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Stereoselective Formal Synthesis of Pseudodistomin C†

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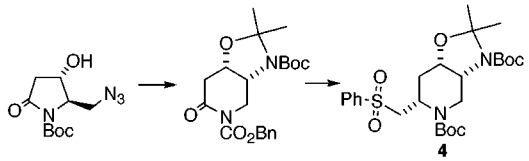
ABSTRACT



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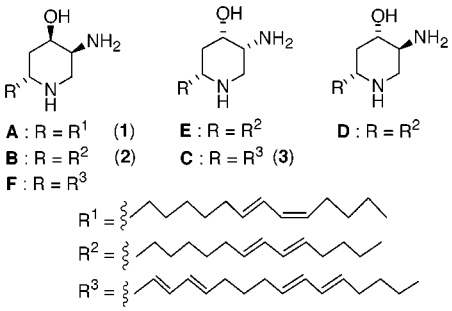
Trisubstituted benzenesulfonylmethylpiperidine 4, in which the substituents are all *cis* to each other, is a direct synthetic precursor of the cytotoxic marine alkaloid pseudodistomin C; it has been synthesized with total diastereoselectivities from (*S*)-pyroglutaminol.

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]

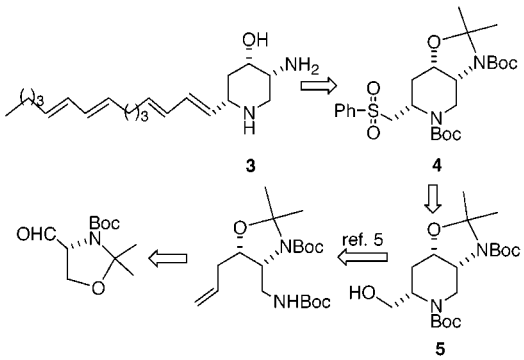
Thus, a diastereo- and enantioselective synthesis of either **4** or **5** was planned through 4-hydroxy-5-*N*-*tert*-butoxycarbonylaminopiperidin-2-one **6**.[7]

Pseudodistomins



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

Scheme 1



† Dedicated to the late Professor H. Nakamura.

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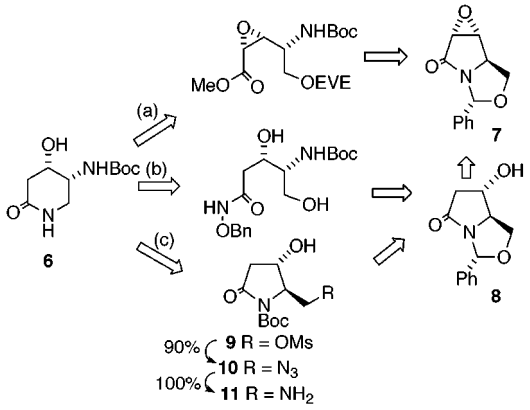
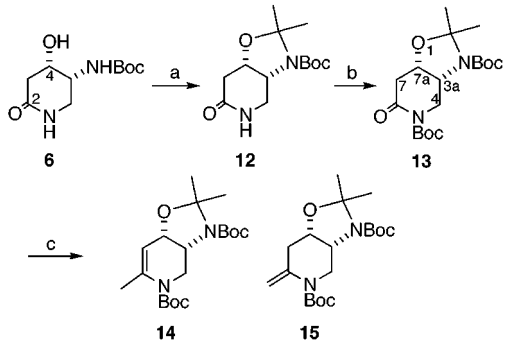
from its derived secondary alcohol **8** prepared from (*S*)-pyroglutaminol,[8,9] as summarized in the Scheme 2.

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

Scheme 3[a]

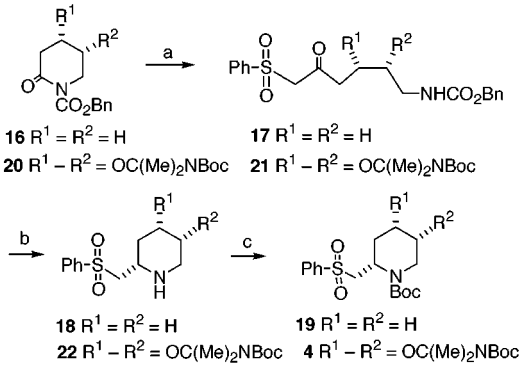


[a] (a) $Me_2C(OMe)_2$,TsOH, acetone (95%); (b) $(Boc)_2O$, DMAP, MeCN (82%); (c) $Cp_2Ti(Me)_2$, 99:1 toluene/pyridine (86%).

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]

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) $PhSO_2CH_2Li$, THF; (b) $H_2/Pd(OH)_2$, MeOH; (c) $(Boc)_2O$, $NaHCO_3$, THF−H_2O.

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.

Acknowledgment. The author is grateful to Professor Jun'ichi Kobayashi for the MS and NMR spectra of **4**, to Jean-François Gallard for recording the NMR spectra, and to Angèle Chiaroni for X-ray analysis of **13**.

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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