Cycloaddition

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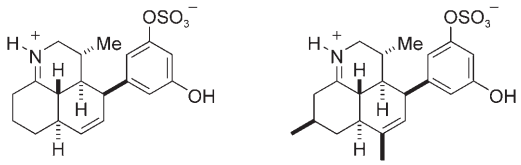
Total Synthesis of (±)-Symbioimine**

*Georgy N. Varseev and Martin E. Maier**

Symbioimine (**1**) is a novel tricyclic iminium alkaloid that was recently isolated from the symbiotic marine dinoflagellate *Symbiodinium* sp.[1] This rather unusual compound occurs in nature as an inner salt of an imine and an aryl sulphuric acid (Scheme 1). Such zwitterionic compounds are very rare,[2,3] and the total synthesis of **1** certainly poses a challenging task.



Scheme 1. Structures of the iminium alkaloids symbioimine (**1**) and neosymbioimine (**2**).

[*] G. N. Varseev, Prof. Dr. M. E. Maier
Institut für Organische Chemie
Universität Tübingen
Auf der Morgenstelle 18, 72076 Tübingen (Germany)
Fax: (+49) 7071-295-137
E-mail: martin.e.maier@uni-tuebingen.de

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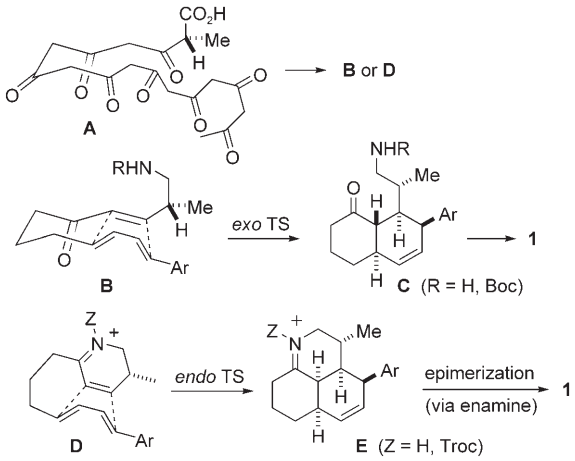
A related compound is the amphoteric neosymbioimine (**2**).[4] Besides its unique structural features, the biological activity of **1** is noteworthy as well: it inhibits the differentiation of progenitor cells (RAW264) into mature osteoclasts with $EC_{50} = 44\ mg\,mL^{-1}$ (116 μM). Therefore, **1** might show the way to a new lead structure in the search for drugs directed at the treatment of osteoporosis. In addition, **1** significantly reduces cyclooxygenase-2 (COX-2) activity at 10 μM.[3]

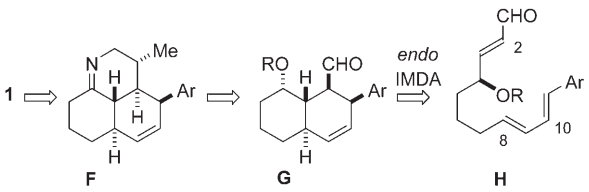
Most likely **1** is constructed through the polyketide pathway, as illustrated with structure **A**, which consists of eight acetate and one propionate groups. The key step in the biosynthesis of **1** might involve an intramolecular Diels–Alder (IMDA) reaction,[5] either of a trienone via an *exo* transition state of type **B** followed by cyclization to an imine (Scheme 2). Alternatively, an *endo* IMDA reaction of a



Scheme 2. Model reactions for biosynthetic key steps towards **1**. Boc = *tert*-butyloxycarbonyl, Troc = trichloroethoxycarbonyl, TS = transition state.

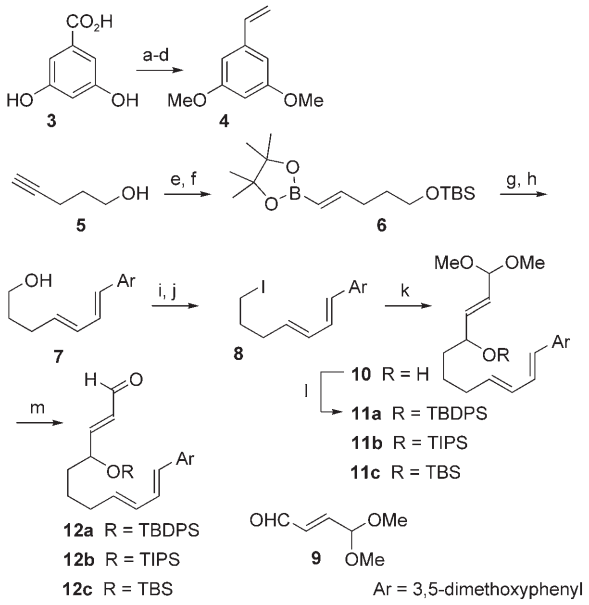
dihydropyridinium cation (compare with transition state **D**) followed by epimerization of the cycloadduct via an enamine might be operative.[4] There is support for the latter mode from a model study by Snider and Che,[6,7] who prepared desulfodeoxysymbioimine through an IMDA reaction of a 2,3-dihydropyridinium cation (Scheme 2; Z = Troc, Ar = Ph). While both routes seem attractive and possible, one should note that the orbital overlap is not ideal as large and small coefficients at the termini do not really match. In fact, we found in preliminary studies that trienone **A** (Scheme 2; R = Boc, Ar = 3,5-dimethoxyphenyl) did not undergo any Diels–Alder reaction, even after heating the substrate in a sealed tube (xylene, 180 °C) for 24 h. Under these conditions, slow decomposition of the substrate was observed.

We reasoned that positioning an electron-withdrawing group on the other side of the double bond should allow for a more facile IMDA reaction (Scheme 3).[8] Some literature precedence indicates that this approach should be feasible.[9] However, a solution for extension of the aldehyde function in the cycloadduct **G** combined with a diastereoselective introduction of the methyl group would have to be found. Herein, we present the realization of these goals.



Scheme 3. Retrosynthetic plan for the synthesis of **1**.

As an initial milestone, we targeted an efficient and large scale synthesis of (*E*,*E*,*E*)-undeca-2,8,10-trienals **12** (structure **H**). A key step of this synthesis is the preparation of the 1-aryl-1,3-*E*,*E*-diene moiety, which might be accessible through a palladium-catalyzed Stille or Suzuki coupling. *E*-Vinyl halide building blocks are required for both methods. However, all attempts to prepare suitable Stille or Suzuki precursors were more or less unsuccessful. Therefore, we turned to the palladium-catalyzed oxygen-promoted Heck-type coupling of alkenes with vinyl boronates.[10,11] Accordingly, the styrene[12–14] **4** and the vinyl boronate[15] **6** were prepared by standard procedures (Scheme 4). Under the reported reaction conditions (5 mol% $Pd(OAc)_2$, dimethylamine (DMA), 23 °C, slow addition of **6**), we got only 30% of the coupling product. We significantly improved the yield for

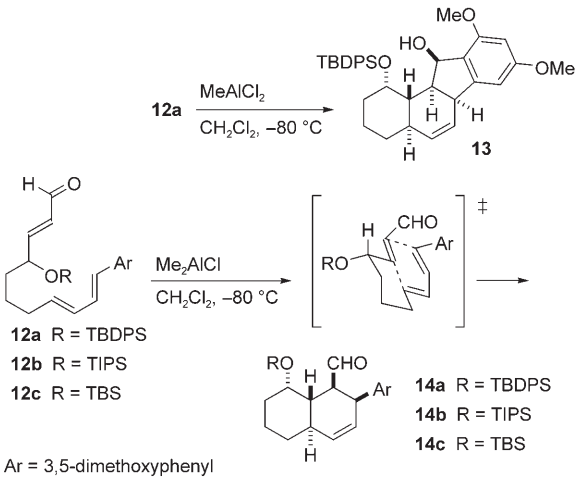


Scheme 4. Synthesis of the Diels–Alder substrates **12**. a) $(CH_3O)_2SO_2$ (3.5 equiv), K_2CO_3, acetone, reflux, 4 h (96%); b) $NaBH_4$ (5 equiv), DME, MeOH, reflux, 1 h (99%); c) CrO_3/pyridine (1.2 equiv), CH_2Cl_2, RT, 24 h (81%); d) $Ph_3PCH_3^+Br^-$ (1.2 equiv), KO*t*Bu (1.4 equiv), THF, −65 °C to RT (96%); e) TBSCl, imidazole, CH_2Cl_2, RT, 24 h (99%); f) catechol borane (1.1 equiv), 70 °C, 12 h, then pinacol (1.2 equiv), 23 °C, 3 h (85%); g) **4** (2 equiv), $Pd(OAc)_2$ (0.1 equiv), Na_2CO_3, DMF, 60 °C, **6** (1 equiv), 24 h; h) HCl, MeOH, 23 °C, 0.5 h (68% from **6**); i) MsCl (1.3 equiv), NEt_3, CH_2Cl_2, −30°, 1 h (98%), j) NaI, acetone, 23 °C, 24 h (93%); k) *t*BuLi (2.5 equiv), then **9** (1.2 equiv), Et_2O, −80 °C, 1 h (60%); l) R_3SiCl (2 equiv), imidazole, CH_2Cl_2, RT, 24 h; m) amberlyst 15, acetone, RT, 40 min (**12a**: 80%, 2 steps; **12b**: 75%; **12c**: 83%). TBS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl, TIPS = triisopropylsilyl, DMF = dimethylformamide, DME = dimethoxyethane, MsCl = methanesulfonyl chloride.

this reaction by using 2 equivalents of **4** and 10 mol% of $Pd(OAc)_2$ in DMF at 60°C. The starting styrene was readily recovered by flash chromatography after acidic cleavage of the TBS group to provide the dienol **7** in 68% yield based on recovered **4** and 59% based on **6**. This reaction is highly regio- and stereoselective, and only the *E*,*E* diene was found to be produced in more than 99% diastereomeric purity.

Continuing with the synthesis, **7** was converted into the iodide **8** in two steps by mesylation (98%) and S_N2 substitution by using NaI in acetone (93%). Transmetalation of **8** with *t*BuLi at −80°C followed by trapping of the organolithium intermediate with the known (2*E*)-4,4-dimethoxybut-2-enal[16] **9**, successfully afforded aldehydes **12** after protection of the hydroxy group with a silicon protecting group followed by hydrolysis of the acetal. Thus, syntheses of all-*E*-undeca-2,8,10-trienals **12** with TBDPS, TIPS, and TBS protecting groups were possible. The synthesis of **12c** was performed on a gram-scale.

With substrates **12** in hand, the Lewis acid catalyzed IMDA reaction was investigated (Scheme 5).[17] A fast



Scheme 5. Lewis acid induced IMDA reaction of trienals **12**.

reaction of **12a** was observed with $MeAlCl_2$ (1 equiv) as the Lewis acid in CH_2Cl_2 at −80°C. However, the reaction did not stop at the stage of the Diels–Alder product. Rather, a subsequent intramolecular Friedel–Crafts reaction of the aldehyde function with the electron-rich aryl ring took place, thus leading to the tetracyclic compound **13** (50% yield). The reaction of **12a** with one equivalent of the weaker Lewis acid Me_2AlCl at −80°C led to a conversion of approximately 60% of **12a** within 24 h to give a 50% yield of the isolated product **14a** as a single diastereomer, and no Friedel–Crafts adducts were observed.

The configuration of **14a** was determined by X-ray analysis (Figure 1). It is interesting to note that both bulky substituents (Ar and $OSiR_3$) are axially oriented relative to the decalin ring. The silicon protecting groups do not significantly affect the outcome of the IMDA reaction. Also, the TIPS- and TBS-protected aldehydes **12b** and **12c** gave a conversion of approximately 50% to the corresponding cycloadducts under these conditions. A higher yield could

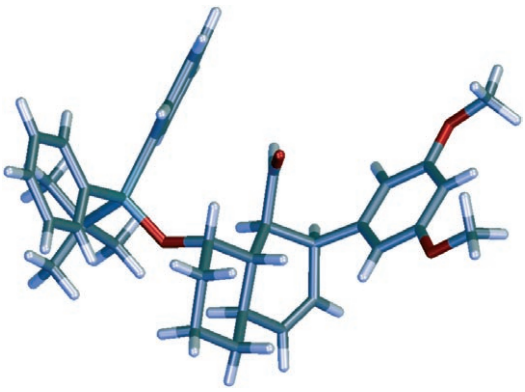
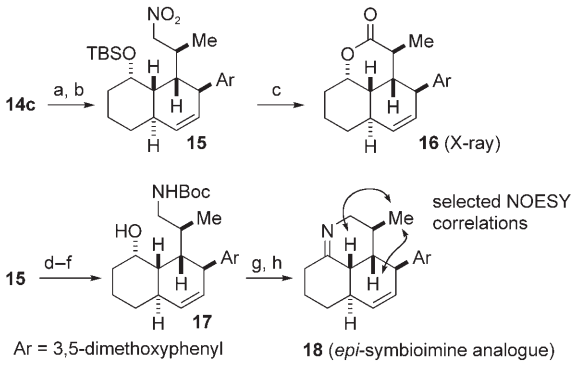


Figure 1. X-ray structure of cycloadduct **14a**.

be realized by using 1.6 equivalents of Me_2AlCl, thus yielding, for example, **12c** in 85% yield on a gram-scale. The cycloadducts already contain four of the five required stereocenters with the correct relative configuration.

For conversion of the aldehyde function into the aminopropyl appendage, several options were considered.[18] In a first attempt, **14c** was subjected to a Henry condensation[19] with nitromethane followed by a Michael addition of the resulting nitroalkene with MeMgBr at −80°C. These transformations proceeded smoothly in good yields and were highly stereoselective and produced the nitro compound **15** (Scheme 6). Attempts to cleave the silyl ether of **15** with TBAF surprisingly gave the corresponding lactol, which was oxidized to lactone **16** with PDC in 65% yield of the isolated product.

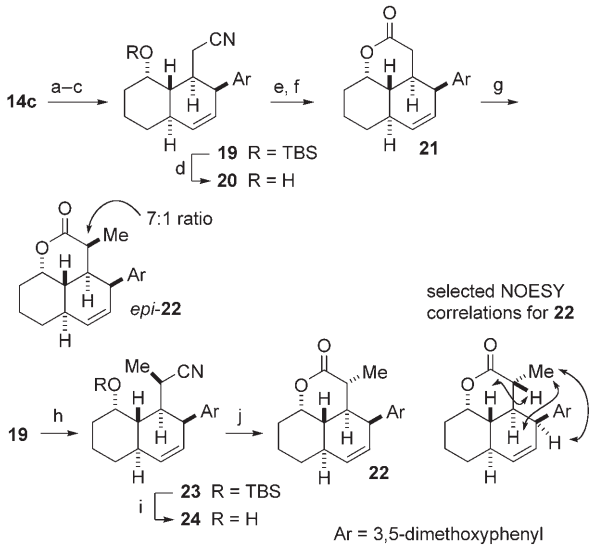


Scheme 6. Extension of cycloadduct **14c** through a tandem Henry Michael addition. a) CH_3NO_2, NH_4OAc, 70°C, 24 h (88%), b) MeMgBr, Et_2O, −80°C, 3 h (70%); c) 1. TBAF, THF, RT, 12 h; 2. PDC, CH_2Cl_2, RT, 24 h (65%); d) $LiAlH_4$, THF, −20°C→RT, 24 h, then reflux, 1 h; e) Boc_2O, NEt_3, MeOH, RT, 0.5 h; f) TBAF, THF, 60°C, 24 h (55%, 3 steps); g) PDC, CH_2Cl_2, RT, 24 h; h) AcCl, MeOH, 50°C, 30 min (80%, 2 steps). TBAF = tetrabutylammonium fluoride, PDC = pyridinium dichromate.

The X-ray structure of lactone **16** showed that two stereocenters were not correct with respect to the natural product (see the Supporting Information). Most likely, the conditions of the Henry reaction caused a base-catalyzed epimerization at the γ-atom of the nitroalkene to give the

thermodynamically favored *trans*-1,2-substituted cyclohexane compound. The stereochemistry of **16** was also evident from NOESY data. To probe the formation of the tetrahydropyridine ring, the nitro group of **15** was reduced with $LiAlH_4$, the amino group protected with Boc anhydride, and the TBS-group cleaved with TBAF to give alcohol **17**. Oxidation of **17** followed by acid-induced Boc cleavage indeed gave imine **18**, an epimeric analogue of **1**.

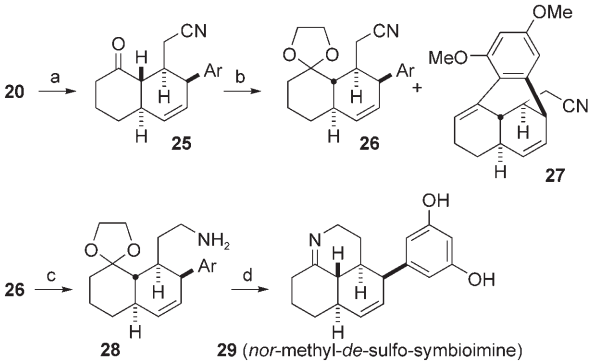
Finally, a practical solution was found starting with a three-step sequence involving the reduction of aldehyde **14c** with $NaBH_4$, conversion of the alcohol into the corresponding mesylate, and nucleophilic substitution of the mesylate with cyanide in dimethyl sulfoxide (DMSO), thus leading to nitrile **19** in more than 90% yield from **14c** (Scheme 7). Removal of



Scheme 7. Diastereoselective alkylation of lactone **21** and nitrile **19**. a) $NaBH_4$, EtOH, RT, 24 h (99%); b) MsCl, NEt_3, CH_2Cl_2, −50°C to RT, 1 h (96%); c) NaCN, DMSO, 50°C, 48 h (95%); d) TBAF, THF, RT, 2 h (98%); e) KOH, EtOH, 80°C, 24 h; f) *p*-TsOH, toluene, 110°C, 1 h (90% for 2 steps); g) LDA (2 equiv), −80°C, 3 h, then MeI (4 equiv), 0.5 h (65%); h) LDA (2 equiv), −80°C, 2 h, then MeI (2 equiv), 0.5 h (92%); i) TBAF, THF, RT, 24 h (92%); j) TMSCl, HCl, toluene, reflux, 48 h (75%). DMSO = dimethyl sulfoxide, LDA = lithium diisopropylamide

the TBS group with TBAF in THF followed by nitrile saponification allowed for the formation of lactone **21**. Although monomethylation of **21** was possible, careful NMR spectroscopic analysis of the major diastereomer showed that methylation had taken place from the wrong side of the enolate. Next, methylation of the nitrile group was investigated. Deprotonation of **19** with LDA (2 equiv) followed by addition of MeI gave a single isomer, tentatively assigned as structure **23**, in 92% yield of the isolated product. Indeed, conversion of **23** into the corresponding lactone allowed for determination of the stereochemistry from the NOESY data (see the NOESY correlations indicated in Scheme 7).

After the diastereoselective introduction of the methyl group had been resolved, a method was sought that would avoid protection of the amino group en route to the tetrahydropyridine. This approach was initially investigated by using hydroxy nitrile **20** (Scheme 8). Dess–Martin oxidation of **20** afforded ketone **25** quantitatively. Ketone **25** was protected with ethylene glycol in toluene to give 68% yield of

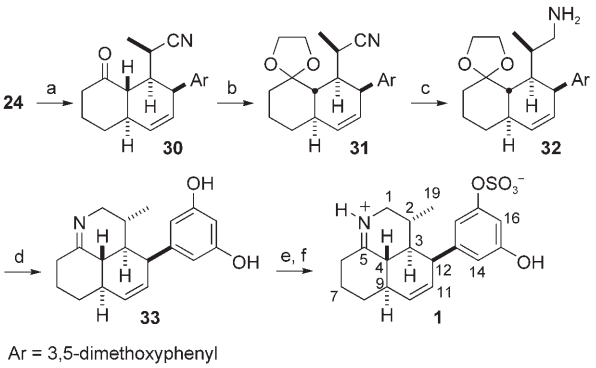


Scheme 8. Synthesis of *nor*-methyl-*de*-sulfo-symbioimine (**29**). a) Dess–Martin periodinane, CH_2Cl_2, RT, 8 h (99%); b) $(CH_2OH)_2$, CSA, toluene, reflux, 12 h, (68% of **26**, 20% of **27**); c) $LiAlH_4$, Et_2O, 0°C to RT, 12 h (87%); d) BBr_3, CH_2Cl_2, −80°C to RT, 24 h (55%). Ar = 3,5-dimethoxyphenyl, CSA = camphorsulfonic acid.

the expected dioxolane **26** and 20% yield of the polycycle **27**, which resulted from attack of the aromatic ring to the keto function. The nitrile group of **26** was then reduced with $LiAlH_4$ to the amine **28**. Cleavage of the aryl methyl ethers, the 1,3-dioxolane, and cyclization to the imine could be achieved in one step using BBr_3 in CH_2Cl_2. Imine **29** is a close analogue of **1**.

Hydroxy nitrile **24** served as starting material for the synthesis of **1**. As before, oxidation to the ketone **30** and protection of the keto function as 1,3-dioxolane led to nitrile **31** (Scheme 9). After reduction of the nitrile to the primary amine, treatment of **32** with BBr_3 generated imine **33**.

The sulfatation of the resorcinol posed a real challenge, as it was not known whether the imine or iminium function would be compatible with the reaction conditions. In addition,



Scheme 9. Completion of the total synthesis of symbioimine (**1**). a) Dess–Martin periodinane, CH_2Cl_2, RT, 8 h (99%); b) $(CH_2OH)_2$, CSA, benzene, reflux, 6 h, (99%); c) $LiAlH_4$, Et_2O, 0°C to RT, 12 h; d) BBr_3, CH_2Cl_2, −80°C to RT, 24 h (55% from **31**); e) SO_3/Py, pyridine, 70°C, 6 h; f) *p*-TsOH, dioxane, H_2O, RT, 3 h (74% from **33**). Py = pyridine.

sulfonation of the aryl ring might take place with SO_3 or related agents. Although sulfate monoesters are less common in nature relative to phosphate monoesters, sulfated biomolecules do have a certain role in cellular events. Typical sulfated biomolecules are carbohydrates, proteins (tyrosines), and steroids.[20,21] The transfer of sulfate groups to hydroxy functions is catalyzed by sulfotransferases, which use 3′-phosphoadenosine 5′-phosphosulfate as the sulfate source. In a laboratory setting, the attachment of the sulfate is preferentially done at the end of the synthesis, as the resulting products are very polar and the sulfate group is somewhat acid labile. Common methods for the preparation of aryl sulfates include the use of SO_3/amine complexes[22] (amine = pyridine, NEt_3) or tetrabutylammonium hydrogen sulfate (Bu_4N^+ HSO_4^-) in presence of dicyclohexyl carbodiimide (DCC).[23] In the case at hand, the treatment of imine **33** with the SO_3/pyridine complex (10 equiv) in pyridine for 6 h at 70 °C afforded about 20 % of the inner salt of **1** and 70 % of a compound that was characterized as a bisulfate derivative of **33**. The bisulfate is a water soluble analogue of **1**, which might also be biologically active. We found that the bisulfate could readily be converted into **1** with *p*-toluenesulfonic acid (*p*-TsOH) in a water/dioxane system at room temperature. Under these conditions, one sulfate group is selectively hydrolyzed to give additional **1** (54 %) and about 10 % of **33**, which could be recovered. The NMR spectra of **1** were found to be identical to the spectra from the isolated natural product.

In summary, we developed an efficient synthesis of (±)-symbioimine (**1**), a novel tricyclic iminium alkaloid. The total synthesis of **1** was accomplished in 22 steps from 3,5-dihydroxy benzoic acid (**5**) in more than 5 % total yield, which corresponds to an average yield of 88 % per step. Our approach features a Lewis acid induced *endo*-IMDA reaction of 2,8,10-*E*,*E*,*E*-trienal **12** and a diastereoselective alkylation of nitrile **19** as key steps. This route opens the way to other symbioimine-type compounds. This study also emphasizes the high reactivity of the electron-rich aryl ring if it comes close to another electrophilic group that yields interesting polycyclic structures. This strategy might actually be of interest in the context of diversity oriented synthesis.[24]

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