

Total Synthesis of ( $\pm$ )-Symbioimine

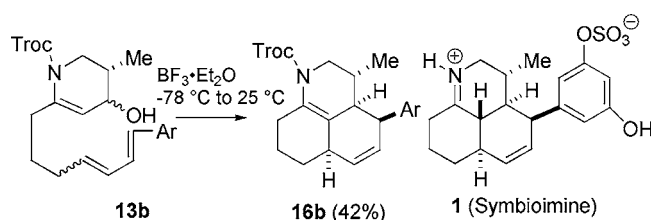
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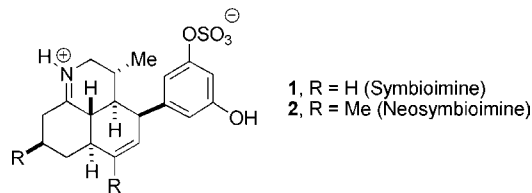
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## ABSTRACT



The synthesis of ( $\pm$ )-symbioimine (**1**) has been completed in only 12 linear steps in 8% overall yield. The key step is the treatment of **13b** with  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  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 ( $\pm$ )-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.<sup>1a,b</sup> Symbioimine (**1**) inhibits the differentiation of RAW264 cells into osteoclasts ( $\text{EC}_{50} = 44 \mu\text{M}$ ) and significantly inhibits cyclooxygenase-2 activity at  $10 \mu\text{M}$ , thus indicating that **1** is a potential antiresorptive and anti-inflammatory drug. Uemura later isolated the dimethyl homologue neosymbioimine (**2**) from the same source.<sup>1c</sup>



We recently reported an efficient biomimetic synthesis of ( $\pm$ )-deoxysymbioimine (**10b**) (see Scheme 1).<sup>2</sup> Treatment of pyridine **3** with TrocCl and then  $\text{EtMgBr}$  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  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  in  $\text{CH}_2\text{Cl}_2$  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  $60^\circ\text{C}$  followed by protonation with TFA afforded symbioimine analogue **10a** in 83% yield.

Unfortunately **5b** could not be prepared by Fowler reduction<sup>3</sup> 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.<sup>4</sup> Wittig reaction of aldehyde **4** with cinnamylidetriphenylphosphorane afforded diene **5b** as a 2:1 *E/Z* mixture that was isomerized with  $\text{I}_2$  in  $\text{CH}_2\text{Cl}_2$  to afford **5b** as a 6:1 *E/Z*

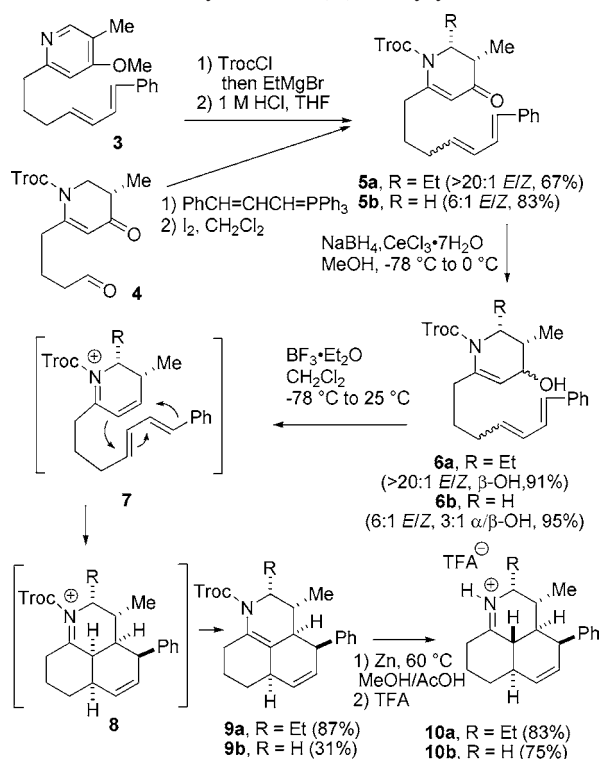
(1) (a) Kita, M.; Kondo, M.; Koyama, T.; Yamada, K.; Matsumoto, T.; Lee, K.-H.; Woo, J.-T.; Uemura, D. *J. Am. Chem. Soc.* **2004**, *126*, 4794–4795. (b) Kita, M.; Uemura, D. *Chem. Lett.* **2005**, *34*, 454–459. (c) Kita, M.; Ohishi, N.; Washida, K.; Kondo, M.; Koyama, T.; Yamada, K.; Uemura, D. *Bioorg.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

### Scheme 1. Synthesis of (±)-Deoxysymbioimine



mixture in 83% yield from **4**. Reduction afforded alcohol **6b** in 95% yield, which was treated with BF<sub>3</sub>·Et<sub>2</sub>O 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.<sup>5</sup> Uemura reported the preparation of bicyclic intermediates by a similar strategy.<sup>6</sup>

The preparation of diene alcohol **13a** was carried out analogously to the preparation of diene alcohol **6b** (see Scheme 2). Wittig reaction of aldehyde **4** with phosphorane **11a**<sup>7,8</sup> followed by equilibration with I<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> afforded

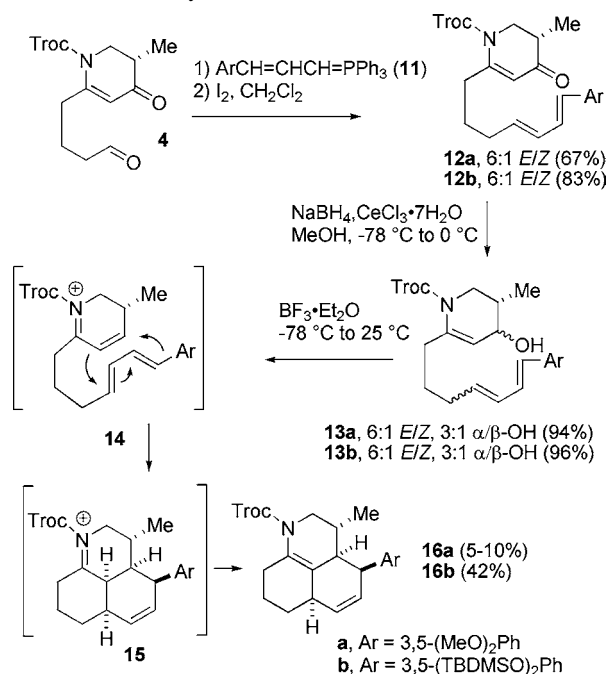
(5) Varseev, G. N.; Maier, M. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 4767–4771.

(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<sub>3</sub>, and reacted with Ph<sub>3</sub>P to give the phosphonium salt.<sup>8</sup> Treatment of the phosphonium salt with *n*-BuLi afforded **11a**.<sup>8</sup>

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

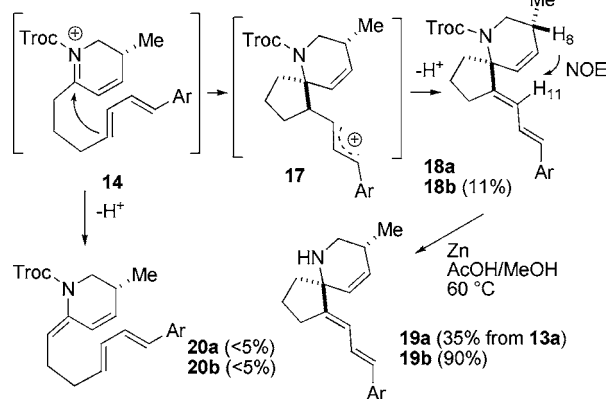
### Scheme 2. Synthesis of Diels–Alder Adducts **15a,b**



dienyl ketone **12a** as a 6:1 *E/Z* mixture in 67% yield. Reduction of the ketone with NaBH<sub>4</sub> and CeCl<sub>3</sub> in MeOH at -78 °C to 0 °C provided **13a** in 94% yield. Unfortunately, treatment of **13a** with BF<sub>3</sub>·Et<sub>2</sub>O 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<sub>3</sub>·Et<sub>2</sub>O (1 equiv) in Et<sub>2</sub>O at -78 to 25 °C gave a ~10:35:1 mixture of **16a**, **18a**, and **20a** in ~46% yield (see Scheme 3). The <sup>1</sup>H NMR spectrum of **18a**

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

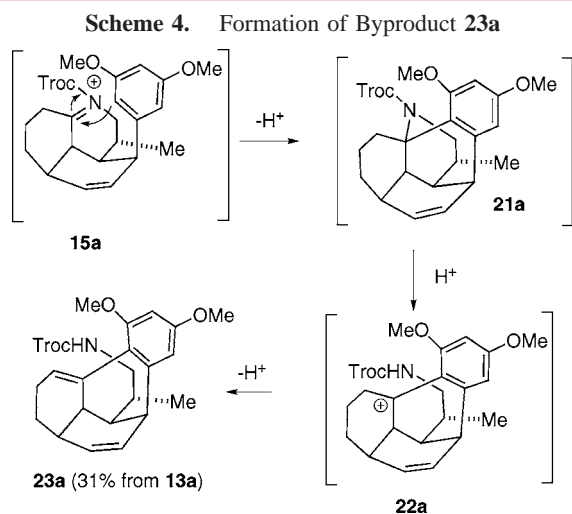


was hard to interpret because of slow rotation about the Troc–N bond. Deprotection of the mixture with activated Zn in AcOH/MeOH at 60 °C for 30 min afforded the free amine **19a** in 35% overall yield from **13a**. Treatment of **13a**

with  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  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  $\text{CH}_2\text{Cl}_2$  gave low yields of a  $\sim 1:2$  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  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (1 equiv) in toluene at  $-78$  to  $25$  °C gave a  $\sim 1:10$  mixture of **16a** and **23a**, from which pure **23a** was isolated in 31% yield (see Scheme 4).



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  $^1\text{H}$ ,  $^{13}\text{C}$ , COSY and 1D NOESY NMR spectra.

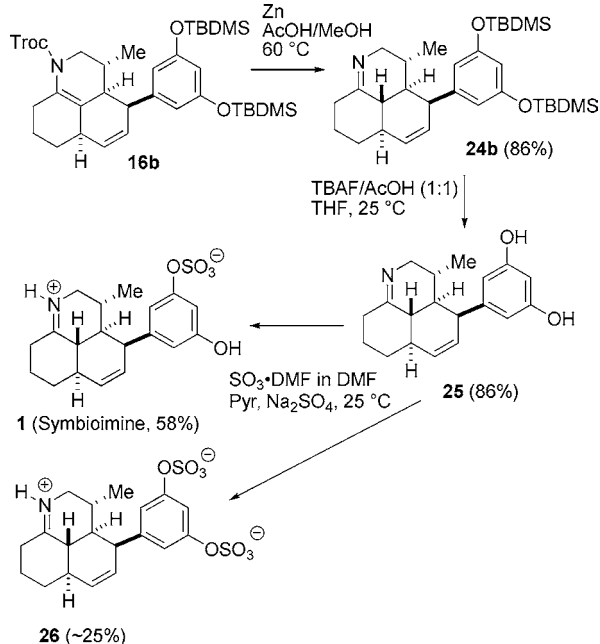
We considered modification of oxygen protecting groups and reaction conditions that would improve the selectivity for the ene carbamate Diels–Alder adduct **16** at the expense of byproducts **18** and **23**. Dihydropyridinium cation **14** cyclizes to give **17** in a polar reaction and undergoes an 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.<sup>9,10</sup> 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  $\text{I}_2$  in  $\text{CH}_2\text{Cl}_2$ . Reduction of the ketone with  $\text{NaBH}_4$  and  $\text{CeCl}_3$  in MeOH at  $-78$  to  $0$  °C afforded 96% of alcohol **13b**. We were delighted to find that treatment of alcohol **13b** with  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  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  $\text{H}_8$  to  $\text{H}_{11}$ . 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.<sup>5</sup> Reaction of **25** with 10 equiv of SO<sub>3</sub>·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.<sup>1,5</sup> We also obtained ~25% of bis-sulfate **26**, which hydrolyzed on concentration to give a mixture of **1**, **25**, and **26**.

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(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<sub>3</sub>, and reacted with Ph<sub>3</sub>P to give the phosphonium salt (80%).<sup>8</sup> 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.

**Acknowledgment.** We thank the NIH (GM50151) for generous financial support.

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

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