Model Studies Towards Azadirachtin: Part 1. Construction of the Crowded C8–C14 Bond by Radical Chemistry**

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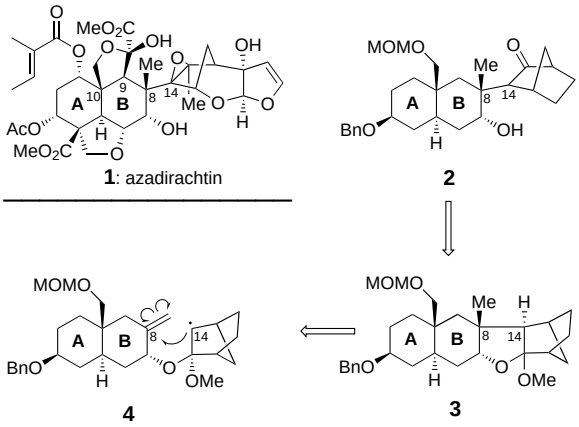
Isolated from the seeds of the neem tree (*Azadirachta indica* Juss.), azadirachtin[1, 2] (**1**, Scheme 1) exhibits potent insect antifeedant activity (active against *Schistocera gregaria* at 0.04 ppm) and growth inhibitory properties across a broad

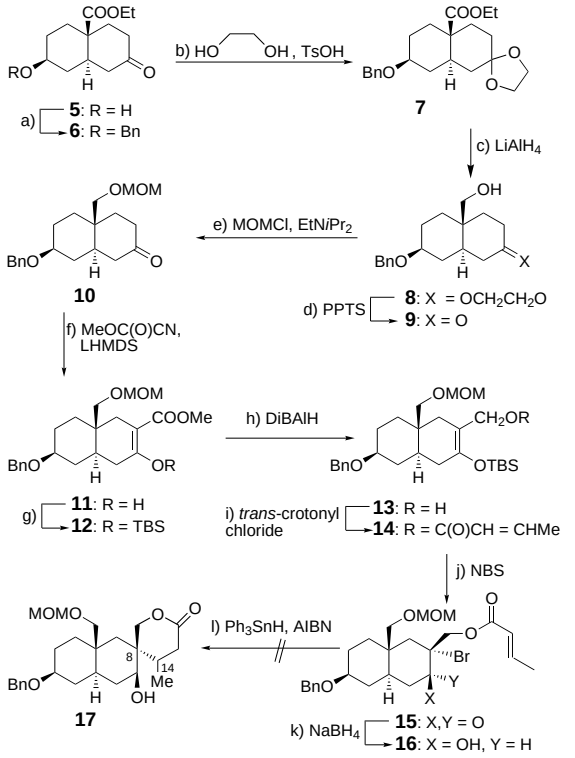


Scheme 1. Molecular structure of azadirachtin (**1**) and radical-based retrosynthesis of model system **2**.

range of insect species while having low mammalian toxicity (nontoxic to rats at doses of 8.5 g kg^{-1}).[3] Because of these important biological actions and its imposing molecular architecture, azadirachtin has elicited considerable interest from the synthetic community.[4] Despite these efforts, however, the molecule of azadirachtin still remains elusive to total synthesis, with its crowded C8–C14 bond bridging its two domains being the main obstacle. In this communication we wish to report our model studies which culminated in a potential solution to the C8–C14 problem based on a tethering strategy followed by a radical-based intramolecular coupling and dismantling of the temporary bridge.

Scheme 1 depicts the targeted model compound **2**, which contains ring systems representing the two structural domains of azadirachtin, and, in retrosynthetic format, the radical-based proposed strategy for the construction of **2**. Thus, it was reasoned that tethering the two domains through a mixed bromoketal would facilitate the intended C8–C14 coupling reaction, upon generation of the radical species **4**, by a 5-*exo*-trig cyclization to furnish **3**. Subsequent collapse of the mixed ketal bridge would then allow the generation of the targeted ring system **2** with the desired C8–C14 bond in place. The successful execution of this strategy was preceded by a number of related studies whose brief description should be instructive.

In search for a suitable *trans*-decalin system as a starting material with an angular substituent and oxygen functionalities on both rings, we found ester **5** (Scheme 2) to be an



Scheme 2. Synthesis of key building block **13** and failure of **16** to undergo 6-*endo*-trig cyclization under radical conditions. a) Benzyl 2,2,2-trichloroacetimidate (1.1 equiv), TfOH (5 mol %), cyclohexane/CH_2Cl_2 (2:1), 25 °C, 4 h, 73 %; b) ethylene glycol (3.0 equiv), TsOH (3 mol %), benzene, Dean-Stark trap, reflux, 3 h, 98 %; c) $LiAlH_4$ (1.5 equiv), THF, 0 °C, 30 min, then reflux, 4 h, 76 %; d) cat. PPTS, wet acetone, 60 °C, 18 h, 100 %; e) MOMCl (2.0 equiv), EtN*i*Pr$_2$ (2.2 equiv), CH_2Cl_2, 25 °C, 4 h, 83 %; f) MeOC(O)CN (1.4 equiv), LHMDS (2.0 equiv), HMPA (1.4 equiv), THF, −78 °C, 30 min, 68 %; g) TBSOTf (4.0 equiv), EtN*i*Pr$_2$ (5.0 equiv), CH_2Cl_2, 25 °C, 4 h, 75 %; h) DiBAlH (4.0 equiv), CH_2Cl_2, −78 °C, 1 h, 62 %; i) *trans*-crotonyl chloride (3.0 equiv), py (10.0 equiv), CH_2Cl_2, 25 °C, 1 h, 99 %; j) NBS (1.1 equiv), CH_2Cl_2, −78 °C, 2 h, 72 %; k) $NaBH_4$ (3.6 equiv), CH_2Cl_2/MeOH (1:1), −50 °C, 1 h, 78 %; l) Ph_3SnH (1.4 equiv), AIBN (0.15 equiv), toluene, 100 °C. TfOH = trifluoromethanesulfonic acid, TsOH = *p*-toluenesulfonic acid, PPTS = pyridinium *p*-toluenesulfonate, MOM = methoxymethyl, LHMDS = lithium bis(trimethylsilyl)amide, HMPA = hexamethylphosphoramide, TBS = *tert*-butyldimethylsilyl, DiBAlH = diisobutylaluminumhydride, py = pyridine, NBS = *N*-bromosuccinimide, AIBN = 2,2′-azobisisobutyronitrile.

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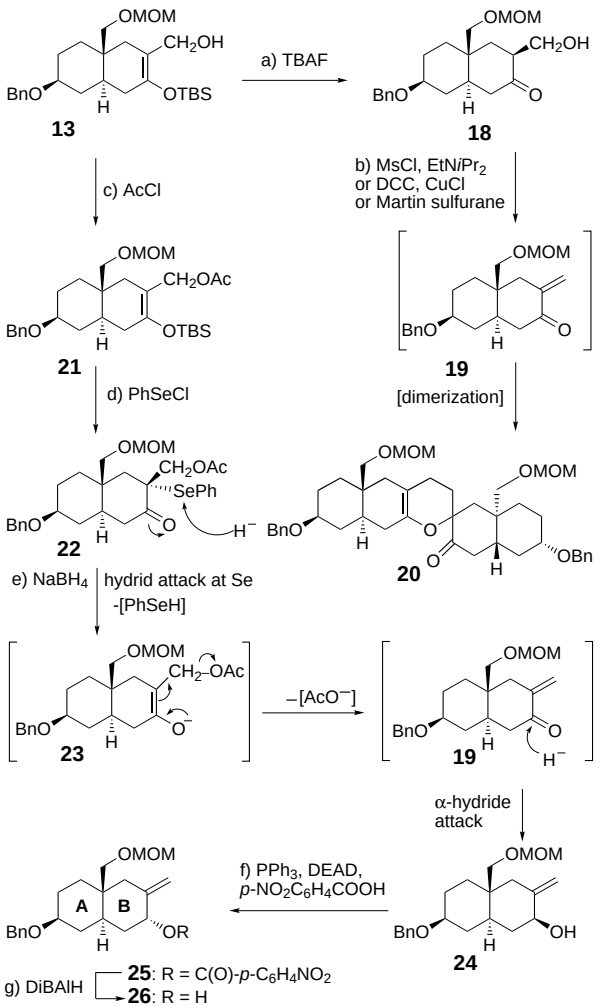
ideal candidate for these studies. This compound is readily available in large quantities, albeit in racemic form, from commercially available starting materials by a three-step modification of a literature procedure.[5] After benzylation of the hydroxy group in **5**, the resulting ketone **6** was protected as the 1,3-dioxolane **7**. Reduction of **7** with $LiAlH_4$ followed by acid-induced hydrolysis of the ethylene ketal furnished hydroxy ketone **9** via intermediate **8** in 76% overall yield. The primary alcohol in compound **9** was then protected as a MOM acetal to produce **10**, which was regioselectively carboxymethylated with Mander's reagent[6] in the presence of LHMDS and HMPA under kinetic conditions ($-78\,^{\circ}C$) to afford enol methyl ester **11** in 68% yield. Silylation of this enol (TBSOTf/EtNiPr$_2$) then led to silyl ether ester **12** (75% yield) whose reduction with DiBAlH furnished primary alcohol **13** in 62% yield.

Our first endeavor into the C8–C14-connected model assembly required bromo acrylate **16** as a possible precursor to a spirocyclic system, **17**, through radical generation and subsequent 6-*endo*-trig cyclization. Precursor **16** was obtained from compound **13** by esterification with *trans*-crotonyl chloride (py, 99% yield), followed by bromination with NBS (72% yield) and $NaBH_4$ reduction (78% yield). However, all attempts to induce ring closure within this compound (**16**) to **17** under radical conditions (tin hydrides, AIBN) failed.[7] These failures led us to conclude that, despite its advantages, the ester bridge was not the best tether for our purposes and that a highly stabilized and congested tertiary radical on the decalin system might not be a sufficiently reactive species to form the C8–C14 bond. Hence, we opted for an alternative strategy in which a ketal linkage was to be used in conjugation with a 5-*exo*-trig cyclization to take place from the "right" domain of the molecule onto the decalin system. The latter mode of cyclization is known to be associated with higher reaction rates than the originally attempted 6-*endo*-trig ring closure[8] and its adoption was, therefore, accompanied by considerable optimism.

The new plan required allylic alcohol **26** as the decalin substrate, a compound that was synthesized from silylenol ether **13** as shown in Scheme 3. Thus, exposure of **13** to TBAF under buffered conditions resulted in the stereoselective formation of ketone **18** in quantitative yield. Attempted dehydration of **18** mediated by MsCl/EtNiPr$_2$, DCC/CuCl,[9] or Martin sulfurane[10] gave only pentacyclic compound **20** in high yield, presumably through a Diels–Alder type dimerization of the resulting enone **19**.[11] To circumvent this hurdle, it became clear that it was necessary to generate and reduce the enone **19** at low temperature. To this end, alcohol **13** was acetylated to silylenol acetate **21** which was then converted, in high yield, to **22** (PhSeCl, $-78\,^{\circ}C$). Ketoselenide **22** was treated with $NaBH_4$ in MeOH/CH_2Cl_2 at $-78\,^{\circ}C$ to furnish allylic alcohol **24** in 98% overall yield from **22**. This remarkable transformation (**22**→**24**) presumably proceeds through the cascade sequence shown in Scheme 3 via intermediates **23** and **19**. The stereochemistry of the newly generated allylic alcohol on ring **B** of compound **24** was inverted by a Mitsunobu-type reaction as modified by Martin[12] followed by DiBAlH reduction of the resulting



Scheme 3. Synthesis of allylic alcohol **26**. a) TBAF (1.1 equiv), THF/AcOH (100:1), 25 °C, 6 h, 100%; b) e.g., MsCl (2.5 equiv), EtNiPr$_2$ (7.5 equiv), CH_2Cl_2, 25 °C, 24 h, 83%; c) AcCl (3.0 equiv), py (10.0 equiv), CH_2Cl_2, 25 °C, 1 h, 67%; d) PhSeCl (1.1 equiv), −78 °C, 1 h, then 25 °C, 1 h; e) $NaBH_4$ (6.8 equiv), CH_2Cl_2/MeOH (1:1), −78 °C, 1 h, then 25 °C, 1 h, 98% (2 steps); f) PPh_3 (3.0 equiv), DEAD (3.0 equiv), *p*-nitrobenzoic acid (2.5 equiv), benzene, 25 °C, 14 h, 78%; g) DiBAlH (3.1 equiv), CH_2Cl_2, −78 °C, 3 h, 79%. TBAF = tetrabutylammonium fluoride, Ms = methanesulfonyl, DEAD = diethyl azodicarboxylate.

p-nitrobenzoate **25** to smoothly lead to the desired product **26** in 79% yield.

The required bromoolefin **28** was obtained as a 1:1 mixture of diastereoisomers (**28a** and **28b**) by coupling of allylic alcohol **26** with enol ether **27** in the presence of Br_2[13] as shown in Scheme 4. This shorter, mixed ketal tether, originally introduced by Stork et al.,[14] was necessary for our intentions to employ a 5-*exo*-trig radical cyclization. In the event, exposure of the diastereomeric mixture of bromoketals **28a** and **28b** to *n*Bu_3SnH/AIBN in toluene at 100 °C produced, in 79% combined yield, a diastereomeric mixture of tetracyclic compounds **29a** and **29b** through a reaction in which the expected C8–C14 bond formation was accompanied by oxidative removal of the MOM group so that the aldehyde function at the angular position was unraveled.

Scheme 5 provides a mechanistic rationale for this interesting cascade sequence that leads from the initially formed

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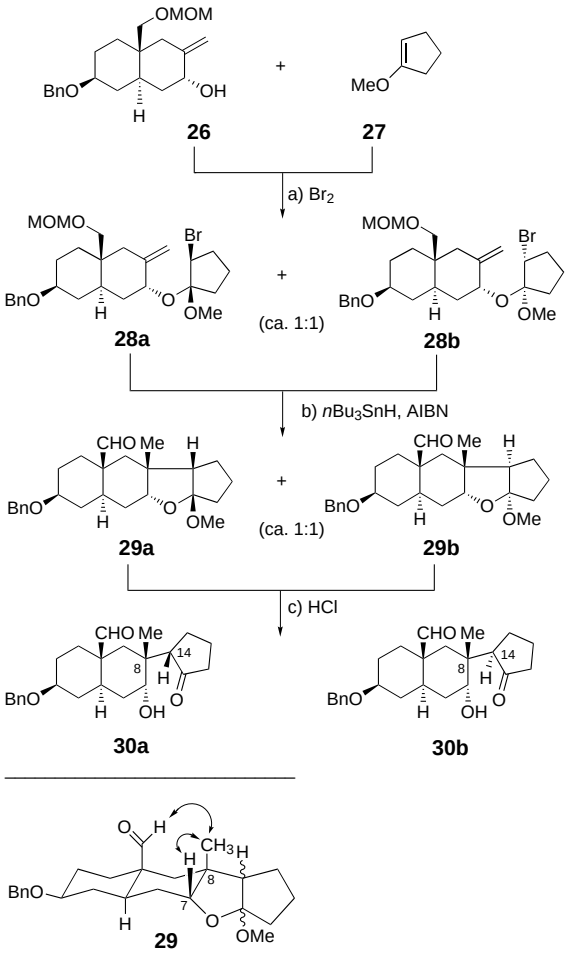
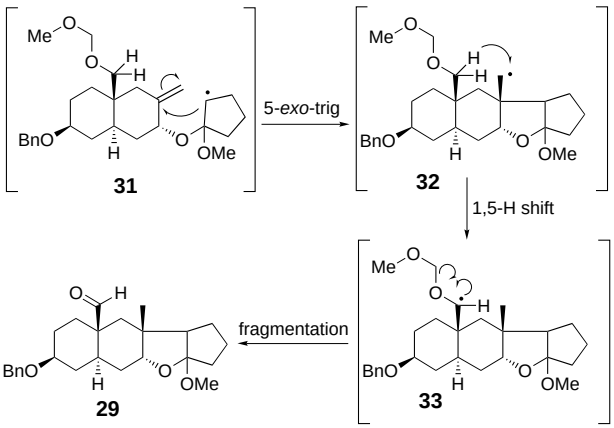


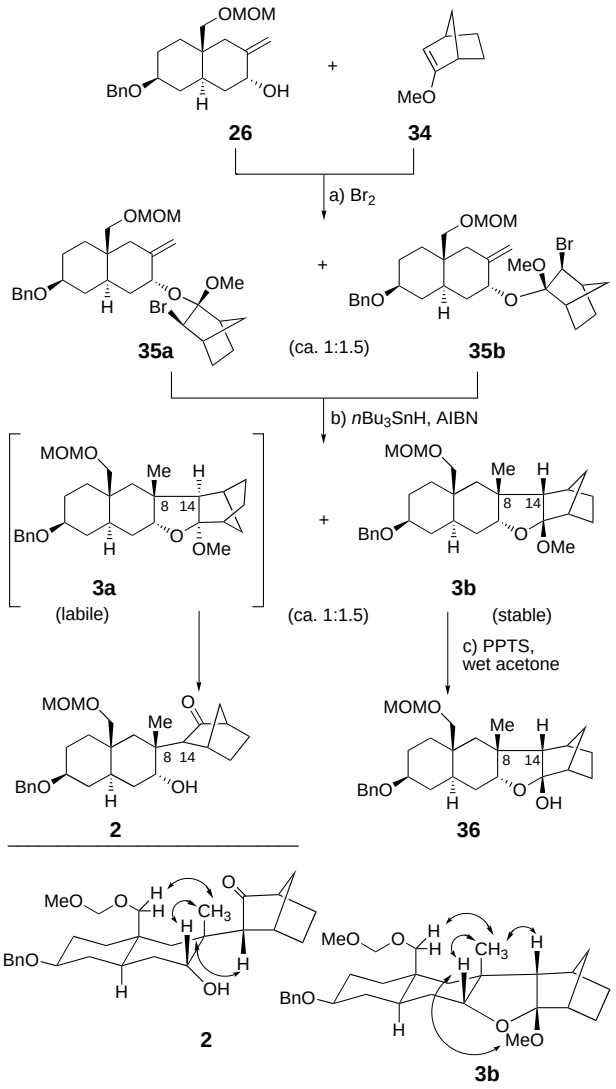
Scheme 4. Synthesis of model systems **30a** and **30b**. a) **27** (10.0 equiv), Br_2 (5.0 equiv), *N*,*N*-dimethylaniline (6.0 equiv), CH_2Cl_2, 25 °C, 12 h, 79% (mixture of diastereoisomers, ca. 1:1); b) nBu_3SnH (1.6 equiv), AIBN (0.14 equiv), 0.004 M in toluene, 12 h, 100 °C, 79%; c) 1 M aq. HCl/THF (1:3.3), 25 °C, 144 h, 70% (separated diastereoisomers, 1:1).



Scheme 5. Postulated mechanism for the radical-based cascade sequence **28** → **29**.

secondary radical **31** to the observed tetracyclic aldehyde **29** via the presumed intermediates **32** and **33** (5-*exo*-trig). The *cis*-stereochemical assignments for both obtained isomers at the newly generated decalin fusion (C7–C8) were based on NOE studies (see structures **29a** and **29b**, Scheme 4). Hydrolysis of the mixture of these two ketals under acidic conditions (aq. HCl, THF) led to the two hydroxy ketoaldehydes **30a** and **30b** (70% combined yield) which were separated by flash column chromatography (silica gel).

These encouraging results prompted us to attempt the construction of a model system closer to the structure of azadirachtin, namely compound **2** (Scheme 6). Thus, coupling of allylic alcohol **26** with racemic 1-methoxynorbornene



Scheme 6. Synthesis of azadirachtin model systems **2**, **3b** and **36**. a) **34** (5.0 equiv), Br_2 (4.3 equiv), *N*,*N*-dimethylaniline (4.65 equiv), CH_2Cl_2, 25 °C, 2 h, 71% (mixture of diastereoisomers, ca. 1.5:1); b) nBu_3SnH (1.3 equiv), AIBN (0.2 equiv), 0.003 M in toluene, 15 min, 110 °C, 70% (mixture of diastereoisomers, ca. 1.5:1); c) PPTS (0.05 equiv), acetone/H_2O (10:1), 65 °C, 72 h, 85%.

(**34**)[15] under the influence of Br_2 furnished a mixture of the two diastereomeric bromoketals **35a** and **35b** (ratio ca. 1:1.5) formed by exclusive addition of bromonium ion to the *exo* face of the norbornene framework as expected (71% total yield). On exposure to nBu_3SnH/AIBN under the above-mentioned conditions, the mixture of bromoketals **35a** and **35b** gave rise to polycyclic systems **3a** and **3b** (ca. 1:1.5 ratio, 70% combined yield) through the desired C8–C14 bond formation. Upon aqueous workup it was observed that the

minor diastereoisomer **3a** was readily converted to the opened hydroxy ketone **2** by hydrolysis. In contrast, the major component **3b** remained intact; it required acidic conditions for its hydrolysis (PPTS, H_2O/acetone, 85% yield), and then lead only to its closed hydroxy tetrahydrofuran form **36** (for selected physical properties of compounds **2** and **36**, see Table 1). This difference in reactivity for the two isomers can be rationalized considering the release of strain involved in going from the closed structure **3a** (C8 methyl group against the two-carbon bridge of the norbornene residue) to the open form **2**, whereas systems **3b** and **36** suffer from no such release of strain. The stereochemical assignments for this series of compounds were based on NOE studies on compounds **2** and **3b** as shown in Scheme 6 (arrows on structures).

Table 1. Selected physical properties of compounds **2** and **36**.

2: Colorless oil; $R_f = 0.28$ (silica, 33% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 3424, 2931, 2860, 1719, 1454, 1155, 1108, 1044\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.32$ (s, 5H), 4.59 (s, 2H), 4.54 (s, 2H), 3.76 (d, $J = 9.9$ Hz, 1H), 3.51 (d, $J = 9.9$ Hz, 1H), 3.44 (m, 1H), 3.40 (d, $J = 2.5$ Hz, 1H), 3.32 (s, 3H), 2.83 (m, 1H), 2.73 (d, $J = 4.4$ Hz, 1H), 2.31 (d, $J = 4.0$ Hz, 1H), 1.84–1.36 (m, 17H), 1.19 ppm (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta =$ 222.1, 139.3, 129.3, 128.2, 128.1, 97.4, 78.0, 76.8, 70.5, 66.1, 64.1, 55.8, 52.3, 41.3, 40.4, 38.4, 36.8, 35.8, 35.0, 34.8, 34.0, 33.7, 27.9, 25.0, 24.5, 24.1 ppm; HRMS (MALDI–FTMS), calcd for $C_{28}H_{40}O_5$ $[M+Na^+]$: 479.2768, found: 479.2776

36: Colorless oil; $R_f = 0.36$ (silica, 33% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 3412, 2931, 2872, 2343, 1448, 1114, 1031\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.32$ (s, 5H), 4.59 (s, 2H), 4.55 (d, $J = 11.7$ Hz, 1H), 4.52 (d, $J =$ 11.7 Hz, 1H); 4.01 (bs, 1H), 3.71 (d, $J = 9.7$ Hz, 1H), 3.54 (d, $J = 9.7$ Hz, 1H), 3.40 (m, 1H), 3.34 (s, 3H), 2.12 (m, 3H), 1.98 (m, 1H), 1.91 (m, 1H), 1.80–1.73 (m, 3H), 1.68 (m, 1H), 1.62–1.54 (m, 8H), 1.46 (bs, 1H), 1.24 (s, 3H), 1.19–1.16 (m, 2H), 0.85 ppm (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 139.3, 129.0, 128.2, 128.1, 114.1, 97.4, 81.4, 77.9, 70.4, 68.1, 65.2, 55.8,$ 44.2, 42.7, 38.0, 37.9, 37.2, 36.3, 36.0, 35.4, 34.2, 31.1, 29.9, 29.8, 27.9, 23.0 ppm; HRMS (MALDI–FTMS), calcd for $C_{28}H_{40}O_5$ $[M+Na^+]$: 479.2768, found: 479.2758

The described chemistry provides a potential solution to the construction of the difficult C8–C14 bond of azadirachtin and paves the way for a total synthesis of this formidable synthetic target. It also provides useful insights into cascade reactions and other processes involving radical cyclizations that may prove useful in other situations where fusions of sterically congested carbon–carbon bonds may be required. In the following communication we report an alternative approach for constructing azadirachtin's most challenging bond, the C8–C14 bridge.[16]

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