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Stereoselective Formal Synthesis of Pseudodistomin C†

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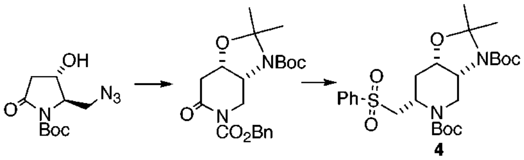
ABSTRACT



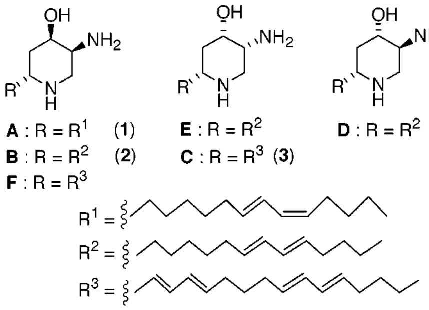
Trisubstituted benzenesulfonylmethylpiperidine 4, in which the substituents are all *cis* to each other, is a direct synthetic precursor of the cytotoxic marine alkaloid pseudodistomin C; it has been synthesized with total diastereoselectivities from (*S*)-pyroglutaminol.

Six members of the pseudodistomin family have been described so far.[1−3] Pseudodistomins A (**1**) and B (**2**) were the first piperidine alkaloids isolated from marine organisms. Pseudodistomin C (**3**) has been extracted from the Okinawan tunicate *Pseudodistoma kanoko* along with **1** and **2** and was shown to possess the absolute configuration 4*S*,5*R*, opposite to those of **1** and **2**.[2] Pseudodistomin C exhibits in vitro cytotoxicity against murine lymphoma L1210 and human epidermoid carcinoma KB cells.[4]

Only one total synthesis of this biologically active product has been achieved by Kobayashi et al. from D-serine derived Garner's aldehyde (Scheme 1).[5] In this synthesis, however, the key intermediates **4** and **5** are obtained with poor diastereo- and enantioselectivities (dr 1.5:1 and ee 60%, respectively), and only a few syntheses of all *cis* *N*-protected 2,4,5-trisubstituted piperidines have been reported.[6]

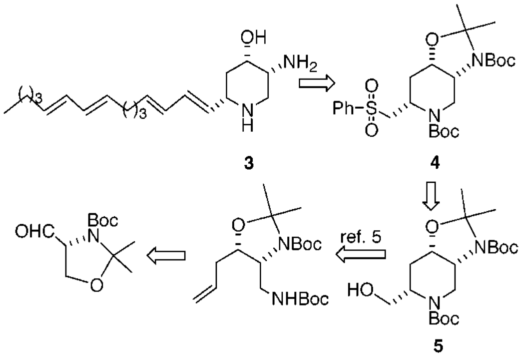
Thus, a diastereo- and enantioselective synthesis of either **4** or **5** was planned through 4-hydroxy-5-*N*-*tert*-butoxycarbonylaminopiperidin-2-one **6**.[7]

Pseudodistomins



Three different ways to this obviously promising intermediate **6** were investigated from the bicyclic epoxide **7** or

Scheme 1



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† Dedicated to the late Professor H. Nakamura.

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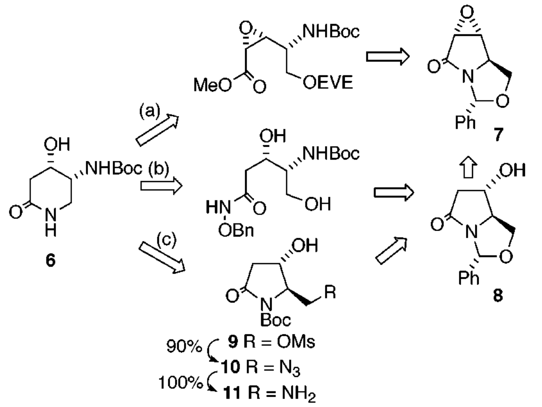
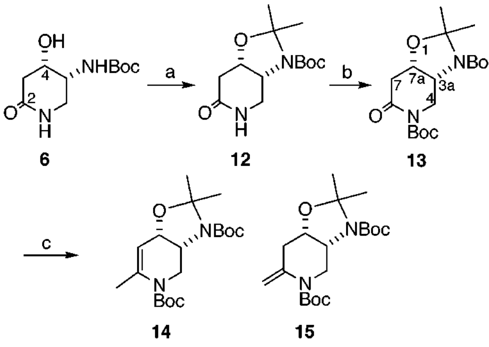
from its derived secondary alcohol **8** prepared from (*S*)-pyroglutaminol,[8,9] as summarized in the Scheme 2.

Scheme 2



According to the most efficient route (c), alcohol **8** was converted first into methanesulfonate ester **9** as previously described.[10] Subsequent displacement of the mesylate by sodium azide in DMF afforded **10** in 90% yield. The reduction of the azido group (H_2−Pd/C 10%) giving **11** was followed by heating in methanol at 65 °C for 24 h. Under these conditions, an intramolecular transamidation[11] of the primary amine was favored by the presence of the *N-tert*-butoxycarbonyl group in pyrrolidinone **11**. Indeed, *N*-protecting carbamates are known to enhance the reactivity of the lactamic carbonyl[12] and translactamization occurred quantitatively, leading to the stable piperidin-2-one **6**. Thus, an effective route to this *cis*-4,5-disubstituted piperidin-2-one was established. With the key intermediate **6** in hand, the introduction of suitable functionalization at C-2 in a *cis* relationship with C-4 and C-5 substituents was attempted, after convenient protections. Accordingly, the hydroxy and *N-tert*-butoxycarbonylamino groups were simultaneously protected as oxazolidine **12** in excellent yield (95%) with 2,2-dimethoxypropane and TsOH; then **12** was treated in acetonitrile with di-*tert*-butyl dicarbonate in the presence of DMAP,[13] giving rise to (3a*R*,7a*S*)-2,2-dimethyl-6-oxoperhydrooxazolo[4,5-*c*]pyridine-3,5-dicarboxylic acid di-*tert*-butyl ester **13** (82%, Scheme 3). In the ^{1}H NMR spectrum of **13**, the small vicinal coupling constants $J_{7,7a}$ and $J_{3a,4}$ of H-7 and H-4 (<3.3 Hz) are consistent with a boat conformation of the molecule which was confirmed by X-ray analysis.[14]

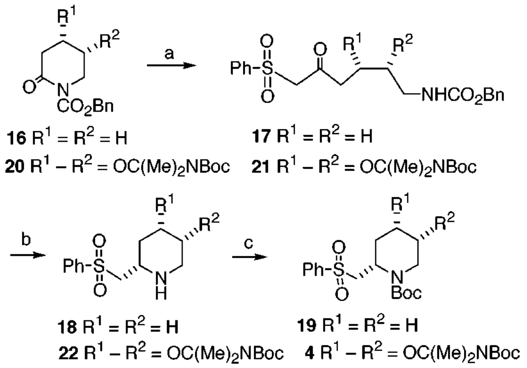
Scheme 3[a]



[a] (a) Me$_2$C(OMe)$_2$,TsOH, acetone (95%); (b) (Boc)$_2$O, DMAP, MeCN (82%); (c) Cp$_2$Ti(Me)$_2$, 99:1 toluene/pyridine (86%).

Introduction of the hydroxymethyl group at C-6 present in compound **5** was initially envisaged by submitting an exomethylene derivative such as **15** to a diastereoselective hydroboration−oxidation reaction.[15] However, despite precautions to avoid isomerization of the created double bond, treatment of lactam **13** with bis(cyclopentadienyl)dimethyltitanium[16] provided only compound **14** (86%). The ^{1}H NMR spectrum of **14** is consistent with an endocyclic unsaturated compound, and the easy formation of the *endo*-enecarbamate prevented this synthetic route from being carried out. As an alternative, the conversion of piperidinone **6** into the advanced phenyl sulfone precursor **4** was investigated as shown in the Scheme 4.

Scheme 4[a]



[a] (a) PhSO$_2$CH$_2$Li, THF; (b) H$_2$/Pd(OH)$_2$, MeOH; (c) (Boc)$_2$O, NaHCO$_3$, THF−H$_2$O.

The opening of *N*-alkoxycarbonyl or *N*-trimethylsilyl lactams with organometallic reagents is well documented.[17]

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Generally, pyrrolidin-2-one *tert*-butyl carbamates react with Grignard reagents at low temperature, providing the corresponding acyclic ketones or cyclic α-hydroxycarbamates in good yields.[17b] However, few literature examples of the use of (benzenesulfonyl)methylmagnesium bromide[18] could be found although effective nucleophilic additions to aldehydes have been described.[19] The experimentation started with (benzenesulfonyl)methyllithium and with the *N*-benzyloxycarbonyl valerolactam **16** as a model. This *N*-protecting group was chosen at this stage to allow a further selective deprotection with polysubstituted piperidinone **6** derivatives. Treatment of **16** with (benzenesulfonyl)methyllithium in THF at −76 °C afforded **17** (68%) without attack of the benzyloxycarbonyl group.[20] Compound **17** was slowly but cleanly converted under H_2 (Pd/C 10%) into piperidine **18**, which was further protected (96%) as the known 1-*tert*-butoxycarbonyl-2-(benzenesulfonyl)methylpiperidine **19** for comparison purposes,[21] and the same scheme was applied to **12** (Scheme 4). Accordingly, piperidinone **12** was *N*-protected with benzylchloroformate to **20** (75%), which adopts the same boat conformation as **13** according to the similarities in their ^{1}H NMR spectra. Treatment of **20** with $PhSO_2CH_2$-Li at −76 °C afforded the corresponding ketone **21**, in a modest unoptimized 41% yield. In this case, the formation of **12** (19%) by attack of the benzyloxycarbonyl group was also observed. *N*-deprotection of **21**, cyclization to the imine intermediate, and subsequent reduction were performed in one step with H_2 in the presence of Pearlman's catalyst, which gave better results than Pd/C, affording the expected all *cis*-trisubstituted piperidine **22** (76%) with total stereoselectivity. The previously described *N*-Boc derivative **4** was obtained in 97% yield; it has been shown to lead to pseudodistomin C **3**, after Julia olefination and classical deprotections.[5]

In conclusion, this work constitutes a valid completely diastereoselective route, not only to natural pseudodistomin C **3** itself but also to structural analogues containing other olefinic side chains, to evaluate their biological activities.

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Supporting Information Available: Experimental procedures for the synthesis of **4** and spectroscopic data for all intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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