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Enantioselective Total Synthesis of (+)-Neosymbioimine

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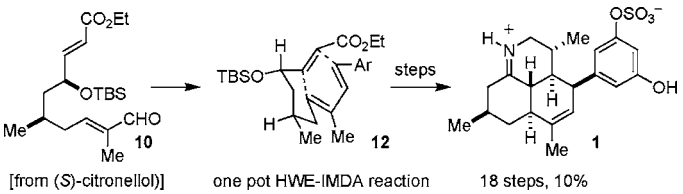
ABSTRACT



The enantioselective total synthesis of (+)-neosymbioimine was accomplished in 18 steps from (−)-(*S*)-citronellol utilizing an organocatalytic α-oxidation of aldehyde 6. The carbon core was constructed by a tandem Horner−Wadsworth−Emmons (HWE) reaction and an intramolecular Diels−Alder cyclization. All double bonds of 12 were made in a stereoselective manner by Wittig-type reactions. Selective formation of the monosulfate monoester was accomplished by one-pot excessive sulfation followed by kinetic hydrolysis of bissulfate 18 in 79% yield.

Neosymbioimine (**1**) is a minor amphoteric metabolite of the symbiotic marine dinoflagellate *Symbiodinium* sp.[1] Like symbioimine (**2**), this alkaloid is composed of a tricyclic iminium core with an attached resorcinol monosulfate unit that causes these molecules to occur as inner salts (Figure 1).[2−4] Organic sulfate monoesters are widespread in biological systems, occurring in proteins, carbohydrates, steroids, and other small molecules.[5,6] In contrast, zwitterionic compounds containing sulfates are still very rare[4] and could be of interest for either organic or medicinal chemistry. For example, the parent compound symbioimine (**2**) inhibits the differentiation of precursor osteoclast cells (RAW264) into mature osteoclasts. Also, it slightly inhibits cyclooxygenase-2 (COX-2) activity. Furthermore, it did not affect cell viability even at 100 μg mL^{-1}.[1,2] Because of their low toxicity, these alkaloids could be used in the development of efficient antiosteoporosis drugs. A concise total synthesis of these metabolites would be of considerable interest to further delineate the biological activity.

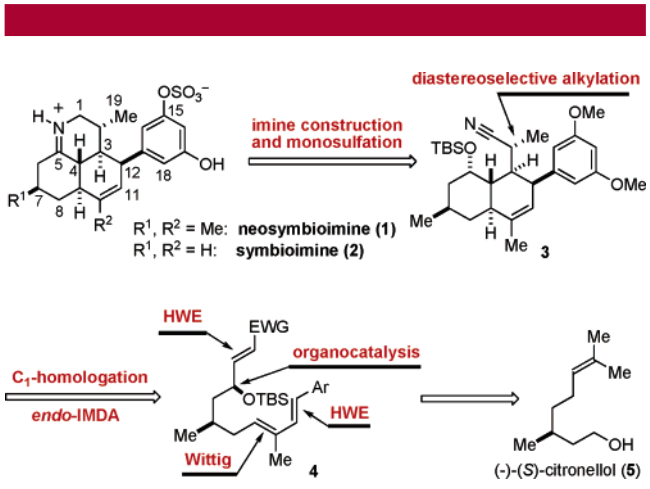


Figure 1. Retrosynthetic analysis for neosymbioimine (**1**).

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Recently, we reported the first total synthesis of (±)-symbioimine (**2**) using an intramolecular *endo*-Diels−Alder (*endo*-IMDA) reaction of an (*E*,*E*,*E*)-undeca-2,8,10-trien-1-al as a key step.[7] Meanwhile, a synthesis of the octalene core of symbioimine, using a related *endo*-IMDA reaction of an (*E*,*E*,*E*)-undeca-2,8,10-trien-1-amide, was reported by Uemura.[8] Another approach to the synthesis of **2** was realized by Snider et al., who prepared (±)-symbioimine through an IMDA reaction of a 2,3-dihydropyridinium cation.[9] Although **2** was synthesized by two different ways, the synthesis of neosymbioimine (**1**) was not published until this time. Herein, we report the first total synthesis of neosymbioimine (**1**) and the assignment of its absolute stereochemistry.

Our retrosynthetic strategy is outlined in Figure 1. The target compound should be available from nitrile **3**, which possesses all stereogenic centers of **1**. The octalene unit of **3** might be accessed by an *endo*-IMDA of triene **4**.[10−12] All double bonds of **4** could be made using Wittig chemistry, and the secondary alcohol function could be introduced by a proline-catalyzed α-hydroxylation of the corresponding aldehyde.[13] As the starting material, we identified (−)-(*S*)-citronellol (**5**), which is readily available from rose oil (ee ca. 92%).[14,15]

Even though C-5 of neosymbioimine is sp^2-hybridized, we planned to temporarily use a secondary alcohol function at this position to guarantee a high diastereoselectivity in the Diels−Alder step. As we found in the symbioimine case, a keto function at C-5 gave a lower *endo*/*exo*-diastereoselectivity in this crucial transformation.[16] On the basis of the results from the symbioimine study, the (*S*)-configuration for the hydroxyl-carrying stereocenter of triene **4** was required.[7] Initially, the alcohol function of (−)-(*S*)-citronellol (**5**) was protected as a TBS ether and the double bond was cleaved by ozonolysis to obtain aldehyde **6** (Scheme 1). Aldehyde **6** was converted to 4-hydroxy-8-silyloxy-enoate **7** by a one-pot MacMillan procedure, including α-hydroxylation followed by Horner−Wadsworth−Emmons (HWE) reaction and cleavage of the N−O bond in 55% yield.[17] The secondary alcohol of enoate **7** was protected with a TBS group, followed by selective liberation of the primary alcohol and its oxidation to provide aldehyde **8**. Wittig reaction of **8** with 2-(triphenylphosphoranylidene)propanal[18] (**9**) gave only the *E*-isomer of aldehyde **10** in 88% yield. In the subsequent condensation of **10** with diethyl 3,5-dimethoxybenzylphosphonate[19] (**11**), we isolated approximately a 1:1 mixture of triene **12** and cyclized product **13**. Heating this mixture in chloroform for 2 h at 60 °C induced conversion of trienoate **12** to **13** to about 95% (by NMR). The conversion did not increase even after 12 h. We assume that only the desired diastereomer of **12** cyclizes under these conditions. The diastereomeric impurity in substrate **12** most likely originates from the minor enantiomer contained in the commercial (−)-(*S*)-citronellol (92% ee).[14] In fact, around 5% of impurity can be seen in the ^{1}H NMR spectra of compounds **7**−**13**. The minor diastereomer of **12** does not cyclize due to the steric hindrance in the transition state (Scheme 2). After reduction of ester **13**, the target alcohol could be easily obtained in pure form. This crucial effect of the methyl group on the IMDA of **12** allowed us to produce enantio- and diastereomerically pure products from the enantioimpure starting compound citronellol.

Mesylation of the primary alcohol derived from cycloadduct **13** followed by S_N2 reaction with sodium cyanide gave nitrile **14** in exellent yield. Methylation of acetonitrile derivative **14** proceeded very cleanly and efficiently, using 2 equiv of LDA and 2 equiv of MeI in THF at −80 °C. Despite the fact that a small amount (10%) of the undesired diastereomer was also formed, pure **3** was isolated in 87% yield on a gram-scale experiment. The structure of nitrile **3**, featuring all stereocenters of the natural product, was confirmed by single-crystal X-ray analysis (Scheme 1). In this molecule, the methyl and propanenitrile groups occupy equatorial positions, whereas the bulky units (Ar, OTBS) are oriented axially. In the ^{1}H NMR spectra of nitrile **3**, the signal of the α-methyl group is shifted toward the high field (δ_H 0.6 ppm) due to the shielding by the aromatic ring current. Concerning the origin of the diastereoselective alkylation, one could argue that the X-ray structure of nitrile **3** shows the available air corridor of the electrophile. Thus, the methyl iodide could approach the nitrile anion above the aryl ring and opposite to the large *tert*-butyldimethylsilyloxy group.

Nitrile **3** was treated with TBAF to remove the TBS group. The obtained alcohol was oxidized to the corresponding

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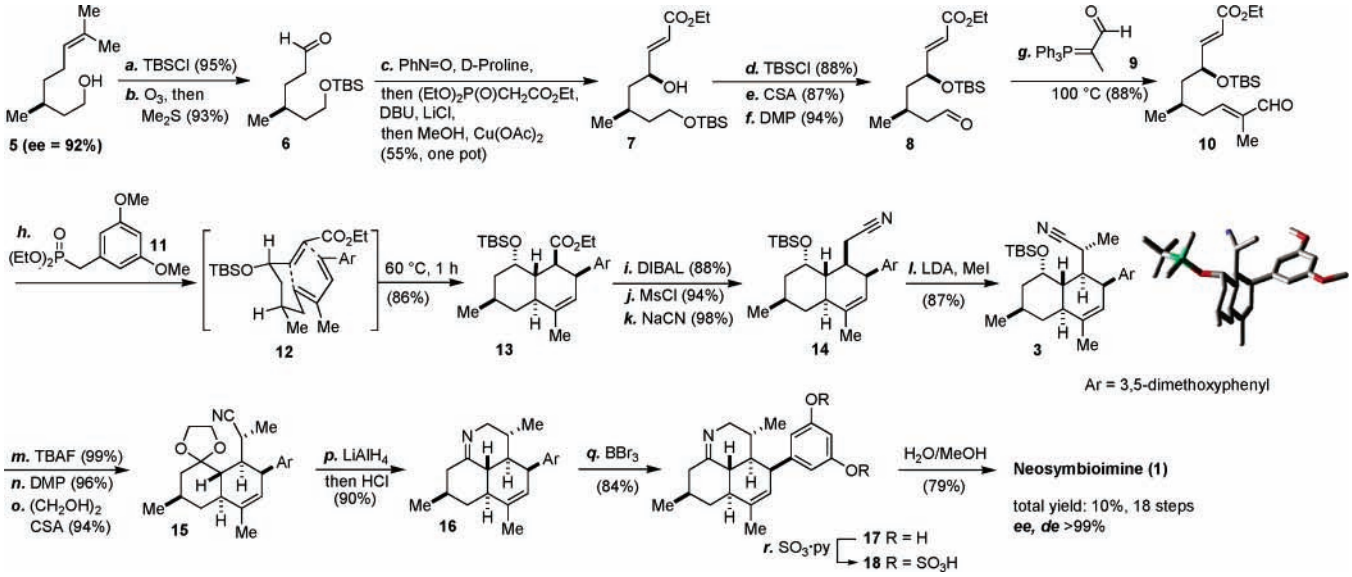
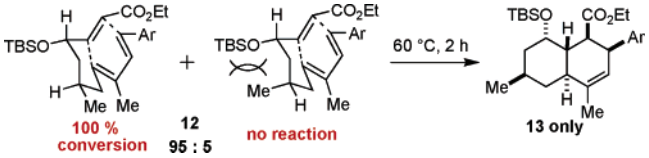
Scheme 1. Synthesis of (+)-Neosymbioimine (**1**) from (−)-(*S*)-Citronellol (**5**)[a]



[a] Reagents and conditions: (a) TBSCl, imidazole, DMF, 23 °C, 12 h (95%); (b) O_3, −78 °C, CH_2Cl_2/MeOH (1:1), then Me_2S, −78 to 20 °C, 16 h (93%); (c) nitrosobenzene (1 equiv), D-proline (0.4 equiv), DMSO, 20 °C, 25 min, then triethylphosphono acetate, DBU, LiCl, 0 °C, 15 min, then MeOH, NH_4Cl, $Cu(OAc)_2$, 24 h; (d) TBSCl, imidazole, DMAP (0.1 equiv), CH_2Cl_2, 23 °C, 14 h (88%); (e) CSA (0.05 equiv), MeOH, 20 °C, 1 h (87%); (f) Dess−Martin periodinane, CH_2Cl_2, 20 °C, 2 h (96%); (g) 2-(triphenylphosphoranylidene)propanal (**9**), toluene, 100 °C, 30 h (88%); (h) diethyl 3,5-dimethoxybenzylphosphonate (**11**), KO^{t}Bu, THF, −78 to 0 °C, then $CHCl_3$, 60 °C, 2 h (86%); (i) HAl(^{i}Bu)$_2$, CH_2Cl_2, 23 °C, 24 h (88%); (j) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h (94%); (k) NaCN, DMSO, 50 °C, 3 days (98%); (l) LDA (2 equiv), THF, −80 °C, 1 h, then MeI (2 equiv), 0.5 h (87%); (m) TBAF, THF, 23 °C, 24 h (99%); (n) Dess−Martin periodinane, CH_2Cl_2, 23 °C, 12 h (96%); (o) $(CH_2OH)_2$, CSA (0.5 equiv), C_6H_6, 80 °C, 10 h (94%); (p) $LiAlH_4$, Et_2O, 23 °C, 24 h, then 3 M HCl, THF, 50 °C, 2 h (90%); (q) BBr_3 (5 equiv), CH_2Cl_2, −80 to 0 °C, 1 h, then 0 °C, 1.5 h (84%); (r) SO_3·Py, pyridine, 60 °C, 24 h, then H_2O/MeOH (1:2), 36 °C, 18 h (79%) brsm. TBS = *tert*-butyldimethylsilyl. DMF = dimethylformamide. DBU = 1,8-diazabicycloundec-7-en. DMAP = 4-dimethylaminopyridine. CSA = camphorsulfonic acid. DMP = Dess−Martin periodinane. DIBAL = diisobutylaluminum hydride. MsCl = methanesulfonyl chloride. LDA = lithium diisopropylamide. TBAF = tetrabutylammonium fluoride. Py = pyridine.

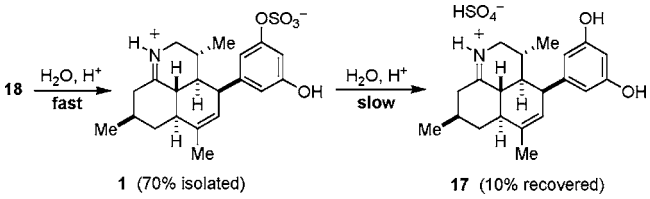
ketone which was protected as 1,3-dioxolane **15** in excellent yield. Reduction of the nitrile to the amine with $LiAlH_4$ followed by acid-catalyzed imine formation gave imine **16**. Finally, the aryl ether functions were cleaved with BBr_3 providing resorcinol **17** in 84% yield.

Scheme 2. Stereochemistry of the IMDA Reaction of Trienoate **12**



As a final challenge, efficient monosulfation of resorcinol **17** remained. Excessive sulfation of **17** with SO_3·py (5 equiv) in pyridine gave bisulfate **18**. As expected, one sulfate group in **18** is more sensitive to hydrolysis (Scheme 3). Accordingly, keeping a solution of **18** in aqueous methanol at 36 °C for 18 h led to complete monohydrolysis of **18** (70% of **1** was isolated). At the same time, neosymbioimine (**1**) was not hydrolyzed significantly (10% of **17** was recovered). It seems that the formation of the inner salt contributes to the stability of the sulfate group. The product was purified by routine flash chromatography, on silica gel using MeOH/$CHCl_3$ as eluent. Synthetic neosymbioimine was identical by NMR to the natural compound. The optical rotation of synthetic neosymbioimine ($[\alpha]^{23}_D$ +172, *c* 0.1, MeOH) correlates well with the authentic one ($[\alpha]^{25}_D$ +149). Thus, the absolute stereochemistry of (+)-neosymbioimine was assigned.

Scheme 3. Selective Monohydrolysis of **18**



In summary, we developed an efficient route to the natural alkaloid (+)-neosymbioimine, starting from readily available (−)-(*S*)-citronellol. The synthetic strategy is based on the extremely facile tandem HWE−IMDA reaction for construction of the neosymbioimine core, which allows for the preparation of significant amounts of **1** in 10% total yield over 18 steps.

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Supporting Information Available: Experimental procedures and characterization for all new compounds reported and copies of NMR spectra for important intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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