Azadirachtin Precursors

Studies Towards the Synthesis of Azadirachtin: Enantioselective Entry into the Azadirachtin Framework through Cascade Reactions**

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As part of a program directed towards the total synthesis of azadirachtin (**1**),[1,2] we have adopted a radical-based approach for the construction of its crowded C8–C14 bond.[3] Herein we report further advances along this path-

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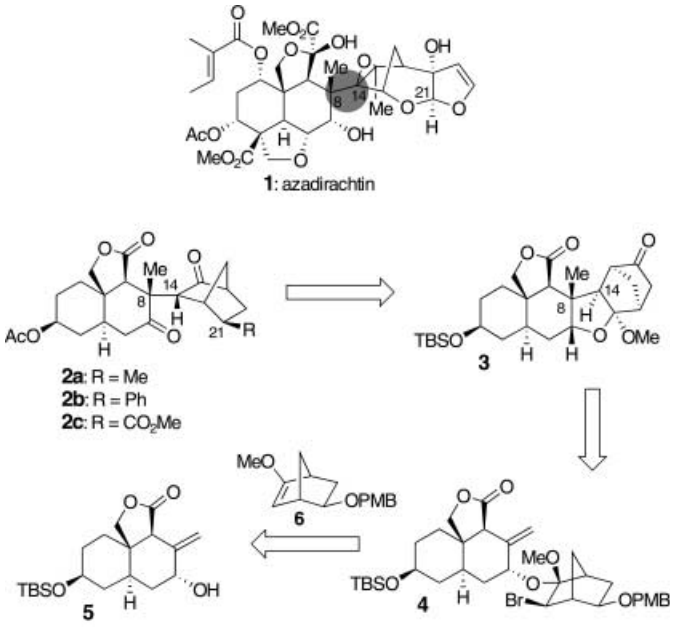
[**] We thank Dr. D. H. Huang and Dr. G. Siuzdak for NMR spectroscopic and mass spectroscopic assistance, respectively, and Dr. Raj Chadha for X-ray crystallographic analysis. This work was financially supported by the National Institutes of Health (USA), The Skaggs Institute for Chemical Biology, predoctoral fellowships from the Division of Organic Chemistry of the ACS sponsored by Novartis and the Division of Medicinal Chemistry of the ACS sponsored by Pfizer (both to A.J.R.), a Feodor Lynen postdoctoral fellowship from the Alexander von Humboldt Foundation (to H.M.), and a postdoctoral fellowship from Bayer AG (to M.F.).

 DOI: 10.1002/ange.200351744

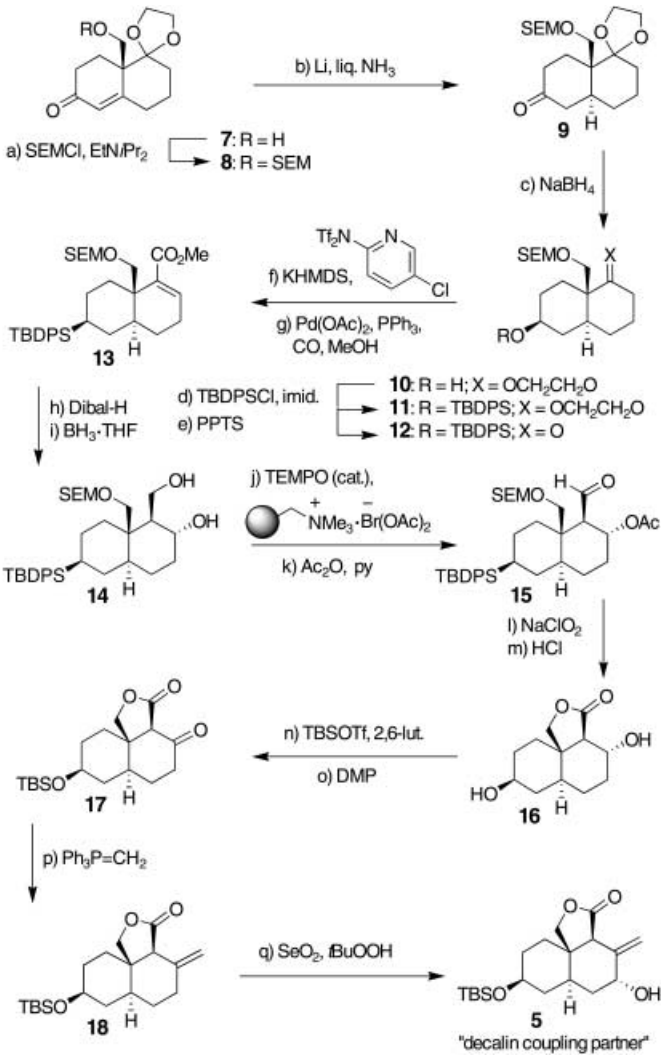
way, including a number of novel cascade reactions and the arrival at suitably functionalized advanced systems **2a–c**, which contain both domains of the target molecule (Scheme 1).



Scheme 1. Retrosynthetic analysis of advanced azadirachtin intermediate **2**.

Scheme 1 outlines the retrosynthetic plan for the enantioselective construction of azadirachtin systems such as **2a–c**, which feature both a functionalized decalin and a bicyclic framework linked together through the C8–C14 bond. It was rationalized that such a compound could be formed through an acid-induced opening of the mixed ketal moiety within the polycyclic compound **3**, followed by suitable elaboration. Lactone **3**, which contains, in principle, enough functionality for a drive towards azadirachtin, was reasoned to arise from a radical cyclization cascade sequence initiated from bromoketal **4**. As originally proposed,[3] bromoketal **4** was to be assembled from the allylic alcohol **5** and methyl enol ether **6**. Hence, enantiocontrolled sequences for the construction of both **5** and **6** were sought.

The synthesis of allylic alcohol **5** is depicted in Scheme 2. Known decalin alcohol **7** (prepared from 1,3-cyclohexanedione with approximately 70% *ee*)[4] was protected as a SEM ether (SEMCl, EtN*i*Pr$_2$, 85% yield), and the resulting enone was subjected to a Birch reduction (Li, liquid NH$_3$, 80% yield) to afford *trans*-decalin system **9**. The ketone functionality of compound **9** was then reduced stereoselectively with NaBH$_4$ (99% yield), and the obtained β-hydroxy compound was silylated (TBDPSCl, imidazole, DMAP, 80% yield), leading to protected compound **11**. The dioxolane system of compound **11** was removed upon treatment with mild acid (PPTS), and the crude ketone was transformed into the corresponding enol triflate (KHMDS, Comin reagent, 72%

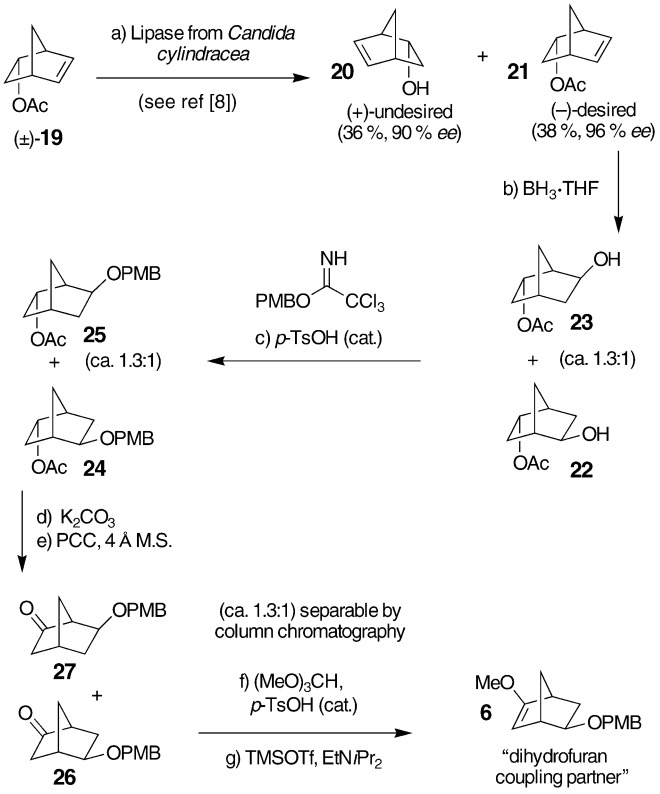


Scheme 2. Enantioselective synthesis of decalin coupling partner **5**. a) SEMCl (1.2 equiv), EtN*i*Pr$_2$ (1.5 equiv), CH_2Cl_2, 25 °C, 20 h, 85%; b) Li (7.0 equiv), liquid NH_3, −78 °C, 1 h, 80%; c) $NaBH_4$ (1.2 equiv), THF/EtOH (1:1), −78→25 °C, 3 h, 99%; d) TBDPSCl (2.0 equiv), imid. (1.5 equiv), DMAP (0.2 equiv), DMF, 25 °C, 24 h, 80%; e) PPTS (0.05 equiv), acetone, 65 °C, 24 h; f) KHMDS (3.5 equiv), Comin reagent (1.2 equiv), THF, −78 °C, 0.5 h, 72% over two steps; g) $Pd(OAc)_2$ (0.3 equiv), PPh_3 (0.6 equiv), CO (1 atm), EtN*i*Pr$_2$ (3.0 equiv), MeOH (50 equiv), DMF, 60 °C, 12 h, 89%; h) DIBAL-H (4.0 equiv), CH_2Cl_2, −78→0 °C, 2 h, 95%; i) BH_3·THF (5.0 equiv), THF, 0 °C, 12 h, 65%; j) TEMPO (0.1 equiv), resin (3.0 equiv), CH_2Cl_2, 25 °C, 2 h; k) Ac_2O (5.0 equiv), py/CH_2Cl_2 (1:4), 25 °C, 0.1 h; l) $NaClO_2$ (5.0 equiv), 2-methyl-2-butene (40 equiv), NaH_2PO_4 (3.5 equiv), *t*BuOH/H_2O (10:1), 25 °C, 2 h; m) HCl (1 N)/dioxane (1:1), 75 °C, 16 h, 83% over four steps; n) TBSOTf (1.1 equiv), 2,6-lut. (1.3 equiv), CH_2Cl_2, 25 °C, 1 h, 72%; o) DMP (1.5 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 25 °C, 3 h, 97%; p) $Ph_3P{=}CH_2$ (8.0 equiv), THF, 25 °C, 12 h, 78%; q) SeO_2 (3.0 equiv), *t*BuOOH (5.0 equiv), CH_2Cl_2, 25 °C, 6 h, 50%. SEM = 2-(trimethylsilyl)ethoxymethyl, TBDPS = *tert*-butyldiphenylsilyl, imid = imidazole, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, PPTS = pyridinium *p*-toluenesulfonate, KHMDS = potassium bis(trimethylsilyl)amide, Comin reagent = 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine, TEMPO = 4-oxo-2,2,6,6-tetramethyl-1-piperidinyloxy (free radical), py = pyridine, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl, DMP = Dess–Martin periodinane.

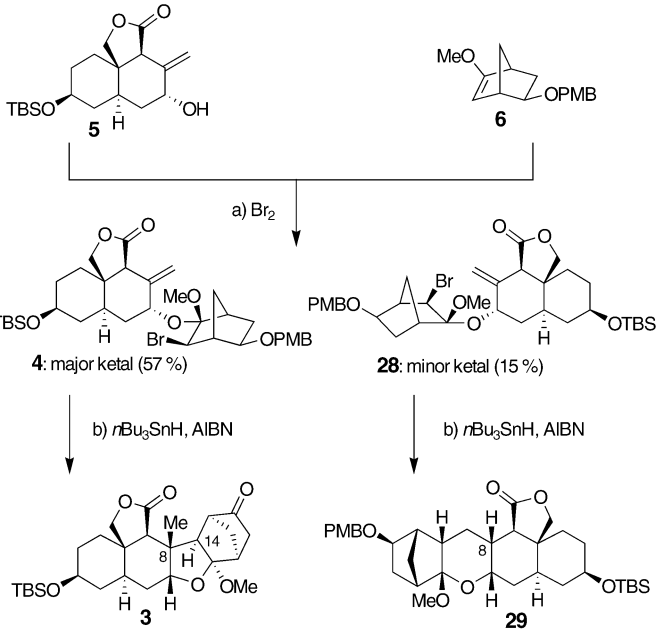
over two steps). The resulting triflate was then engaged in a palladium-catalyzed carbonylation reaction to afford α,β-unsaturated methyl ester **13** in 89% yield.[5] Reduction of **13** with DIBAL-H (95% yield), followed by regio- and stereoselective hydroboration led to diol **14** in 65% yield after basic workup. This diol was then selectively oxidized to the corresponding hydroxyaldehyde through a polymer-assisted TEMPO-catalyzed oxidation procedure[6] and subsequently acetylated (Ac_2O, Et_3N) to produce aldehyde acetate **15**. Further oxidation to the carboxylic acid, followed by treatment of the resulting compound with aqueous HCl in dioxane, gave rise to dihydroxy lactone **16** (83% yield over four steps). Diol **16** was then selectively protected as a TBS ether (72% yield), which was oxidized to the dicarbonyl system **17** with DMP (97% yield). Finally, selective olefination of the ketone functionality of **17** ($Ph_3P=CH_2$, 78% yield) followed by regio- and stereoselective allylic oxidation of the resulting **18** as effected by SeO_2 and *t*BuOOH afforded the desired allylic alcohol **5** in 50% yield.[7]

The enantioselective synthesis of the required enol ether **6** is shown in Scheme 3. A known resolution procedure was used to prepare the desired *endo* acetate **21** from racemic acetate **19** in 38% yield with high enantioselectivity (96% *ee*).[8] Hydroboration (BH_3·THF) of the C=C bond in **21** followed by basic workup with hydrogen peroxide resulted in an inseparable mixture of regioisomeric alcohols (**22**/**23** ≈ 1:1.3) in 78% combined yield. This mixture was protected with a PMB group to provide **24** and **25**, the acetate was removed (K_2CO_3, MeOH, 84% yield over two steps), and the resulting alcohols were oxidized to the corresponding ketones **26** and **27** upon treatment with PCC (88% combined yield). The desired ketone **26** was separated from its unwanted isomer **27** by flash column chromatography (silica gel), and then transformed into the targeted enol ether **6** by first constructing its dimethyl ketal ($(MeO)_3CH$, *p*-TsOH, 98% yield) and then eliminating one molecule of MeOH under the conditions reported by Gassman et al. (TMSOTf/Et*N*iPr_2, 57% yield).[9]

With both building blocks **5** and **6** in hand, the next task was the tethering of the two domains through a ketal bridge. As depicted in Scheme 4, treatment of enol ether **6** with bromine in CH_2Cl_2 in the presence of *N*,*N*-dimethylaniline at



Scheme 3. Enantioselective synthesis of bicyclic methyl enol ether **6** (dihydrofuran coupling partner). a) See reference [8]; b) BH_3·THF (1.0 equiv), THF, 0°C, 1 h; then NaOH (1 M; 5.0 equiv), aqueous H_2O_2 (30 wt%; 5.0 equiv), 30 min, 78%; c) *p*-methoxybenzyltrichloroacetimidate (2.0 equiv), *p*-TsOH (0.1 equiv), CH_2Cl_2, 25°C, 10 h; d) K_2CO_3 (0.5 equiv), MeOH, 25°C, 8 h, 84% over two steps; e) PCC (2.5 equiv), M.S. (4 Å), CH_2Cl_2, 25°C, 1 h, 88%; f) $(MeO)_3CH$ (1.5 equiv), *p*-TsOH (0.05 equiv), MeOH, 25°C, 3 h, 98%; g) TMSOTf (1.1 equiv), Et*N*iPr_2 (1.2 equiv), CH_2Cl_2, −20→25°C, 16 h, 57%. PMB = *p*-methoxybenzyl, *p*-TsOH = *p*-toluenesulfonic acid monohydrate, PCC = pyridinium chlorochromate.



Scheme 4. Radical cascade-based construction of the C8–C14 bond of azadirachtin; construction of **3** and **29**. a) Br_2 (1.0 equiv), *N*,*N*-dimethylaniline (2.0 equiv), CH_2Cl_2, **6** (1.3 equiv), **5** (1.0 equiv), −78→0°C, 12 h, 72% combined yield; b) nBu_3SnH (1.3 equiv), AIBN (0.5 equiv) in toluene (0.01 M), 110°C, 15 h, 75% (**4**), 74% (**29**). AIBN = 2,2′-azobisisobutyronitrile.

−78°C, followed by addition of allylic alcohol **5** at that temperature, afforded bromoketal **4** as the major product (57%) together with bromoketal **28** as a minor product (15%).[10] Individual treatment of these ketals with nBu_3SnH and AIBN (0.01M in toluene, 110°C) led to hexacyclic products **3** (75%, desired product for azadirachtin; see Table 1) and **29** (74%), respectively. Interestingly, loss of

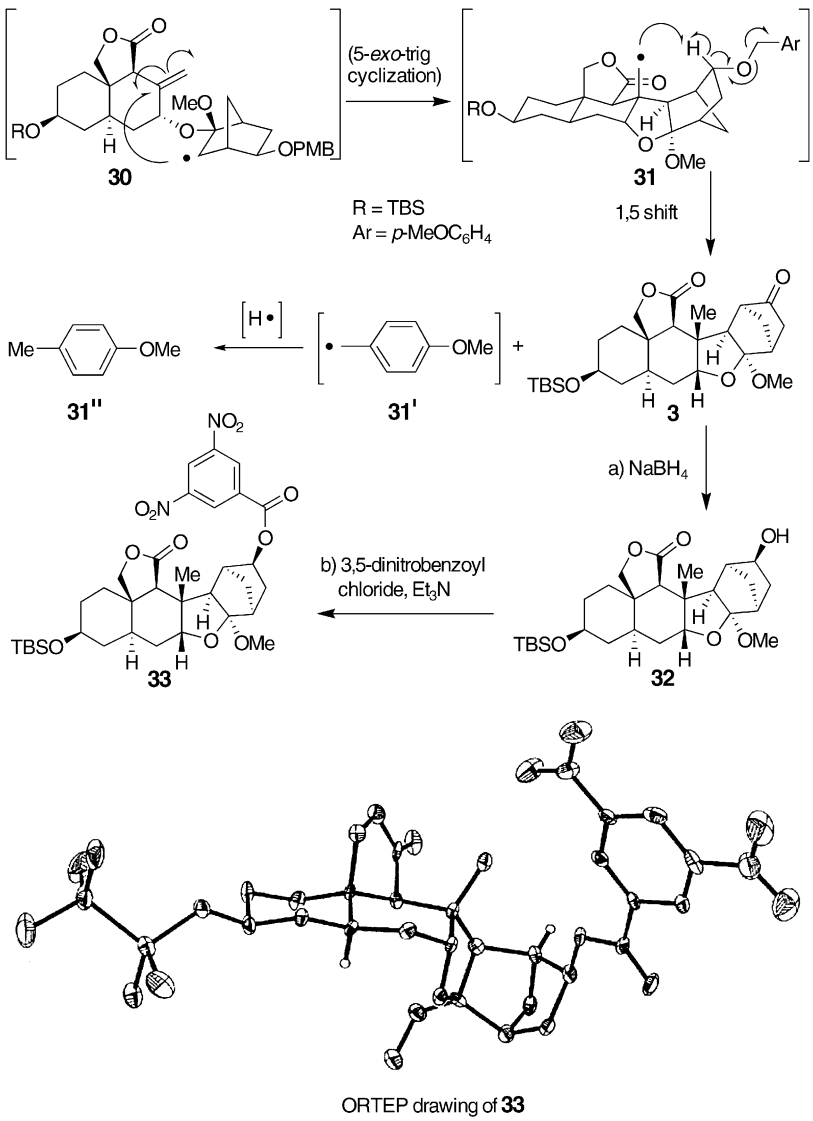
the PMB ether and concomitant conversion into a ketone accompanied the 5-*exo*-trig cyclization to give **3** from the major bromoketal **4**. Also of interest is the fact that the minor ketal underwent cyclization in a 6-*endo*-trig manner to afford **29** as opposed to the expected 5-*exo*-trig cyclization.[11]

A mechanistic explanation for the intriguing transformation of **4** into **3** is shown in Scheme 5. Thus, the secondary radical generated from **4** (i.e. **30**) undergoes the expected 5-*exo*-trig cyclization to forge the C8–C14 bond, leading to the highly reactive primary radical **31**. The proximity of the radical center within **31** to the hydrogen atom on the carbon atom that bears the PMB ether, five bonds away, coupled with the overall rigidity and reactivity of the system, apparently allows the indicated 1,5 H shift, with concomitant oxidative rupture of the benzyl bond, leading to the observed product **3** and *p*-methoxytoluene (**31″**), which presumably arises from the intermediate radical species **31′**.[12] To confirm the structure of **3**, a suitably crystalline derivative for X-ray crystallographic analysis was sought and found in the 3,5-dinitrobenzoate **33**. The latter compound was obtained by a stereoselective reduction of **3** with $NaBH_4$ (80% yield) followed by reaction with 3,5-dinitrobenzoyl chloride and Et_3N in the presence of DMAP (85% yield). Indeed, the X-ray crystallographic analysis of **33** revealed its structure (see ORTEP drawing, Scheme 5) and, by extension, that of **3**.

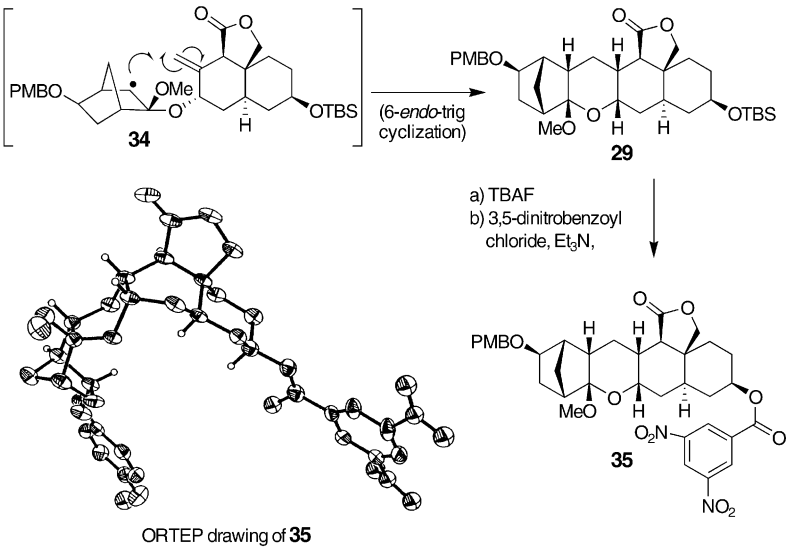
The radical cyclization reaction of the minor bromoketal (**28**, Scheme 4) was also intriguing in that it apparently proceeded through a 6-*endo*-trig cyclization of the initially formed radical **34** to form hexacycle **29** as shown in Scheme 6.[13] The structure of **29** was unambiguously assigned by X-ray crystallographic analysis of the 3,5-dinitrobenzoate derivative **35**, obtained by desilylation of **29** (100% yield) and ester formation (80% yield; see ORTEP structure in Scheme 6).

Modeling studies (ball and stick) with **28** indicate that a 5-*exo*-trig cyclization would be associated with a severe steric interaction between the methoxy group and the olefinic site in contrast to a 6-*endo*-trig mode of ring closure, which is devoid of such interactions. Similar modeling with the major bromoketal **4**, on the other hand, shows that the expected 5-*exo*-trig cyclization does not suffer from the methoxy–olefin steric interaction, explaining the difference in the behavior of the two diastereomeric bromoketals.

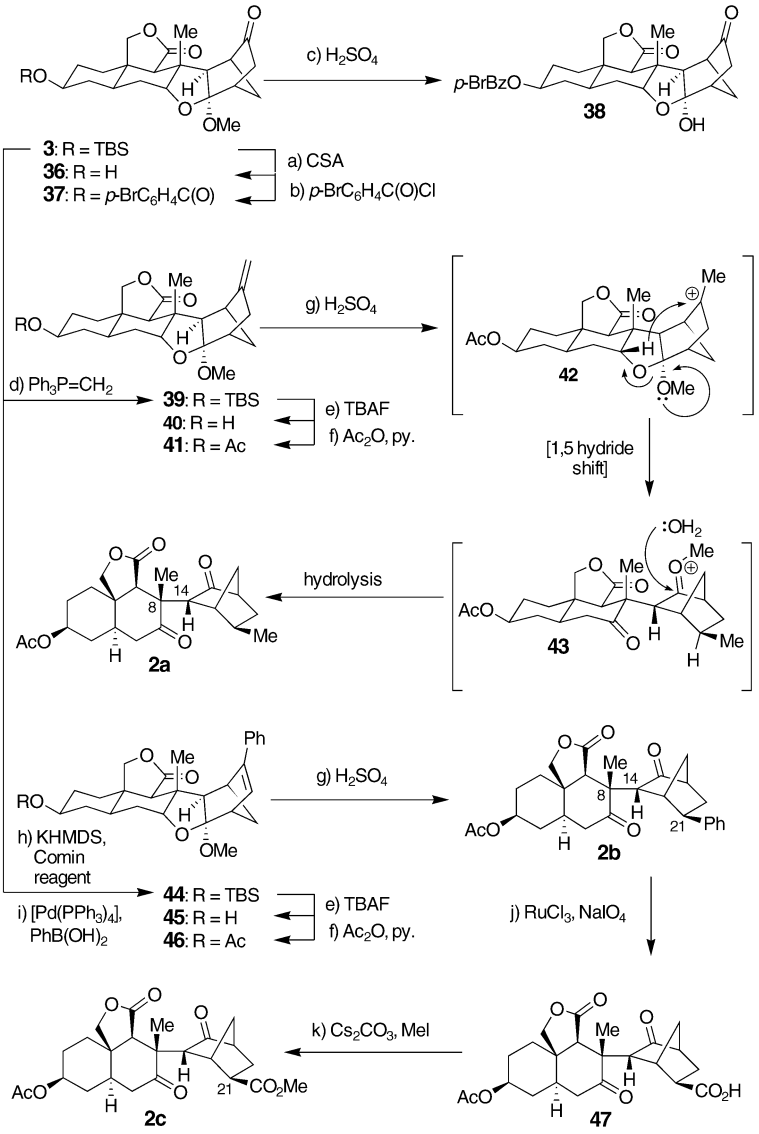
A significant finding in this study was the demonstration of the rupture of the mixed ketal bridge employed to facilitate C8–C14 bond formation (Scheme 7). These studies began with an attempt to hydrolyze the mixed ketal within **3**, or variants thereof, only to realize the intransigence of the resulting lactol towards opening to the desired hydroxyketone form. The sequence **3**→**36**→**37**→**38** (desilylation, *p*-bromobenzoate formation, and treatment with H_2SO_4) is illustrative of these forays. This intransigence is in contrast to previous observations with similar compounds,[3] and underscores the subtle intricacies of reactivity within the azadirachtin scaffold. In an effort to probe further these structure-based reactivity patterns, polycycle **3** was modified to its olefinic counterpart **39** through Wittig olefination (62% yield), desilylation (→**40**, 91% yield), and acetylation (→**41**, 90% yield). Gratifyingly, **41** was smoothly converted into diketone **2a** (see Table 1) in 80% yield upon exposure to H_2SO_4 in CH_2Cl_2 at 0°C.[14] To explain this unusual transformation we invoke an initial protonation of the olefinic bond leading to a



Scheme 5. Proposed cascade sequence for the formation of **3** from major ketal **4** and structural proof of product. a) $NaBH_4$ (4.0 equiv), MeOH, 0°C, 1 h, 80%; b) 3,5-dinitrobenzoyl chloride (2.0 equiv), Et_3N (4.0 equiv), DMAP (0.2 equiv), CH_2Cl_2, 25°C, 12 h, 85%.



Scheme 6. Structural proof of polycycle **29**. a) TBAF (3.0 equiv), THF, 25 °C, 4 h, 100%; b) 3,5-dinitrobenzoyl chloride (2.0 equiv), Et_3N (5.0 equiv), DMAP (0.2 equiv), CH_2Cl_2, 25 °C, 12 h, 80%. TBAF = tetrabutylammonium fluoride.



Scheme 7. Hydrolysis of mixed ketal polycycles and synthesis of **2a**–**c**. a) CSA (2.0 equiv), MeOH, 25 °C, 1 h, 90%; b) 4-bromobenzoyl chloride (2.0 equiv), Et_3N (5.0 equiv), DMAP (0.2 equiv), CH_2Cl_2, 25 °C, 12 h, 81%; c) H_2SO_4 (5.0 equiv), CH_2Cl_2, 0 °C, 0.5 h, 85%; d) $Ph_3P{=}CH_2$ (10.0 equiv), THF, 25 °C, 15 h, 62%; e) TBAF (3.0 equiv), THF, 40 °C, 0.5 h, 91%; f) Ac_2O (10.0 equiv), DMAP (1.0 equiv), py, 25 °C, 6 min, 90%; g) H_2SO_4 (5.0 equiv), CH_2Cl_2, 0 °C, 10 min, 80% (**2a**), 81% (**2b**); h) KHMDS (3.0 equiv), Comin reagent (2.0 equiv), THF, −78 °C, 1 h, 65%; i) $[Pd(PPh_3)_4]$ (0.1 equiv), $PhB(OH)_2$ (5.0 equiv), Cs_2CO_3 (10.0 equiv), DMF/MeOH (10:1), 80 °C, 1 h, 78%; j) $RuCl_3$ (0.5 equiv), $NaIO_4$ (20.0 equiv), $CH_3CN/CCl_4/H_2O$ (1:1:1), 25 °C, 24 h; k) Cs_2CO_3 (5.0 equiv), MeI (10.0 equiv), DMF, 25 °C, 2 h, 80% over two steps. CSA = camphorsulfonic acid.

tertiary carbocation (**42**, see Scheme 7) which then triggers an oxidative 1,5 hydride transfer with concomitant rupture of the oxygen bridge between the two domains of the molecule. Subsequent hydrolysis of the resulting intermediate **43** then leads to the observed product **2a**.

In an extension of this concept and to obtain a functional handle at what will become C21 of azadirachtin, a second foray was designed and executed. Hence, compound **3** (Scheme 7) was transformed into styrene derivative **44** via its enol triflate (KHMDS, Comin reagent, 65% yield) and through a Suzuki reaction ($[Pd(PPh_3)_4]$, $PhB(OH)_2$, 78% yield). The TBS group within **44** was then replaced by an acetate group to afford **46** via **45** (82% for two steps). Exposure of **46** to H_2SO_4 as above gave **2b**, presumably through the same cascade mechanism that led to **2a**. The phenyl ring of the latter intermediate (**2b**) was then oxidatively degraded[15] by the action of $RuCl_3$ and $NaIO_4$ to reveal carboxylic acid **47**, whose methylation afforded advanced intermediate **2c** (80% yield over two steps) equipped with a synthetically useful handle at C21.

The described chemistry represents considerable progress toward the azadirachtin structure and its congeners. Specifically, a sequence based on intramolecular radical chemistry followed by a cation-induced rupture of an initially formed bridge enabled the construction of the suitably functionalized system **2c**, setting the stage for further advances towards this formidable target. Furthermore, the observed radical- and ionic-based cascade sequences may prove

Table 1: Selected data for **3** and **2a**.

3: Colorless oil; $[\alpha]_D = -14°$ ($c = 0.10$ in $CHCl_3$); $R_f = 0.27$ (silica, 25% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 2930, 2861, 1766, 1742, 1508, 1461, 1249\ cm^{-1}$; ^1H NMR (600 MHz, C_6D_6): $\delta = 3.71$ (d, $J = 9.7$ Hz, 1H), 3.69–3.67 (m, 1H), 3.58–3.50 (m, 1H), 3.37 (d, $J = 9.7$ Hz, 1H), 3.13 (s, 3H), 2.83 (d, $J = 4.4$ Hz, 1H), 2.56 (s, 1H), 2.40 (br s, 1H), 2.32 (br s, 1H), 2.16 (dd, $J = 17.9$, 4.8 Hz, 1H), 1.88–1.80 (m, 1H), 1.61–1.42 (m, 5H), 1.39–1.22 (m, 3H), 1.14 (s, 3H), 1.03 (d, $J = 10.5$ Hz, 1H), 0.96 (s, 9H), 0.95–0.88 (m, 1H), 0.82–0.74 (m, 1H), −0.02 ppm (s, 6H); ^{13}C NMR (150 MHz, C_6D_6): $\delta = 215.1, 171.3, 115.1, 85.2, 71.1, 68.4, 67.7, 54.8, 54.1, 51.0, 42.5, 41.3, 41.1, 39.9, 38.8, 38.1, 35.6, 32.2, 30.4, 28.2, 26.0, 18.1, 16.5, -4.5, -4.6$ ppm; HRMS (MALDI, FTMS), calcd for $C_{27}H_{42}O_6Si$ [M+Na^+]: 513.2643, found: 513.2631

2a: Colorless oil; $[\alpha]_D = -34°$ ($c = 0.23$ in $CHCl_3$); $R_f = 0.52$ (silica, 50% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 2958, 2868, 1765, 1730, 1454, 1371, 1243\ cm^{-1}$; ^1H NMR (600 MHz, C_6D_6): $\delta = 4.43–4.38$ (m, 1H), 3.66 (d, $J = 9.6$ Hz, 1H), 3.48 (dd, $J = 9.6$, 2.2 Hz, 1H), 2.92 (s, 1H), 2.74 (d, $J = 4.0$ Hz, 1H), 2.62–2.58 (m, 1H), 2.52 (d, $J = 4.0$ Hz, 1H), 2.21–2.15 (m, 1H), 1.94–1.91 (m, 1H), 1.74–1.70 (m, 1H), 1.67 (s, 3H), 1.65 (d, $J = 3.5$ Hz, 1H), 1.63 (d, $J = 3.5$ Hz, 1H), 1.56–1.53 (m, 1H), 1.38–1.18 (m, 5H), 1.07–1.03 (m, 1H), 1.02–0.98 (m, 1H), 0.96 (s, 3H), 0.77 (d, $J = 7.0$ Hz, 3H), 0.58–0.52 ppm (m, 1H); ^{13}C NMR (125 MHz, C_6D_6): $\delta = 215.5, 207.1, 175.5, 169.0, 70.6, 68.6, 60.2, 58.5, 53.4, 50.4, 46.0, 43.3, 40.2, 38.6, 35.4, 34.7, 34.1, 34.0, 30.2, 27.2, 22.2, 20.7, 20.4$ ppm; HRMS (MALDI, FTMS), calcd for $C_{23}H_{30}O_6$ [M+H^+]: 403.2115, found: 403.2118

useful in other contexts within the general theme of molecular complexity and diversity construction.

Received: April 24, 2003 [Z51744]

Keywords: asymmetric synthesis · azadirachtin · domino reactions · hydride shift · natural products · radicals

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