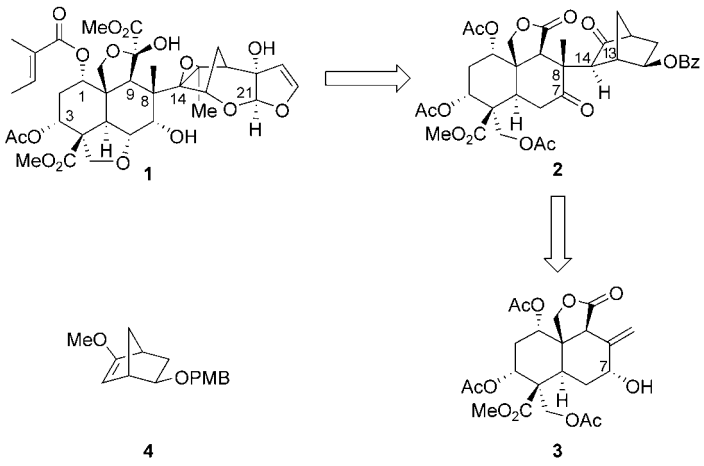
Natural Products Synthesis (1)

Studies toward the Synthesis of Azadirachtin, Part 1: Total Synthesis of a Fully Functionalized ABC Ring Framework and Coupling with a Norbornene Domain**

K. C. Nicolaou, Pradip K. Sasmal, A. J. Roecker, Xiao-Wen Sun, Sunil Mandal, and Antonella Converso*

We recently embarked on a program directed towards the total synthesis of azadirachtin (**1**, Scheme 1), the remarkable



1 **2** **3** **4**

Scheme 1. Retrosynthetic analysis of azadirachtin (**1**).

antifeedant agent isolated from the Neem tree[1] and currently in use as an insecticide.[2] Our radical-based approach towards this unusually challenging target molecule (see Scheme 1) was validated by a number of model studies,[3–5] which, however, left much to be desired in terms of functionalities on the crowded decalin system of the natural product. Herein we report the total synthesis of a fully functionalized ABC decalin intermediate **3** and its coupling with a suitable norbornene system **4** to afford a C7–C13 linked product, which was elaborated into the advanced intermediate **2** and whose structural disposition might allow its eventual conversion into azadirachtin (**1**). In the following Communication in this issue,[6] we describe both the total synthesis and semisynthesis of a different decalin intermediate and its elaboration into a close precursor of the target molecule, as well as some interesting reactions made possible by the special proximity effects that uniquely characterize the azadirachtin structural motif.[7]

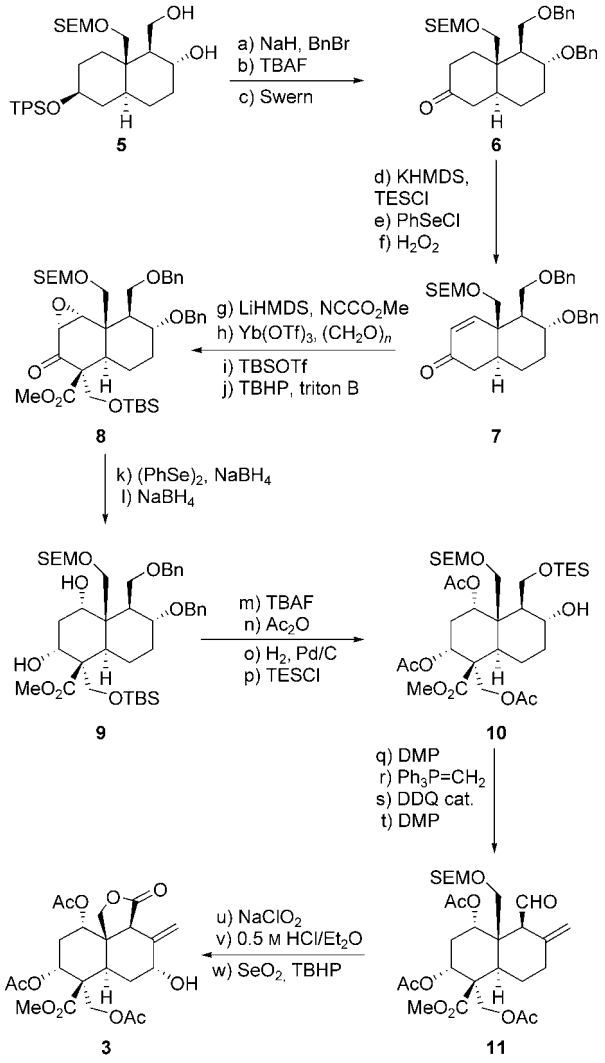
According to our previously disclosed strategy,[3–5] azadirachtin (**1**) was to be approached through a path marked by key intermediates such as **2**, **3**, and **4** as retrosynthetically outlined in Scheme 1. Crucial to the success of such a plan is the availability of fully functionalized advanced decalin systems such as **3**, which have the potential to yield azadirachtin upon coupling with norbornene derivatives such as **4** followed by appropriate elaboration.

The fundamental strategy for the synthesis of the norbornene precursor **4** has already been reported in a previous Communication.[5] The construction of the fully functionalized decalin system **3** in its enantiomerically pure form is depicted in Scheme 2. Thus, starting from enantiopure compound **5**,[5] ketone **6** was produced by dibenzylation (for abbreviations and conditions, see legends in schemes) followed by desilylation and Swern oxidation of the resulting secondary alcohol. Ketone **6** was then converted into enone **7** in 81% overall yield for the three-step sequence with a regioselectivity of approximately 10:1. Subsequent functionalization of **7** by Mander carboxylation[8] followed by aldol reaction of the resulting β-ketoester with paraformaldehyde in the presence of $Yb(OTf)_3$ led to the corresponding hydroxyester, whose hydroxy group was protected as a TBS ether (69% yield for three steps). Subsequent epoxidation of the enone moiety of the so-obtained intermediate by TBHP in the presence of triton B furnished, stereoselectively, epoxide **8** in 87% yield. The required 1,3-diaxial diol system within the growing substrate was established first by regioselective opening of the epoxide moiety of **8** (91% yield) with PhSeNa (generated in situ from PhSeSePh and $NaBH_4$)[9] and then stereoselective reduction ($NaBH_4$) of the intermediate hydroxyketone to afford the desired compound **9** in 63% yield. Selective removal of the TBS group, peracetylation, debenzylation, and finally, regioselective monoprotection of the primary alcohol of the resulting diol as a TES ether yielded alcohol **10** in 74% yield over four steps. The hydroxy compound **10** was then oxidized with DMP, and the resulting ketone was olefinated with $Ph_3P=CH_2$ prior to removal of the TES group in the presence of catalytic DDQ.[10] The primary alcohol was then oxidized to the corresponding aldehyde **11** (once again with DMP) in 65% overall yield over the four steps. The targeted coupling partner **3** was finally obtained from the latter intermediate **11** in 48% overall yield,[11] by the following sequence: 1) oxidation with $NaClO_2$, 2) exposure to ethanolic HCl (0.5 M), and 3) allylic oxidation with SeO_2 and TBHP.

[*] Prof. Dr. K. C. Nicolaou, Dr. P. K. Sasmal, A. J. Roecker, Dr. X.-W. Sun, Dr. S. Mandal, Dr. A. Converso
Department of Chemistry and
The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-2469
E-mail: kcn@scripps.edu
and
Department of Chemistry and Biochemistry
University of California, San Diego
9500 Gilman Drive, La Jolla, CA 92093 (USA)

[**] We thank Dr. D. H. Huang and Dr. G. Siuzdak for NMR spectroscopic and mass spectrometric assistance, respectively. Financial support for this work was provided by grants from the National Institutes of Health (USA) and the Skaggs Institute for Chemical Biology, and a predoctoral fellowship from the Division of Organic Chemistry of the American Chemical Society sponsored by Novartis (to A.J.R.).

 DOI: 10.1002/ange.200500216



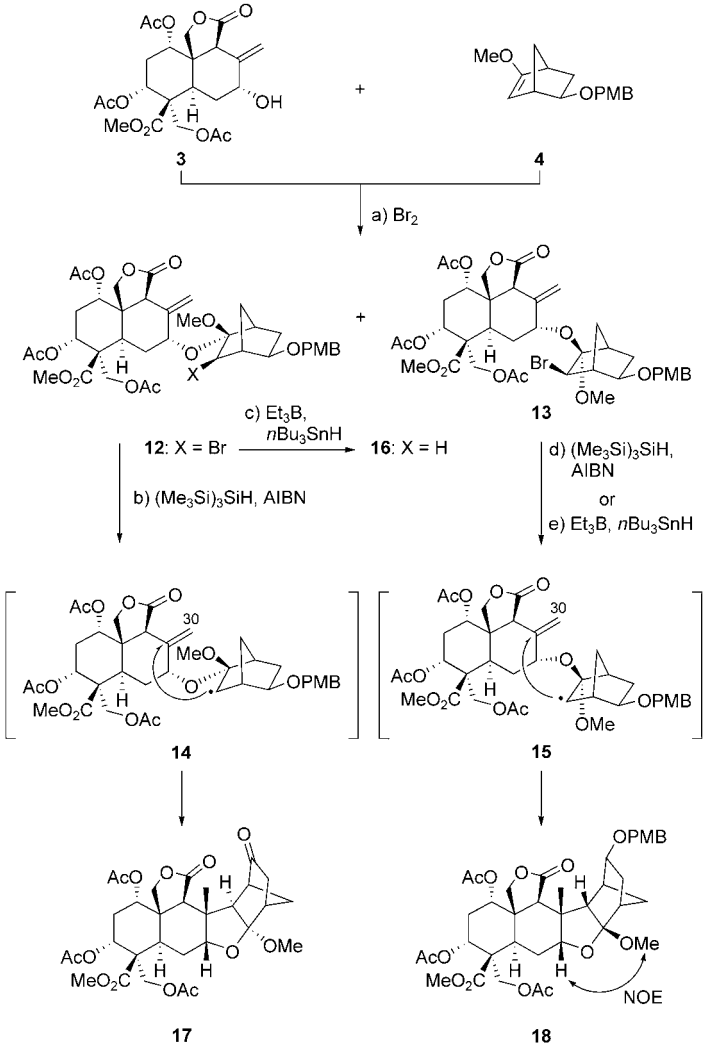
Scheme 2. Construction of decalin fragment **3**. Reagents and conditions: a) NaH (6.0 equiv), BnBr (4.0 equiv), nBu_4NI (0.2 equiv), THF/DMF (3:1), 25 °C, 24 h; b) TBAF (2.0 equiv), THF, 25 °C, 15 h, 91 % over two steps; c) $(COCl)_2$ (1.5 equiv), DMSO (3.0 equiv), Et_3N (6.0 equiv), −78→25 °C, CH_2Cl_2, 1 h, 89 %; d) KHMDS (1.5 equiv), TESCl (1.5 equiv), THF, −78 °C, 30 min; e) PhSeCl (1.1 equiv), CH_2Cl_2, −78 °C, 30 min; f) H_2O_2 (30 % v/v, 3.0 equiv), THF, 0→25 °C, 1 h, 80 % over three steps; g) LiHMDS (2.0 equiv), $NCCO_2Me$ (1.5 equiv), THF, −78 °C, 6 h, 93 %; h) $(CH_2O)_n$ (20 equiv), $Yb(OTf)_3$ (2.0 equiv), THF, 25 °C, 2 h; i) TBSOTf (1.5 equiv), 2,6-lutidine (2.5 equiv), CH_2Cl_2, −78 °C, 30 min, 74 % over two steps; j) triton B (2.0 equiv), aqueous TBHP (70 %; 10 equiv), THF, 25 °C, 16 h, 87 %; k) $(PhSe)_2$ (3.0 equiv), $NaBH_4$ (6.0 equiv), EtOH, 25 °C, 0.5 h, 91 %; l) $NaBH_4$ (8.0 equiv), $MeOH/CH_2Cl_2$ (1:15), 25 °C, 24 h, 63 %; m) TBAF (1.5 equiv), THF, 0→25 °C, 1 h; n) Ac_2O (6.0 equiv), Et_3N (10 equiv), DMAP (0.4 equiv), CH_2Cl_2, 25 °C, 6 h, 92 % over two steps; o) Pd/C (10 %; 20 wt %), H_2 (1 atm), EtOH, 25 °C, 16 h, 98 %; p) TESCl (1.0 equiv), Et_3N (2.0 equiv), CH_2Cl_2, 0→25 °C, 2 h, 82 %; q) DMP (1.5 equiv), $NaHCO_3$ (1.5 equiv), CH_2Cl_2, 0→25 °C, 2 h, 91 %; r) $Ph_3P=CH_2$ (5.0 equiv), diethyl ether, 25 °C, 2 h, 80 %; s) DDQ (0.1 equiv), THF/H_2O (9:1), 25 °C, 2 h, 97 %; t) DMP (1.5 equiv), CH_2Cl_2, 0→25 °C, 2 h, 92 %; u) $NaClO_2$ (4.0 equiv), NaH_2PO_4 (4.0 equiv), 2-methyl-2-butene (75 equiv), $THF/tBuOH/H_2O$ (2:4:1), 25 °C, 1 h; v) 0.5 M HCl, $EtOH/Et_2O$ (1:1), 0→25 °C, 6 h, solvent evaporated; then, Ac_2O (6.0 equiv), Et_3N (10 equiv), DMAP (0.4 equiv), CH_2Cl_2, 25 °C, 6 h, 94 % over two steps; w) SeO_2 (5.0 equiv), TBHP (10 equiv), CH_2Cl_2, 25 °C, 6 h, 51 %. Bn = benzyl, DMF = *N*,*N*-dimethylformamide, TBAF = tetra-*n*-butylammonium fluoride, DMSO = dimethyl sulfoxide, HMDS = hexamethyldisilazane, TES = triethylsilyl, OTf = trifluoromethanesulfonate, TBS = *tert*-butyldimethylsilyl, triton B = benzyltrimethylammonium hydroxide, TBHP = *tert*-butyl hydroperoxide, DMAP = 4-(dimethylamino)pyridine, DMP = Dess–Martin periodinane, DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone.

With **3** in hand, we were now poised to test the key bromoketalization[12] reaction between this substrate and norbornene enol ether **4**, a reaction that had shown rather capricious behavior during our previous model studies. Upon considerable experimentation, it was found that the optimum conditions for this coupling required addition of Br_2 to norbornene derivative **4** in CH_2Cl_2 at −78 °C followed by the sequential addition of *N*,*N*-dimethylaniline and allylic alcohol **3**, and warming slowly to 0 °C. Chromatographic resolution of the rather complex mixture of products led to the isolation and characterization of two diastereomeric bromoketals (ca. 1:1 ratio, 80 % combined yield), whose NMR spectroscopic analysis revealed structures **12** and **13** (Scheme 3). The ratio of the two isomers was found to be dependent on reaction time, temperature, and, apparently, on the steric environment around the attacking allylic alcohol moiety, since previous[4,5] and subsequent[6] experiments with other decalin allylic alcohol substrates led to different results. Scheme 4 provides a possible explanation for these results by invoking an oxonium ion intermediate **4b** derived from the rupture of the initially formed bromonium ion **4a** as the temperature is raised to 0 °C. Attack on oxonium ion **4b** from the *exo* face is now possible, and leads to the formation of the *epi*-C13 bromoketal (azadirachtin numbering) **4d** (Scheme 4) or **13** (Scheme 3).

Both bromoketals **12** and **13** were subjected to radical cyclization conditions[13] to afford the desired hexacyclic products **17** and **18** (Table 1) in 70 and 76 % yield, respectively (Scheme 3). The structures and stereochemistries of **17** and **18** were unambiguously assigned by NMR spectroscopy (^1H,^{13}C-COSY, ROESY, and HMQC). Interestingly, only compound **13** generated the desired polycycle **18** upon treatment with nBu_3SnH–Et_3B[14] at room temperature, whereas compound **12** gave, exclusively, reduction to **16**. This observation suggests that, while the radical formed from **12** (i.e. **14**) requires higher temperature to access the appropriate transition state for ring closure, the radical obtained from **13** resides in a more privileged position to attain the required transition state for cyclization, which apparently takes place even at ambient temperature.

Interestingly, the primary radicals initially formed from **14** and **15** only undergo the 5-*exo*-trig mode of ring closure. The alternative 6-*endo*-trig mode of reaction is also available in principle and, indeed, is observed with other substrates, as we shall describe in more detail in the following Communication in this issue.[6] In the present instance the secondary radical thus formed through the action of $(Me_3Si)_3SiH$–AIBN undergoes ring closure, leading to a primary radical, which in turn undergoes an intramolecular 1,5-H shift (see 30-H (azadirachtin numbering) in structures **14** and **15**) to afford ketone **17**, in the case of **14**, or undergoes an intermolecular quench to yield PMB ether **18** in the case of **15**.

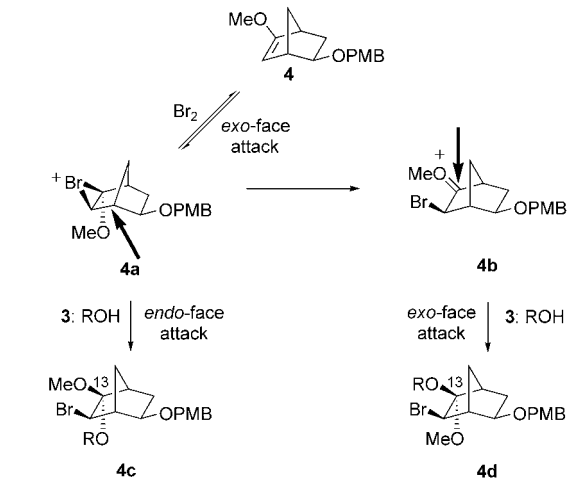
The stereochemistry of the newly generated stereogenic centers within **18** was confirmed by ^1H NMR NOE studies (see Scheme 3). As further proof of its structure, compound **17** was also constructed from the previously synthesized[5] intermediate **19** as shown in Scheme 5. Thus, **19** was converted into compound **20** by protection as a BOM ether, desilylation, and oxidation under Swern conditions. Regioselective unsa-



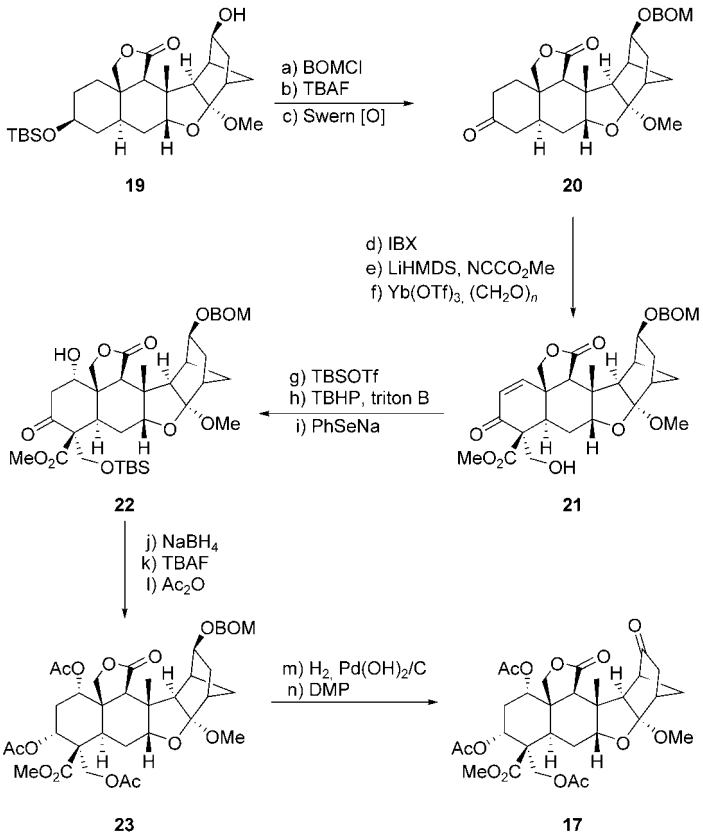
Scheme 3. Coupling of decalin system **3** with norbornene derivative **4** and synthesis of hexacyclic compounds **17** and **18**. Reagents and conditions: a) Br_2 (1.5 equiv), *N*,*N*-dimethylaniline (2.0 equiv), **4** (2.0 equiv), CH_2Cl_2, −78 °C, 10 min; then **3**, −78→0 °C over 2 h, 0 °C, 1 h, **12** (38%) and **13** (42%); b) $(Me_3Si)_3SiH$ (2.0 equiv), AIBN (1.0 equiv), toluene (0.007 M), 110 °C, 30 min, 70%; c) Et_3B (5.0 equiv), nBu_3SnH (5.0 equiv), CH_2Cl_2, 25 °C, 1 h, 80%; d) $(Me_3Si)_3SiH$ (2.0 equiv), AIBN (1.0 equiv), toluene (0.007 M), 110 °C, 30 min, 76%; e) Et_3B (5.0 equiv), nBu_3SnH (5.0 equiv), CH_2Cl_2, 25 °C, 1 h, 80%. AIBN = 2,2′-azobisisobutyronitrile.

turation of ketone **20** with IBX,[15] followed by sequential treatment with LiHDMS/$NCCO_2Me$ and $Yb(OTf)_3/(CH_2O)_n$, furnished hydroxyenone **21**, whose protection with TBS, stereoselective epoxidation, and reductive epoxide opening (PhSeNa, 81% over two steps) led to β-hydroxyketone **22**. Following stereoselective reduction (30%) of **22** with $NaBH_4$, desilylation and then peracetylation of the resulting triol afforded triacetate **23**. Finally, hydrogenolysis of the BOM protecting group from intermediate **23** followed by oxidation with DMP furnished the desired hexacyclic ketone **17**, whose spectroscopic and chromatographic properties matched those of a sample obtained from the more convergent and expedient route depicted in Scheme 3.

In the final phase of this study, it was important to demonstrate the cleavage of the temporary bridge that was so

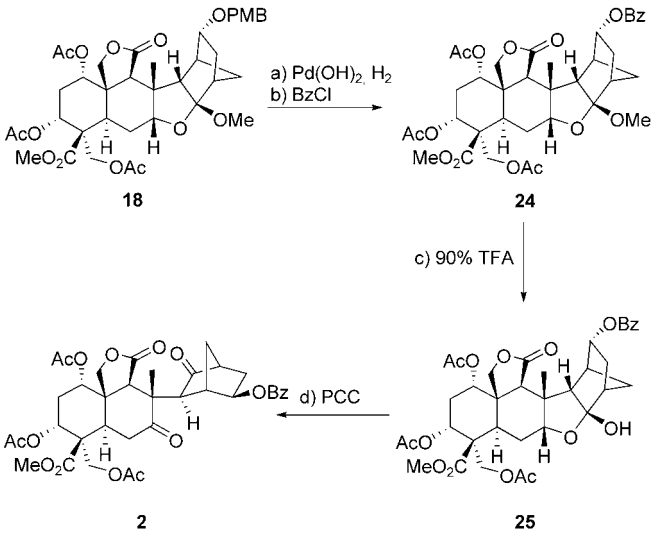


Scheme 4. Proposed mechanism for bromoketalization of **3** and **4**.



Scheme 5. Construction of hexacyclic compound **17** from **19**. Reagents and conditions: a) BOMCl (5.0 equiv), iPr_2NEt (10 equiv), DMF, 40 °C, 24 h, 96%; b) TBAF (2.0 equiv), THF, 25 °C, 12 h, 94%; c) $(COCl)_2$ (2.0 equiv), DMSO (3.0 equiv), Et_3N (4.0 equiv), −78→25 °C, CH_2Cl_2, 1 h, 74%; d) IBX (1.5 equiv), DMSO, 65 °C, 36 h, 75%; e) LiHMDS (1.5 equiv), $NCCO_2Me$ (1.2 equiv), HMPA (1.5 equiv), THF, −78 °C, 3 h, 65%; f) $(CH_2O)_n$ (5.0 equiv), $Yb(OTf)_3$ (2.0 equiv), THF, 25 °C, 1 h, 72%; g) TBSOTf (1.1 equiv), 2,6-lutidine (2.0 equiv), CH_2Cl_2, −78 °C, 1 h, 90%; h) triton B (2.0 equiv), aqueous TBHP (70%; 10 equiv), THF, 25 °C, 16 h; i) PhSeNa (3.0 equiv), EtOH, 25 °C, 4 h, 81% over two steps; j) $NaBH_4$ (8.0 equiv), THF, 25 °C, 30 min, 30%; k) TBAF (1.5 equiv), THF, 0→25 °C, 1 h; l) Ac_2O (6.0 equiv), Et_3N (10 equiv), DMAP (0.4 equiv), CH_2Cl_2, 25 °C, 6 h, 80% over two steps; m) $Pd(OH)_2/C$ (20%; 10 wt%), H_2 (1 atm), EtOH, 25 °C, 1 h; n) DMP (2.0 equiv), CH_2Cl_2, 0→25 °C, 2 h, 90% over two steps. BOM = benzyloxymethyl, IBX = *o*-iodoxybenzoic acid, HMPA = hexamethylphosphoramide.

instrumental in forming the challenging C8–C14 bond as a prelude to further advances toward azadirachtin. Towards this end, the hexacyclic compound **18** was first converted into the benzoate **24** (by protecting-group exchange through hydrogenolysis and benzoylation) and followed by hydrolysis to hemiketal **25** in 75% overall yield (Scheme 6). Finally, hemiketal **25** was oxidized with PCC to afford diketone **2** (Table 1) in 80% yield. Diastereomer **17** has not, as yet, been advanced further.



Scheme 6. Conversion of hexacyclic compound **18** into advanced pentacyclic intermediate **2**. Reagents and conditions: a) $Pd(OH)_2/C$ (20%; 10 wt%), H_2 (1 atm), EtOH, 25 °C, 1 h; b) BzCl (3.0 equiv), Et_3N (6.0 equiv), DMAP (0.1 equiv), CH_2Cl_2, 0→25 °C, 4 h; c) aqueous TFA (90%), 65 °C, 3 h, 75% over three steps; d) PCC (15 equiv), DCE, 65 °C, 16 h, 80%. Bz = benzoyl, TFA = trifluoroacetic acid, PCC = pyridinium chlorochromate, DCE = 1,2-dichloroethane.

The described chemistry provides solutions to a number of challenges posed by the decalin domain of azadirachtin (**1**) and brings the realization of the synthesis of this molecule within close range. In the following Communication in this issue,[6] we describe further studies that place this goal even closer, but from a different angle.

Received: January 19, 2005
Published online: April 21, 2005

Keywords: asymmetric synthesis · natural products · protecting groups · radical reactions · total synthesis

Table 1: Selected physical properties for compounds **2**, **17**, and **18**.

2: $R_f = 0.29$ (silica gel, EtOAc/hexanes 1:1); $[\alpha]_D^{32} = -28.0$ ($c = 0.6$, CH_2Cl_2); IR (film): $\tilde{\nu}_{max} = 2923, 2851, 1780, 1745, 1717, 1451, 1376, 1231, 1112, 1048, 963\ cm^{-1}$; ^1H NMR (500 MHz, C_6D_6): $\delta = 8.02$ (d, $J = 7.7$ Hz, 2H), 7.58 (t, $J = 7.7$ Hz, 1H), 7.46 (t, $J = 7.7$ Hz, 2H), 5.52 (t, $J = 2.9$ Hz, 1H), 5.16 (d, $J = 7.0$ Hz, 1H), 4.83 (t, $J = 2.9$ Hz, 1H), 4.41 (A of ABq, $J = 10.6$ Hz, 1H), 4.35 (B of ABq, $J = 10.6$ Hz, 1H), 4.29 (A of ABq, $J = 10.5$ Hz, 1H), 4.00 (B of ABq, $J = 10.5$ Hz, 1H), 3.82 (s, 3H), 3.22–3.09 (m, 2H), 2.97 (br s, 1H), 2.93 (d, $J = 2.2$ Hz, 1H), 2.67 (dd, $J = 15.7$, 2.9 Hz, 1H), 2.65 (s, 1H), 2.58 (d, $J = 4.0$ Hz, 1H), 2.44 (dt, $J = 17.0$, 3.5 Hz, 1H), 2.38–2.30 (m, 2H), 2.13–1.95 (m, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 1.99 (s, 3H), 1.29 ppm (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): $\delta = 214.3, 207.3, 174.0, 172.4, 170.2, 169.9, 169.5, 166.1, 133.4, 130.0, 129.7, 128.6, 77.0, 69.5, 67.3, 66.3, 65.8, 53.9, 53.3, 51.0, 49.2, 48.0, 47.6, 41.6, 34.8, 33.0, 32.9, 32.8, 29.9, 27.6, 23.2, 21.2, 21.0, 20.6$ ppm; HRMS (MALDI): calcd for $C_{36}H_{40}O_{14}Na$: 719.2310 [M+Na^+], found 719.2311

17: $R_f = 0.11$ (silica gel, EtOAc/hexane 1:1); $[\alpha]_D^{32} = -44.5$ (CH_2Cl_2, $c = 0.14$); IR (film): $\tilde{\nu}_{max} = 2954, 2922, 2851, 1778, 1743, 1730, 1439, 1375, 1320, 1234, 1050, 938, 736, 604\ cm^{-1}$; ^1H NMR (600 MHz, C_6D_6): $\delta = 5.63$ (br s, 1H), 4.89 (br s, 1H), 4.39 (d, $J = 10.5$ Hz, 1H), 4.23 (d, $J = 10.5$ Hz, 1H), 3.76 (d, $J = 9.6$ Hz, 1H), 3.63 (s, 1H), 3.42 (d, $J = 9.6$ Hz, 1H), 3.14 (s, 3H), 3.10 (s, 3H), 3.05 (s, 1H), 2.98 (dd, $J = 13.8$, 3.6 Hz, 1H), 2.85 (d, $J = 4.8$ Hz, 1H), 2.46 (br s, 1H), 2.28 (br s, 1H), 2.21–2.17 (m, 2H), 2.05 (dt, $J = 13.8$, 3.6, 1H), 1.69 (s, 3H), 1.68 (s, 3H), 1.67–1.66 (m, 1H), 1.62 (s, 3H), 1.59–1.51 (m, 3H), 1.14 (s, 3H), 1.09 ppm (d, $J = 10.2$ Hz, 1H); ^{13}C NMR (150 MHz, C_6D_6): $\delta = 214.9, 175.3, 172.5, 169.7, 169.1, 168.6, 115.3, 84.4, 69.6, 67.4, 67.4, 66.8, 66.1, 53.9, 51.9, 51.4, 50.3, 50.0, 46.4, 41.4, 40.4, 39.7, 38.7, 27.8, 27.7, 22.3, 20.5, 20.5, 20.1, 16.3$ ppm; HRMS (ESI-TOF): calcd for $C_{30}H_{38}O_{13}Na^+$ [M+Na^+]: 629.2204; found: 629.2205

18: $R_f = 0.26$ (silica gel, EtOAc/hexane 1:1); $[\alpha]_D^{32} = +1.4$ (CH_2Cl_2, $c = 0.14$); IR (film): $\tilde{\nu}_{max} = 2934, 2851, 1777, 1745, 1612, 1513, 1440, 1372, 1318, 1231, 1182, 1047, 823, 736\ cm^{-1}$; ^1H NMR (600 MHz, C_6D_6): $\delta = 7.27$ (d, $J = 8.4$ Hz, 2H), 6.80 (d, $J = 8.4$ Hz, 2H), 5.69 (br s, 1H), 4.82 (br s, 1H), 4.44 (d, $J = 11.4$ Hz, 1H), 4.43 (d, $J = 10.2$ Hz, 1H), 4.41 (d, $J = 10.2$ Hz, 1H), 4.36 (d, $J = 11.4$ Hz, 1H), 3.95 (br s, 1H), 3.87 (d, $J = 10.0$ Hz, 1H), 3.63 (d, $J = 6.0$ Hz, 1H), 3.56 (d, $J = 10.0$ Hz, 1H), 3.33 (s, 3H), 3.24 (s, 1H), 3.13 (br s, 1H), 3.11 (s, 3H), 3.04 (s, 3H), 3.02 (dd, $J = 13.8$, 3.0 Hz, 1H), 2.40 (d, $J = 3.6$ Hz, 1H), 2.36 (br d, $J = 16.8$ Hz, 1H), 2.08 (br d, $J = 16.8$ Hz, 1H), 2.03–1.96 (m, 4H), 1.91 (d, $J = 9.6$ Hz, 1H), 1.68 (s, 3H), 1.60 (s, 3H), 1.53 (br s, 1H), 1.48 (dd, $J = 9.6$, 3.0 Hz, 1H), 1.44 (s, 3H), 1.11 ppm (s, 3H); ^{13}C NMR (150 MHz, C_6D_6): $\delta = 176.1, 172.6, 169.6, 169.0, 168.9, 159.6, 131.3, 129.7, 117.1, 114.0, 81.3, 81.2, 71.0, 70.8, 67.1, 66.6, 66.5, 63.6, 54.7, 52.0, 50.6, 50.2, 46.4, 43.6, 43.0, 42.0, 37.9, 33.2, 33.0, 28.5, 27.5, 25.8, 22.2, 20.7, 20.3, 20.0$ ppm; HRMS (ESI-TOF): calcd for $C_{38}H_{48}O_{14}Na^+$ [M+Na^+]: 751.2936; found: 751.2932

[1] For isolation, see: a) J. H. Butterworth, E. D. Morgan, *J. Chem. Soc. Chem. Commun.* **1968**, 23–24; for structure determination, see: b) J. N. Bilton, H. B. Broughton, P. S. Jones, S. V. Ley, Z. Lidert, E. D. Morgan, H. S. Rszepa, R. N. Sheppard, A. M. Z. Slawin, D. J. Williams, *Tetrahedron* **1987**, *43*, 2805–2815; c) W. Kraus, M. Bokel, A. Bruhn, R. Cramer, I. Klaiber, A. Klenk, G. Nagl, H. Pohnl, H. Sadlo, B. Vogler, *Tetrahedron* **1987**, *43*, 2817–2830; d) C. J. Turner, M. S. Tempesta, R. B. Taylor, M. G. Zagorski, J. S. Termini, D. R. Schroeder, K. Nakanishi, *Tetrahedron* **1987**, *43*, 2789–2804.

[2] a) V. H. Guerrini (Australia), PCT Int. Appl., WO 19901211, **1991** [*Chem. Abstr.* **1991**, *116*, 2316]; b) P. H. Hull (Australia), PCT Int. Appl., WO 9105561, **1991** [*Chem. Abstr.* **1991**, *115*, 108578]; c) J. A. Klocke, M. S. Lee, R. B. Yamasaki (Native Plants, Inc., USA)., Eur. Pat. Appl., EP 308044, **1989** [*Chem. Abstr.* **1989**, *112*, 153732]; d) Z. Lidert (Rohm and Haas Co., USA), Eur. Pat. Appl. EP 311284, **1989** [*Chem. Abstr.* **1989**, *111*, 92333]; e) G. Stix, *Sci. Am.* **1992**, *266*, 132; f) B. Corradi (Italy), Eur. Pat. Appl., Ep 1293122, **2003** [*Chem. Abstr.* **2003**, *138*, 200347]; g) T. R. Govindachari, G. Gopalakrishnan, *J. Indian Chem. Soc.* **1998**, *75*, 655–661; h) H. Gong, H. Xu, (People Rep. China), application CN 1468625, **2004**; i) A. J. Mordue, *Neem: Today and in the New Millennium* **2004**, 229–242; j) E. D.

Morgan, *Neem: Today and in the New Millennium* **2004**, 21 – 32; k) P. D. K. Jayanthi, A. Verghese, *Entomon* **2004**, *29*, 45 – 50; l) S. R. Moorty, A. D. Kumar (Fortune Bio-Tech Limited, India), application US 6733802, **2004** [*Chem. Abstr.* **2004**, *140*, 352064].

[3] K. C. Nicolaou, M. Follmann, A. J. Roecker, K. W. Hunt, *Angew. Chem.* **2002**, *114*, 2207 – 2210; *Angew. Chem. Int. Ed.* **2002**, *41*, 2103 – 2106.

[4] K. C. Nicolaou, A. J. Roecker, M. Follmann, R. Baati, *Angew. Chem.* **2002**, *114*, 2211 – 2214; *Angew. Chem. Int. Ed.* **2002**, *41*, 2107 – 2110.

[5] K. C. Nicolaou, A. J. Roecker, H. Monenschein, P. Guntupalli, M. Follmann, *Angew. Chem.* **2003**, *115*, 3765 – 3770; *Angew. Chem. Int. Ed.* **2003**, *42*, 3637 – 3642.

[6] K. C. Nicolaou, P. K. Sasmal, T. V. Koftis, A. Converso, E. Loizidou, F. Kaiser, A. J. Roecker, C. C. Dellios, X.-W. Sun, G. Petrovic, *Angew. Chem.* **2005**, *117*, 3513 – 3518; *Angew. Chem. Int. Ed.* **2005**, *44*, 3447 – 3452, following Communication in this issue.

[7] For earlier synthetic studies from other groups, see: a) A. Murai, *J. Toxicol. Toxin Rev.* **2003**, *22*, 617 – 632; b) T. Fukuzaki, S. Kobayashi, T. Hibi, T. Ikuma, J. Ishihara, N. Kanoh, A. Murai, *Org. Lett.* **2002**, *4*, 2877 – 2880; c) T. Durand-Reville, L. B. Gobbi, B. L. Gray, S. V. Ley, J. S. Scott, *Org. Lett.* **2002**, *4*, 3847 – 3850; d) Y. Yamamoto, J. Ishihara, N. Kanoh, A. Murai, *Synthesis* **2000**, 1894 – 1906; e) S. V. Ley, C. E. Gutteridge, A. R. Pape, C. D. Spilling, C. Zumbrunn, *Synlett* **1999**, 1295 – 1297; f) H. Schlesiger, E. Winterfeld, *Chirality* **1997**, *9*, 454 – 458; g) H. Watanabe, T. Watanabe, K. Mori, T. Kitahara, *Tetrahedron Lett.* **1997**, *38*, 4429 – 4432; h) A. A. Denholm, L. Jennens, S. V. Ley, A. Wood, *Tetrahedron* **1995**, *51*, 6591 – 6604; i) K. J. Henry Jr., B. Fraser-Reid, *J. Org. Chem.* **1994**, *59*, 5128 – 5129; j) S. V. Ley, A. A. Denholm, A. Wood, *Nat. Prod. Rep.* **1993**, *10*, 109 – 157; k) H. Kolb, S. V. Ley, *Tetrahedron Lett.* **1991**, *32*, 6187 – 6190; l) Y. Nishikimi, T. Iimori, M. Sodeoka, M. Shibasaki, *J. Org. Chem.* **1989**, *54*, 3354 – 3359; m) M. G. Brasca, H. B. Broughton, D. Craig, S. V. Ley, A. A. Somovilla, P. L. Toogood, *Tetrahedron Lett.* **1988**, *29*, 1853 – 1856.

[8] S. R. Crabtree, W. L. A. Chu, L. N. Mander, *Synlett* **1990**, 169 – 170.

[9] M. Miyashita, T. Suzuki, A. Yoshikoshi, *Tetrahedron Lett.* **1987**, *28*, 4293 – 4296.

[10] K. Tanemura, T. Suzuki, T. Horaguchi, *J. Chem. Soc. Perkin Trans. 1* **1992**, 2997 – 2998.

[11] A. F. Barrero, S. Arseniyadis, J. F. Quilez Dell Moral, M. Mar Herrador, M. Valdivia, D. Jimenez, *J. Org. Chem.* **2002**, *67*, 2501 – 2508.

[12] For selected previous bromoketalization reactions, see: a) A. Srikrishna, G. Sundarababu, *Tetrahedron* **1990**, *46*, 7901 – 7910; b) J. D. White, P. Theramongkol, C. Kuroda, J. R. Engebrecht, *J. Org. Chem.* **1988**, *53*, 5909 – 5921; c) G. Stork, R. Mook, Jr., S. A. Biller, S. D. Rychnovsky, *J. Am. Chem. Soc.* **1983**, *105*, 3741 – 3742; d) G. Stork, R. Mook, Jr., *J. Am. Chem. Soc.* **1983**, *105*, 3720 – 3722.

[13] J. M. Kanabus-Kaminska, J. A. Hawari, D. Griller, C. Chatgilialoglu, *J. Am. Chem. Soc.* **1987**, *109*, 5267 – 5268.

[14] K. Miura, Y. Ichinose, K. Nozaki, K. Fugami, K. Oshima, K. Utimoto, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 143 – 147.

[15] K. C. Nicolaou, T. Montagnon, P. S. Baran, Y. L. Zhong, *J. Am. Chem. Soc.* **2002**, *124*, 2245 – 2258.

