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Total Synthesis of (±)-Symbioimine

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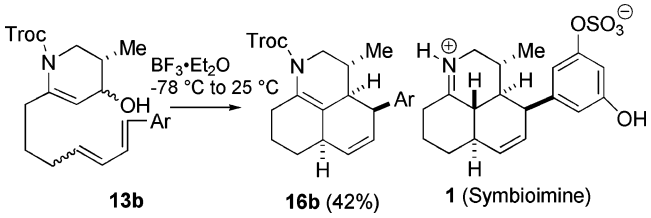
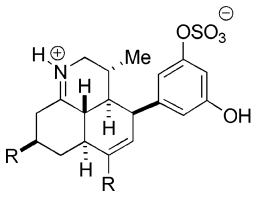
ABSTRACT



The synthesis of (±)-symbioimine (1) has been completed in only 12 linear steps in 8% overall yield. The key step is the treatment of 13b with BF_3·Et_2O to generate *N*-carboalkoxydihydropyridinium cation 14b, which undergoes a novel stereospecific intramolecular Diels–Alder reaction to give adduct 16b in 42% yield. Cleavage of the *N*-Troc group of 16b afforded imine 24b stereospecifically. Cleavage of the TBDMS ethers and sulfation provided (±)-symbioimine (1).

Uemura and co-workers recently reported the isolation of the novel tricyclic iminium sulfate symbioimine (**1**) from a cultured marine dinoflagellate *Symbiodinium* sp.[1a,b] Symbioimine (**1**) inhibits the differentiation of RAW264 cells into osteoclasts (EC_{50} = 44 μM) and significantly inhibits cyclooxygenase-2 activity at 10 μM, thus indicating that **1** is a potential antiresorptive and anti-inflammatory drug. Uemura later isolated the dimethyl homologue neosymbioimine (**2**) from the same source.[1c]



1, R = H (Symbioimine)
2, R = Me (Neosymbioimine)

We recently reported an efficient biomimetic synthesis of (±)-deoxysymbioimine (**10b**) (see Scheme 1).[2] Treatment of pyridine **3** with TrocCl and then EtMgBr gave a methoxydihydropyridine that was hydrolyzed with HCl to give ketone **5a** in 67% yield (see Scheme 1). Reduction of the ketone afforded alcohol **6a** in 91% yield, which was treated with BF_3·Et_2O in CH_2Cl_2 to generate *N*-alkoxycarbonyl dihydropyridinium cation **7a**, which underwent the desired intramolecular Diels−Alder reaction through an *endo* transition state from the face opposite the two alkyl groups to give adduct **8a**. Loss of a proton provided ene carbamate **9a** in 87% yield from **6a**. Deprotection of **9a** with activated Zn in AcOH/MeOH at 60 °C followed by protonation with TFA afforded symbioimine analogue **10a** in 83% yield.

Unfortunately **5b** could not be prepared by Fowler reduction[3] of pyridine **3** (treatment with TrocCl and a hydride reducing agent). We therefore developed an alternate route to **5b** from aldehyde **4**, which is readily available in six steps and 53% overall yield from ethyl acetoacetate.[4] Wittig reaction of aldehyde **4** with cinnamylidenetriphenylphosphorane afforded diene **5b** as a 2:1 *E*/*Z* mixture that was isomerized with I_2 in CH_2Cl_2 to afford **5b** as a 6:1 *E*/*Z*

(1) (a) Kita, M.; Kondo, M.; Koyama, T.; Yamada, K.; Matsumoto, T.; Lee, K.-H.; Woo, J.-T.; Uemura, D. *J. Am. Chem. Soc.* **2004**, *126*, 4794−4795. (b) Kita, M.; Uemura, D. *Chem. Lett.* **2005**, *34*, 454−459. (c) Kita, M.; Ohishi, N.; Washida, K.; Kondo, M.; Koyama, T.; Yamada, K.; Uemura, D. *Bioorg. Med. Chem.* **2005**, *13*, 5253−5258.

(2) Snider, B. B.; Che, Q. *Angew. Chem., Int. Ed.* **2006**, *45*, 932−935.

(3) (a) Fowler, F. W. *J. Org. Chem.* **1972**, *37*, 1321−1323. (b) Raucher, S.; MacDonald, J. E. *Synth. Commun.* **1980**, *10*, 325−331. (c) Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1981**, *46*, 4836−4842. (d) Sundberg, R. J.; Hamilton, G.; Trindle, C. *J. Org. Chem.* **1986**, *51*, 3672−3679. (e) Zhao, G.; Deo, U. C.; Ganem, B. *Org. Lett.* **2001**, *3*, 201−203.

(4) Our original procedure required two steps to hydrolyze a dioxolane protecting group by first converting it to a dimethyl acetal. The sequence has been shortened one step by alkylating ethyl acetoacetate with 3-bromo-1,1-dimethoxypropane rather than 2-(2-bromoethyl)-1,3-dioxolane so that the acetal exchange is not necessary. Full details are provided in the Supporting Information.

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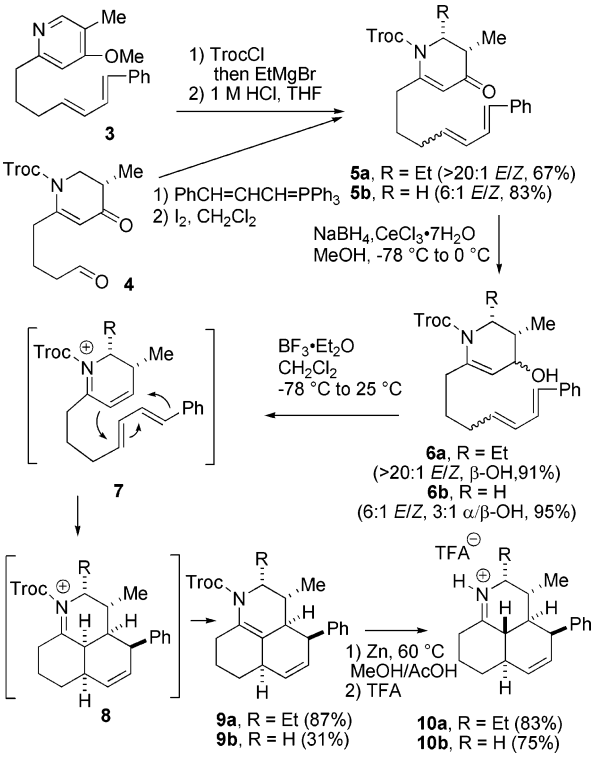
Scheme 1. Synthesis of (±)-Deoxysymbioimine



mixture in 83% yield from **4**. Reduction afforded alcohol **6b** in 95% yield, which was treated with BF_3•Et_2O as described above for **6a** to afford the desired Diels−Alder adduct **9b** in only 31% yield. Deprotection of **9b** with activated Zn in AcOH/MeOH at 60 °C and protonation with TFA afforded (±)-deoxysymbioimine (**10b**) in 75% yield.

To complete the synthesis of (±)-symbioimine (**1**), we needed to adapt this chemistry to a bis-oxygen-substituted aromatic ring and optimize the intramolecular Diels−Alder reaction, which gave the ethyl homologue **9a** in 87% yield, but gave deoxysymbioimine precursor **9b** in only 31% yield. While this work was in progress, Varseev and Maier reported the synthesis of (±)-symbioimine via an intramolecular Diels−Alder reaction of an unsaturated aldehyde, followed by elaboration of the heterocyclic ring in 22 steps.[5] Uemura reported the preparation of bicyclic intermediates by a similar strategy.[6]

The preparation of diene alcohol **13a** was carried out analogously to the preparation of diene alcohol **6b** (see Scheme 2). Wittig reaction of aldehdye **4** with phosphorane **11a**[7,8] followed by equilibration with I_2 in CH_2Cl_2 afforded

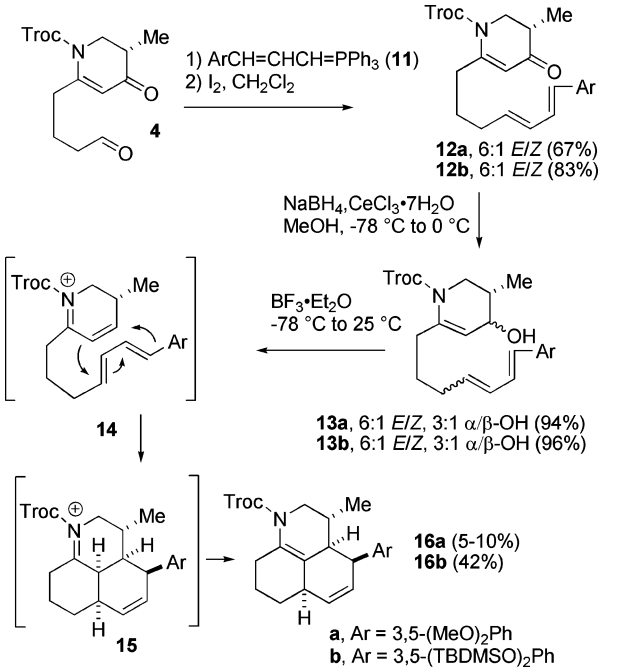
(5) Varseev, G. N.; Maier, M. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 4767−4771.

(6) Sakai, E.; Araki, K.; Tamkamura, H.; Uemura, D. *Tetrahedron Lett.* **2006**, *47*, 6343−6345.

(7) Wittig reaction of 3,5-dimethoxybenzaldehyde with methyl triphenylphosphoranylideneacetate afforded the cinnamate ester that was reduced to the alcohol with DIBAl-H, converted to the bromide with PBr_3, and reacted with Ph_3P to give the phosphonium salt.[8] Treatment of the phosphonium salt with *n*-BuLi afforded **11a**.[8]

(8) Taira, S.; Danjo, H.; Imamoto, T. *Tetrahedron Lett.* **2002**, *43*, 8893−8896.

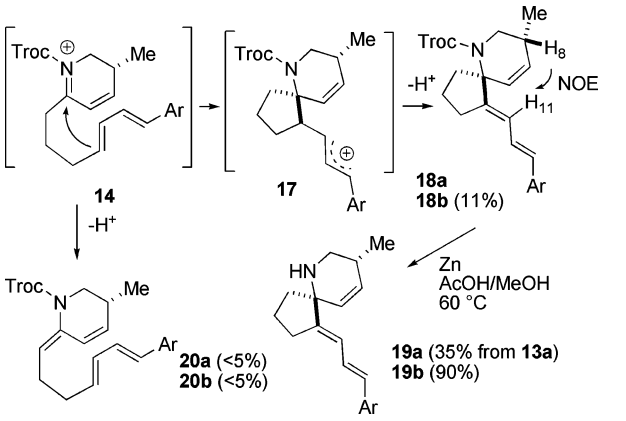
Scheme 2. Synthesis of Diels−Alder Adducts **15a**,**b**



dienyl ketone **12a** as a 6:1 *E*/*Z* mixture in 67% yield. Reduction of the ketone with $NaBH_4$ and $CeCl_3$ in MeOH at −78 °C to 0 °C provided **13a** in 94% yield. Unfortunately, treatment of **13a** with BF_3•Et_2O under a variety of conditions gave only 5−10% of the 3,5-dimethoxyphenyl Diels−Alder product **16a**. We looked carefully at the structures of the byproducts to understand this reaction better and hopefully improve the yield of the Diels−Alder reaction.

Reaction of **13a** with BF_3•Et_2O (1 equiv) in Et_2O at −78 to 25 °C gave a ∼10:35:1 mixture of **16a**, **18a**, and **20a** in ∼46% yield (see Scheme 3). The ^{1}H NMR spectrum of **18a**

Scheme 3. Formation of Byproducts **18** and **20**



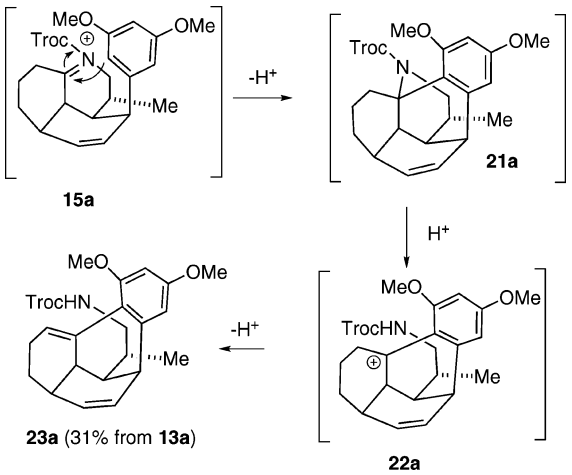
was hard to interpret because of slow rotation about the Troc−N bond. Deprotection of the mixture with activated Zn in AcOH/MeOH at 60 °C for 30 min afforded the free amine **19a** in 35% overall yield from **13a**. Treatment of **13a**

with BF_3·Et_2O generates dihydropyridinium cation **14a**, which undergoes both the desired Diels−Alder reaction to give **15a** and a stepwise cyclization from the less hindered top face to give allylic cation **17a**, which loses a proton to give the conjugated diene **18a**. The stereochemistry of **18a** and **19a** was assigned by analogy to **18b** (see below). Minor byproduct **20a** is formed by loss of a proton from dihydropyridinium cation **14a**. Diels−Alder reaction in CH_2Cl_2 gave low yields of a ~1:2 mixture of **16a** and **18a**.

Having established the structure of **18**, we can rationalize the formation of the ethyl-substituted Diels−Alder adduct **9a** in 87% yield, while the parent adduct **9b** is formed in only 31% yield. Presumably, the ethyl group sterically retards the stepwise addition of the diene to the iminium cation, so that byproducts analogous to **18** are formed from iminium salt **7b**, but not from the ethyl homologue **7a**. The substituents on the aryl group do not play a crucial role in this side reaction.

Reaction of **13a** with BF_3·Et_2O (1 equiv) in toluene at −78 to 25 °C gave a ~1:10 mixture of **16a** and **23a**, from which pure **23a** was isolated in 31% yield (see Scheme 4).

Scheme 4. Formation of Byproduct **23a**



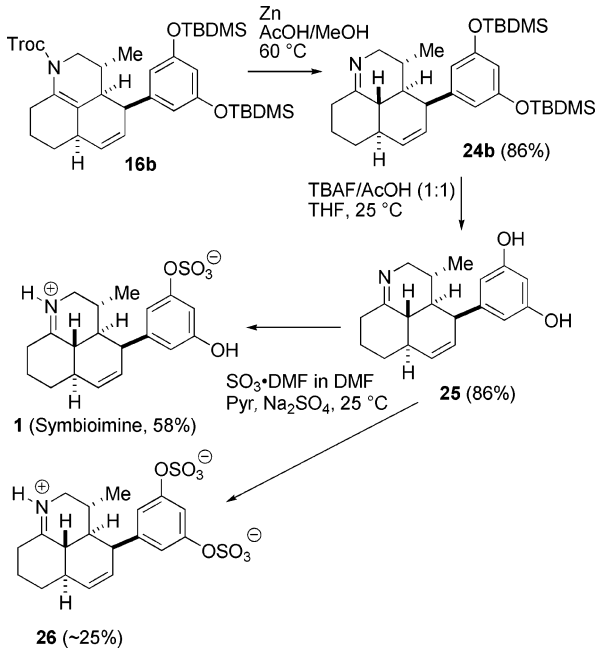
In the less polar solvent toluene, the stepwise addition to give **18a** does not occur. The desired Diels−Alder adduct **15a** is formed, but reacts further to give byproduct **23a**. The electron-rich dimethoxyphenyl ring of the Diels−Alder adduct iminium salt **15a** is close to the iminium cation. Friedel−Crafts addition followed by loss of a proton affords **21a**, which is protonated on nitrogen and undergoes C−N bond cleavage to give stabilized benzylic cation **22a**, which loses a proton to give **23a**. The structure of **23a** was assigned by careful analysis of the ^1H, ^{13}C, COSY and 1D NOESY NMR spectra.

We considered modification of oxygen protecting groups and reaction conditions that would improve the selectivity for the ene carbamate Diels−Alder adduct **16** at the expense of byproducts **18** and **23**. Dihydropyridinium cation **14** cyclizes to give **17** in a polar reaction and undergoes an intramolecular cycloaddition to give **15** in a concerted reaction. Use of nonpolar solvents such as toluene favors the Diels−Alder product **15** at the expense of **18**. Byproduct **23** is formed by Friedel−Crafts cyclization of the Diels−Alder adduct **15** prior to loss of a proton to form **16**. We thought that this cyclization should be slower with larger protecting groups on oxygens. TBDMS was chosen for initial examination because it is large and easily removed after the Diels−Alder reaction.

Phosphorane **11b** was prepared analogously to **11a** from 3,5-bis(TBDMSO)-benzaldehyde.[9,10] Reaction of aldehyde **4** with ylide **11b** gave dienyl ketone **12b** in 83% yield as a 6:1 mixture of *E*/Z isomers after equilibration with I_2 in CH_2Cl_2. Reduction of the ketone with $NaBH_4$ and $CeCl_3$ in MeOH at −78 to 0 °C afforded 96% of alcohol **13b**. We were delighted to find that treatment of alcohol **13b** with BF_3·Et_2O in 1:1 benzene/toluene at −42 °C for 20 min followed by slow warming to 25 °C over 20 min provided the desired ene carbamate **16b** in 42% yield (49% based on *E*-isomer), only 11% of byproduct **18b**, and <5% of **20b**. Friedel−Crafts reaction to give **23b** did not take place. The spectral data for **16b** corresponded closely to those for deoxysymbioimine precursor **9b**. The stereochemistry of the diene and the heterocyclic ring of **18b** was assigned based on the NOE from H_8 to H_{11}. Deprotection of **18b** gave **19b** in 90% yield.

Deprotection of the Troc group of **16b** with Zn in AcOH/MeOH at 60 °C provided imine **24b** in 86% yield (see Scheme 5). Deprotection of the TBDMS groups proved

Scheme 5. Completion of the Symbioimine (**1**) Synthesis



challenging but was achieved by treatment with TBAF/AcOH (1:1, 2 equiv) in THF at 25 °C for 15 min. The product was separated from tetrabutylammonium salts by extraction from water at neutral pH into ether to give desulfato symbioimine **25** in 86% yield with spectral data identical with those

reported by Varseev and Maier.[5] Reaction of **25** with 10 equiv of SO_3·DMF (2 M in DMF) and anhydrous sodium sulfate in pyridine afforded a mixture of (±)-symbioimine (**1**) and the bis-sulfate **26** in quantitative yield. Reverse-phase HPLC separation gave pure (±)-symbioimine (**1**) in 58% yield with spectral data identical with those reported.[1,5] We also obtained ~25% of bis-sulfate **26**, which hydrolyzed on concentration to give a mixture of **1**, **25**, and **26**.

(9) Guiso, M.; Marra, C.; Farina, A. *Tetrahedron Lett.* **2002**, *43*, 597−598.

(10) Wittig reaction of 3,5-bis(TBDMSO)-benzaldehyde with methyl triphenylphosphoranylideneacetate afforded the cinnamate ester (91%) that was reduced to the alcohol (95%) with DIBAl-H, converted to the bromide (80%) with PBr_3, and reacted with Ph_3P to give the phosphonium salt (80%).[8] Treatment of the phosphonium salt with *n*-BuLi afforded **11b**. Full details are provided in the Supporting Information.

In conclusion, we have completed the synthesis of (±)-symbioimine in only 12 linear steps in 8% overall yield. The key step is the novel stereospecific intramolecular Diels−Alder reaction of **14b**, with an *N*-carboalkoxydihydropyridinium cation as the dienophile, which gave adduct **16b** in 42% yield. This convergent sequence starting from aldehyde **4** and ylide **11b** is readily amenable to preparation of analogues for further biological evaluation.

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Supporting Information Available: Full experimental details and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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