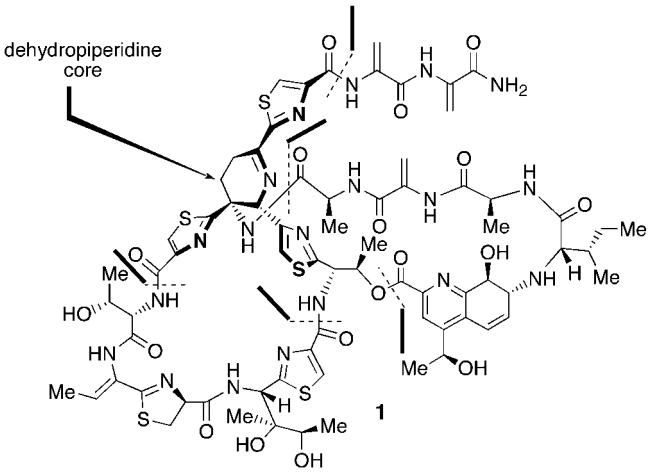
A Biomimetically Inspired Synthesis of the Dehydropiperidine Domain of Thiostrepton**

K. C. Nicolaou,* Marta Nevalainen, Brian S. Safina, Mark Zak, and Stephan Bulat

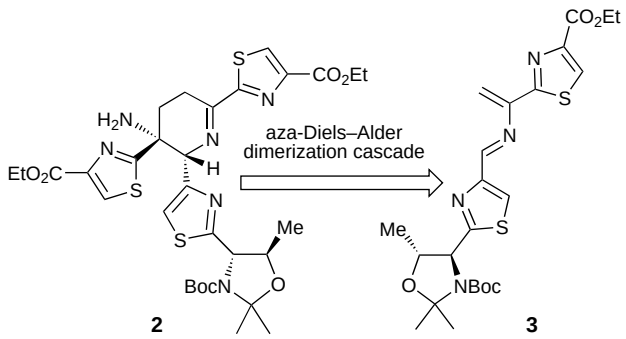
Dedicated to Professor Ralph F. Hirschmann on the occasion of his 80th birthday

In the preceding communication,[1] we described a stereoselective construction of the macrocycle of thiostrepton (**1**)[2] which incorporates the quinaldic acid moiety of the molecule.[3a] Herein we report an expedient synthesis of the

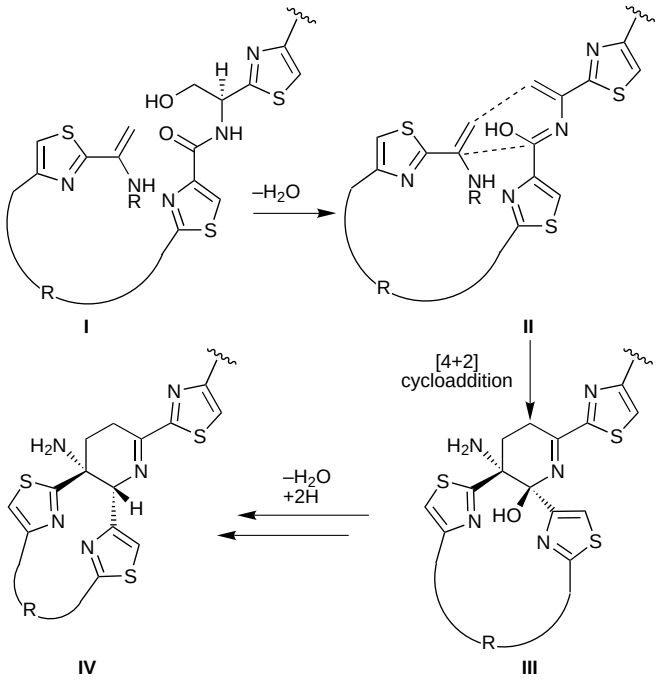


dehydropiperidine domain **2** (Scheme 1)[3b] of this complex antibiotic based on a biomimetic strategy involving a cascade reaction, which features a striking dimerization of a designed azadiene **3**, through a hetero-Diels–Alder reaction,[4] followed by hydrolytic excision of the superfluous thiazole moiety.

Based on some elegant biosynthetic studies, Floss and coworkers[5] suggested a hetero-Diels–Alder reaction (Scheme 2, **II**→**III**) as a key step in the biosynthesis of thiostrepton (**1**). Specifically, it was proposed that a precursor such as **I** (Scheme 2), upon elimination of a water molecule,



Scheme 1. Retrosynthetic analysis of the dehydropiperidine core **2**.



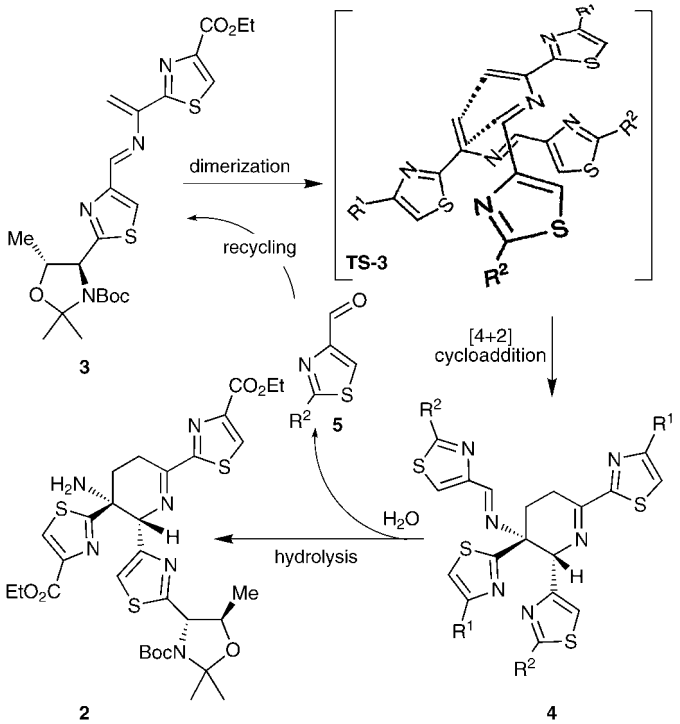
Scheme 2. Postulated biosynthesis of the dehydropiperidine domain of thiostrepton (**1**). R = peptide backbone.

gives rise to the hydroxy azadiene system **II**, which undergoes an intramolecular [4+2] cycloaddition reaction to afford hydroxydehydropiperidine system **III**. Subsequent 1,4 dehydration then furnishes a conjugated azadiene system, whose 1,4 reduction leads to the thiostrepton structure **IV** (Scheme 2).

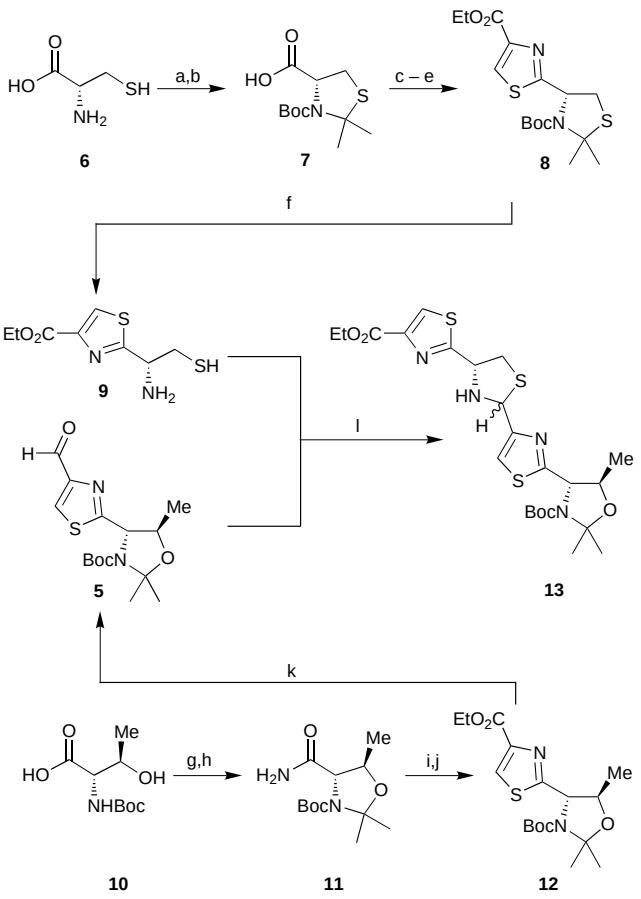
Inspired by this fascinating hypothesis, we sought to devise a chemical route for the construction of dehydropiperidine moiety **2** of thiostrepton, as shown in Scheme 3. Our proposed strategy involved the design of a cascade sequence whereby a suitable precursor would generate the 2-azadiene **3**,[6] whose dimerization[7] through a hetero-Diels–Alder cyclization would proceed through a pathway in which the conjugated imino-olefin system of one molecule would act as the diene and the olefinic unit of another molecule would serve as the dienophile (Scheme 3, **TS-3**). Although no facial selectivity was anticipated in this process, the *endo* rule was expected to prevail, thus leading to the desired *trans* relationship between the two adjacent thiazole rings in structure **4**. Whether the remote chiral Boc acetonide moiety of **3** would exert any

[*] Prof. Dr. K. C. Nicolaou, Dr. M. Nevalainen, B. S. Safina, M. Zak, Dr. S. Bulat
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
Department of Chemistry and Biochemistry
University of California, San Diego
9500 Gilman Drive, La Jolla, CA 92093 (USA)
E-mail: kcn@scripps.edu

[**] We thank Drs. D. H. Huang and L. Pasternack, G. Suizdak, and R. Chadja for NMR spectroscopic, mass spectrometric, and X-ray crystallographic assistance, respectively. Financial support for this work was provided by The Skaggs Institute for Chemical Biology, the National Institutes of Health (USA), fellowships from The Academy of Finland (M.N.), The Skaggs Institute for Research (M.Z.), and Bayer AG (S.B.), and grants from Abbott, Amgen, Array Biopharma, Boehringer-Ingelheim, Glaxo, Hoffmann-LaRoche, DuPont, Merck, Novartis, Pfizer, and Schering Plough.



Scheme 3. Proposed biomimetic strategy for the laboratory synthesis of the dehydropiperidine domain **2**. $R_1 = CO_2Et$, $R_2 =$ Boc acetonide threonine side chain. Boc = *tert*-Butoxycarbonyl.



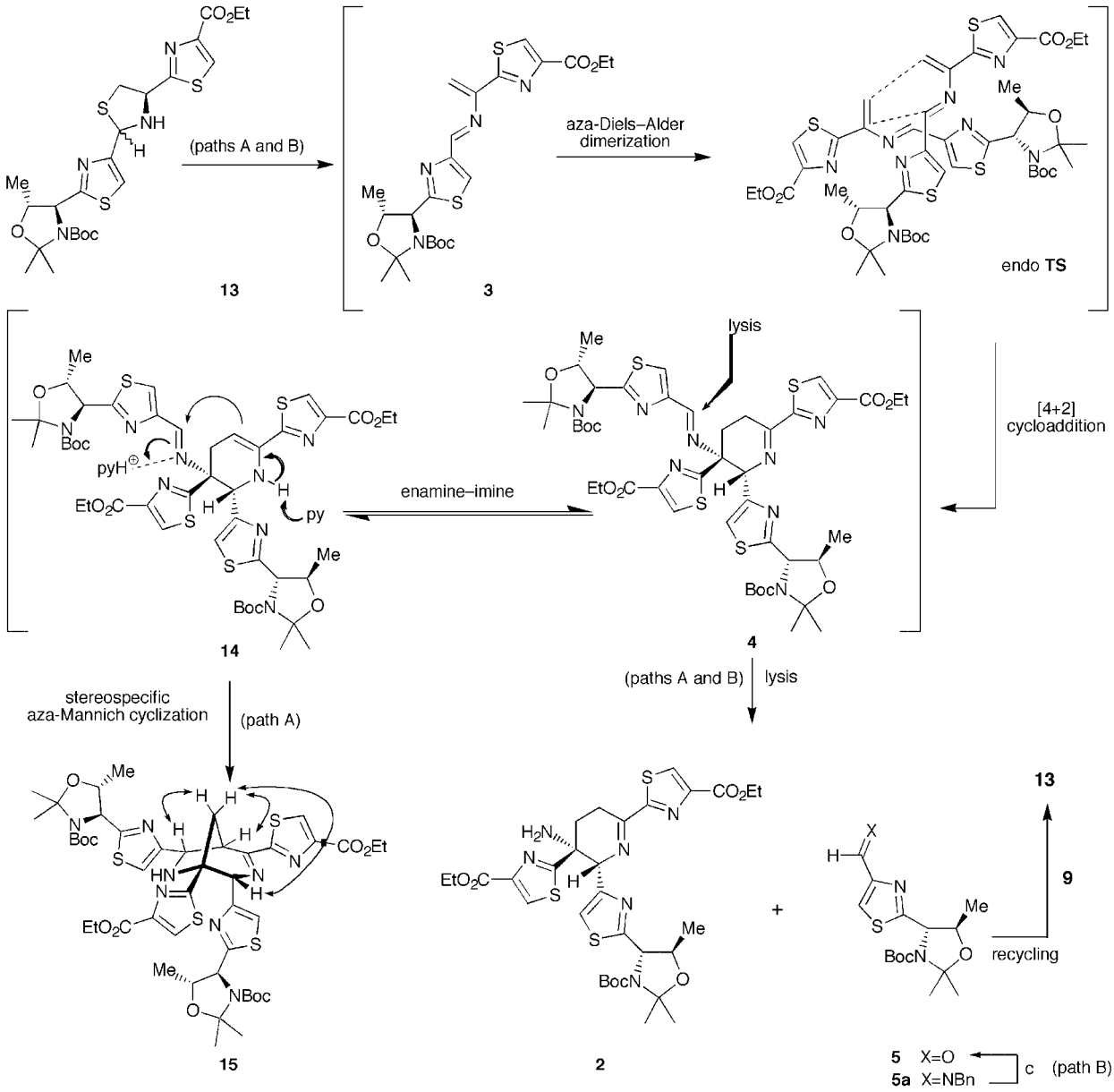
Scheme 4. Synthesis of thiazolidine **13**. Reagents and conditions: a) acetone, 60 °C, 2 h, 99 %; b) Boc_2O (1.2 equiv), *i*Pr_2NEt (1.1 equiv), MeCN, 25 °C, 48 h, 40 %; c) DCC (1.1 equiv), HOSu (1.1 equiv), THF, 0 °C, 3 h; then NH_3 (aqueous, 28 %), 0 °C, 30 min, 65 %; d) Lawesson's reagent (0.6 equiv), DME, 25 °C, 12 h, 85 %; e) $BrCH_2COCO_2Et$ (3.0 equiv), $KHCO_3$ (3.0 equiv), THF, 25 °C, 24 h; then TFAA (1.5 equiv), pyridine (3.0 equiv), 0 °C, 3 h, 90 %; f) TFA/CH_2Cl_2 (3:1), 25 °C, 3 h; then EtOH/H_2O (1:1), 25 °C, concentration in vacuo, 98 %; g) $(MeO)CMe_2$ (22.0 equiv), *p*-TsOH (0.1 equiv), CH_2Cl_2, 25 °C, 24 h, 91 %; h) $ClCO_2Et$ (1.1 equiv), Et_3N (1.1 equiv), THF, 0 °C, 30 min; then NH_3 (aqueous, 28 %), 0 °C, 1.5 h, 78 %; i) Lawesson's reagent (0.6 equiv), benzene, 80 °C, 1 h, 85 %; j) $BrCH_2COCO_2Et$ (3.0 equiv), $NaHCO_3$ (8.0 equiv), DME, 25 °C, 24 h; then TFAA (4.0 equiv), pyridine (9.0 equiv), 0 °C, 1 h, 90 %; k) DIBAL (2.0 equiv), toluene, −78 °C, 2 h, 87 %; l) **9**·TFA (1.0 equiv), **5** (1.0 equiv), $KHCO_3$ (3.0 equiv), EtOH/H_2O (1:1), 25 °C, 12 h, 90 %. Boc = *tert*-butoxycarbonyl; DCC = 1,3-dicyclohexylcarbodiimide; HOSu = *N*-hydroxysuccinimide; DME = dimethoxyethane; TFAA = trifluoroacetic anhydride; TFA = trifluoroacetic acid; *p*-TsOH = *p*-toluenesulfonic acid.

stereochemical control on the expected [4+2] cycloaddition was an open question. Subsequent hydrolysis of the labile exocyclic imine functionality of **4** was then expected to generate the desired dehydropiperidine system **2**, with the concomitant release of thiazole aldehyde **5**. Thiazole **5** would be recycled back into **3** thus, in principle, increasing the efficiency of the overall process.

To implement this strategy we chose thiazolidine compound **13** (Scheme 4) as a suitable precursor for the required 2-azadiene system **3** (Scheme 2). The convergent synthesis of **13** proceeded from L-cysteine (**6**) and L-threonine (**10**), as shown in Scheme 4. Thus, the amino acids **6** and **10** were converted into their Boc acetonide derivatives **7** and **11**, respectively, by known procedures.[8] Acetonides **7** and **11** were then converted into **8** and **12**, respectively, by means of the modified Hantzsch thiazole-forming reaction.[9] Removal of the Boc group from intermediate **8** under acidic conditions (TFA) and subsequent concentration in the presence of EtOH and H_2O led to complete removal of the generated acetone and the isolation of amino thiol **9** in 98 % yield. On the other hand, DIBAL reduction of ethyl ester **12** furnished aldehyde **5** cleanly (87 % yield). Finally, condensation of fragments **9** and **5** in EtOH/H_2O (1:1) in the presence of $KHCO_3$ proceeded smoothly to afford the desired thiazolidine **13** in 90 % yield.

With thiazolidine **13** in hand, we were now in a position to test the hypothesis of the hetero-Diels–Alder reaction proposal as part of the cascade leading to the projected dehydropiperidine system **2**. Indeed, exposure of a solution of **13** in pyridine to Ag_2CO_3 and catalytic amounts of DBU at −15 °C led to the rupture of the thiazolidine moiety and generation of the 2-azadiene system **3**, which underwent spontaneous [4+2] cycloaddition to afford the coveted dehydropiperidine system **4**, apparently as a mixture with its tautomeric form, enamine **14** (Scheme 5, path A).[6c, 7] Upon quenching with water at −15 °C, the desired dehydropiperidine fragment **2** (22 %), aldehyde **5** (20 %), and [3.2.1]-bridged bicycle **15** (63 %, see Table 1 for data) were obtained. Whereas the origin of **2** and **5** can be attributed to a simple imine hydrolysis of imino compound **4**, the formation of **15** must be the result of a stereospecific aza-Mannich cyclization within **14**, as designated by the arrows in Scheme 5. The relative stereochemistry of **15** was established on the basis of NOE studies (Scheme 5), and later confirmed by X-ray

  0044-8249/02/11411-2022 $ 20.00+.50/0 *Angew. Chem.* **2002**, *114*, Nr. 11



Scheme 5. Hetero-Diels–Alder dimerization cascade. Reagents and conditions: path A. a) Ag_2CO_3 (1.1 equiv), DBU (0.2 equiv), pyridine, −15 °C, 1 h; b) H_2O, 10 min; products: **15** (63%, ca. 1:1 ratio of diastereomers), **2** (22%, ca. 1:1 ratio of diastereomers), **5** (20%); path B. a) Ag_2CO_3 (1.1 equiv), DBU (0.2 equiv), $PhCH_2NH_2$ (1.0 equiv), pyridine, −15 °C, 1 h; b) H_2O, 10 min; c) silica gel, 25 °C, CH_2Cl_2/AcOEt (1:1); products: **15** (trace); **2** (60%, ca. 1:1 ratio of diastereomers); **5** (68%). DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

crystallographic analysis (of **16**, see below). Although the Diels–Alder reaction proceeded both in a regioselective and *endo*-selective manner, it showed no facial selectivity and, therefore, compounds **4**, **14**, **15**, and **2** are mixtures of diastereomers (ca. 1:1) with regards to the relative stereochemistry of the core substituents and those already existing on the remote chiral Boc acetonide moiety.

To further establish the stereochemistry of the [3.2.1]-bridged system **15**, and, therefore, that of its precursors, the rather labile imine **15** was subjected to reduction with $NaCNBH_3$ in the presence of AcOH/EtOH, which led to its more stable amino counterpart **16** (Table 1) in 85% yield (Scheme 6). Compound **16** was chromatographically purified to a single diastereomer and crystallized from hexanes/ethyl acetate. X-ray crystallographic analysis (Figure 1) confirmed its absolute stereochemistry, which was also clear from NOE experiments (see arrows in **16**, Scheme 6).

To improve the yield of the targeted tertiary amine **2**, we chose transimination as a possible means to excise the undesired fragment **5** from the dimerization product **4**, and thus suppress the aza-Mannich reaction that leads to **15**. Indeed, the addition of stoichiometric amounts of benzylamine to the reaction mixture led to **2** (60%), **5** (68%, after hydrolysis of the resulting imine **5a**), and only traces of **15** (see Scheme 5, path B).

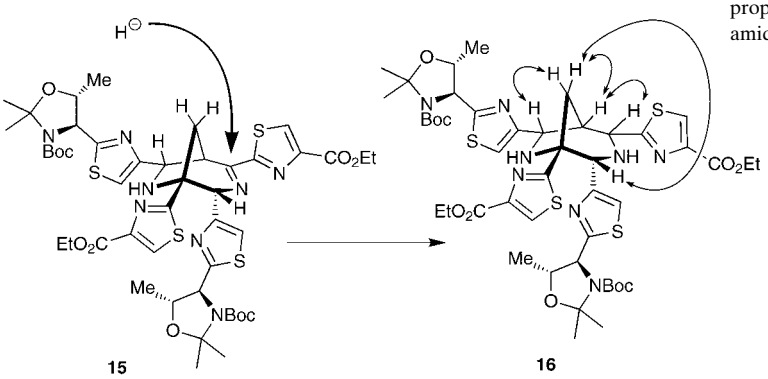
In further experiments (Scheme 7), the imine functionality of **2** (ca. 1:1 mixture of diastereomers) was reduced with $NaCNBH_3$–AcOH in EtOH to afford the corresponding

  0044-8249/02/11411-2023 $ 20.00+.50/0

Table 1. Selected data for compounds **15** and **16**.

15. $R_f = 0.32$ (silica gel, CH_2Cl_2/EtOAc, 1:1); $[\alpha]_D^{20} = -29.8$ ($c = 2.2$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3354, 3005, 2991, 1702, 1478, 1367, 1208, 1131, 1096, 756\ cm^{-1}$; ^1H NMR (600 MHz, CD_3CN, 70 °C): $\delta = 8.13$ (s, 1H), 8.02 (s, 1H), 7.55 (s, 1H), 7.42 (s, 1H), 6.02 (s, 1H), 5.04 (m, 1H), 4.58 (d, $J =$ 7.4 Hz, 1H), 4.46 (d, $J = 7.0$ Hz, 1H), 4.40–4.25 (m, 5H), 3.96 (m, 1H), 3.80 (m, 1H), 2.80 (d, $J = 11.4$ Hz, 1H), 2.58 (dd, $J = 11.4$, 3.5 Hz, 1H), 1.59 (s, 3H), 1.59 (s, 3H), 1.55 (s, 3H), 1.55 (s, 3H), 1.51 (s, 3H), 1.40–1.05 ppm (m, 30H); ^{13}C NMR (125 MHz, CD_3CN, 70 °C): $\delta = 178.2$, 171.1, 169.0, 165.2, 161.7, 161.1, 154.1, 153.6, 151.9, 148.2, 148.1, 148.0, 131.6, 131.1, 128.2, 118.9, 116.8, 116.0, 95.1, 95.0, 80.5, 80.3, 78.5, 77.5, 73.0, 72.1, 67.2, 66.0, 65.9, 61.4, 61.2, 45.2, 41.3, 28.1, 27.9, 28.0–27.0 (b), 25.7 (b), 18.2, 17.5, 14.0, 14.0 ppm; HRMS (MALDI): calcd for $C_{46}H_{60}N_8O_{10}S_4$ [M+Na$^+$]: 1035.3214; found: 1035.3293

16. $R_f = 0.24$ (silica gel, CH_2Cl_2/EtOAc, 1:1); $[\alpha]_D^{20} = -39.7$ ($c = 1.6$, $CHCl_3$); IR (film): $\tilde{\nu}_{max} = 3400, 2979, 1702, 1366, 1210, 1090, 754\ cm^{-1}$; ^1H NMR (600 MHz, CD_3CN, 70 °C): $\delta = 7.94$ (s, 1H), 7.89 (s, 1H), 7.13 (s, 1H), 7.04 (s, 1H), 4.95 (d, $J = 4.4$ Hz, 1H), 4.89 (s, 1H), 4.82 (br s, 1H), 4.72 (d, $J = 8.0$ Hz, 1H), 4.65 (d, $J = 6.5$ Hz, 1H), 4.64 (s, 1H), 4.36 (q, $J = 7.0$ Hz, 2H), 4.32 (q, $J = 7.0$ Hz, 2H), 4.04 (m, 1H), 3.95 (m, 1H), 3.83 (bs, 1H), 3.47 (t, $J = 4.0$ Hz, 1H), 2.71 (d, $J = 11.4$ Hz, 1H), 2.64 (dd, $J = 11.4$, 4.4 Hz, 1H), 1.63 (s, 6H), 1.56 (s, 3H), 1.55 (s, 3H), 1.40–1.25 ppm (m, 30H); ^{13}C NMR (150 MHz, CD_3CN, 70 °C): $\delta = 173.5$, 171.5, 162.2, 161.9, 154.8, 154.5, 148.4, 147.3, 128.2, 127.9, 117.2, 95.6, 95.6, 78.1, 77.6, 69.8, 66.8, 66.7, 65.5, 62.8, 62.7, 61.5, 61.5, 46.7, 45.9, 28.5, 28.4, 28.0–27.0 (br), 26.5, 26.3, 20.8, 20.2, 19.7, 18.3, 14.4, 14.4 ppm; HRMS (MALDI): calcd for $C_{46}H_{62}N_8O_{10}S_4$ [M+Na$^+$]: 1037.3364; found: 1037.3371



Scheme 6. Stereospecific reduction of the imine functionality in **15** and structural assignment of **16** by NMR spectroscopy (see indicated NOE interactions). Reagents and conditions: $NaCNBH_3$ (2.0 equiv), AcOH/EtOH (1:1), 25 °C, 2 h, 85%.

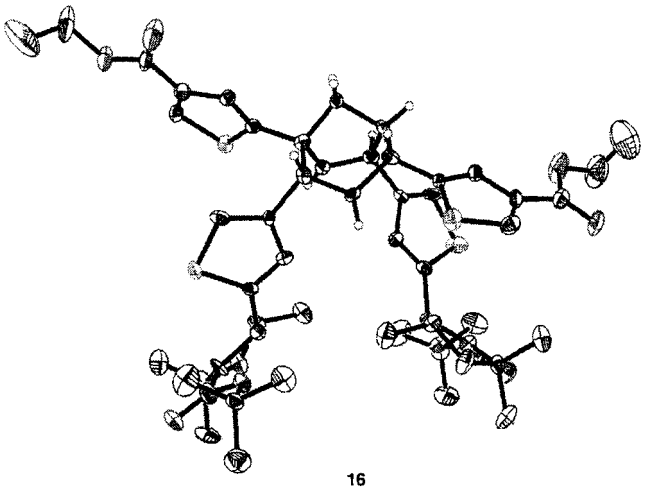
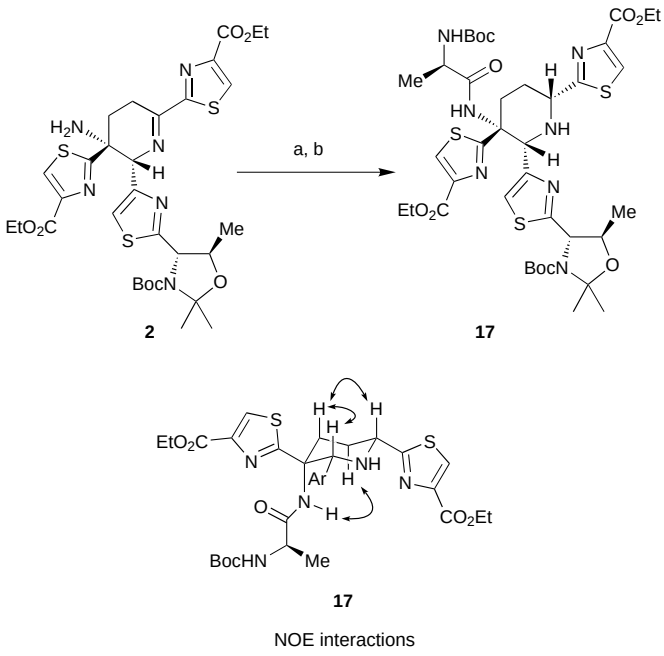


Figure 1. ORTEP diagram of **16**.



Scheme 7. Stereospecific reduction, coupling of **2**, and stereochemical assignment of **17** by NOE studies. Reagents and conditions: a) $NaCNBH_3$ (2.0 equiv), AcOH/EtOH (1:1), 25 °C, 2 h; b) HOAt (1.1 equiv), EDC (1.1 equiv), H-Ala-NBoc (1.1 equiv), DMF, 0 → 25 °C, 19 h, 82% over two steps. HOAt = 1-hydroxy-7-azabenzotriazole; EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; DMF = *N*,*N*-dimethylformamide.

diamine, whose selective coupling with H-Ala-NBoc in the presence of EDC–HOAt led to peptide **17** (82% yield, ca. 1:1 mixture of diastereomers).[3b] The stereochemistry of **17** and therefore of **2** became clear from NOE studies, as indicated in Scheme 7 (arrows in **17**).

In conclusion, we devised and experimentally demonstrated a biomimetic approach to the unusual dehydropiperidine domain of thiostrepton (**1**) based on a novel intermolecular hetero-Diels–Alder reaction followed by imine hydrolysis. Refinements of this cascade reaction with regards to efficiency and stereochemical control are anticipated and should facilitate the total synthesis of this challenging target. Furthermore, other modifications of this hetero-Diels–Alder reaction, including heterodimerizations and intramolecular versions, are currently considered as alternative approaches to thiostrepton. The described synthetic technology also appears to be amenable to the construction of a wide range of novel and biologically relevant heterocycles, including complex structures such as the [3.2.1]-bridged systems **15** and **16** for biological screening purposes.

Received: March 15, 2002 [Z18904]

[1] K. C. Nicolaou, B. S. Safina, C. Funke, M. Zak, F. J. Zécri, *Angew. Chem.* **2002**, *114*, 2017–2020; *Angew. Chem. Int. Ed.* **2002**, *41*, 1937–1940, preceding communication.

[2] Isolation: a) J. F. Pagano, M. J. Weinstein, H. A. Stout, R. Donovick, *Antibiot. Ann.* **1955–1956**, 554–559; b) J. Vandeputte, J. D. Dutcher, *Antibiot. Ann.* **1955–1956**, 560–561; c) B. A. Steinberg, W. P. Jambor, L. O. Suydam, *Antibiot. Ann.* **1955–1956**, 562–565; structure determination: d) C. S. Bond, M. P. Shaw, M. S. Alphey, W. N. Hunter, *Acta*

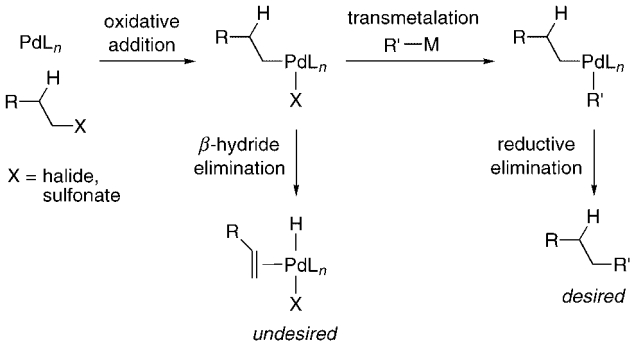
  0044-8249/02/11411-2024 $ 20.00+.50/0

Crystallogr. Sect. D **2001**, *57*, 755 – 758; e) B. Anderson, D. C. Hodgkin, M. A. Viswamitra, *Nature* **1970**, *225*, 233 – 235.
[3] For other related synthetic studies towards thiostrepton, see: a) S. Higashibayashi, T. Mori, K. Shinko, K. Hashimoto, M. Nakata, *Heterocycles* **2002**, *57*, 111 – 122; b) S. Higashibayashi, K. Hashimoto, M. Nakata, *Tetrahedron Lett.* **2002**, *43*, 105 – 110.
[4] For reviews, see: a) "Hetero-Diels – Alder Methodology in Organic Chemistry": D. L. Boger, S. M. Weinreb in *Organic Synthesis*, *Vol. 47*, Academic Press, San Diego, **1987**, p. 386; b) "Stereoselective Heterocyclic Synthesis I": L. F. Tietze, G. Kettschau, *Top. Curr. Chem.* **1997**, *189*, 1 – 120.
[5] U. Mocek, Z. Zeng, D. O'Hagan, P. Zhou, L.-D. G. Fan, J. M. Beale, H. G. Floss, *J. Am. Chem. Soc.* **1993**, *115*, 7992 – 8001.
[6] For some recent examples of Diels – Alder reactions of 2-azadienes, see: a) F. Palacios, E. Herrán, G. Rubiales, J. M. Ezpeleta, *J. Org. Chem.* **2002**, *67*, 2131 – 2135; b) F. Palacios, C. Alonso, P. Amezua, G. Rubiales, *J. Org. Chem.* **2002**, *67*, 1941 – 1946; c) T. M. V. D. Pinho e Melo, R. Fausto, A. M. d'A. Rocha Gonsalves, *J. Org. Chem.* **1998**, *63*, 5350 – 5355, and references therein.
[7] For similar dimerizations, see: a) G. Wulff, H. T. Klinken, *Tetrahedron* **1992**, *48*, 5985 – 5990; b) G. Wulff, H. G. Lindner, H. Bohnke, A. Steigel, H. T. Klinken, *Liebigs Ann. Chem.* **1989**, 527 – 531; c) G. Wulff, H. Böhnke, *Angew. Chem.* **1986**, *98*, 101 – 102; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 90 – 92.
[8] a) K. Okumura, Y. Nakamura, C.-g. Shin, *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1561 – 1569; b) D. S. Kemp, R. I. Carey, *J. Org. Chem.* **1989**, *54*, 3640 – 3646; c) K. Okumura, H. Saito, C. Shin, J. Yoshimura, K. Uemura, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1863 – 1870.
[9] C. Holzapfel, G. J. Pettit, *J. Org. Chem.* **1985**, *50*, 2323 – 2327.

A Method for Palladium-Catalyzed Cross-Couplings of Simple Alkyl Chlorides: Suzuki Reactions Catalyzed by $[Pd_2(dba)_3]/PCy_3$**

Jan H. Kirchhoff, Chaoyang Dai, and Gregory C. Fu*

Palladium-catalyzed cross-couplings of organic electrophiles with main-group organometallic compounds serve as straightforward, powerful methods for carbon – carbon bond formation, and such processes are routinely used in fields ranging from materials science to natural product synthesis.[1] The overwhelming majority of studies of metal-catalyzed cross-couplings have employed a halide or sulfonate as the electrophile and a organometallic reagent as the nucleophile in which the carbon atoms to be coupled are all sp^2-hybridized (e.g., for the synthesis of biaryls). In contrast, reports of successful couplings of simple halides/sulfonates bound to sp^3-hybridized carbon atoms are very rare.[2] Two of the likely reasons that have hampered the utilization of these important families of electrophiles are: 1) slow oxidative addition of the alkyl halide/sulfonate to palladium, and 2) if oxidative addition has indeed taken place, β-hydride elimination of the resulting alkyl – palladium complex, in preference to cross-coupling (Scheme 1).



Scheme 1. Palladium-catalyzed cross-coupling of an alkyl halide/sulfonate.

It is critical to point out that three studies in particular have, however, described noteworthy progress in overcoming this considerable limitation in the scope of metal-catalyzed cross-coupling reactions. In a pioneering investigation in 1992, Suzuki et al. discovered that $[Pd(PPh_3)_4]$ can catalyze couplings of alkyl iodides with alkyl boranes at 60 °C in yields as high as 71 %.[3, 4] Furthermore, we established last year that $Pd(OAc)_2/PCy_3$ effects Suzuki reactions of alkyl bromides at room temperature.[5] Finally, in a series of reports beginning in 1995, Knochel et al. have demonstrated that a nickel-based catalyst can promote cross-couplings of alkyl bromides and iodides with organozinc reagents.[6] Although each of these studies represents an important development, even collectively they provide a solution to only a small subset of the coupling processes of interest.

Thus, there is still a very substantial need for the development of catalysts to cross-couple alkyl halides. Since there has been essentially no success to date in any palladium- or nickel-catalyzed coupling of simple alkyl chlorides, in contrast to iodides or bromides, they represent a particularly significant challenge.[2, 7] In view of our recent progress in developing mild conditions for Suzuki reactions of alkyl bromides,[5] we decided to determine if we might also be able to contribute to solving the problem of coupling alkyl chlorides. In this communication, we describe the advances that we have made toward this objective [Eq. (1); 9-BBN = 9-borabicyclo[3.3.1]-nonane].

$$R_{alkyl}\text{—Cl} \quad \underset{\text{1.2 equiv}}{\text{R—(9-BBN)}} \quad \xrightarrow[\text{1.1 CsOH} \cdot \text{H}_2\text{O}\ \text{dioxane, 90 °C}]{\text{5\% [Pd}_2\text{(dba)}_3\text{]}\ \text{20\% PCy}_3} \quad R_{alkyl}\text{—R} \qquad (1)$$

[*] Prof. Dr. G. C. Fu, Dr. J. H. Kirchhoff, Dr. C. Dai
Department of Chemistry
Massachusetts Institute of Technology
Cambridge, MA 02139 (USA)
Fax: (+1) 617-258-7500
E-mail: gcf@mit.edu

[**] dba = (*E*,*E*)-dibenzylideneacetone, Cy = cyclohexyl. We thank Dr. Matthew R. Netherton for helpful discussions and Johnson Matthey Inc. for supplying palladium compounds. Support has been provided by the Deutsche Akademie der Naturforscher Leopoldina (Leopoldina fellowship to J.H.K., BMBF-LPD 9901/8-48), Bristol-Myers Squibb, the National Institutes of Health (National Institute of General Medical Sciences, R01-GM62871), the Natural Sciences and Engineering Research Council of Canada (postdoctoral fellowship to C.D.), and Novartis. Funding for the MIT Department of Chemistry Instrumentation Facility has been provided in part by NSF CHE-9808061 and NSF DBI-9729592.

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