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Asymmetric Synthesis of Polyhydroxylated *N*-Alkoxypiperidines by Ring-Closing Double Reductive Amination: Facile Preparation of Isofagomine and Analogues

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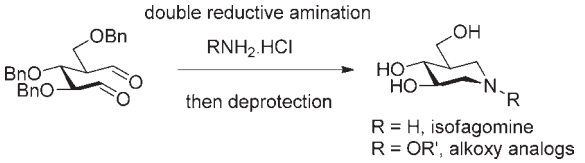
ABSTRACT



A de novo synthesis of novel polyhydroxylated *N*-alkoxypiperidines based on the ring-closing double reductive amination of 1,5-dialdehydes, obtained by oxidative cleavage of cyclopentene derivatives, with O-substituted hydroxylamines is reported. Isofagomine was accessed by cleavage of the N–O bond of an *N*-alkoxypiperidine.

In connection with ongoing projects in our laboratory we required a rapid entry into optically pure polyhydroxylated piperidines and their N-substituted analogues with particular emphasis on the N-alkoxy derivatives. We report here on the development of such a method based on the ring-closing double reductive amination of protected hydroxylated 1,5-dialdehydes and its application to the synthesis of the potent glycosidase inhibitor isofagomine.

Inspired by the first synthesis of isofagomine by Bols in 1994,[1] which employed a ring-closing double reductive amination of a dialdehyde with ammonia, we envisaged the preparation of N-alkoxy analogues by a related strategy employing O-substituted hydroxylamines as the amine component. With the exception of a single example described by Hindsgaul[2] using hydroxylamine itself, to our knowledge such a protocol has not been reported previously.

The Bols isofagomine synthesis accessed the requisite dialdehyde in four allegedly difficult steps[3] from the Cerny epoxide,[4] which itself was traditionally obtained somewhat laboriously from glucose until an improved protocol was reported by Guo in 2003 starting from D-glucal.[5] Requiring a maximum of flexibility and a concise synthesis, we

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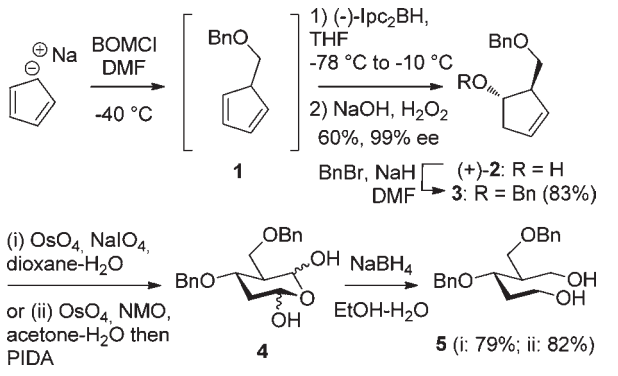
opted instead for a de novo asymmetric synthesis from readily available starting materials. In particular, we were attracted to an approach revolving around the desymmetrization of cyclopentadiene to give an optically enriched functionalized cyclopentene derivative followed by oxidative cleavage to yield the necessary dialdehyde.

The cyclopentene derivative (+)-**2** has been described several times in the literature, mainly in the course of the synthesis of nucleoside analogues.[6] Its preparation begins with the alkylation of the cyclopentadienyl anion with benzyloxymethyl chloride, leading to intermediate **1**, known to be prone to isomerization when generated from sodium cyclopentadienylide, followed by desymmetrizing enantioselective hydroboration with (−)-diisopinocampheylborane ((−)-Ipc_2BH).[7] As reported by Corey, this problem can be avoided by means of thallium cyclopentadienylide,[6b] but we preferred the recent Gellman procedure,[6e] which overcomes the racemization problem with the sodio derivative by working in DMF at −40 °C. In our hands, this afforded the required cyclopentene (+)-**2** with a satisfactory 60% yield and 99% enantiomeric purity on a 40 mmol scale (Scheme 1). Subsequent protection of **2** as the benzyl ether **3**,[6g,8] in the standard manner, provided a model with which to evaluate the overall strategy.

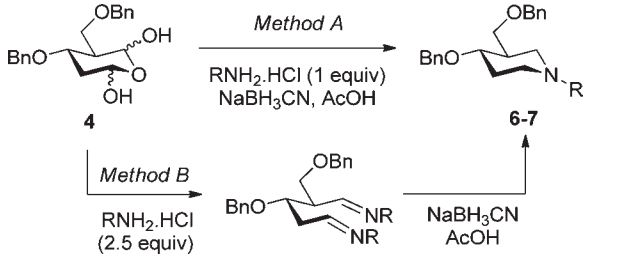
Scheme 1. Preparation of the Model Dialdehyde **4**



Oxidative cleavage of olefin **3** was first evaluated under classical conditions, with sodium periodate and osmium tetroxide in a mixture of dioxane and water. The so-formed dialdehyde exists in admixture with the various diastereomeric forms of the cyclic hydrate **4** and was reduced to the diol **5** with sodium borohydride[9] to assess the efficiency of the oxidative cleavage. In this manner diol **5** was formed in 79% yield, whereas the use of Nicolaou's recent modification[10] that employs osmium tetroxide/*N*-methylmorpholine *N*-oxide followed by treatment with phenyliodine diacetate (PIDA) afforded diol **5** in 82% overall yield after reduction with sodium borohydride.

The key ring-closing double reductive amination of dialdehyde **4** was validated under classical Borch conditions with benzylamine,[11] when the targeted piperidine **6** was obtained in 71% yield (Table 1, entry 1). We then turned to the use of alkoxyamines, whose use in ring-closing double reductive aminations appears not to have been reported previously. *O*-Benzylhydroxylamine was investigated first with 1.1 equiv of freshly prepared dialdehyde, affording the *N*-alkoxypiperidine **7** in 46% yield (Table 1, entry 2). When 1.5 equiv of dialdehyde was employed (Table 1, entry 3), the cyclic alkoxyamine **7** was obtained in 54% yield, while the use of 2 equiv of dialdehyde gave a 57% yield (Table 1, entry 4). Using such conditions, however, we were unable to improve the yield beyond 60%, and consequently we moved to a two-step process. In this higher yielding protocol 2.5 equiv of hydroxylamine was first added to generate the intermediate dioxime (Table 1, method B) and on completion (LC-MS, ∼ca. 2.5 h) the reductant was added, resulting in the clean formation of the target alkoxyamine **7** in 81% yield (Table 1, entry 5). The presence of molecular sieves was necessary for the efficient generation of the double oxime (Table 1, entry 6).

Table 1. Ring-Closing Double Reductive Amination of **4** with Benzylamine and *O*-Benzylhydroxylamine



entry	method[a]	R	R'CHO/RNH_2	product	yield (%)[b]
1	ref 11b	Bn	1.2/1	**6**	71
2	A	OBn	1.1/1	**7**	46
3	A	OBn	1.5/1	**7**	54
4	A	OBn	2/1	**7**	57
5	B	OBn	1/2.5	**7**	81
6	B	OBn	1/2.5	**7**	0[c]

[a] Method A: $RNH_2 \cdot HCl$ (1 equiv), $NaBH_3CN$ (5 equiv), AcOH (20 equiv), MS 3 Å, MeOH (0.04 M). Method B: $RNH_2 \cdot HCl$ (2.5 equiv), MS 3 Å, MeOH (0.25 M) then $NaBH_3CN$ (5 equiv), AcOH (10 equiv). [b] Isolated yields. [c] Reaction performed without molecular sieves.

With conditions for the ring-closing double reductive amination established, we next focused on the synthesis of more functionalized dialdehydes, for which double reductive

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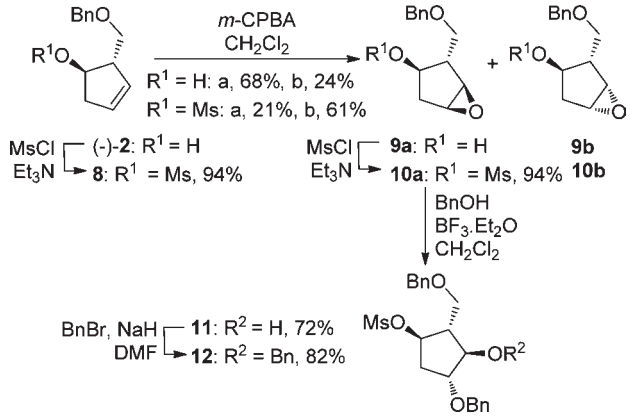
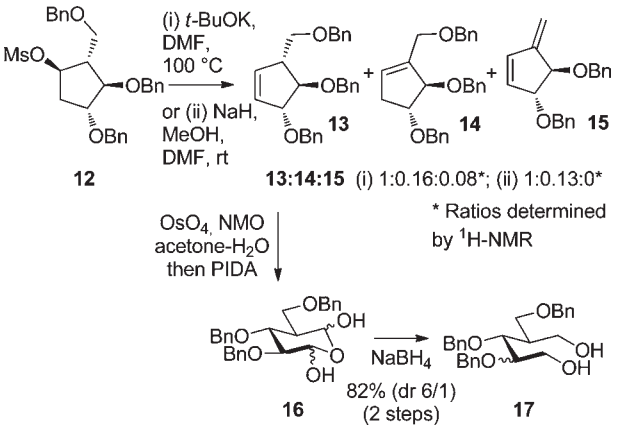
Scheme 2. Preparation of a Highly Functionalized Cyclopentane



Scheme 3. Synthesis of Functionalized Dialdehyde **16**



amination with hydroxylamines would provide trisubstituted *N*-alkoxypiperidines analogous to isofagomine. The synthesis commenced from (−)-**2**, obtained analogously to its enantiomer (+)-**2** (Scheme 1). Subsequently, on the basis of a recent strategy developed by Meier,[6f] alcohol (−)-**2** was converted to the mesylate **8** in excellent yield, and the double bond was subjected to epoxidation with *m*-CPBA (Scheme 2), leading to the formation of two diasteromeric epoxides **10** in a 1:3 ratio in favor of the undesired isomer **10b**. Fortunately, hydroxyl-directed *m*-CPBA epoxidation of cyclopentene (−)-**2**, in a manner analogous to a related Sharpless epoxidation,[6d] furnished in good yield a separable mixture of epoxides **9a**,**b** in a 3:1 ratio favoring the desired isomer. Mesylation then afforded the compound **10a** in 94% yield, which, on treatment with benzyl alcohol in the presence of $BF_3 \cdot OEt_2$, underwent regioselective opening of the epoxide to give **11** as a single diastereoisomer in good yield. Protection of the resulting alcohol function with benzyl bromide in the presence of NaH then provided the functionalized cyclopentane **12** in 82% yield (Scheme 2).

The base-assisted elimination of the mesylate from **12** was first investigated with potassium *tert*-butoxide in polar aprotic solvents, as Meier[6f] had identified *t*-BuOK to afford the Hofmann product preferentially in a series of closely related compounds, due to the sterically hindered nature of the base. Under the Meier conditions (*t*-BuOK, DMF, 100 °C) mesylate **12** gave three different products, namely the Hofmann and Saytzeff products **13** and **14**, respectively, and a product **15** resulting from the elimination of the benzyloxy group. As determined by ^{1}H NMR spectroscopy on the crude reaction mixture, the required regioisomer **13** was favored under these conditions (Scheme 3), and decreasing the temperature to ambient improved the ratio further to 1:0.1:0.02. Surprisingly, however, the best results were obtained with the less basic, less hindered sodium methoxide as base at room temperature,[12] when formation of the over-elimination product **15** was suppressed and the Hofmann and Saytzeff products were obtained in a ratio of 1:0.13, enabling the isolation of cyclopentene **13** in 72% yield. Subsequent oxidation with the NMO/OsO_4/PIDA system gave the corresponding hydrated dialdehyde **16**, which was characterized after reduction to the diol **17** with sodium borohydride (Scheme 3). Interestingly, diol **17** was obtained as a 6:1 mixture of two unassigned diastereoisomers but, as revealed by the subsequent ring-closing cyclizations which were epimerization free, the loss of stereochemical integrity occurred during the reduction step. In subsequent work, the dialdehyde was used without characterization in the ring-closing reductive amination step immediately following flash chromatography over silica gel.

Ring-closing double reductive amination was first investigated with benzylamine in the presence of sodium cyanoborohydride, which resulted in formation of the protected isofagomine derivative **18**, albeit in a low 18% yield (Table 2, entry 1). Interestingly, in view of this low yield, the *N*-benzyloxypiperidine **19** was prepared by ring-closing double reductive amination with *O*-benzylhydroxylamine under the previously optimized conditions in an excellent 84% yield (Table 2, entry 2). The subsequent use of a variety of N-substituted hydroxylamines in this manner demonstrates that this protocol nicely accommodates the presence of protected sugar, ester, alkyne, allyl and benzyl functionalities in the hydroxylamine component, giving a range of novel piperidine derivatives. Thus, *O*-(*p*-methoxybenzyl)hydroxylamine and *O*-allylhydroxylamine provided the piperidines **20** and **21** in excellent 90% and 89% yields, respectively (Table 2, entries 4 and 5). Reductive amination with the sugar-derived hydroxylamine[13] furnished the corresponding pseudodisaccharide **22** in 70% yield (Table 2, entry 6). The functionalized piperidines **23** and **24** were obtained uneventfully in 76% and 72% yields from ester- and

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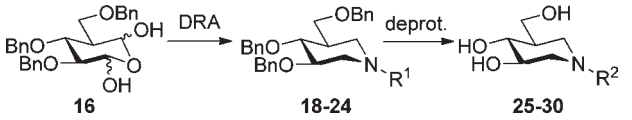
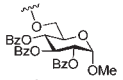
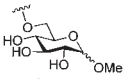
Table 2. Synthesis of Isofagomine and Some N-Alkoxy Derivatives



entry	R^1	yields[a]	R^2	yields[a]
1	Bn	**18**, 18%	H	-[b]
2	OBn	**19**, 84%	H	**25**, 72%[c]
3			OBn	**26**, 90%[d]
4	OPMB	**20**, 90%	OH	**27**, 96%[d]
5	OAll	**21**, 89%	OAll	**28**, 88%[d]
6		**22**, 70%		**29**, 61%[e]
7		**23**, 76%		**30**, 45%[d,f]
8		**24**, 72%	-[g]	-[g]

[a] Isolated yields. [b] Isofagomine **25** was obtained from **19** (entry 2). [c] BBr_3, CH_2Cl_2. [d] BCl_3, CH_2Cl_2. [e] (i) NaOMe, MeOH; (ii) BCl_3, CH_2Cl_2. [f] Obtained as a 1.9:1 mixture of ethyl and methyl esters, respectively (see the Supporting Information). [g] The presence of alkyne is not compatible with BCl_3 deprotection.

alkyne-carrying hydroxylamines, respectively (Table 2, entries 7 and 8). From a practical standpoint, it must be noted that the ^{1}H NMR spectra of the various *N*-alkoxypiperidines obtained in this manner were complex when recorded at room temperature, due to the existence of several conformers, but showed a single time-averaged structure when recorded at 100 °C in d_7-DMF.[14]

Exposure of these *N*-alkoxypiperidine derivatives to BCl_3 cleanly removed the benzyl groups, resulting in the formation of the target *N*-alkoxypiperidines, all of which are analogues of isofagomine characterized by the presence of a N−O bond linked to various functional groups (Table 2, entries 3−7). The simple *N*-hydroxyisofagomine **27** was obtained from **20** in excellent yield, as the PMB group of the hydroxylamine was labile to the BCl_3 conditions (Table 2, entry 4). The PMB group can also be orthogonally removed from **20** by simple treatment with TFA (see the Supporting Information). Finally, deprotection of **19** with BBr_3 rather than BCl_3 removed the ether functionality in the standard manner and additionally effected cleavage of the hydroxylamine N−O to afford isofagomine itself (**25**) in 72% yield (Table 2, entry 2).

Overall, a de novo asymmetric entry into two series of *N*-hydroxy- and *N*-alkoxypiperidines, analogues of isofagomine, has been developed on the basis of a novel strategy of ring-closing double reductive amination on a functionalized dialdehyde with O-substituted hydroxylamines. Isofagomine, a non-natural aza sugar[15] analogous to fagomine, with a spectrum of biological activities that includes inhibition of β-glucosidase[16] and hepatic glycogen phosphorylase[17] with potential for the treatment of Gaucher's disease,[18] was obtained by cleavage of the N−O bond of an N-alkoxy derivative with BBr_3. This synthesis of isofagomine compares favorably with many of the numerous approaches described in the literature.[9,19]

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Supporting Information Available. Text and figures giving experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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