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Tetrahedron Letters 47 (2006) 6343–6345
Tetrahedron Letters

Stereoselective construction of the octalin unit of symbioimine using an intramolecular Diels–Alder reaction

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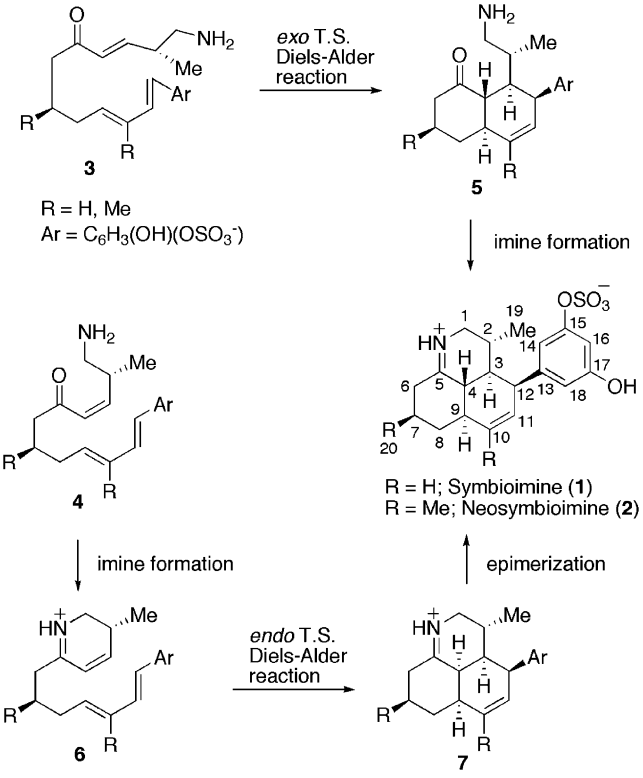
Received 21 June 2006; revised 5 July 2006; accepted 6 July 2006

Abstract—The octalin unit of symbioimine (**1**) has been synthesized stereoselectively via an intramolecular Diels–Alder reaction.

A number of natural products with unique structures and biological activities are found in marine organisms. However, the true origins of these metabolites are not completely clear.[1–3] It is suggested that the possible producer of secondary metabolites would be microalgae, bacteria, and fungi, and they are carried through a symbiosis and a food chain. We have been interested in bioactive metabolites produced by marine symbiotic microorganisms. In our search for biologically active compounds, we recently isolated unique amphoteric iminium compounds, symbioimine (**1**) and neosymbioimine (**2**) from a cultured marine dinoflagellate *Symbiodinium* sp. (Scheme 1).[4–6] Symbioimine (**1**) inhibits osteoclastogenesis in the murine monocytic cell line RAW264 ($EC_{50} = 44$ μg/mL). Meanwhile, it does not affect the cell viability even at 100 μg/mL. Thus, **1** is thought to be a drug candidate for the prevention and treatment of osteoporosis in postmenopausal women. Moreover, **1** also inhibits cyclooxygenase-2 (COX-2) activity (32%) at 10 μM, indicating that **1** may be useful for the development of new anti-inflammatory drugs.[5,6] We originally suggested the biogenetic pathway of **1** and **2** as shown in Scheme 1.[6] An *exo* transition state intramolecular Diels–Alder (IMDA) reaction of (*E*)-enone **3** would provide cycloadduct **5**. The subsequent imine formation of **5** could construct the carbon framework of symbioimines. Moreover, it can be also considered that the tricyclic system could be synthesized from (*Z*)-enone



Scheme 1. Plausible biomimetic pathway to symbioimines.

4. Symbioimines could be synthesized via imine formation and an *endo* transition state IMDA reaction of 2,3-dihydropyridinium cation **6**, followed by epimerization. Very recently, Snider et al. reported the synthesis of

Keywords: Symbioimine; Intramolecular Diels–Alder reaction; Stereoselective construction; Octalin unit.
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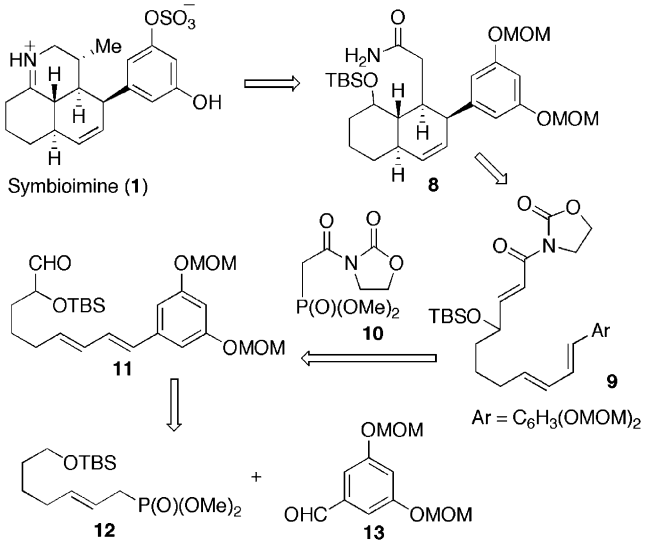
0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.07.012

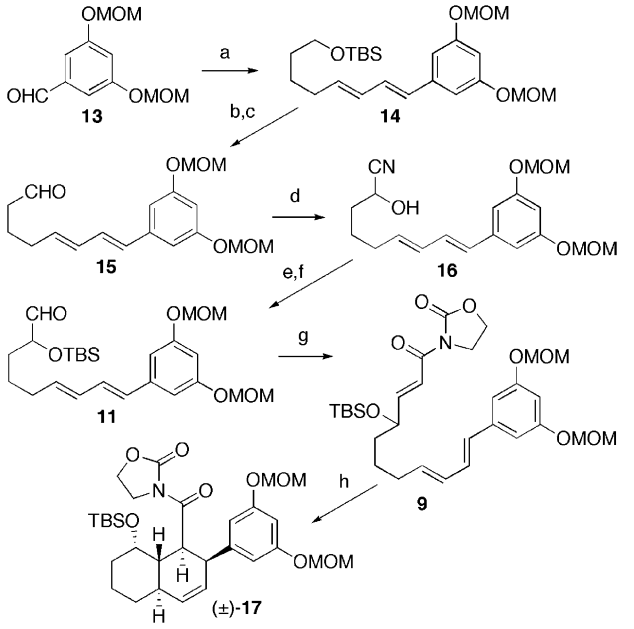
(±)-deoxysymbioimine using the IMDA reaction with a 2,3-dihydropyridinium cation as the dienophile.[7] In this letter, we wish to report a highly stereoselective construction of the octalin unit of **1** using the IMDA reaction with an acrylimide as the dienophile.[8]

Evans and co-workers developed the enantioselective Diels–Alder reaction catalyzed by bis(oxazoline) copper complexes with an acrylimide as the dienophile.[9] We planned to use this methodology for the stereoselective construction of the octalin unit of **1**. Before the examination of the enantioselective Diels–Alder reaction by using Evans protocol, we decided to utilize the allylic stereogenic center for the asymmetric induction of the newly formed chiral centers.[10] That is why we chose an acrylimide as the dienophile. Retrosynthetic analysis of **1** is shown in Scheme 2. Iminium ring formation and the introduction of methyl substituent would be carried out in the later stage. Bicyclic compound **8** would be synthesized by using the IMDA reaction of acrylimide **9**. Compound **9** can be broken down into phosphonate **10** and aldehyde **11**. The Horner–Wadsworth–Emmons reaction of phosphonate **12** and benzaldehyde **13** would provide the carbon framework of aldehyde **11**.

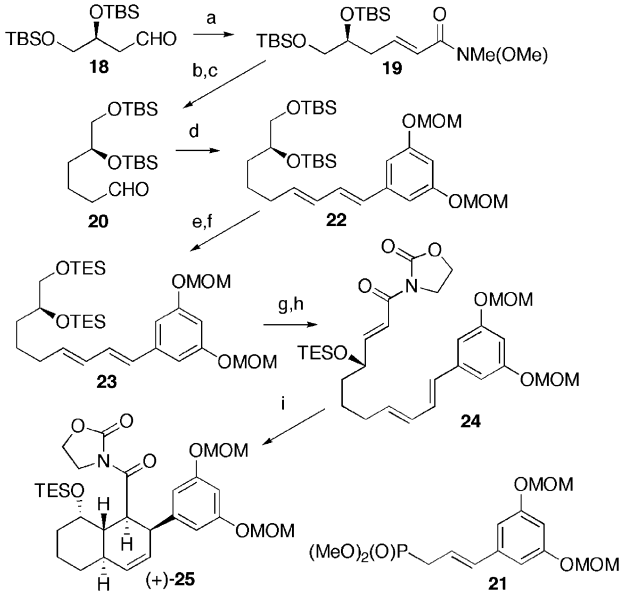
Based on the retrosynthetic analysis, diastereoselective construction of the octalin unit of **1** was investigated (Scheme 3). The Horner–Wadsworth–Emmons reaction of the known benzaldehyde **13**,[11] prepared from 3,5-dihydroxybenzaldehyde, and phosphonate **12** gave the desired coupling product **14** possessing the *E*,*E*-diene moiety in 80% yield. Removal of the silyl protecting group with TBAF followed by IBX oxidation afforded aldehyde **15**. Treatment of **15** with acetone cyanohydrin in the presence of titanium(IV) isopropoxide provided cyanohydrin **16**.[12] After the resulting alcohol was protected with *tert*-butyldimethylsilyl chloride, reduction of the nitrile group with diisobutylaluminium hydride was carried out to provide aldehyde **11**. Compound **11** was converted to trienimide **9**, which is the precursor of Diels–Alder reaction, by the Horner–Wadsworth–Emmons elongation with the phosphonate reagent **10**.[9] IMDA reaction of **9** proceeded smoothly under the conditions of reflux in toluene to give the desired product (±)-**17** as a single stereoisomer.



Scheme 2. Retrosynthetic analysis of symbioimine (**1**).



Scheme 3. Synthesis of (±)-**17**. Reagents and conditions: (a) **12**, ^{t}BuOK, THF, −78 °C to rt, 80%; (b) TBAF, THF, rt; (c) IBX, DMSO, rt, quant. (two steps); (d) acetone cyanohydrin, $Ti(O^{i}Pr)_4$, THF, rt, 67%; (e) TBSCl, imidazole, DMAP, DMF, rt, quant.; (f) DIBALH, CH_2Cl_2, −78 °C, 94%; (g) **10**, Et_3N, LiCl, CH_3CN, rt, 91%; (h) toluene, reflux, quant.



Scheme 4. Synthesis of (+)-**25**. Reagents and conditions: (a) $Ph_3P{=}CHC(O)NMe(OMe)$, CH_2Cl_2, rt, 88%; (b) H_2, Pd–C, EtOAc, rt, 96%; (c) DIBALH, THF, −30 °C to rt, 92%; (d) **21**, ^{n}BuLi, HMDS, THF, −78 °C to rt, 80%; (e) TBAF, THF, rt; (f) TESCl, imidazole, DMAP, rt, 86% (two steps); (g) $(COCl)_2$, DMSO, CH_2Cl_2, −78 to −40 °C, then Et_3N, −78 °C to rt; (h) **10**, Et_3N, LiCl, CH_3CN, rt, 60% (two steps); (i) toluene, 80 °C, quant.

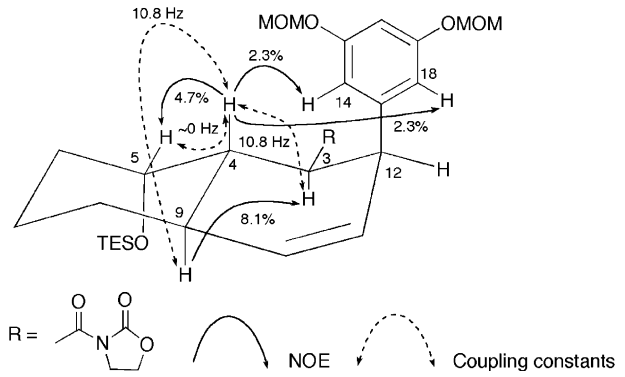


Figure 1. Structural determination of (+)-**25**.

Next, the examination on the enantioselective construction of the octalin segment was carried out (Scheme 4). The known aldehyde **18**,[13] prepared from L-malic acid, was subjected to the Wittig reaction with *N*-methoxy-*N*-methyl-2-(triphenylphosphoranylidene)acetamide[14] to give the unsaturated Weinreb amide **19** in 88%. After the hydrogenation of **19** was carried out in the presence of Pd–C, the amide moiety was reduced with diisobutylaluminium hydride to provide aldehyde **20**. After treatment of **20** with phosphonate **21** gave the coupling product **22** in 80% yield, bis-TBS ether **22** was converted to bis-TES ether **23**. Primary TES ether was selectively oxidized to the corresponding aldehyde under Swern condition,[15] and then oxadolidinone moiety was introduced to give the trienimide **24**. Compound **24** was subjected to the diastereoselective IMDA reaction to provide imide (+)-**25**, which possesses the desired stereochemistries, as a single stereoisomer.

The absolute stereochemistries of (+)-**25** were determined by ^{1}H–^{1}H coupling constants and NOE experiments (Fig. 1). The small magnitude of the coupling constant ($J_{4,5} = \sim 0$ Hz) and NOE for H-4/H-5 were observed, suggesting that H-4 was in the *syn* relationship to H-5. Three protons, H-3, H-4, and H-9 were considered to be in all-axial orientations with each other based on the large coupling constant ($J_{3,4} = 10.8$ Hz and $J_{4,9} = 10.8$ Hz) and NOE observation for H-3/H-9. The aromatic ring moiety would be placed in an axial conformation because NOE for H-4/H-14 and H-4/H-18 were observed.

In conclusion, the highly stereoselective construction of the octalin unit of **1** was executed by using the IMDA reaction with an acrylimide as the dienophile. Further studies toward the total synthesis of symbioimines are in progress.

Acknowledgments

This work was supported in part by a Grant-in-Aid for Creative Scientific Research (16GS0206) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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