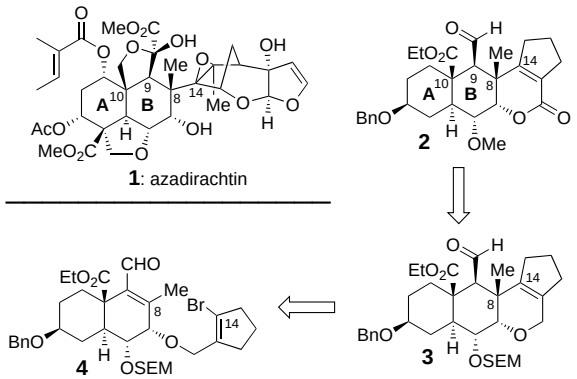
Model Studies Towards Azadirachtin: Part 2. Construction of the Crowded C8–C14 Bond by Transition Metal Chemistry**

K. C. Nicolaou,* A. J. Roecker, Markus Follmann, and Rachid Baati

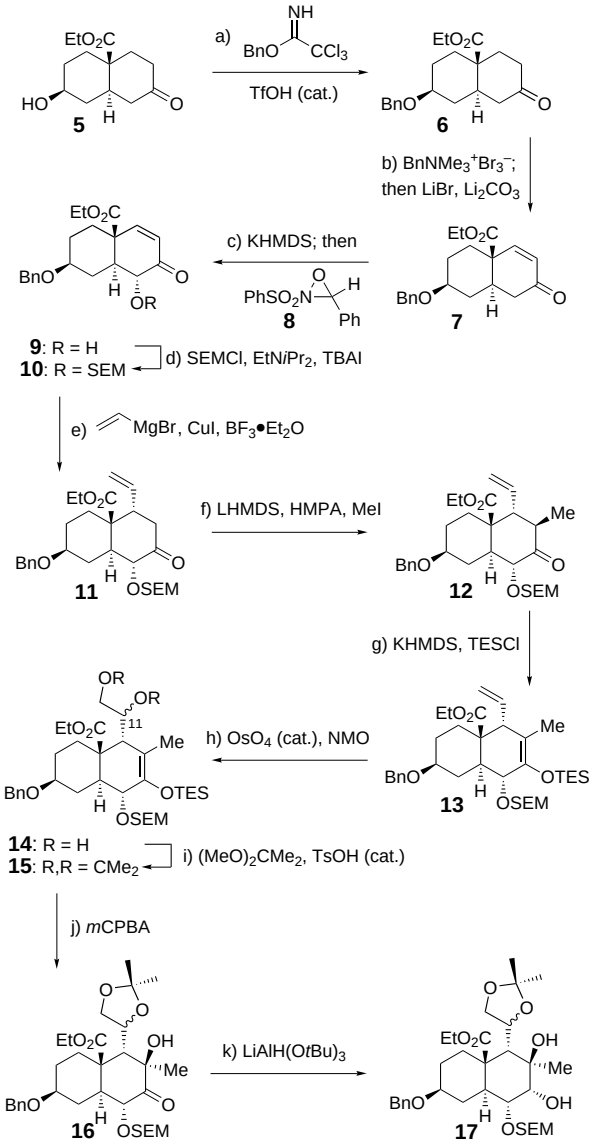
In the preceding communication,[1] we described our radical-based studies in the azadirachtin area providing a possible solution to the molecule's crowded C8–C14 bond problem. Herein, we wish to report an alternative strategy based on activated transition metal intermediates that may also offer a facile entry into the difficult C8–C14 linkage that bridges the two main domains of azadirachtin (**1**, Scheme 1).[2]



Scheme 1. Structure of azadirachtin (**1**) and model systems **2** and **3**.

To explore the application of transition-metal-based chemistry toward azadirachtin's C8–C14 bond, we defined model systems **2** and **3** as the targets of this investigation, and substrate **4** as their precursor (see Scheme 1). The latter compound includes within its structure an α,β-unsaturated aldehyde moiety as a Michael acceptor and a vinyl bromide as a progenitor to a metal species. These two functionalities are joined through a tether that could potentially be cleaved after the crucial C8–C14 bond formation. To test the above hypothesis, a suitable **AB** decalin precursor relevant to azadirachtin was sought and found in intermediate **17** (Scheme 2) as described below.

Synthesis of the required decalin fragment **17** commenced with benzylation of the known alcohol **5**[3] under acidic conditions to afford **6** in 73% yield. The resulting ketone **6**



Scheme 2. Construction of key building block **17**. a) Benzyl 2,2,2-trichloroacetimidate (1.1 equiv), TfOH (0.05 equiv), 25 °C, 3 h, 73%; b) benzyltrimethylammonium tribromide (1.05 equiv), THF, 0 °C, 1 h; then LiBr (5.0 equiv), Li_2CO_3 (5.0 equiv), DMF, 110 °C, 3 h, 95%; c) KHMDS (1.2 equiv), **8** (1.1 equiv), THF, −78 °C, 1 h, 60%; d) SEMCl (2.0 equiv), EtN*i*Pr$_2$ (2.0 equiv), TBAI (1.0 equiv), CH_2Cl_2, 25 °C, 24 h, 78%; e) vinylmagnesium bromide (5.0 equiv), CuI (5.0 equiv), $BF_3 \cdot Et_2O$ (5.0 equiv), THF, −78 °C, 1 h, 97%; f) LHMDS (1.5 equiv), HMPA (2.0 equiv), MeI (10.0 equiv), THF, −40 → −5 °C, 12 h, 60%; g) KHMDS (1.5 equiv), TESCl (1.5 equiv), THF, −40 °C, 1 h, 90%; h) OsO_4 (0.05 equiv), NMO (5.0 equiv), acetone/H_2O (10:1), 25 °C, 48 h, 86%; i) TsOH (0.001 equiv), 2,2-dimethoxypropane (neat), 25 °C, 24 h, 87%; j) *m*CPBA (5.0 equiv), CH_2Cl_2, 25 °C, 24 h, 81%; k) LiAlH(O*t*Bu)$_3$ (2.5 equiv), THF, 0 °C, 1 h, 86%. Bn = benzyl, HMPA = hexamethylphosphoramide, KHMDS = potassium bis(trimethylsilyl)amide, LHMDS = lithium bis(trimethylsilyl)-amide, *m*CPBA = *meta*-chloroperbenzoic acid; NMO = 4-methylmorpholine *N*-oxide, SEM = 2-(trimethylsilyl)ethoxymethyl, TBAI = tetrabutylammonium iodide, TES = triethylsilyl, TfOH = trifluoromethanesulfonic acid, TsOH = *para*-toluenesulfonic acid.

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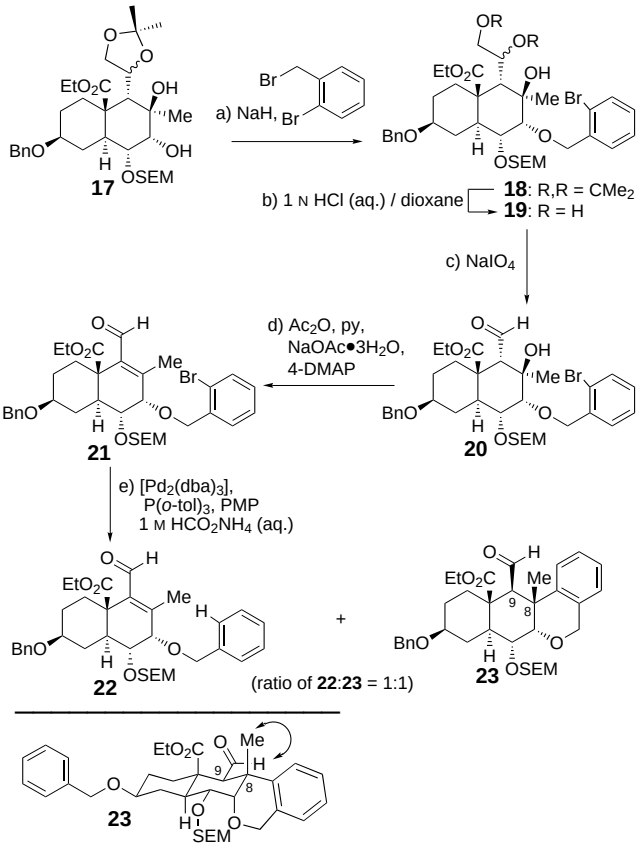
was then regioselectively brominated with benzyltrimethylammonium tribromide, and the intermediate α-bromoketone was heated in DMF in the presence of LiBr and Li_2CO_3 at 110 °C to furnish enone **7** in 95% overall yield through elimination of HBr.[4] Hydroxylation of **7** was accomplished upon treatment with KHMDS followed by the addition of Davis oxaziridine[5] **8** to exclusively afford equatorial alcohol **9** in 60% yield. This α-hydroxyketone, **9**, was protected as a SEM ether, which was then efficiently engaged in a conjugate addition reaction with the cuprate derived from vinylmagnesium bromide and CuI in the presence of $BF_3 \cdot Et_2O$ to afford vinyl compound **11** as a single diastereomer in 97% yield.[6] The observed diastereoselectivity in this reaction presumably results from the bulky neighboring ester moiety which plays a decisive role in exerting stereochemical control in this and several subsequent steps as will be described below. Regioselective methylation of ketone **11** was effected upon exposure to LHMDS, HMPA, and MeI to yield compound **12** with complete selectivity for the axial methyl group (60% yield). The triethylsilyl enol ether **13** was then generated efficiently (90% yield) and regioselectively from **12** by deprotonation with KHMDS and quenching with TESCl. Chemoselective dihydroxylation of **13** then afforded diol **14** as a mixture of diastereomers (ca. 12:1, 80% combined yield). Although the stereochemical identity of the two diastereomers of **14** is presently unknown, it is of no consequence, as the newly generated stereocenter (C11) will be removed at a later stage in the synthesis. The 1,2-diol **14** was then protected as the acetonide **15** by exposure to 2,2-dimethoxypropane and catalytic amounts of TsOH (87% yield). This triethylsilyl enol ether **15** was subsequently converted to hydroxy ketone **16** by a Rubottom-type epoxidation[7] in excellent yield (81%) and with complete diastereoselectivity, presumably because of the bulky neighboring acetonide moiety. Finally, reduction of hydroxyketone **16** with $LiAlH(OtBu)_3$ proceeded through equatorial hydride attack to afford the axial secondary alcohol **17** in 86% yield.

As a first attempt to effect the desired bridging of the two azadirachtin model domains, diol **17** was converted to precursor **21** which contains the two reactive functionalities (Scheme 3). Thus, selective benzylation of the secondary hydroxy group in **17** afforded *o*-bromobenzyl ether **18** in 75% yield whose acetonide group was removed by exposure to aqueous HCl in dioxane at 40 °C to afford triol **19** (80% yield). Oxidative cleavage of the generated 1,2-diol system of **19** with $NaIO_4$ furnished aldehyde **20** in quantitative yield. Dehydration of **20** in the desired endocyclic sense required exposure to Ac_2O/pyridine in the presence of $NaOAc \cdot 3H_2O$ and 4-DMAP, and afforded the targeted intermediate **21** in 73% yield. This set the stage for the projected intramolecular coupling reaction. In the event, exposure of bromoenal **21** to catalytic amounts of $[Pd_2(dba)_3]$ in the presence of P(*o*-tol)$_3$, PMP and HCO_2NH_4 in toluene/THF at 60 °C led to the formation of equimolar amounts of the reduced product **22** (where the bromine atom was replaced by a hydrogen atom) and the bridged tetracyclic system **23** (100% combined yield).[8] The latter compound was formed as a single diastereomer and with the desired C8–C9 stereochemistry characteristic of the azadirachtin structure.



Scheme 3. Synthesis of tetracycle **23** via Pd^0-catalyzed cyclization. a) NaH (3.0 equiv), 2-bromobenzyl bromide (1.7 equiv), THF, 25 °C, 24 h, 75%; b) dioxane:1N HCl (aq.) (5:1, 0.01M), 40 °C, 1 h, 80%; c) $NaIO_4$ (1.5 equiv), THF/H_2O (2:1), 25 °C, 24 h, 100%; d) $NaOAc \cdot 3H_2O$ (15.0 equiv), 4-DMAP (3.0 equiv), Ac_2O/py (1:1), 50 °C, 24 h, 73%; e) $[Pd_2(dba)_3]$ (0.5 equiv), P(*o*-tol)$_3$ (1.0 equiv), PMP (10.0 equiv), toluene/THF/1M HCO_2NH_4 (aq.) (6:2:1), 60 °C, 11 h, 100%. dba = dibenzylideneacetone, 4-DMAP = 4-dimethylaminopyridine, PMP = 1,2,2,6,6-pentamethylpiperidine, py = pyridine.

The relative stereochemistry at the C8 and C9 positions was established by nOe studies as shown in Scheme 3 (see arrows on structure **23**). This thermodynamically favored outcome implies an axial orientation for the palladium species in the transition state on C9 after the obligatory migratory insertion and release of the palladium upon donation of a formate ligand from HCO_2NH_4 followed by reductive elimination with retention of stereochemistry. This encouraging result led to the pursuit of a closer analogue to azadirachtin as described below.

The second targeted precursor in these investigations was the α,β-unsaturated aldehyde **28** equipped with a cyclohexene vinyl bromide ether moiety (Scheme 4). This intermediate was constructed in an expedient manner following similar chemistry to that utilized for the synthesis of **21** described above. On exposure of precursor **28** to palladium catalysis as mentioned above for the conversion of **21** to **23**, however, only the reduced product **29** was obtained and in quantitative yield. Failing to improve the situation in favor of the desired tetracyclic compound **31** by varying the conditions, we opted to generate the more reactive iodine counterpart of vinyl bromide **28**. To this end, we selected the method[9] that

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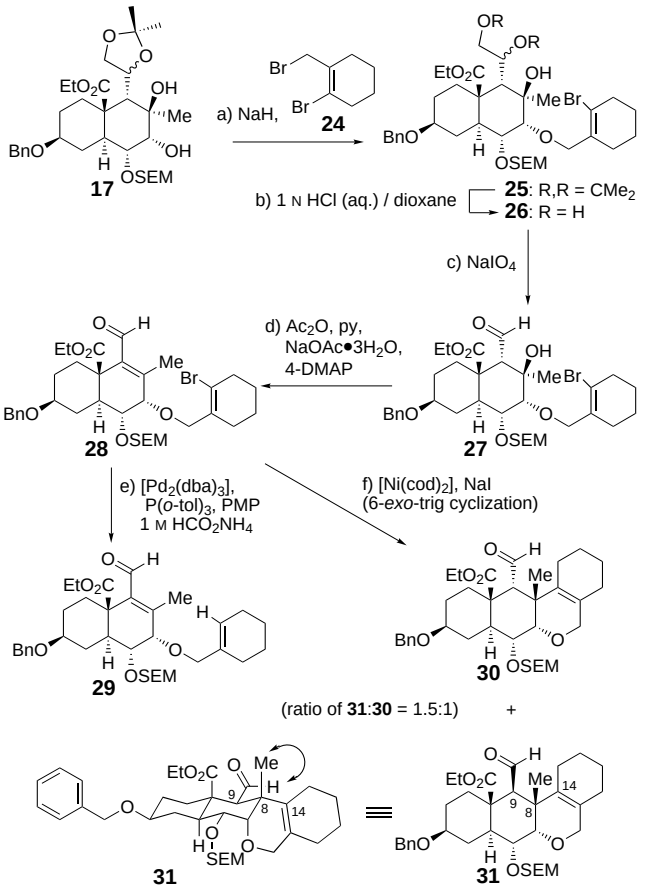
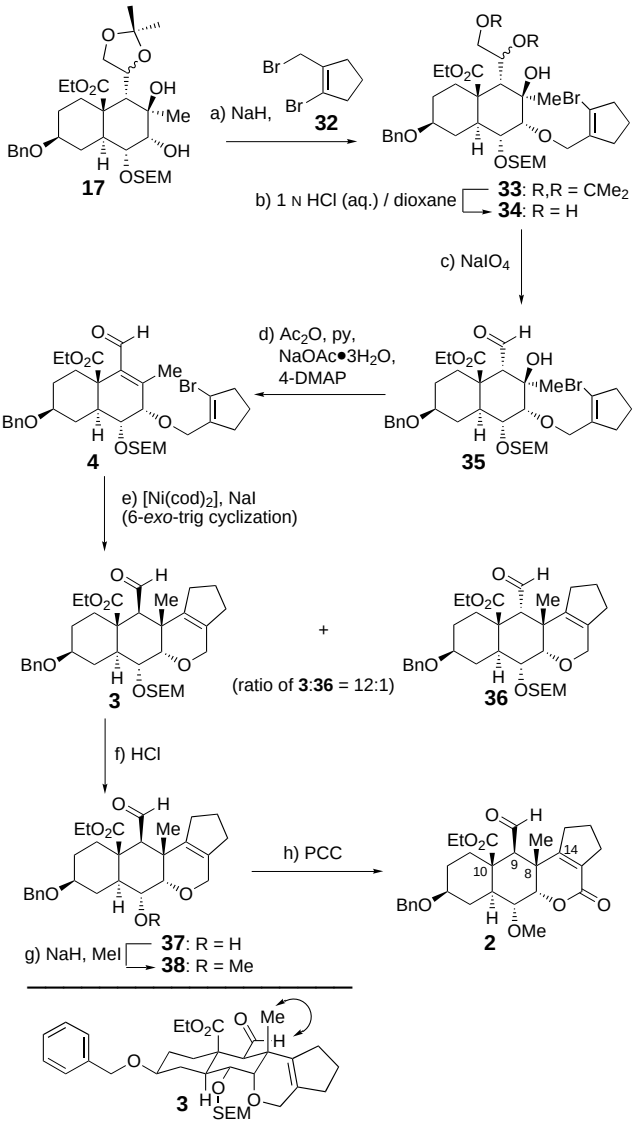


Scheme 4. Synthesis of tetracycles **30** and **31** by Ni^0-mediated cyclization. a) NaH (3.0 equiv), **24** (1.7 equiv), THF, 25 °C, 24 h, 60 %; b) dioxane:1N HCl (aq.) (5:1, 0.01M), 40 °C, 1 h 74 %; c) $NaIO_4$ (1.5 equiv), THF/H_2O (2:1), 25 °C, 24 h, 100 %; d) $NaOAc \cdot 3H_2O$ (15.0 equiv), 4-DMAP (3.0 equiv), Ac_2O/py (1:1), 50 °C, 24 h, 70 %; e) $[Pd_2(dba)_3]$ (0.5 equiv), P(*o*-tol)$_3$ (1.0 equiv), PMP (10.0 eqiuv), toluene/THF/1M HCO_2NH_4 (aq.) (6:2:1), 60 °C, 11 h, 100 %; f) $[Ni(cod)_2]$ (6.0 equiv), NaI (10.0 equiv), DMF, 80 °C, 2 h, 60 %. cod = 1,5-cyclooctadiene.



Scheme 5. Synthesis of tetracycles **3** and **36** by Ni^0-mediated cyclization and further elaboration of **3** to **2**. a) NaH (3.0 equiv), **32** (1.7 equiv), THF, 25 °C, 24 h, 63 %; b) dioxane:1N HCl (aq.) (5:1, 0.01M), 40 °C, 1 h, 74 %; c) $NaIO_4$ (1.5 equiv), THF/H_2O (2:1), 25 °C, 24 h, 100 %; d) $NaOAc \cdot 3H_2O$ (15.0 equiv), 4-DMAP (3.0 equiv), Ac_2O/py (1:1), 50 °C, 24 h, 67 %; e) $[Ni(cod)_2]$ (6.0 equiv), NaI (10.0 equiv), DMF, 80 °C, 2 h, 55 %; f) 1N HCl (aq.)/dioxane (3:1), 50 °C, 6 h, 85 %; g) NaH (10.0 equiv), MeI (10.0 equiv), THF, 50 °C, 2 h, 89 %; h) PCC (5.0 equiv), CH_2Cl_2, 50 °C, 24 h, 79 % at 56 % conversion. PCC = pyridinium chlorochromate.

requires $[Ni(cod)_2]$/NaI and proceeded to employ **28** as the substrate for the desired transformation. It was to our pleasant surprise that upon heating **28** in the presence of $[Ni(cod)_2]$ and NaI in DMF at 80 °C we observed the formation of the two diastereomers **30** and **31** in 60 % total yield (ca. 1:1.5 ratio). Although nickel-mediated Heck-type processes are known in the literature,[10] the ability of this reaction to form quaternary centers is, to the best of our knowledge, unprecedented. Also unprecedented is the use of α,β-unsaturated aldehydes in such nickel-facilitated coupling reactions. Once again, the desired *syn* stereochemistry of the two newly generated centers at C8 and C9 in the two diastereomers (**30** and **31**) was determined by NOE studies (see arrows on structure **31**, Scheme 4). The next step was to employ a cyclopentene ring on the "right wing" of the molecule as an even closer relative to azadirachtin and aimed both for the crowded C8–C14 bridge and the proper C8–C9 *syn* stereochemistry.

Scheme 5 outlines our final endeavor into the azadirachtin landscape, beginning with the coupling of diol **17** with cyclopentene dibromide **32**[11] and elaboration of the resulting product **33** to precursor **4** via intermediates **34** and **35** according to the standard sequence developed for the other two precursors (**21** and **28**) discussed above. The critical 6-*exo*-trig cyclization of **4** proceeded smoothly ($[Ni(cod)_2]$/NaI) and led to the desired stereoisomer **3** contaminated with a small amount of its C9-epimer (**36**, ca. 12:1 ratio, 55 % total yield). Again, nOe studies established the designated stereochemistry for the two compounds **3** and **36** (see arrows on structure **3**, Scheme 5). To advance the tetracyclic allylic ether **3** to its lactone counterpart **2**, it was necessary, for compatibility reasons, to exchange the SEM group for a Me substituent. PCC oxidation of the allylic ether moiety within **38** then furnished model system **2** (79 % yield based on 56 %

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Table 1. Selected physical properties of compounds **2** and **3**.

2: Colorless oil; $R_f = 0.56$ (silica, 50% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 2924, 2866, 1717$ (overlapping signals), 1458, 1383, 1360, 1263, 1199, 1142, 1090 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.95$ (d, $J = 2.9$ Hz, 1H), 7.34–7.32 (m, 4H), 7.29–7.25 (m, 1H), 4.59 (d, $J = 9.9$ Hz, 1H), 4.51 (d, $J = 9.9$ Hz, 1H), 4.34 (d, $J = 2.2$ Hz, 1H), 4.26–4.20 (m, 2H), 4.02 (dd, $J =$ 9.5, 2.2 Hz, 1H), 3.46 (s, 3H), 3.42–3.37 (m, 1H), 2.66–2.60 (m, 1H), 2.54–2.48 (m, 3H), 2.30–2.23 (m, 2H), 2.03–1.98 (m, 2H), 1.95–1.88 (m, 2H), 1.43–1.39 (m, 1H), 1.32 (s, 3H), 1.30 (t, $J = 5.9$ Hz, 3H), 1.27–1.23 (m, 2H), 1.17–1.14 ppm (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 200.0$, 173.4, 164.9, 162.5, 138.6, 129.7, 128.4, 127.6, 127.5, 81.0, 76.4, 75.1, 70.2, 61.5, 60.0, 57.7, 48.8, 41.7, 38.8, 35.7, 34.2, 30.1, 29.7, 28.6, 28.3, 21.2, 16.0, 14.0 ppm; HRMS (MALDI–FTMS), calcd for $C_{29}H_{36}O_7$ $[M+Na^+]$: 519.2353, found: 519.2359

3: Colorless oil; $R_f = 0.48$ (silica, 25% EtOAc in hexanes); IR (thin film): $\tilde{\nu}_{max} = 2931, 2846, 1727, 1717, 1448, 1364, 1243, 1200, 1097, 1055\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.97$ (d, $J = 5.2$ Hz, 1H), 7.33–7.30 (m, 4H), 7.28–7.25 (m, 1H), 4.86 (d, $J = 7.0$ Hz, 1H), 4.79 (d, $J = 7.0$ Hz, 1H), 4.55 (d, $J = 11.8$ Hz, 1H), 4.49 (d, $J = 11.8$ Hz, 1H), 4.44 (dd, $J = 11.4$, 3.3 Hz, 1H), 4.29 (bd, $J = 15.4$ Hz, 1H), 4.25–4.17 (m, 2H), 4.09 (bd, $J =$ 15.0 Hz, 1H), 3.80–3.75 (m, 1H), 3.64–3.59 (m, 1H), 3.38 (d, $J = 3.0$ Hz, 1H), 3.37–3.32 (m, 1H), 2.39–2.34 (m, 1H), 2.35 (d, $J = 5.1$ Hz, 1H), 2.20–2.16 (m, 2H), 2.11–2.05 (m, 2H), 1.98–1.93 (m, 2H), 1.90–1.85 (m, 1H), 1.84–1.78 (m, 2H), 1.31 (t, $J = 7.3$ Hz, 3H), 1.27–1.23 (m, 2H), 1.21 (s, 3H), 1.14–1.09 (m, 1H), 1.00–0.93 (m, 2H), 0.02 ppm (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 203.2$, 173.9, 139.4, 138.8, 134.9, 128.3, 127.6, 127.4, 95.1, 80.2, 74.1, 70.0, 67.4, 65.1, 61.1, 60.8, 49.1, 41.3, 38.6, 35.9, 31.9, 31.8, 29.7, 28.7, 28.5, 22.3, 18.2, 16.4, 14.1, −1.4 ppm; HRMS (MALDI–FTMS), calcd for $C_{34}H_{50}O_7Si$ $[M+Na^+]$: 621.3218, found: 621.3218

conversion) (for selected physical properties of compounds **2** and **3**, see Table 1).

The described chemistry may hold the key to a successful total synthesis of azadirachtin (**1**) by providing the basis for the construction of the C8–C14 bridge. Furthermore, this study may serve as the foundation for future developments in carbon–carbon bond forming reactions, particularly in sterically congested situations and in the construction of quaternary centers.

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[1] 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, preceding communication.

[2] For isolation, structural elucidation, and previous synthetic studies in the area of azadirachtin (**1**), see literature cited in ref. [1].

[3] a) D. Nasipuri, R. Roy, G. Sarkar, M. Guha, *J. Indian Chem. Soc.* **1966**, *43*, 383–390; b) J. B. Jones, D. R. Dodds, *Can. J. Chem.* **1987**, *65*, 2397–2404.

[4] J. F. Templeton, L. Lin, Y. Ling, H. Majgier-Baranowska, K. Marat, *J. Chem. Soc. Perkin Trans. 1* **1997**, 2037–2044.

[5] For a general review on oxaziridines, see: F. A. Davis, B. C. Chen, *Chem. Rev.* **1992**, *92*, 919–934.

[6] a) K. Maruyama, Y. Yamamoto, *J. Am. Chem. Soc.* **1977**, *99*, 8068–8070; b) K. Maruyama, Y. Yamamoto, *J. Am. Chem. Soc.* **1978**, *100*, 3240–3241.

[7] G. M. Rubottom, J. M. Gruber, *J. Org. Chem.* **1978**, *43*, 1599–1602.

[8] R. Grigg, V. Sridharan, S. Sukirthalingam, *Tetrahedron Lett.* **1991**, *32*, 3855–3858.

[9] M. C. J. M. Hooijdonk, T. H. A. Peters, S. F. Vasilevsky, L. Brandsma, *Synth. Commun.* **1994**, *24*, 1261–1263.

[10] a) D. Sole, Y. Chancho, A. Llebaria, J. M. Moreto, A. Delgado, *J. Am. Chem. Soc.* **1994**, *116*, 12133–12134; b) D. Sole, J. Bonjoch, J. Bosch, *J. Org. Chem.* **1996**, *61*, 4194–4195.

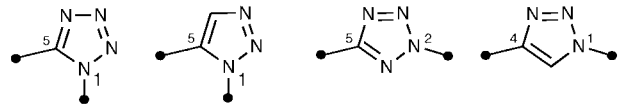
[11] T. Rajamannar, K. K. Balasubramanian, *Tetrahedron Lett.* **1988**, *29*, 5789–5792.

A Click Chemistry Approach to Tetrazoles by Huisgen 1,3-Dipolar Cycloaddition: Synthesis of 5-Sulfonyl Tetrazoles from Azides and Sulfonyl Cyanides**

Zachary P. Demko and K. Barry Sharpless*

Dedicated to Professor Rolf Huisgen

Stable in strongly acidic and basic media, as well as to oxidizing and reducing conditions, tetrazoles readily tolerate a wide range of chemical environments,[1] and new uses for this unique family of heterocycles continue to emerge in both materials science,[2] and pharmaceutical applications. They can serve as metabolically stable surrogates for a carboxylic acid group,[3] as precursors to a variety of nitrogen-containing heterocycles by Huisgen rearrangement,[4] and as simple lipophilic spacers displaying two substituents in the appropriate manner. In the latter example, the connectivity patterns of the embedded tetrazole units bear a striking resemblance to those of their 1,2,3-triazole analogues (Scheme 1).



Scheme 1. Spacial display of substituents in disubstituted tetrazoles and triazoles.

However, despite these structural similarities, the triazoles are much easier to synthesize, thanks to the direct Huisgen 1,3-dipolar cycloaddition route to triazoles ($RN_3 + RC{\equiv}CR$).[5] It has been argued that this [2+3] cycloaddition is among the rare organic reactions which approach perfection, or ideal "click-chemistry" status,[6] with many consequent applications.[7] The analogous [2+3] route to tetrazoles ($RN_3 + RC{\equiv}N$) is reliable for intramolecular cases,[8] but the existing intermolecular precedents for this process are neither general nor practical (see below).

Every chemist is familiar with the personal activation barrier to running "difficult" reactions, and it is well known that the value of a reaction increases dramatically if it is simple to perform. Therefore, uncovering a simple [2+3] fu-

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

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