Studies toward the Synthesis of Azadirachtin, Part 2: Construction of Fully Functionalized ABCD Ring Frameworks and Unusual Intramolecular Reactions Induced by Close-Proximity Effects**

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In the preceding Communication in this issue[1] we described the total synthesis of a potential decalin precursor to azadirachtin (**1**),[2] its coupling to a suitable norbornene fragment **4** (Scheme 1), and the elaboration of the product to an advanced intermediate along the path to this synthetic target. Herein we report the total synthesis and semisynthesis from azadirachtin of a more advanced decalin system **3**, its coupling to the same norbornene fragment **4**, and the elaboration of the resulting product to an advanced intermediate for the total synthesis of azadirachtin (Scheme 1). This report also includes a number of unusual reactions induced by proximity effects and special steric factors highlighting the unique characteristics of the azadirachtin scaffold.

Having successfully synthesized tricyclic decalin system **5**, (Scheme 1) and explored its chemistry toward azadirachtin (**1**) as described in the preceding Communication,[1] we turned our attention to the more advanced tetracyclic decalin precursor **3**, which bears the tetrahydrofuran ring system of **1** within its structure. Our plan to synthesize the targeted intermediate **3** required key building block **6** (Scheme 2) as

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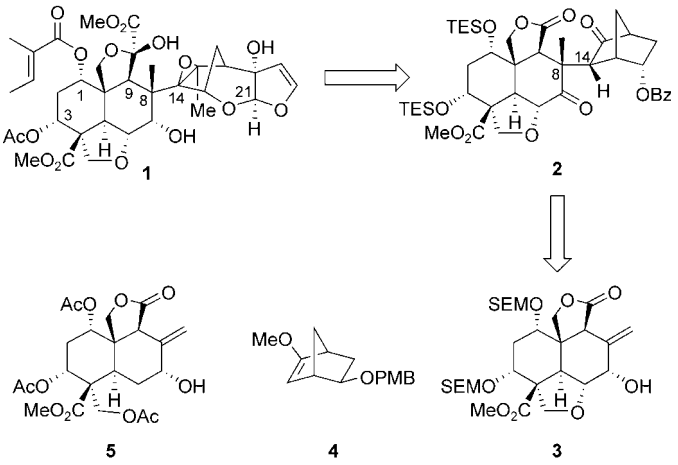
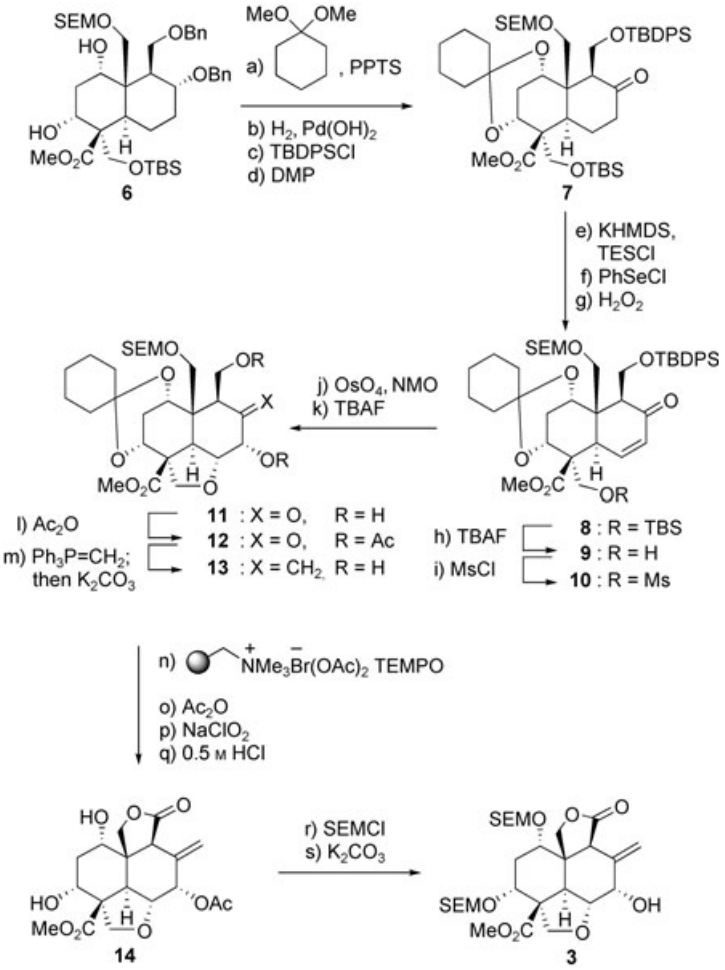


Scheme 1. Structure of azadirachtin (**1**) and possible precursors **3** and **5**.

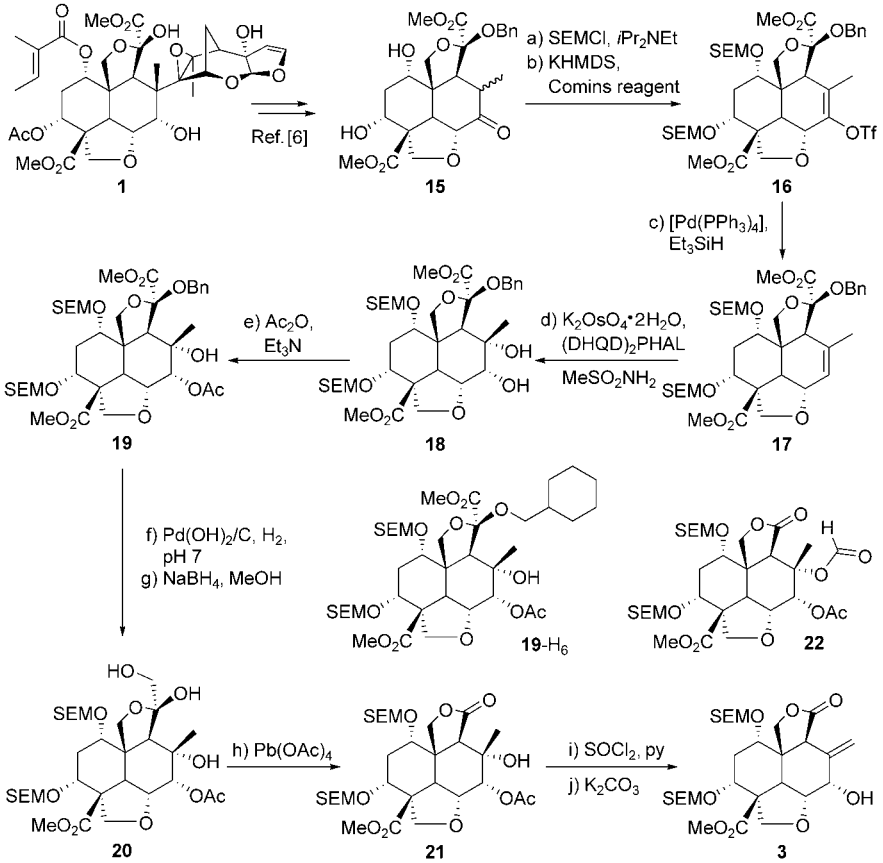


Scheme 2. Total synthesis of hydroxylactone **3**. Reagents and conditions: a) 1,1-dimethoxycyclohexane (4.0 equiv), PPTS (8.0 equiv), benzene, 80 °C, 4 h, 74 %; b) Pd/C (10 %; 40 wt %), $NaHCO_3$ (10 equiv), H_2 (1 atm), EtOAc, 25 °C, 24 h, 91 %; c) TBDPSCl (1.5 equiv), Et_3N (3.0 equiv), DMAP (0.1 equiv), CH_2Cl_2, 0 °C, 2 h, 94 %; d) DMP (1.5 equiv), $NaHCO_3$ (2.0 equiv), CH_2Cl_2, 0→25 °C, 2 h, 91 %; e) KHMDS (1.5 equiv), TESCl (1.5 equiv), THF, −78 °C, 30 min; f) PhSeCl (1.1 equiv), CH_2Cl_2, −78 °C, 30 min; g) H_2O_2 (3.0 equiv), THF, 0→25 °C, 1 h, 95 % over three steps; h) TBAF (1.5 equiv), THF, 0→25 °C, 2 h, 94 %; i) MsCl (2.0 equiv), Et_3N (4.0 equiv), DMAP (0.1 equiv), CH_2Cl_2, 0 °C, 2 h; j) OsO_4 (0.2 equiv), NMO (2.0 equiv), *t*BuOH/THF/H_2O (5:5:1), 25 °C, 24 h, 95 % over two steps; k) TBAF (1.5 equiv), THF, 25 °C, 3 h, 96 %; l) Ac_2O (8.0 equiv), Et_3N (12 equiv), DMAP (0.2 equiv), CH_2Cl_2, 0→25 °C, 2 h, 95 %; m) 1. $Ph_3P{=}CH_2$ (8.0 equiv), Et_2O, 0→25 °C, 6 h, 93 %; 2. K_2CO_3 (6.0 equiv), MeOH, 25 °C, 5 h, 92 %; n) TEMPO (0.8 equiv), polystyrene-supported bromite resin (6.0 equiv), CH_2Cl_2, 0 °C, 2 h, 75 %; o) Ac_2O (5.0 equiv), Et_3N (10 equiv), DMAP (0.2 equiv), CH_2Cl_2, 0→25 °C, 1 h, 92 %; p) $NaClO_2$ (4.0 equiv), NaH_2PO_4 (5.0 equiv), 2-methyl-2-butene (75 equiv), THF/*t*BuOH/H_2O (2:4:1), 25 °C, 1 h; q) HCl (0.5 M), EtOH/Et_2O (1:1), 0→25 °C, 3 h, 75 % over two steps; r) SEMCl (6.0 equiv), *i*Pr_2NEt (12 equiv), *n*Bu_4NI (4.0 equiv), $CHCl_3$, 61 °C, 8 h, 89 %; s) K_2CO_3 (10 equiv), MeOH, 25 °C, 2 h, 99 %. PPTS = pyridinium *p*-toluene sulfonate, TBDPS = *tert*-butyldiphenylsilyl, DMAP = 4-(dimethylamino)pyridine, DMP = Dess–Martin periodinane, HMDS = hexamethyldisilazide, TES = triethylsilyl, TBAF = tetra-*n*-butylammonium fluoride, Ms = mesyl, NMO = *N*-methylmorpholine *N*-oxide, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxyl radical, SEM = 2-(trimethylsilyl)ethoxymethyl.

the starting point, a compound that had been encountered as an enantiopure substance in our previous expeditions.[1] This diol **6** was first protected as a cyclohexanone ketal, the two benzyl protecting groups were cleaved, the resulting primary hydroxy group was selectively silylated, and finally the remaining secondary alcohol was oxidized with DMP to afford ketone **7** in 58 % overall yield. Compound **7** was then converted into enone **8** by the standard, three-step protocol in 95 % overall yield and thence into mesylate **10** via hydroxy compound **9** by desilylation followed by mesylation of the primary alcohol. The OsO_4–NMO-induced dihydroxylation of enone **10** proceeded stereoselectively from the less-hindered α face and was accompanied by internal S_N2-type mesylate displacement, affording the expected tetrahydrofuran derivative in 95 % yield over two steps. Desilylation of the latter intermediate with TBAF furnished dihydroxyketone **11** in 96 % yield. This substance was then converted into the exocyclic olefin **13** via its diacetate **12** (95 %) by a Wittig reaction with $Ph_3P{=}CH_2$ (93 %) followed by deacetylation with K_2CO_3 in MeOH (92 %). This three-step process was adopted after encountering difficulties with the attempted, but failed, direct olefination of **11**. The primary alcohol of diol **13** was selectively oxidized to the corresponding hydroxyaldehyde through a TEMPO-catalyzed oxidation procedure (75 %).[3] The remaining secondary hydroxy function was protected as an acetoxy group, and the aldehyde moiety was further oxidized to the acetate carboxylic acid. Exposure of the latter to 0.5 M ethanolic HCl gave the dihydroxylactone **14** through cleavage of both the ketal and the silyl protecting groups and ring closure (69 % overall yield). Lactone **14** crystallized from CH_2Cl_2/hexanes as colorless crystals (m.p. 240–241 °C) and X-ray crystallographic analysis[4] confirmed the ring framework and stereochemical features of this compound (Figure 1). Finally, protection of both free hydroxy groups within **14** with SEMCl (89 % yield) followed by treatment with K_2CO_3 in MeOH led to the coveted hydroxylactone **3** in 99 % yield.

Having completed the construction of hydroxylactone **3**, we then contemplated obtaining this same key intermediate

from the natural product **1** through semisynthesis. The aim of the degradation exercise of azadirachtin (**1**) to this key decalin fragment was not only to enrich our supplies of the target compound **2** for the purposes of our total synthesis efforts, but also to discover certain, unexpected or suspected, intricacies of the azadirachtin molecule that may be either of general interest or prove to be of some use in aiding our sail towards the natural product. In our search for an expedient route to **3** from **1** we made use of the work of Ley and coworkers,[5–7] who developed a four-step degradation sequence from **1** to **15**,[6] the tetracyclic compound that served as a beachhead for our expeditions (Scheme 3). Thus, the two hydroxy groups within **15** were protected as SEM ethers by reaction with SEMCl in the presence of iPr$_2$NEt, and the resulting bis-SEM-protected ketone was converted into olefin **17** by a regioselective transformation into the corresponding triflate **16** and then reduction of the latter compound with Et$_3$SiH in the presence of [Pd(PPh$_3$)$_4$] (47% overall yield for three steps). Manual molecular modeling suggested the α face of the double bond of **17** as the more accessible site, and this bias was greatly enhanced by the asymmetric dihydroxylation of this compound with K_2OsO_4 and (DHQD)$_2$PHAL in the presence of $MeSO_2NH_2$ in 96% yield, leading to 1,2-diol **18** as the exclusive product. Landing an acetate group on the secondary alcohol of **18** proved trivial, as treatment of this compound with Ac$_2$O, DMAP and Et$_3$N furnished monoacetate **19** (98% yield) as expected. Debenzylation of compound **19** required carefully controlled conditions (10% Pd(OH)$_2$/C, MeOH-H$_2$O, pH 7, H$_2$), otherwise an unusual reaction took place, namely the reduction of the benzene ring to afford the corresponding cyclohexylmethyl ether derivative **19**-H$_6$ (10% Pd(OH)$_2$/C, EtOH, H$_2$, 98% yield, **23**/**19**-H$_6$ ≈ 2.6:1). The origin of this remarkable mode of reactivity of benzyl ether derivative **19** remains unknown. Facilitated by the neighboring hydroxy group, the reduction with NaBH$_4$ of the carbomethoxy group of the debenzylation product derived from **19** proceeded smoothly to afford triol **20** in good yield. The Pb(OAc)$_4$-induced cleavage of the 1,2-diol system within **20** gave γ-lactone **21** in 70% overall yield from **19** for the three steps. Finally, exposure of **21** to SOCl$_2$ in the presence of pyridine led to the corresponding exocyclic olefin, which was treated with K$_2$CO$_3$ to give the targeted allylic alcohol **3** in 85% overall yield.



Scheme 3. Semisynthesis of hydroxylactone fragment **3** from **1**. Reagents and conditions: a) SEMCl (6.0 equiv), iPr$_2$NEt (12 equiv), nBu$_4$NI (4.0 equiv), CHCl$_3$, 60 °C, 8 h, 89%; b) Comins reagent (2.0 equiv), KHMDS (0.5 M in toluene, 2.0 equiv), THF, −78 °C, 30 min, 56%; c) [Pd(PPh$_3$)$_4$] (0.2 equiv), Et$_3$SiH (3.0 equiv), LiCl (3.0 equiv), DMF, 55 °C, 24 h, 95%; d) K_2OsO_4·H$_2$O (0.2 equiv), (DHQD)$_2$PHAL (0.5 equiv), K$_3$Fe(CN)$_6$ (3.0 equiv), $MeSO_2NH_2$ (1.0 equiv), K$_2$CO$_3$ (3.0 equiv), tBuOH/H$_2$O (3:2), 2 h, 96%; e) Ac$_2$O (5.0 equiv), Et$_3$N (10 equiv), DMAP (1.0 equiv), CH$_2$Cl$_2$, 0→25 °C, 8 h, 98%; f) Pd(OH)$_2$/C (1:1 w/w), H$_2$O/MeOH (1:2), pH 7, H$_2$, 25 °C, 2 h; g) NaBH$_4$ (10 equiv), MeOH, 0→25 °C, 4 h; h) Pb(OAc)$_4$ (2.0 equiv), CH$_2$Cl$_2$, 0 °C, 2 h, 70% over three steps; i) SOCl$_2$ (20 equiv), py, 0→25 °C, 8 h, 86%; j) K$_2$CO$_3$ (10 equiv), MeOH, 25 °C, 2 h, 99%. Comins reagent = 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine, DMF = *N*,*N*-dimethylformamide, (DHQD)$_2$PHAL = 1,4-bis(9-*O*-dihydroquinidinyl)phthalazine, py = pyridine.

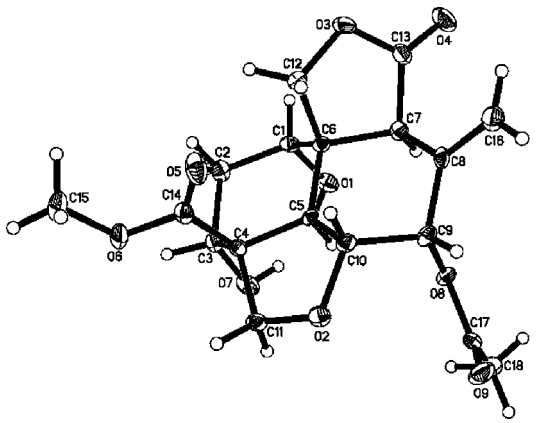
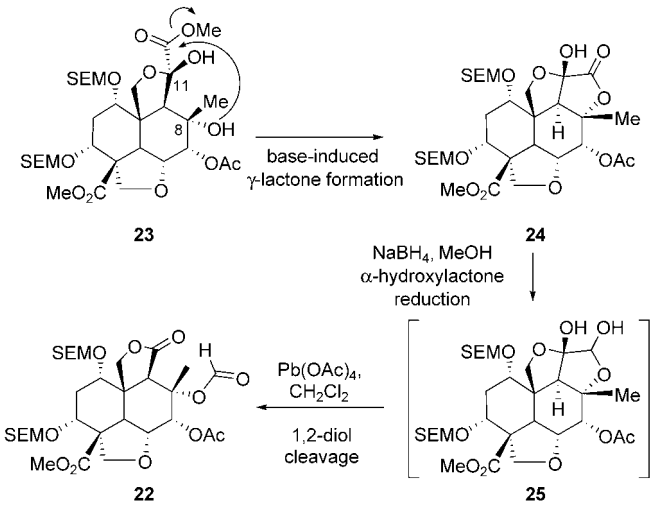
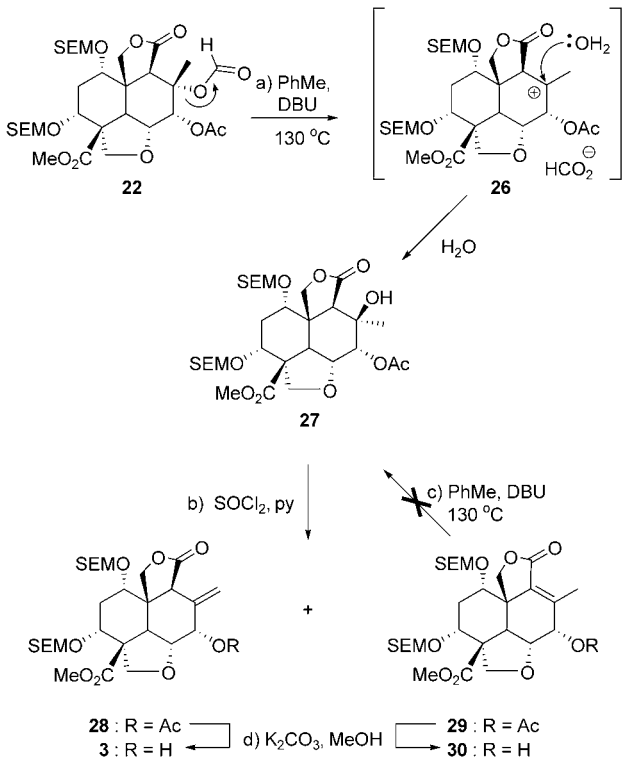


Figure 1. ORTEP drawing of **14** at the 30% probability level.

En route to allylic alcohol **3** from compound **19**, a noteworthy reaction was observed which led to a number of subsequent developments of equal interest. When the crude reaction mixture from hydrogenation of **19** was subjected to the intended reduction of the methyl ester with NaBH$_4$ followed by 1,2-diol cleavage with Pb(OAc)$_4$ on a large scale, the γ-lactone formate **22** was obtained, together with the desired γ-lactone alcohol **21** in approximately equimolar amounts and good overall yield. As shown in Scheme 4, we



Scheme 4. An unexpected $Pb(OAc)_4$-induced carbonyl migration and preparation of formate **22**. Reagents and conditions: $NaBH_4$ (10 equiv), MeOH, 0 °C→25 °C, 30 min; then $Pb(OAc)_4$ (10 equiv), CH_2Cl_2, 0→25 °C, 2 h, 95% over three steps.



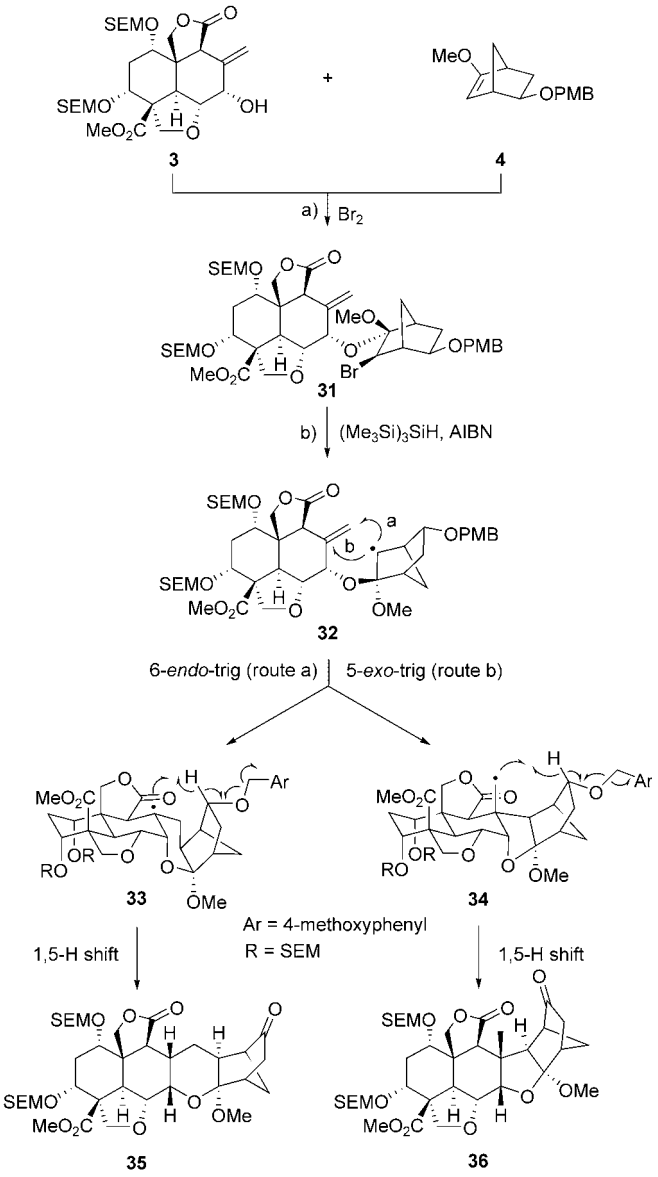
Scheme 5. An unexpected, DBU-induced inversion of configuration and preparation of 8-*epi* hydroxy compound **27** and allylic acetates **28** and **29**. Reagents and conditions: a) DBU (20 equiv), toluene, reflux, 4 h, 70%; b) $SOCl_2$ (20 equiv), py, 0→25 °C, 8 h, 71%; c) DBU (20 equiv), toluene, reflux, 10 h; d) K_2CO_3 (10 equiv), MeOH, 25 °C, 2 h, 99%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

hypothesized that this rather unusual outcome might be due to the propensity of the incipient diol **23** to form pentacyclic lactone **24** by attack of the C8 tertiary hydroxy group at the neighboring C11-carbomethoxy moiety with subsequent expulsion of a molecule of MeOH. Exposure of **24** to $NaBH_4$ would then result in the C11-OH-assisted reduction of the newly formed γ-lactone ring, yielding bis-hemiketal **25**, which could be oxidatively cleaved in the next step by $Pb(OAc)_4$ to give the observed formate lactone **22**. In support of this hypothesis we synthesized the postulated intermediate **24** from **23** and converted it exclusively into formate **22** by the proposed two-step sequence in 95% overall yield.

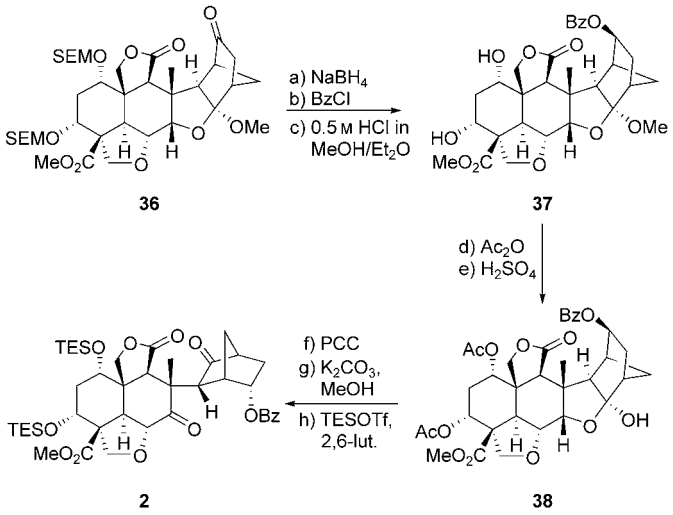
The fortuitous availability of formate **22** inspired a potential entry into the α,β-unsaturated γ-lactone series of decalin fragments (e.g. compound **30**, Scheme 5) as possible partners in coupling reactions with the norbornene-type precursors of azadirachtin (e.g. **4**). Thus, **22** was heated in refluxing toluene in the presence of DBU in the hope that the α,β-unsaturated lactone **29** would be obtained by elimination of the formate ester group (see Scheme 5). Instead, however, compound **27** was observed as the only product (70%). This C8-inverted tertiary alcohol **27** is presumably the product of ionization of the formate group to carbocation **26** followed by its immediate quenching by traces of moisture present in the reaction medium (**22**→**26**→**27**, Scheme 5). The nonpolar nature of the solvent employed (toluene) accounts for the observed inversion of configuration at C8, the tight ion pair formed between the decalin cationic domain and the leaving formate anion ensuring total blockade of the already hindered decalin α face. An alternative plausible mechanism, namely that involving stereoselective conjugate addition of water to an initially formed α,β-unsaturated γ-lactone (i.e. **29**, the compound targeted in the first place), has been ruled out by the failure of **29** to undergo addition of water upon exposure to the same reaction conditions. Unexpected as it was, the C8-*epi* alcohol **27** offers the only point of entry found so far, even after considerable experimentation, into the α,β-unsaturated γ-lactone series of decalin fragments. This was converted into **29** by exposure to $SOCl_2$ in the presence of pyridine in a reaction that also produced the exocyclic olefinic acetate **28** in a combined yield of 71% (**28**/**29** ≈ 2:1). Allylic alcohols **3** and **30**, obtained by treatment of this mixture with K_2CO_3 in MeOH, were conveniently separated by silica gel chromatography.

Allylic alcohol **3**, which was now available through two different routes, was then subjected to bromoketalization with norbornene derivative **4** under the conditions described in the preceding Communication[1] and remarkably afforded a single bromoketal **31** in 76% yield (Scheme 6).[10] It is interesting to recall that the bromoketalization of the previously employed decalin substrate **5**, which lacks the tetrahydrofuran system, led to a mixture of two diastereomeric bromoketals in approximately 1:1 ratio.[1] From this contrast, it is apparent that the distribution of the two isomers in these reactions is dictated not only by the reaction time and temperature, but also, and most profoundly, by the nature of the decalin partner.[8]

It was again found that $(Me_3Si)_3SiH$ served as an excellent H-atom donor in the radical-based cyclization of bromoketal **31**, yielding heptacyclic compounds **35** and **36** (Table 1) in 32 and 42% yield, respectively.[9] In this case, the secondary radical **32**, initially generated from **31**, underwent both the 6-*endo*-trig and the 5-*exo*-trig modes of ring closure,[8] thus leading to the tertiary and primary radicals **33** and **34**. These,



Scheme 6. Bromoketalization of hydroxylactone **3** with norbornene derivative **4** and elaboration of the product into **35** and **36**. Reagents and conditions: a) Br_2 (1.5 equiv), *N*,*N*-dimethylaniline (2.0 equiv), K_2CO_3 (10 equiv), **4** (2.0 equiv), CH_2Cl_2, −78 °C, 10 min; then **3**, −78→0 °C over 2 h, 0 °C, 1 h, 76%; b) $(Me_3Si)_3SiH$ (2.0 equiv), AIBN (1.0 equiv), toluene (0.007 M), 110 °C, 30 min, **35** (32%) **36** (42%); AIBN = 2,2′-azobisisobutyronitrile.

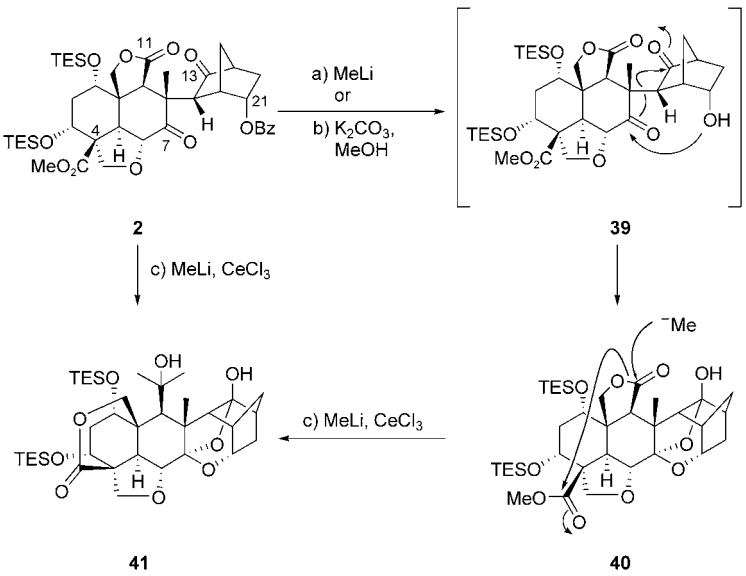


Scheme 7. Conversion of heptacyclic compound **36** into advanced system **2**. Reagents and conditions: a) $NaBH_4$ (5.0 equiv), MeOH, 0 °C, 15 min, 88%; b) BzCl (7.0 equiv), DMAP (5.0 equiv), pyridine, 60 °C, 5 h; c) 0.5 M HCl, MeOH/Et_2O (1:1), 0→25 °C, 6 h, 72% over two steps; d) Ac_2O (8.0 equiv), Et_3N (12 equiv), DMAP (0.4 equiv), CH_2Cl_2, 0→25 °C, 6 h, 79%; e) H_2SO_4 (5.0 equiv), CH_2Cl_2, 0 °C, 30 min; f) PCC (15 equiv), DCE, 65 °C, 16 h, 60% over two steps; g) K_2CO_3 (10 equiv), MeOH, 25 °C, 30 min; h) TESOTf (10 equiv), 2,6-lutidine (20 equiv), CH_2Cl_2, −78→25 °C, 24 h, 62% over two steps. Bz = benzoyl, PCC = pyridinium chlorochromate, DCE = 1,2-dichloroethane, OTf = trifluoromethanesulfonate.

in turn, undergo a 1,5-H shift (as shown in Scheme 6), to afford ketones **35** and **36**, respectively, upon oxidative cleavage of the PMB ether group. This behavior again reveals the controlling power of the decalin system in deciding the fate of these chemical species.

From the two intermediates **35** and **36**, only the latter is potentially productive in the campaign towards azadirachtin. To this end, we needed to demonstrate the facile cleavage of the temporary bridge that enabled the formation of the crucial C8–C14 bond in the first place. The heptacyclic ketone **36** (Scheme 7) was reduced with $NaBH_4$ in MeOH, exclusively from the *exo* side, to afford the corresponding alcohol, which was benzoylated and then desilylated under acidic conditions to furnish dihydroxy benzoate **37** in 63% overall yield. Exposure of diol **37** to Ac_2O, Et_3N, and DMAP gave the corresponding bisacetate (79% yield), which was subsequently converted into hemiketal **38**. Finally, oxidation of **38** with PCC, cleavage of the acetate group, and TES protection furnished diketone **2** (Table 1) in 37% yield for the four steps.

In the course of our drive towards azadirachtin (**1**), we became keenly, and sometimes painfully, aware of the unique behavior of this natural product due to the oxygen-rich nature of its skeleton and the close proximity of its numerous functional groups. In addition to the above-mentioned incidents, we consider it of interest to reveal one more example that speaks to this point. Scheme 8 shows the outcome of the reaction of diketone **2** with MeLi. It became apparent that initial loss of the benzoyl protecting group at C21 unmasked the secondary alcohol function, which was then in a position to attack the C7 carbonyl group, presumably forming a hemiketal. The existence of the latter compound was evidently transient under the reaction conditions, as a further ring closure ensued, this time on the C13 carbonyl carbon atom, to give the highly congested cagelike ketal/hemiketal **40** in 72% overall yield. Lactone **40** did not constitute the end of the journey in this cascade in the presence of $CeCl_3$. In this case, further attack by MeLi at the C11 lactone carbonyl function produced a free primary alcohol group, which was then able to reach across the decalin system to attack the C4 carbomethoxy residue to generate a second lactone ring with the expulsion of a methoxy group, furnishing, upon further addition of MeLi, the impressively



Scheme 8. Intriguing cascade sequences with azadirachtin-type scaffolds. Reagents and conditions: a) MeLi (5.0 equiv), Et_2O, −78 °C, 2 h, 72%; b) K_2CO_3 (10 equiv), MeOH, 25 °C, 36 h, 91%; c) MeLi (5.0 equiv), $CeCl_3$ (5.0 equiv), Et_2O, 0 °C, 8 h, 80%.

compact polycycle **41** in 80% overall yield from **2**. The stable ketal/hemiketal **40** was also the exclusive product (91% yield) of the reaction of benzoate **2** with K_2CO_3 in MeOH.

The described chemistry represents our most recent and important advancements toward the total synthesis of azadirachtin (**1**) and at the same time reveals some of the inner intricacies of this uniquely crowded and highly functionalized molecular architecture. Further progress towards congeners of azadirachtin is sure to be frustrated or facilitated by these intricacies.

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Table 1: Selected physical properties for compounds **2**, **35**, and **36**.

2: $R_f = 0.50$ (silica gel, EtOAc/hexane 1:2); $[\alpha]_D^{32} = -23.0$ ($c = 0.3$, $CHCl_3$); IR (film) $\tilde{\nu}_{max} = 2955, 2876, 1782, 1763, 1752, 1742, 1717, 1458, 1273, 1162, 1113, 1019, 874, 813, 716\ cm^{-1}$; ^1H NMR (600 MHz, C_6D_6): $\delta = 7.87$ (d, $J = 7.5$ Hz, 2H), 7.51 (t, $J = 7.5$ Hz, 1H), 7.42 (t, $J = 7.5$ Hz, 2H), 5.57 (ddd, $J = 10.2$, 9.0, 4.2 Hz, 1H), 5.01 (d, $J = 14.4$ Hz, 1H), 4.62 (d, $J = 10.5$ Hz, 1H), 4.44 (br s, 1H), 4.13 (d, $J = 8.4$ Hz, 1H), 4.06 (d, $J = 8.4$ Hz, 1H), 3.91 (s, 1H), 3.83 (d, $J = 10.5$ Hz, 1H), 3.76 (s, 3H), 3.73 (br s, 1H), 3.11 (br d, $J = 3.0$ Hz, 1H), 3.02 (br s, 1H), 2.99 (d, $J = 14.4$ Hz, 1H), 2.85 (br d, $J = 4.8$ Hz, 1H), 2.66 (dt, $J = 13.2$, 4.2 Hz, 1H), 2.41 (ddd, $J = 13.2$, 10.2, 4.8 Hz, 1H), 2.02 (br d, $J = 15.6$ Hz, 1H), 1.90 (br d, $J = 15.6$ Hz, 1H), 1.87 (br d, $J = 10.8$ Hz, 1H), 1.78 (br d, $J = 10.8$ Hz, 1H), 1.37 (s, 3H), 0.97 (t, $J = 7.8$ Hz, 9H), 0.96 (t, $J = 8.4$ Hz, 9H), 0.66 (q, $J = 7.8$ Hz, 6H), 0.61 ppm (q, $J = 8.4$ Hz, 6H); ^{13}C NMR (150 MHz, C_6D_6): $\delta = 212.7, 202.0, 175.4, 174.0, 166.7, 132.9, 130.0, 129.5, 128.5, 76.1, 74.4, 74.3, 70.8, 69.9, 66.5, 56.5, 55.3, 54.5, 53.3, 52.6, 52.0, 48.0, 45.0, 42.6, 36.6, 36.2, 30.8, 20.8, 7.0, 7.0, 4.7$ ppm; HRMS (ESI TOF): calcd for $C_{42}H_{61}O_{11}Si_2^+$ [M+H^+]: 797.3747; found: 797.3748

35: $R_f = 0.25$ (silica gel, EtOAc/hexanes 1:1); $[\alpha]_D^{31} = -30.0$ ($c = 0.3$, CH_2Cl_2); IR (film): $\tilde{\nu}_{max} = 2952, 2926, 1780, 1743, 1724, 1437, 1249, 1163, 1054, 836\ cm^{-1}$; ^1H NMR (500 MHz, C_6D_6): $\delta = 4.75$ (d, $J = 7.0$ Hz, 1H), 4.70 (dd, $J = 9.2$, 1.0 Hz, 1H), 4.63 (d, $J = 6.6$ Hz, 1H), 4.56 (d, $J = 6.6$ Hz, 1H), 4.45 (t, $J = 2.6$ Hz, 1H), 4.32 (d, $J = 11.0$ Hz, 1H), 4.31 (d, $J = 6.6$ Hz, 1H), 4.23 (dd, $J = 11.0$, 1.5 Hz, 1H), 4.17 (d, $J = 7.7$ Hz, 1H), 3.93 (ddd, $J = 10.6$, 9.5, 5.8 Hz, 1H), 3.79 (d, $J = 8.1$ Hz, 1H), 3.69–3.62 (m, 3H), 3.53–3.44 (m, 3H), 3.41 (s, 3H), 3.39 (dd, $J = 11.5$, 1.5 Hz, 1H), 3.15 (s, 3H), 2.50 (d, $J = 2.5$ Hz, 1H), 2.34 (dd, $J = 5.1$, 2.2 Hz, 1H), 2.23–2.13 (m, 4H), 1.72 (br d, $J = 11.3$ Hz, 1H), 1.53 (dd, $J = 17.8$, 4.5 Hz, 1H), 1.51 (br d, $J = 12.0$ Hz, 1H), 1.42 (dd, $J = 12.8$, 3.8 Hz, 1H), 1.35 (dt, $J = 16.2$, 2.9 Hz, 1H), 1.23 (br d, $J = 10.6$ Hz, 1H), 1.19–1.05 (m, 2H), 0.87 (d, $J = 7.7$ Hz, 1H), 0.85 (d, $J = 8.1$ Hz, 1H), 0.08 (s, 9H), −0.04 ppm (s, 9H); ^{13}C NMR (125 MHz, C_6D_6): $\delta = 214.1, 177.6, 173.9, 116.8, 93.5, 93.2, 88.0, 77.4, 73.0, 71.3, 70.0, 69.2, 66.1, 65.6, 59.9, 57.7, 54.9, 51.6, 51.4, 48.5, 43.9, 40.8, 40.1, 38.6, 37.2, 36.6, 29.4, 26.9, 18.1, 18.0, −1.3, −1.4$ ppm; HRMS (MALDI): calcd for $C_{36}H_{58}O_{12}Si_2Na$: 761.3359 [M+Na^+]; found: 761.3350

36: $R_f = 0.36$ (silica gel, EtOAc/hexanes 1:1); $[\alpha]_D^{31} = -24.0$ ($c = 0.3$, CH_2Cl_2); IR (film): $\tilde{\nu}_{max} = 2953, 2924, 1766, 1741, 1725, 1438, 1317, 1248, 1169, 1098, 1032, 836\ cm^{-1}$; ^1H NMR (500 MHz, C_6D_6): $\delta = 4.76$ (d, $J = 7.0$ Hz, 1H), 4.61 (d, $J = 7.0$ Hz, 1H), 4.59 (d, $J = 6.6$ Hz, 1H), 4.39–4.37 (m, 1H), 4.37 (d, $J = 6.6$ Hz, 1H), 4.33–4.27 (m, 3H), 4.17 (d, $J = 10.3$ Hz, 1H), 4.07 (d, $J = 7.7$ Hz, 1H), 3.96 (ddd, $J = 11.0$, 9.5, 5.9 Hz, 1H), 3.71 (s, 1H), 3.64 (ddd, $J = 11.0$, 9.9, 5.9 Hz, 1H), 3.56 (br t, $J = 2.4$ Hz, 1H), 3.54–3.46 (m, 4H), 3.37 (s, 3H), 3.10 (s, 3H), 3.05 (d, $J = 4.4$ Hz, 1H), 2.42 (d, $J = 3.7$ Hz, 1H), 2.38 (d, $J = 4.0$ Hz, 1H), 2.31 (dd, $J = 18.0$, 4.8 Hz, 1H), 2.13 (dt, $J = 16.1$, 2.6 Hz, 1H), 1.68–1.61 (m, 1H), 1.48 (dd, $J = 18.0$, 4.8 Hz, 1H), 1.39 (dt, $J = 16.1$, 2.9 Hz, 1H), 1.21 (s, 3H), 1.18–1.05 (m, 3H), 0.88 (d, $J = 8.4$ Hz, 1H), 0.87 (d, $J = 7.7$ Hz, 1H), 0.10 (s, 9H), 0.03 ppm (s, 9H); ^{13}C NMR (125 MHz, C_6D_6): $\delta = 215.0, 176.3, 174.1, 116.0, 93.6, 92.5, 85.0, 73.9, 72.8, 72.3, 70.5, 69.8, 67.3, 66.2, 65.6, 53.9, 53.8, 51.6, 51.1, 49.1, 47.5, 46.6, 42.0, 39.9, 38.9, 35.2, 27.1, 18.2, 18.1, 16.5, −1.3, −1.4$ ppm; HRMS (MALDI): calcd for $C_{36}H_{58}O_{12}Si_2Na$: 761.3359 [M+Na^+]; found: 761.3366

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[10] **Note added in proof**: After submission of this manuscript, we isolated the other bromoketal diastereomer in approximately 10% yield from experiments carried out on a larger scale.

