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Total Synthesis of (±)-Symbioimine

Yefen Zou, Qinglin Che, and Barry B. Snider

Department of Chemistry MS 015, Brandeis University, Waltham, Massachusetts 02454-9110

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 $\text{BF}_3 \cdot \text{Et}_2\text{O}$ 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 (±)-symbioimine (**1**).

Uemura and coworkers 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 ($\text{EC}_{50} = 44 \mu\text{M}$) 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.^{1c}

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 $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in CH_2Cl_2 to generate *N*-alkoxycarbonyl dihydropyridinium cation **7a**, which underwent the desired intramolecular Diels-Alder reaction through an *endo* transition state

snider@brandeis.edu.

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>.

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 MeOH/AcOH at 60 °C followed by protonation with TFA afforded symbioimine analogue **10a** in 83% yield.

Unfortunately **5b** could not be prepared by Fowler reduction³ 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 I₂ in CH₂Cl₂ to afford **5b** as a 6:1 *E/Z* mixture in 83% yield from **4**. Reduction afforded alcohol **6b** in 95% yield, which was treated with BF₃•Et₂O as described above for **6a** to afford the desired Diels-Alder adduct **9b** in only 31% yield. De-protection of **9b** with activated Zn in AcOH/MeOH at 60 °C and protonation with TFA afforded (±)-deoxysymbioimine (**10b**) in 75% yield.

In order 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 Uemera 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 aldehyde **4** with phosphorane **11a**^{7,8} followed by equilibration with I₂ in CH₂Cl₂ afforded dienyl ketone **12a** as a 6:1 *E/Z* mixture in 67% yield. Reduction of the ketone with NaBH₄ and CeCl₃ in MeOH at -78 °C to 0 °C provided **13a** in 94% yield. Unfortunately, treatment of **13a** with BF₃•Et₂O 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 BF₃•Et₂O (1 equiv) in Et₂O at -78 °C to 25 °C gave a ~10:35:1 mixture of **16a**, **18a**, and **20a** in ~46% yield (see Scheme 3). The ¹H NMR spectrum of **18a** 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 BF₃•Et₂O 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** were 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 CH₂Cl₂ 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 BF₃•Et₂O (1 equiv) in toluene at -78 °C to 25 °C gave a ~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 ^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 non-polar 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 $-78\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$ 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 $-42\text{ }^\circ\text{C}$ for 20 min followed by slow warming to $25\text{ }^\circ\text{C}$ 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** were 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 $60\text{ }^\circ\text{C}$ provided imine **24b** in 86% yield (see Scheme 5). Deprotection of the TBDMS groups proved challenging but was achieved by treatment with TBAF/AcOH (1:1, 2 equiv) in THF at $25\text{ }^\circ\text{C}$ 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 to that reported by Varseev and Maier.⁵ Reaction of **25** with 10 equiv of $\text{SO}_3\cdot\text{DMF}$ (2 M in DMF) and anhydrous sodium sulfate in pyridine afforded a mixture of ($\pm$)-symbioimine (**1**) and the bis sulfate **26** in quantitative yield. Reverse phase HPLC separation gave pure ($\pm$)-symbioimine (**1**) in 58% yield with spectral data identical to 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**.

In conclusion, we have completed the synthesis of ($\pm$)-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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.
 Synthesis of (±)-Deoxysymbioimine

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

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

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

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