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Intramolecular Mitsunobu reaction in the regio- and stereoselective synthesis of *cis*-4,5-disubstituted piperidin-2-ones

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Abstract

Enantiopure *cis*-4,5-disubstituted piperidin-2-ones were synthesized through the cyclization of *O*-benzyl hydroxamates under Mitsunobu conditions, followed by samarium diiodide reduction.

Keywords: polysubstituted piperidinones; hydroxamates; Mitsunobu reaction; samarium diiodide.

Polysubstituted piperidines are common structural sub-units in numerous natural products and drugs. As this class of compounds exhibit a wide range of biological activities,[1] regio- and stereoselective syntheses of enantiopure substituted piperidines are a target of particular interest.[2] Thus, many structural analogues of pyranose-type azasugars, particularly 2-substituted 3,4,5-trihydroxypiperidines with transition-state like half-chair conformation, have been synthesized and studied as glycosidase inhibitors.[3,4] Among the 2,4,5-trisubstituted members, (4*S*,5*S*)-5-acetamido-4-hydroxypipecolic acids **1** are weak sialidase inhibitors,[5] whereas pseudodistomins A, B, F (**2**) and E, C (**3**) are known for their activity as calmodulin antagonists and/or their cytotoxicity against L1210 leukemia cells.[6,7] In these marine piperidines isolated from tunicates, a *cis* relationship is observed between the substituents at C-4 and C-5.[6,7] Focusing our interest on this characteristic structural feature, we report here a new route to the diastereo- and enantioselective construction of *cis*-4,5-disubstituted piperidin-2-ones, the amide carbonyl of which allows further functionalization.

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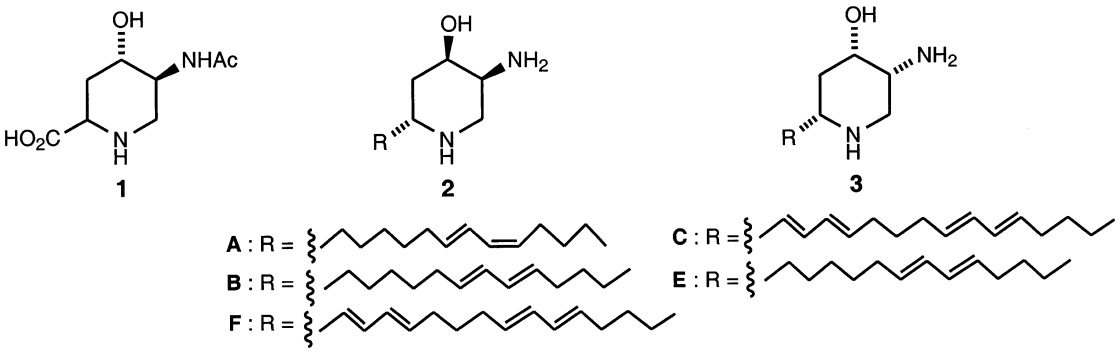
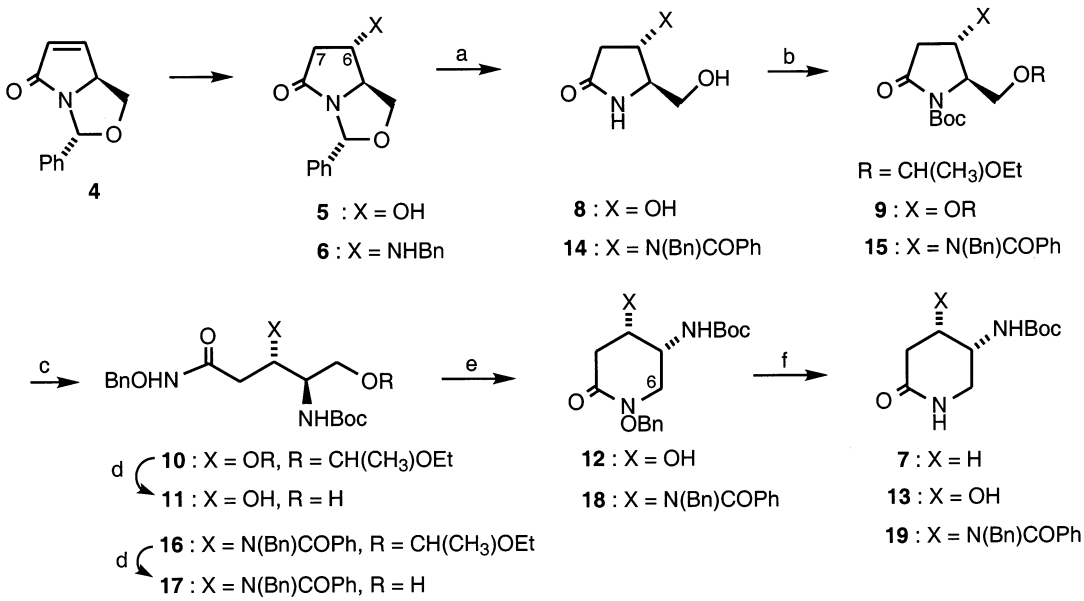
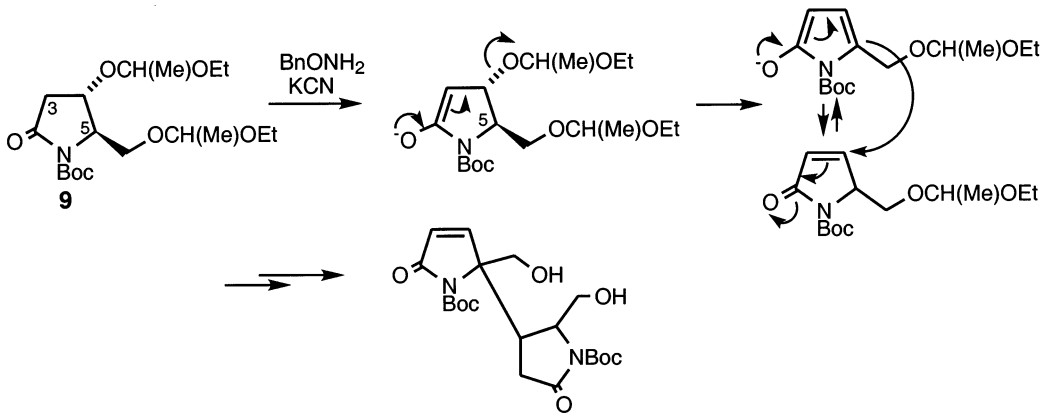


Starting from the rigid bicyclic α,β-unsaturated lactam **4** derived from inexpensive (*S*)-pyroglutaminol, the synthetic route, summarized in the general Scheme 1, took advantage of the high diastereoselectivity observed in the substitution at C-6. The 6*S*-hydroxy derivative **5** was obtained by regiospecific opening of 6*R*,7*R*-epoxide with SmI_2 at −78°C (83% for two steps),[8] whereas the 6*S*-*N*-benzylamino compound **6** resulted from stereospecific conjugate addition of *N*-benzylamine (88%).[9] The nitrogen of the targeted piperidin-2-ones could be introduced by the opening of *N*-*tert*-butoxycarbonylpyrrolidin-2-one rings with *O*-benzylhydroxylamine to form hydroxamates. The low p*K* of *O*-benzyl hydroxamates, indeed, is known to induce a good chemoselectivity towards an intramolecular Mitsunobu reaction of substrates also containing carbamate functions. This selectivity has been widely used in β and ω-lactam formation,[10,11] and has been extended in our laboratory to δ-lactam preparation, as exemplified by the synthesis of enantiopure (*S*)-5-aminopiperidin-2-one **7**.[12]



Scheme 1. Reagents and conditions (all the reactions were performed at room temperature): (a) CF_3CO_2H, H_2O–THF 1:1; (b) (i) ethylvinylether, CCl_3CO_2H, CH_2Cl_2; (ii) $(Boc)_2O$, DMAP, CH_3CN; (c) $BnONH_2$, H_2O, Na_2CO_3; (d) 0.1N HCl; (e) PPh_3, DEAD, THF; (f) SmI_2, THF

Accordingly, the alcohol **5** gave rise quantitatively to the diol **8** after hydrolysis of the oxazolidine protection with aqueous trifluoroacetic acid in THF. The diol **8** was converted into suitably protected *N*-Boc pyrrolidin-2-one **9** by classical methods (89% for two steps, Scheme 1). At first, *O*-benzyl hydroxamate **10** was obtained from **9** (40%) by triisobutylaluminum mediated transamidation[13] with *O*-benzylhydroxylamine, but this reaction was unreliable and *N*-Boc deprotection was observed in some cases. The cleavage in the presence of a catalytic amount of potassium cyanide,[14] or using lithium amide as the nucleophile, led to a mixture of products resulting from deprotonation at C-3 with β-elimination. The major product resulted from Michael addition of an unsaturated lactam to another molecule, providing a dimeric compound characterized after deprotection of the hydroxyl groups (Scheme 2).[15] The opening of the γ-lactam ring with the amine in the presence of H_2O and Na_2CO_3 was preferred, following our recently developed method.[14] Under these conditions, however, the reaction with **9** is very slow and was stopped before completion to avoid a possible β-elimination of the functional group at C-4. Compound **10** was isolated in 60% yield, together with starting **9** (25%).



Scheme 2.

A selective Mitsunobu reaction with *O*-deprotected diol **11** (100% from **10**) was performed in THF at room temperature using 1.2 equiv. of reagents (PPh_3, DEAD) and provided **12** (68%). Previous cyclization through selective Mitsunobu reaction with unprotected amino-polyols leading to five-membered rings has been described in pyridine as solvent.[16] In the NMR spectra of the cyclization product **12**, the chemical shifts of C-6-H_2 (^{13}C: $\delta = 49.8$ ppm), consistent with a NCH_2 methylene, prove that *N*-alkylation occurred versus *O*-alkylation. The N–O bond of **13** was cleanly cleaved by SmI_2 in THF at room temperature,[17,18] and the required piperidinone **13** was obtained in 84% yield (Scheme 1).

A similar scheme was applied to the synthesis of the protected *cis*-4,5-diamino piperidin-2-one **19** as an analogue. The 6-*N*-benzylamino derivative **6** led, after *N*-benzoylation (PhCOCl, 2.4 equiv., CH_2Cl_2, Et_3N, rt, 95%) and acid hydrolysis (100%), to the γ-lactam **14**, which was converted into *N*-Boc pyrrolidinone **15** (70% for two steps). The γ-lactam ring of **15** was smoothly opened with *O*-benzylhydroxylamine to afford the pentanamide **16** (72%) and unreacted **15** (11%). These compounds gave broad signals in ^1H NMR, probably owing to the presence of conformers. By intramolecular alkylation under Mitsunobu reaction conditions, the primary alcohol **17** (100% from **16**) gave rise efficiently to 4,5-disubstituted piperidin-2-one **18** (82%). This compound was treated with SmI_2 to afford the 4,5-disubstituted piperidin-2-one **19**

in good yield (84%). In this way, *cis* cyclic vicinal diamines in diastereomerically and enantiomerically pure form become accessible and could be useful as scaffolds to synthesize not only more complex molecules but also new metal chelating agents.[20]

In conclusion, a synthesis of new enantiopure 4-substituted 5-(*N*-Boc)aminopiperidin-2-ones of defined 4*S* and 5*R* configurations was developed taking advantage of stereospecific functionalization of the versatile bicyclic α,β-unsaturated lactam **4**.

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