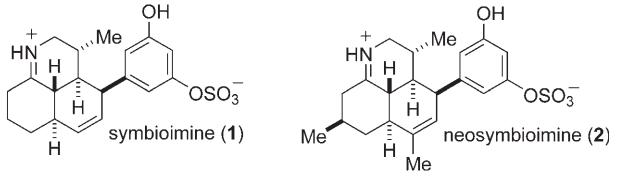
Biomimetic Synthesis

DOI: 10.1002/ange.200605160

Enantioselective Total Synthesis of the Osteoclastogenesis Inhibitor (+)-Symbioimine**

*Justin Kim and Regan J. Thomson**

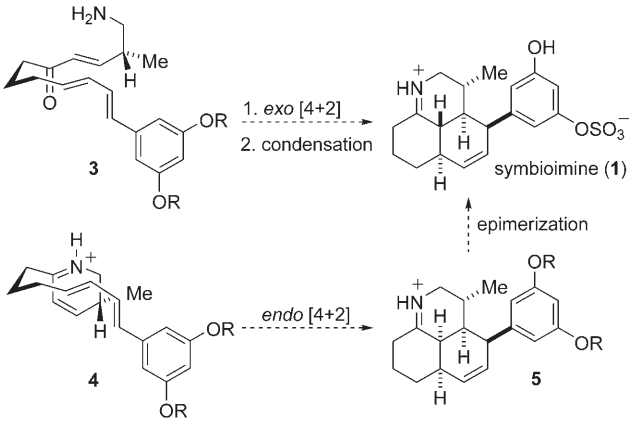
The isolation, structural determination, and biological activity of the unusual tetracyclic alkaloid, symbioimine (**1**), was reported by the research group of Uemura in 2004 (Scheme 1).[1] The alkaloid **1** was isolated from *Symbiodinium* sp., a culture from a marine dinoflagellate that has a



Scheme 1. The structures of symbioimine (**1**) and neosymbioimine (**2**).

symbiotic relationship with the acoel flatworm *Amphiscolops* sp., and inhibits osteoclastogenesis in RAW264 cells ($EC_{50} = 44\ \mu g\,mL^{-1}$) while maintaining cell viability at concentrations up to $100\ \mu g\,mL^{-1}$. As such, symbioimine (**1**) or analogues may offer a new opening to the development of preventative treatments for osteoporosis. Further studies by the research group of Uemura have revealed that **1** inhibits cyclooxygenase-2 activity, suggesting that this zwitterion may also find use as an anti-inflammatory therapeutic agent. Neosymbioimine (**2**), a compound related to **1**, was reported in 2005.[1c]

Several hypotheses regarding the biogenetic origin of the 6,6,6-tricyclic iminium ring system present within **1** and **2** have been suggested. In the initial study, Uemura and co-workers suggested a plausible pathway based on an *exo*-selective Diels–Alder reaction akin to the conversion of **3** into **1** as



Scheme 2. Proposed biosynthetic pathways to symbioimine (**1**).

shown in Scheme 2.[1a] It seemed unlikely to us that the cyclization of **3** would proceed with *exo* selectivity in the absence of an enzyme. Furthermore, we expected that face selectivity of the dienophile that arises from the methyl group would be poor. In light of these considerations we sought to investigate an alternative route that would proceed with greater diastereoselectivity in the key bond-forming event. An *endo*-selective cyclization of the cyclic iminium species **4** should occur with high facial selectivity, and thus the predicted major diastereomer **5** would arise from an addition opposite the methyl substituent. Epimerization of the resultant ring system from all-*cis*-fused to all-*trans*-fused arrangements should be driven by favorable thermodynamics (**5**→**1**). During the course of our own investigation, Uemura and co-workers published a similar idea,[1c] and Snider and Che reported a model study in which an *N*-acyl iminium ion underwent a selective Diels–Alder reaction followed by epimerization.[2] Two additional studies by the research groups of Maier and Uemura have explored alternative cycloaddition strategies,[3] and the former group recently published a synthesis of racemic **1**. Very recently Snider and co-workers reported the second total synthesis of racemic **1** based on their strategy of the cycloaddition of an acyl iminium ion.[4] Herein we report the results of our own efforts that have culminated in the first enantioselective synthesis of (+)-symbioimine (**1**).

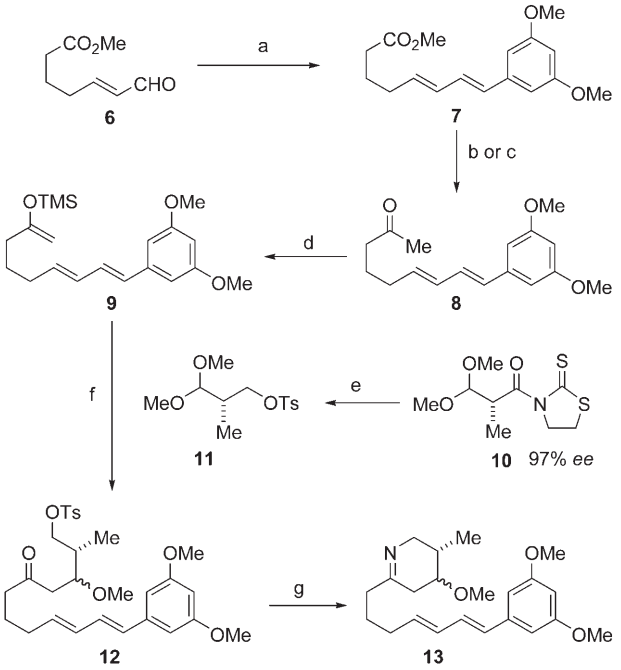
As a result of the ease with which dihydropyridine derivatives are oxidized or can disproportionate,[5] we planned to access the desired cyclic iminium ion (**4**, R = Me) in a one-pot cascade sequence than began with the tetrahydropyridine **13**. We hoped that exposure of **13** to either Brønsted or Lewis acids would effect elimination, followed by cycloaddition and epimerization to afford the skeleton of the natural product. From the beginning, we elected to protect

[*] Prof. R. J. Thomson
Department of Chemistry
Northwestern University
2145 Sheridan Rd, Evanston, IL 60208 (USA)
Fax: (+1) 847-467-2184
E-mail: r-thomson@northwestern.edu
J. Kim
Department of Chemistry & Chemical Biology
Harvard University
12 Oxford St, Cambridge, MA 02138 (USA)

[**] We thank Prof. D. Uemura and Dr. M. Kita for providing an authentic sample of (+)-symbioimine. A portion of this work was conducted at Harvard University and Prof. D. A. Evans is gratefully acknowledged for support. This work was supported by Northwestern University (NU), the NU Analytical Services Laboratory (NSF grants DMR0114235 and CHE9871268), and the Mass Spectrometry Laboratory at the University of Illinois, Chicago.

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

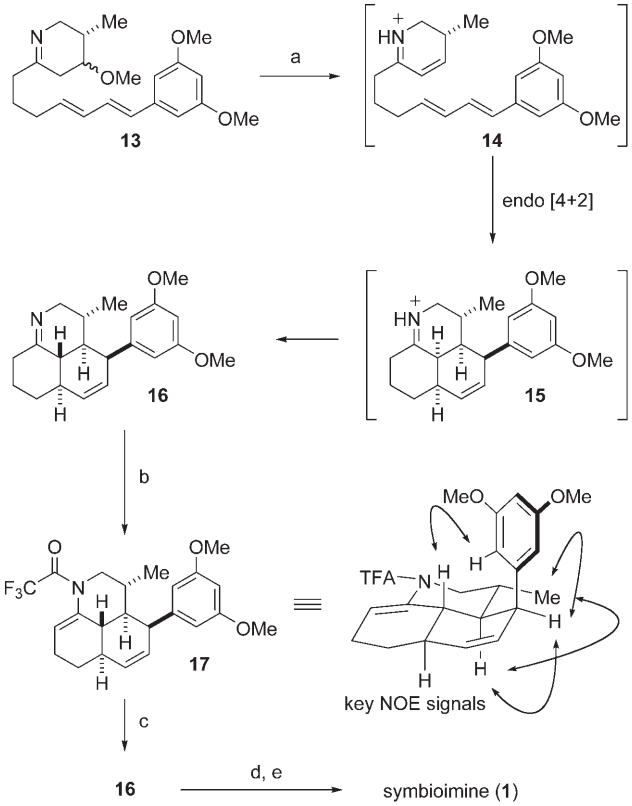
the phenolic groups as the corresponding methyl ethers, with the reason that double deprotection and selective sulfation conditions could be found once our key cycloaddition had been achieved. The synthesis of imine **13** is outlined in Scheme 3.



Scheme 3. Synthesis of the precursor to the Diels–Alder reaction **13**. a) Dimethyl 3,5-dimethoxybenzylphosphonate, NaHMDS, 82%; b) MeMgCl, NHMe(OMe)·HCl, 70%; c) *i*PrMgCl, NHMe(OMe)·HCl; MeMgCl, 90% (2 steps) d) LDA, TMSCl, Et_3N, 99%; e) $LiBH_4$; TsCl, py, 61% (2 steps); f) **9** + **11**, TMSOTf, 2,6-di-*tert*-butylpyridine, 58%; g) NaN_3; solid-supported Ph_3P, 98% (2 steps). HMDS = hexamethyldisilazide, LDA = lithium diisopropylamide, py = pyridine, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl, Ts = toluenesulfonyl.

A Horner–Wadsworth–Emmons reaction between the known aldehyde **6**[6] and dimethyl 3,5-dimethoxybenzylphosphonate[7] provided the desired diene **7** with high levels of *E*/*Z* selectivity (>11:1) and in good yield (82%). Preparation of methyl ketone **8** could be achieved in 70% yield by a one-step protocol using NHMe(OMe)·HCl and excess MeMgCl.[8] On a larger scale it was more convenient to use a two-step procedure which involved the initial isolation of the intermediate Weinreb amide, and its subsequent conversion into the methyl ketone **8** (90% yield, two steps). Silylation of **8** by using the Corey protocol[9] afforded enol silane **9** (70% yield, two steps). We proposed to couple **9** with dimethyl acetal **11**, which was readily prepared from the thione **10**[10] (97% *ee*), by reduction and tosylation (61% yield, two steps). In the event, exposure of a 2:1 ratio of **9** and **11** to TMSOTf in the presence of 2,6-di-*tert*-butylpyridine provided the desired adduct **12** in 58% yield (based on the tosylate **11**). Treatment of **12** with NaN_3, followed by a Staudinger reduction and aza-Wittig reaction delivered the imine **13** in excellent yield (98%, two steps).[11]

Our initial efforts sought to effect thermal elimination of methanol from **13**, but only decomposition products that resulted from oxidation were observed. During this time, Kishi and co-workers reported an intramolecular Diels–Alder reaction mediated by a Brønsted acid of an exocyclic unsaturated imine en route to the marine toxin gymnodimine.[12] However, no reaction was observed when we exposed **13** to the conditions reported by Kishi and co-workers (pH 6.5 buffer). Nevertheless, further exploration revealed a set of conditions that did effect the desired cascade sequence (Scheme 4). Heating **13** in a 0.5 M solution of TFA at



Scheme 4. Diels–Alder cascade reaction and completion of the synthesis. a) 0.5 M TFA (4:1 water/THF), 50 °C; b) TFAA, Et_3N, 25–37% (2 steps); c) K_2CO_3/MeOH, 99%; d) 1.0 M BBr_3, 82%; e) SO_3·py, py, 27%. TFA = trifluoroacetic acid, TFAA = trifluoroacetic anhydride.

50 °C for 24 h provided the desired cycloadduct **16**, presumably by the pathway outlined in Scheme 4. Analysis of the ^1H NMR spectrum of the unpurified reaction mixture revealed that the cyclization afforded a single diastereoisomer. For ease of purification, the reaction mixture was treated with trifluoroacetic anhydride, and in this manner acetamide **17** was isolated in 25–37% yield from **13**. Tentative proof of the stereochemistry was obtained at this juncture by observing key NOE signals within **17** (see Scheme 4). Trifluoroacetamide **17** could be converted back into **16** by using a mild methanolysis (K_2CO_3/MeOH). Brief exposure of **16** to an excess of 1.0 M boron tribromide for one hour cleanly provided the corresponding bisphenol derivative. Sulfation using the modified conditions reported by Maier and co-

workers provided **1** in 27% yield ($[\alpha]_D$ +251 ($c = 0.15$, DMSO) [lit. $[\alpha]_D$ +245 ($c = 0.1$, DMSO)]). The spectroscopic data (^{1}H and ^{13}C NMR, MS) of synthetic **1** corresponded with those of the natural product.[13]

Our Diels–Alder sequence is distinctive relative to the previously reported approaches to symbioimine (**1**) because it proceeds via iminium ion intermediates[14,15] rather than acyl iminium ions[2] or ketones.[3] As such, the reaction provides direct support that such an intramolecular [4+2] cycloaddition reaction may be involved in the biosynthesis of **1**. The moderate yield obtained is probably a result of the generation of pyridine derivatives that could not be completely avoided. Notably we did not isolate any of the unusual structures that were reported by Snider and co-workers[4] during the cycloadditions of the acyl iminium ions, although these cannot be completely ruled out. More importantly, this example of a rare cycloaddition of a dihydropyridinium ion is a step towards the expansion of the use of these entities in complex molecule synthesis. From a synthetic standpoint, the direct conversion of **13** into **16** represents a significant increase in structural complexity: two new rings and four stereocenters are formed in a diastereoselective manner from the presence of a single methyl substituent. The overall brevity of the sequence detailed here suggests that it may be useful for the synthesis of analogues of **1** and in the identification of structure–activity relationships with respect to osteoclastogenesis inhibition. Such research efforts will become increasingly more important because of the increase in elderly populations around the world.

Received: December 21, 2006
Revised: January 24, 2007
Published online: March 15, 2007

Keywords: biomimetic synthesis · cycloaddition · Diels–Alder reaction · natural products · total synthesis

[1] a) M. Kita, M. Kondo, T. Koyama, K. Yamada, T. Matsumoto, K. Lee, J. Woo, D. Uemura, *J. Am. Chem. Soc.* **2004**, *126*, 4794–4795; b) M. Kita, D. Uemura, *Chem. Lett.* **2005**, 454–459; c) M. Kita, N. Ohishi, K. Washida, M. Kondo, T. Koyama, K. Yamada, D. Uemura, *Bioorg. Med. Chem.* **2005**, *13*, 5253–5258.

[2] B. B. Snider, Q. Che, *Angew. Chem.* **2006**, *118*, 946–949; *Angew. Chem. Int. Ed.* **2006**, *45*, 932–935.

[3] a) G. N. Varseev, M. E. Maier, *Angew. Chem.* **2006**, *118*, 4885–4889; *Angew. Chem. Int. Ed.* **2006**, *45*, 4767–4771; b) E. Sakai, K. Araki, H. Takamura, D. Uemura, *Tetrahedron Lett.* **2006**, *47*, 6343–6345.

[4] Y. Zou, Q. Che, B. B. Snider, *Org. Lett.* **2006**, *8*, 5605–5608.

[5] a) R. F. Francis, C. D. Crews, B. S. Scott, *J. Org. Chem.* **1978**, *43*, 3227–3230; b) R. J. Sundberg, D. S. Grierson, H.-P. Husson, *J. Org. Chem.* **1984**, *49*, 2400–2404; c) N. Naiman, H. Rollema, E. Johnson, N. Castagnoli, Jr., *Chem. Res. Toxicol.* **1990**, *3*, 133–138.

[6] M. A. Ciufolini, S. Zhu, *J. Org. Chem.* **1998**, *63*, 1668–1675.

[7] J. Drew, M. Letellier, P. Morand, A. G. Szabo, *J. Org. Chem.* **1987**, *52*, 4047–4052.

[8] J. M. Williams, R. B. Jobson, N. Yasuda, G. Marchesini, U.-H. Dolling, E. J. J. Grabowski, *Tetrahedron Lett.* **1995**, *36*, 5461–5464.

[9] E. J. Corey, A. W. Gross, *Tetrahedron Lett.* **1984**, *25*, 495–498.

[10] D. A. Evans, R. J. Thomson, *J. Am. Chem. Soc.* **2005**, *127*, 10506–10507.

[11] a) H. Staudinger, J. Meyer, *Helv. Chim. Acta* **1919**, *2*, 635–646; b) M. Vaultier, N. Knouzi, R. Carrie, *Tetrahedron Lett.* **1983**, *24*, 763–764.

[12] J. W. Johannes, S. Wenglowsky, Y. Kishi, *Org. Lett.* **2005**, *7*, 3997–4000.

[13] See the Supporting Information for experimental procedures and spectroscopic data for all compounds.

[14] For examples of 5,6-dihydropyridinium ions as dienophiles, see: a) J. E. Baldwin, D. R. Spring, R. C. Whitehead, *Tetrahedron Lett.* **1998**, *39*, 5417–5420; b) K. Jakubowicz, K. Ben Abdeljelil, M. Herdemann, M.-T. Martin, A. Gateau-Olesker, A. Al-Mourabit, C. Marazano, B. C. Das, *J. Org. Chem.* **1999**, *64*, 7381–7387; c) J. E. Baldwin, T. D. W. Claridge, A. J. Culshaw, F. A. Heupel, V. Lee, D. R. Spring, R. C. Whitehead, *Chem. Eur. J.* **1999**, *5*, 3154–3161; d) M. Herdemann, A. Al-Mourabit, M.-T. Martin, C. Marazano, *J. Org. Chem.* **2002**, *67*, 1890–1897.

[15] For the use of 3,4-dihydropyridinium ions as dienes in biomimetic Diels–Alder reactions, see: R. B. Ruggeri, M. M. Hansen, C. H. Heathcock, *J. Am. Chem. Soc.* **1988**, *110*, 8734–8736.

