that the stereochemistry at C7 does not affect the yields. The stereochemistry of **13a** and **13b** was confirmed by NOE experiment and the coupling constants of their ^{1}H-NMR spectra. Following the success of this cyclization, we started synthetic study towards **2** which has all the substituents on B-ring in proper stereochemistry.

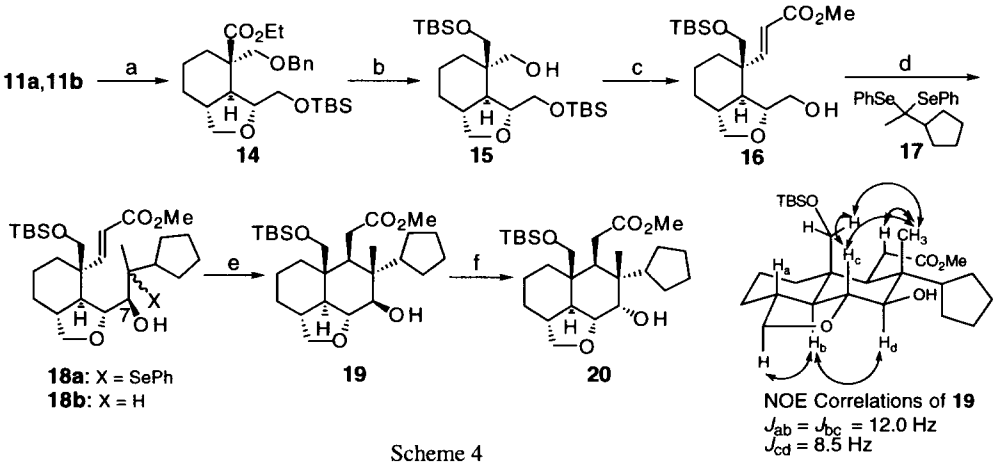


Scheme 3

Hydrogenation followed by alkylation with benzyl chloromethyl ether of the mixture of **11a** and **11b** at the α-position of the ester group gave stereoselectively **14** (Scheme 4). The hydrogenated product of **11b** was not alkylated and was recovered in this reaction. Reduction of the ester group of **14** with lithium aluminum hydride gave the alcohol which was then converted into **15** by silylation and subsequent hydrogenolysis of the benzyl ether. Swern oxidation[6] of **15** followed by Wittig reaction gave the unsaturated ester whose less hindered *t*-butyldimethylsilyl group was selectively removed by acid hydrolysis using acetic acid to give the monool (**16**). Swern oxidation[6] of **16** gave the corresponding aldehyde which was treated with the organolithium reagent prepared from selenoacetal **17**[7] to give the selenide (**18a**) as a diastereomeric mixture. This reaction was thought to proceed in a chelation-controlled manner, and the epimers at C7 were not obtained.

Though the radical cyclization of **18a** was expected to be much more difficult than that of **12a,b** owing to the severe steric repulsion between CH_3 and $TBSOCH_2$ groups, the reaction proceeded by warming **18a** with

n-Bu_3SnH (3 eq) and a catalytic amount of AIBN in toluene (14 mM) to give stereoselectively the required decalin (**19**) in a 28% yield, together with the deselenized products (**18b**, ~60%). The stereochemistry of **19** was confirmed by NOE experiment and coupling constants of its ^{1}H-NMR spectrum as shown in Scheme 4. Neither slow addition of the reagents nor high dilution condition improved the yield of **19**. Oxidation of the secondary α-hydroxyl group with Dess-Martin reagent[8] followed by reduction of the resulting ketone with borane *t*-butylamine complex gave the α-alcohol (**20**) and **19** (3:1).

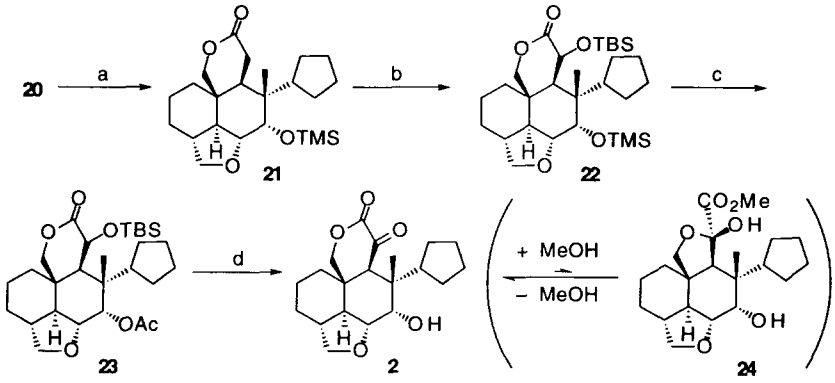


Scheme 4

a) i) H_2, PtO_2, quant.; ii) LDA; BOMCl, TMEDA, 61%. b) i) LAH, 78%; ii) TBSCl, imidazole, quant.; iii) H_2, $Pd(OH)_2$-C, 97%. c) i) $(COCl)_2$, DMSO; Et_3N; ii) methyl (triphenylphosphoranylidene)acetate, 76% (2 steps); iii) AcOH-H_2O-THF (2:1:2), r.t., 1 d, 93%. d) i) $(COCl)_2$, DMSO; Et_3N, quant.; ii) **17**, *n*-BuLi /THF, -110℃~-45℃, 32% (42% recovery). e) *n*-Bu_3SnH, AIBN / toluene, 110℃, 1 h, 28%. f) i) Dess-Martin reagent, 89%; ii) *t*-$BuNH_2$•BH_3, 72% (+ 24% of **19**).

Desilylation of **20** with HF in aqueous acetonitrile proceeded with simultaneous lactonization to give the δ-lactone which was then converted into the trimethylsilyl ether (**21**) (Scheme 5). Oxidation at the α-position of the lactone carbonyl group employing KHMDS / Davis reagent[9] or LDA / MoO_5•pyridine•DMPU complex[10] failed to give the desired product. We then attempted oxidation via silyl ketene acetal. The lactone (**21**) was treated with *t*-butyldimethylsilyl triflate and triethylamine to give the intermediate silyl ketene acetal which was then oxidized with Davis reagent[11] to give the desired product (**22**) in acceptable yield. For the last steps of our synthesis, **22** was converted into the acetate (**23**) by treatment with HF in aqueous acetonitrile followed by acetylation. Desilylation of **23** with TBAF, oxidation of the alcohol with Dess-Martin reagent[8] and methanolysis of the acetate gave the hydroxyl-α-ketolactone (**2**). On treatment with acid or base in methanol, **2** remained intact and the hemiacetal **24** could not be obtained. Probably the equilibrium lies by far to **2** under the methanolysis condition because of the steric repulsion between the hydroxyl group and the axial methyl group of **24**.[12] Thus we complete this model study.

In summary, we synthesized the decalin unit of azadirachtin which has full functionality on B-ring. Especially, this is the first example of the C-C bond formation corresponding to the C8-C14 bond linking the left and the right hand parts of azadirachtin. Improvement of the yield of radical cyclization and functionalization of A-ring towards the total synthesis of azadirachtin (**1**) is now in progress.



Scheme 5

a) i) HF / aq MeCN; ii) TMSCl, imidazole, 87% (2 steps). b) i) TBSOTf, Et_3N; ii) 2-benzenesulfonyl-3-phenyloxaziridine / CH_2Cl_2, r.t., 45% (2 steps). c) i) HF / aq MeCN; ii) Ac_2O, DMAP, pyridine, 85% (2 steps). d) i) TBAF; ii) Dess-Martin reagent; iii) K_2CO_3, MeOH, 80% (3 steps).

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12. Although a trace amount of a single less polar product could be observed on TLC during the reaction, it disappeared after the work-up. Regeneration of **2** from this new spot on SiO_2 TLC was also observed by two-dimensional development. On the other hand, in the case of azadirachtin itself, the 5-membered ring hemiacetal structure is stabilized by the hydrogen bonding between the hemiacetal hydroxyl group and the epoxide oxygen of the right hand part.

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