Cycloaddition Reactions

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Synthesis of (±)-Deoxysymbioimine Using an Intramolecular Diels–Alder Reaction with an *N*-Alkoxycarbonyl 2,3-Dihydropyridinium Cation as the Dienophile**

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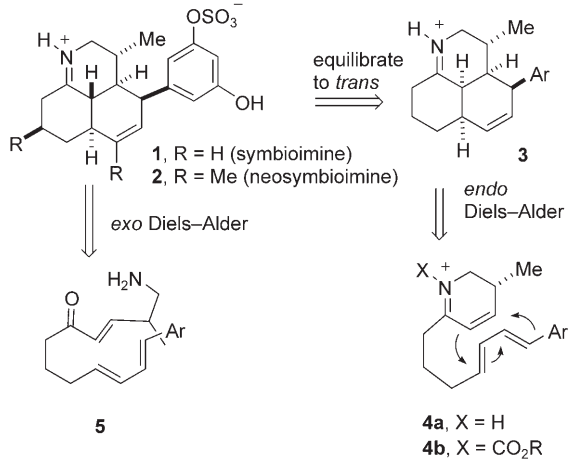
Uemura et al. recently reported the isolation of the novel tricyclic iminium sulfate symbioimine (**1**) from a cultured symbiotic marine dinoflagellate *Symbiodinium* sp.[1a,b] Symbioimine (**1**) inhibits the differentiation of RAW264 cells into osteoclasts ($EC_{50} = 44\ \mu M$) and significantly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

Uemura et al. originally suggested that the biogenesis of **1** might involve an intramolecular Diels–Alder (IMDA) reaction of enone **5** through an *exo* transition state followed by cyclization to generate the imine (see Scheme 1).[1a,b] While our investigation was in progress, he suggested that the IMDA reaction of dihydropyridinium cation **4a** through an *endo* transition state would give **3** with a *cis* ring fusion, which could readily epimerize to give **1** with a *trans* ring fusion.[1c]



Scheme 1. Retrosynthetic intramolecular Diels–Alder routes to symbioimine (**1**).

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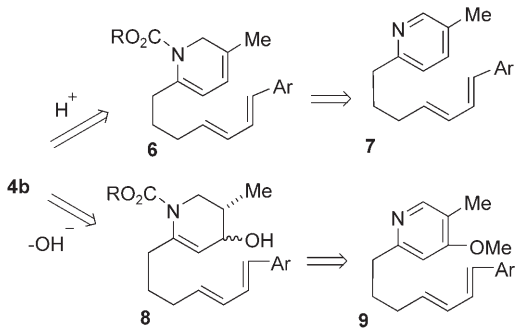
We considered both of these routes for the synthesis of **1**. IMDA reactions of *trans*-enones analogous to **5** give mainly the *endo* adduct,[2] rather than the *exo* adduct needed for the preparation of **1**. Furthermore, it did not appear likely that the methyl substituent of **5** would control the facial selectivity of the IMDA reaction, so mixtures of isomers would be obtained. *cis*-Enones analogous to **4** are known to give *endo* adducts analogous to **3**.[3] Furthermore, the methyl group of **4** will block the bottom face of the dihydropyridinium cation so that the IMDA reaction should occur selectively on the desired top face. Sammakia and co-workers very recently developed a related IMDA reaction of a cyclic oxocarbenium ion for the synthesis of (−)-dihydrocompactin.[4]

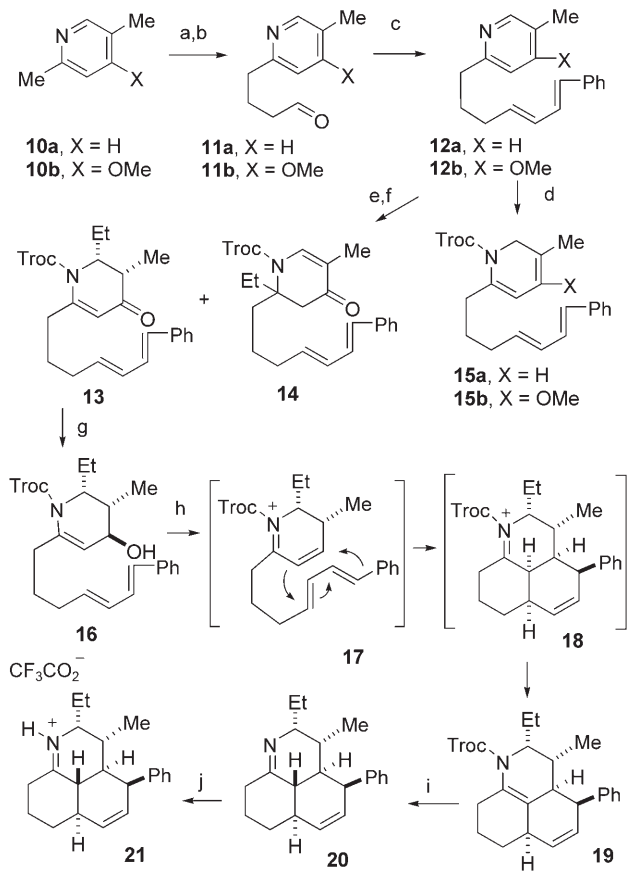
Dihydropyridinium cation **4a** is a plausible intermediate in the biosynthesis of **1**, but is not an attractive synthetic intermediate. Although dihydropyridinium cations have seen limited use as dienophiles,[5] they disproportionate readily to give pyridines and tetrahydropyridines.[6] *N*-Alkoxycarbonyl dihydropyridinium cation **4b** will not disproportionate and is more electron deficient, and therefore a more reactive dienophile. Cation **4b** might be available by protonation of dihydropyridine **6**, which can be prepared from pyridine **7** by a Fowler reduction with a chloroformate ester and $NaBH_4$ or $NaBH_3CN$ (see Scheme 2).[7] Alternatively, cation **4b** might be accessible by loss of the hydroxide moiety from tetrahydropyridinol **8**, which can be prepared by Fowler reduction of pyridine **9**, hydrolysis of the enol ether, and reduction of the ketone.



Scheme 2. Retrosynthetic routes to *N*-alkoxycarbonyl dihydropyridinium cation **4b** from pyridines **7** and **9**.

Deprotonation[8] of the 2-methyl group of 2,5-dimethylpyridine (**10a**) with *n*BuLi in THF at 0 °C, alkylation with 2-(2-bromoethyl)-1,3-dioxolane, and hydrolysis of the acetal afforded aldehyde **11a** (88%; see Scheme 3). A Horner–Emmons Wittig reaction with diethyl cinnamylphosphonate afforded **12a** as a 20:1 mixture of the *E*/Z isomers (95%). Treatment of pyridine **12a** with TrocCl and $NaBH_3CN$ afforded an inseparable 2:1 mixture of the desired dihydropyridine **15a** and the 1,4-dihydro isomer. Unfortunately, treatment of this mixture with acid under a variety of conditions did not generate any IMDA adduct, thus suggesting that protonation of dihydropyridine **15a** on the carbon atom bearing the methyl group to generate the *N*-alkoxycarbonyl dihydropyridinium cation is not facile.

We therefore turned our attention to the preparation of tetrahydropyridinol **8**. Deprotonation[9] of the 2-methyl group



Scheme 3. a) *n*BuLi (1 equiv), THF; then 2-(2-bromoethyl)-1,3-dioxolane (1 equiv), 4 h; b) 1 M HCl, 25 °C, 1 h (**11a**: 88%, **11b**: 84%; two steps); c) LDA (1 equiv), diethyl (*E*)-cinnamylphosphonate (1 equiv), THF, 0 °C, 1 h; then aldehyde **11**, −78 °C, 1 h, 25 °C, 12 h (**12a**: 95%, **12b**: 82%); d) $NaBH_3CN$ (3 equiv), TrocCl (3 equiv), THF, 25 °C, 30 min (**15a**: 40% and 1,4-dihydropyridine: 20%, **15b**: 0%); e) TrocCl (2 equiv), THF, −78 °C, 1 h; then EtMgBr (2 equiv), −78 °C, 30 min; 25 °C, 1 h; f) 1 M HCl, 30 min (**13**: 67%, **14**: 18%; two steps); g) $NaBH_4$ (1 equiv) $CeCl_3 \cdot 7H_2O$ (1.25 equiv), MeOH, −78 °C, 30 min; 0 °C, 30 min (91%); h) $BF_3 \cdot Et_2O$ (1.2 equiv), CH_2Cl_2, −78 °C, 10 min; 25 °C, 30 min (87%); i) activated Zn dust, 1:1 MeOH/AcOH, 60 °C, 30 min; then K_2CO_3 (83%); j) TFA (1 equiv) (100%). LDA = lithium diisopropylamide, Troc = 2,2,2-trichloroethoxycarbonyl.

of 4-methoxy-2,5-dimethylpyridine (**10b**)[10] with *n*BuLi in THF at −20 °C, alkylation with 2-(bromoethyl)-1,3-dioxolane, and hydrolysis of the acetal afforded aldehyde **11b** (84%). A Horner–Emmons Wittig reaction with diethyl cinnamylphosphonate afforded **12b** (82%). Unfortunately, all attempts to effect Fowler reduction of **12b** to give **15b** were unsuccessful. Although **12b** is not useful for the preparation of deoxysymbioimine, it was useful for the preparation of the ethyl-substituted analogue **16** of tetrahydropyridinol **8**, which allowed us to validate this IMDA approach to symbioimine.

The addition of Grignard reagents to pyridines and chloroformate esters is more facile and general than the Fowler reduction.[11] We therefore treated **12b** with EtMgBr and TrocCl in THF at −78 °C to give a mixture of dienyl ethers that were hydrolyzed with 1 M HCl to give the desired enone **13** (67%) and the regioisomer **14** (18%). Only the *cis* isomer of **13**[12] was isolated, thus suggesting that protonation of the dienyl ether occurs selectively from the face opposite the ethyl group. Luche reduction[13] of enone **13** gave a single stereoisomeric tetrahydropyridinol **16**[12] in 91% yield.

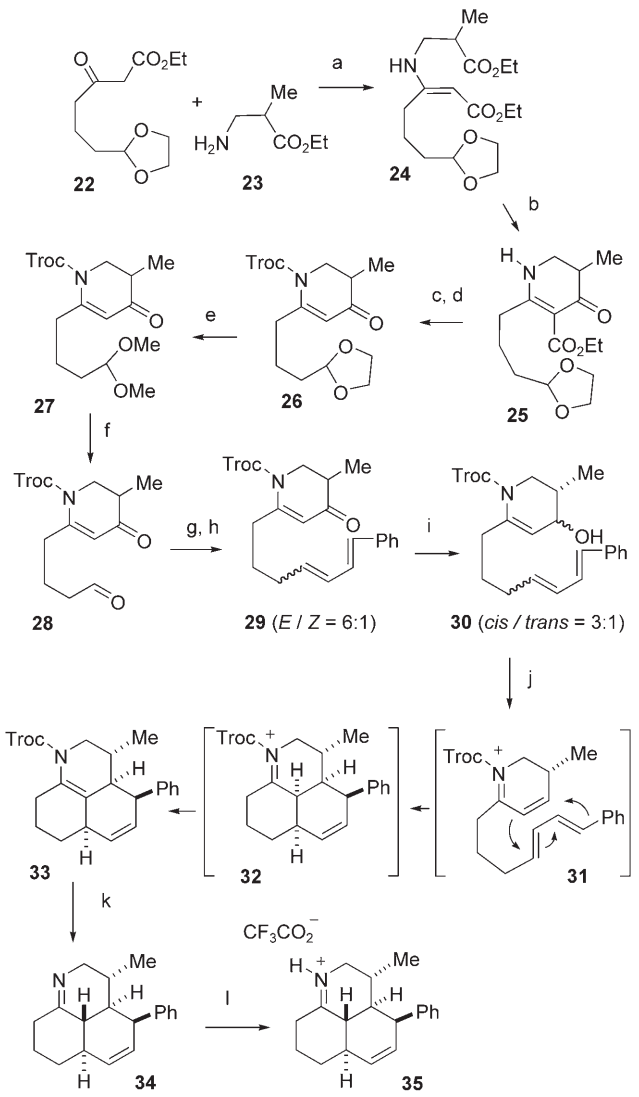
Treatment of alcohol **16** with $BF_3 \cdot Et_2O$ in CH_2Cl_2 at −78–25 °C cleanly afforded the desired tricyclic adduct **19** (87%).[12] Loss of the hydroxide moiety provided the *N*-alkoxycarbonyl dihydropyridinium cation **17**, which underwent the desired IMDA reaction through an *endo* transition state from the face opposite the two alkyl substituents to give adduct **18**. Loss of a proton gave ene carbamate **19**.[12] Reductive cleavage of the Troc group with activated Zn[14] in MeOH/AcOH at 60 °C for 30 min and neutralization with K_2CO_3 afforded imine **20** (83%), which slowly tautomerized to give a 2.5:1 mixture of imine **20** and the enamine corresponding to **19**. Treatment of this mixture with one equivalent of trifluoroacetic acid (TFA) afforded symbioimine analogue **21**[12] quantitatively.

The efficient conversion of **16** into **21** established that the IMDA reaction of **17** gave exclusively *endo* adduct **18**, in which the diene added to the unhindered face of the dihydropyridinium cation. Epimerization occurred readily on deprotection to give exclusively **21** with symbioimine stereochemistry. This behavior suggests that loss of the hydroxide moiety from tetrahydropyridinol **8** will give **4b**, which will undergo the desired IMDA reaction to give the symbioimine skeleton. We therefore turned our attention to alternate routes to tetrahydropyridinol **8**.

Condensation of β-keto ester **22**[15] with β-amino ester **23**[16] in toluene containing acetic acid at reflux afforded enamine **24** (96%; see Scheme 4). Dieckmann condensation of **24** with NaH in THF at reflux provided dihydropyridinone **25** (97%).[17] Hydrolysis[18] of the ethyl ester with aqueous NaOH in MeOH at reflux followed by decarboxylation on neutralization proceeded in 94% yield. Treatment of the dihydropyridinone with *n*BuLi and TrocCl afforded the desired *N*-Troc dihydropyridinone **26** in 96% yield.[19]

Direct deprotection of **26** to give aldehyde **28** was unsuccessful. The acidic conditions needed to cleave the dioxolane also effected an intramolecular aldol reaction of **28**.[20,21] Fortunately, treatment of **26** with pyridinium *p*-toluenesulfonate (PPTS) in MeOH at 65 °C afforded the more easily cleaved dimethyl acetal **27** (95%), which was cleaved to form the desired aldehyde **28** (87%) with PPTS in wet acetone at 55 °C. Aldehyde **28** decomposed on attempted Horner–Emmons Wittig reaction with diethyl cinnamylphosphonate. Fortunately, reaction with the less basic cinnamylidinetriphenylphosphorane[22] afforded **29**, albeit as a 2:1 mixture of the *E*/*Z* isomers. Isomerization with I_2 in CH_2Cl_2 afforded **29** as a 6:1 mixture of the *E*/*Z* isomers in 83% yield from **28**. Luche reduction afforded the requisite tetrahydropyridinol **30**[12] as an inseparable 3:1 mixture of *cis*/*trans* isomers in 95% yield.

Treatment of tetrahydropyridinol **30** with $BF_3 \cdot Et_2O$ in CH_2Cl_2 at −78 °C formed dihydropyridinium cation **31**, which gave the desired tricyclic adduct **33** in 31% yield based on the *E* isomer of **30**.[12] It is not clear why the IMDA reaction of **31** to give **32** proceeded in much lower yield than that of the ethyl homologue **17**. The unstable by-products that were formed from **30** were difficult to characterize. Deprotection of **33** with



Scheme 4. a) **22** (1 equiv), **23** (1 equiv), toluene, HOAc, reflux, 2 h (96%); b) NaH (3 equiv), THF, reflux, 3 h (97%); c) 1:1 MeOH/25% aqueous NaOH, reflux, 12 h (94%); d) *n*BuLi (1.1 equiv), THF, −78 °C, 30 min; then TrocCl (1.05 equiv), −78 °C, 30 min; 25 °C, 20 min (96%); e) PPTS (0.25 equiv), MeOH, 65 °C, 12 h (95%); f) PPTS (0.3 equiv), wet acetone, 55 °C, 3 h (87%); g) cinnamyltriphenylphosphonium chloride (1 equiv), *n*BuLi (1 equiv), THF, 0 °C, 1 h, cool to −78 °C; then aldehyde **28**, −78 °C, 30 min; 25 °C, 2 h (83%, *E*/*Z* = 2:1); h) I_2 (cat.), CH_2Cl_2, 25 °C, 1 h (100%, *E*/*Z* = 6:1); i) $NaBH_4$ (1 equiv) $CeCl_3 \cdot 7H_2O$ (1.25 equiv), MeOH, −78 °C, 30 min; 0 °C, 30 min (95%, *cis*/*trans* = 3:1); j) $BF_3 \cdot Et_2O$ (1.1 equiv), CH_2Cl_2, −78 °C, 10 min; 25 °C, 20 min (31% based on *E* isomer); k) activated Zn dust, MeOH/AcOH (1:1), 60 °C, 30 min; then K_2CO_3 (75%); l) TFA (1 equiv; 100% yield).

Zn in MeOH/AcOH at 60 °C followed by neutralization with K_2CO_3 afforded imine **34** (75%). Addition of TFA (1 equiv) afforded deoxysymbioimine (**35**) quantitatively. The ^1H and ^{13}C NMR spectral data of **35** correspond very closely to those of **1** except for the expected differences in the aromatic region.[12]

The convergent sequence from **22** and **23** to deoxysymbioimine (**35**) proceeds in 13% overall yield despite the 31% yield of the key IMDA reaction. We are currently optimizing the IMDA reaction of **31**, using the dienes obtained from aldehyde **28** and other Wittig reagents for the synthesis of symbioimine and oxygenated analogues, and exploring whether enantiomerically pure products can be obtained starting with optically pure amino ester **23**.[16c]

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[12] Stereochemical assignments based on coupling constants and NOE interaction studies are presented in detail in the Supporting Information.

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