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A facile approach to chiral 1,4-benzodioxane toward the syntheses of doxazosin, prosympal, piperoxan, and dibozane

Abdul Rouf *, Mushtaq A. Aga, Brijesh Kumar, Subhash Chandra Taneja *

CSIR-Indian Institute of Integrative Medicine, Canal Road, Jammu 180001, India

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ABSTRACT

The process describes the concise synthesis of (*R*/*S*)-enantiomers of doxazosin, an antidepressant drug and α-adrenergic receptor antagonists like prosympal, piperoxan, and dibozane in practical yields from easily available (*R*)-2,3-*O*-cyclohexylidene-D-glyceraldehyde and (*S*)-3-(benzyloxy)propane-1,2-diol.

The 1,4-benzodioxane derivatives are found in a wide variety of natural products[1] and therapeutic agents possessing important biological activities.[2] They are known to possess the interesting biological properties like α-adrenergic blocking,[3] antigastric,[4] spasmolytic,[5] antipsychotic,[6] anxiolytic,[7] and hepatoprotective[8] properties. These activities are influenced by the absolute configuration of the 1,4-benzodioxane unit.[9] Enantiomerically pure 1,4-benzodioxan-2-carboxylic acid **1** and 2-hydroxymethyl-1,4-benzodioxane **2** derivatives (Fig. 1) are important intermediates of various drug molecules. These compounds could also be used as intermediates for very useful synthetic transformations.[10]

The reported methods for the synthesis of benzodioxane containing molecules typically involve the use of chiral building blocks from the 'chiral pool', such as glycerol or glycidol derivatives,[11] via condensation of catechol with chiral glycidol,[12] by Sharpless epoxidation of 1-aryloxy-4-hydroxy-2-butene substrate[13]and chemoenzymatic methods, involving kinetic resolutions of 1,4-benzodioxan-2-carboxylic acid,[14] its ethyl ester,[15] 2-hydroxymethyl-1,4-benzodioxane,[16] or accomplished after conversion of the enantiomers into diastereoisomers.[17] Another approach used the cycloaddition of a variety of *O*-quinones with dienophiles, either directly or via a two-step process involving a hetero-Diels–Alder reaction, followed by a [3,3]-sigmatropic rearrangement.[18] The most recent examples are the palladium-catalyzed asymmetric cyclization of benzene-1,2-diol with allylic biscarbonates,[19] the palladium catalyzed intramolecular cyclization of non-racemic 1-(2-bromophenyl)glycerol,[20] and Cu_2O-catalyzed ring-opening and coupling of epoxides.[21]

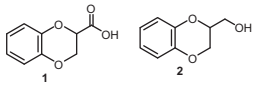

Figure 1. 1,4-Benzodioxan-2-carboxylic acid **1** and 2-hydroxymethyl-1,4-benzodioxane **2** derivatives.

Recently our group has also reported the chemoenzymatic approach toward the synthesis of enantiomerically pure isomers of doxazosin, piperoxan, prosympal, and dibozane containing 1,4-benzodioxane unit.[22] Even though the enzymatic processes are environment friendly and mild, the maximum yield of an enantiomer is only 50%. In this Letter an efficient and facile alternative for the preparation of these bioactive molecules from a cheap and easily available raw material that is, (*R*)-2,3-cyclohexylideneglyceraldehyde **8** and (*S*)-3-(benzyloxy)propane-1,2-diol **11** is described. Earlier, 1,4-benzodioxanes have also been chemically synthesized by various methods using chiral glyceraldehydes[23,9] or epoxides,[12] the present method offers a more facile and practical approach to the preparation of chiral 1,4-benzodioxanes.

The syntheses of chiral 1,4-benzodiaxane and the downstream products that is, doxazosin **3**, piperoxan **4**, prosympal **5,** and dibozane **6** are based upon commercially available and inexpensive (*R*)-**8**[24] and (*S*)-**11**.[25]

For the synthesis of (*S*)-hydroxymethyl-1,4-benzodioxane **2**, the methodology initiated was the reduction of (*R*)-2,3-*O*-cyclohexylidene-D-glyceraldehyde **8** (obtained via protection of D-mannitol

* Corresponding authors.
E-mail addresses: roufiiim@rediffmail.com (A. Rouf), drsctaneja@gmail.com, sctaneja@iiim.ac.in (S.C. Taneja).

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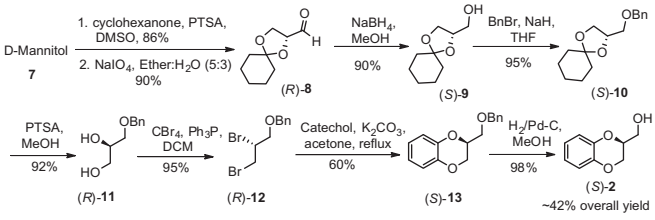
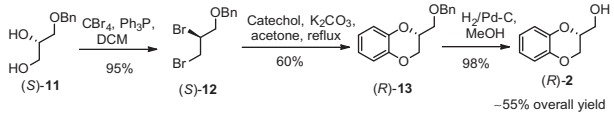
and C–C bond scissoring) by sodium borohydride followed by benzyl protection to generate (*S*)-2-((benzyloxy)methyl)-1,4-dioxaspirodecane **10**. The deprotection of the cyclohexylidene group of (*S*)-**10** with *p*-toluenesulfonic acid (PTSA) led to the formation of (*R*)-3-(benzyloxy)propane-1,2-diol **11**. An attempt was made to directly couple the optically active diol-**11** with catechol under Mitsunobu conditions. However, the reaction was unsuccessful, therefore the hydroxyl groups were substituted by bromine through Appel reaction (CBr_4/triphenylphosphine)[26] to form (*R*)-((2,3-dibromopropoxy)methyl)benzene **12** in 95% yields. Under the basic conditions, the coupling of catechol and dibromo (*R*)-**12** was successfully accomplished to yield the intermediate (*S*)-2-(benzyloxymethyl)-1,4-benzodioxane **13** in 60% yield, which was hydrogenated (H_2/Pd-C, MeOH) to form the intermediate (*S*)-hydroxymethyl-1,4-benzodioxane **2** in ~42% overall yield from (*R*)-**8**, which was thereafter used for further transformations (Scheme 1).

The nature provides only D-sugars and hydroxymethyl-1,4-benzodioxane **2** with the (*S*)-configuration can be obtained from D-mannitol through (*R*)-aldehyde **8**. However, for the preparation of (*R*)-hydroxymethyl-1,4-benzodioxane **2**, the synthesis was initiated from the commercially available (*S*)-benzyl-l,2-propanediol **11**,[27] by following the same reaction sequence described for (*S*)-**2** isomer (bromination, coupling and deprotection) in ~55% overall yield from (*S*)-**11** (Scheme 2).

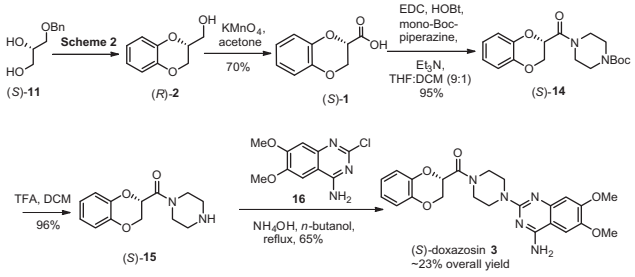
For the preparation of (*S*)-doxazosin **3**, (*R*)-hydroxymethyl-1,4-benzodioxane **2** [obtained from (*S*)-**11**] was oxidized with permanganate ($KMnO_4$) to form the enantiomerically pure acid (*S*)-**1**, and coupled with mono-Boc-piperazine to form (*S*)-**14** in 95% yield. The earlier reported methods[15b] used unprotected piperazine in which side product diamide is formed, while the present method afforded the desired amide in higher yields. The deprotection of



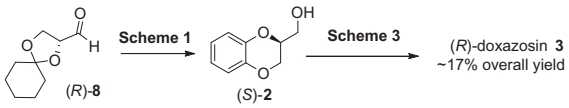
Scheme 1. Synthesis of (*S*)-hydroxymethyl-1,4-benzodioxane.



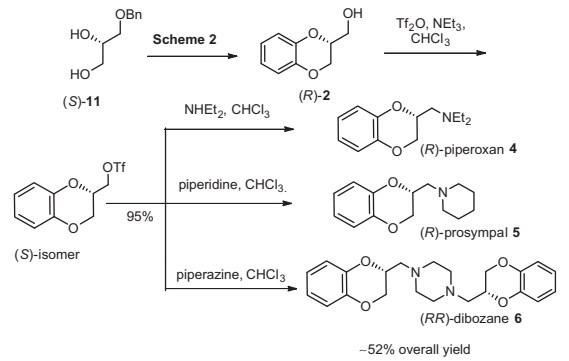
Scheme 2. Synthesis of (*R*)-hydroxymethyl-1,4-benzodioxane.



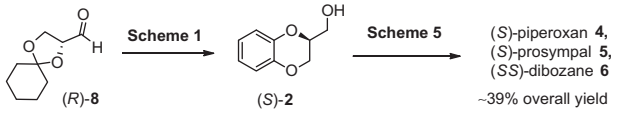
Scheme 3. Synthesis of (*S*)-doxazosin.



Scheme 4. Synthesis of (*R*)-doxazosin.



Scheme 5. Synthesis of (*R*)-isomers of **4**, **5** and **6**.



Scheme 6. Synthesis of (*S*)-isomers of **4**, **5** and **6**.

the *tert*-butoxy carbonyl group (Boc) was accomplished by trifluoroacetic acid in dichloromethane furnishing piprazinamide (*S*)-**15**, which was then coupled with 4-amino-2-chloro-6,7-dimethoxyquinazoline **16** in *n*-butanol to give (*S*)-doxazosin **3** in 65% yield with 99% ee (23% overall yield, Scheme 3).

For the synthesis of (*R*)-doxazosin **3**, (*S*)-hydroxymethyl-1,4-benzodioxane **2** [obtained from aldehyde (*R*)-**8**, Scheme 1] was oxidized to (*R*)-1,4-benzodioxan-2-carboxylic acid **1**, and thereafter converted to (*R*)-doxazosin **3** (99% ee) following the same reaction sequence described for (*S*)-doxazosin with ~17% overall yield (Scheme 4).

The synthesis of target bioactive molecules **4,5,6** by the substitution of the hydroxyl group with respective nucleophiles was optimized via triflation. Thus, the hydroxyl group was reacted with trifluoromethane sulfonic anhydride (triflic anhydride-Tf_2O) in chloroform to form activated triflates and then substituted with respective amines, that is, diethyl amine for piperoxan **4**, piperidine for prosympal **5**, and piperazine for dibozane **6** in one step. The reaction occurred cleanly in high yields (95%) without any by-product formation (Scheme 5). The preparation of (*R*)-isomers of **4**, **5,** and **6** from (*R*)-hydroxymethyl-1,4-benzodioxane **2** is depicted in Scheme 5 with ~52% overall yields.

While the (*S*)-isomers of **4,5,6** were prepared from the (*S*)-hydroxymethyl-1,4-benzodioxane **2** by the procedure discussed for (*R*)-isomers in ~39% overall yield (Scheme 6).

In conclusion an efficient and facile methodology has been demonstrated for the synthesis of (*R*/*S*)-isomers of doxazosin **3**, piperoxan **4**, prosympal **5**, and dibozane **6** from the (*R*/*S*)-3-(benzyloxy)propane-1,2-diol via a common intermediate **2**.

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Supplementary data

Supplementary data (experimental procedure and copies of ^{1}H and ^{13}C NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.09.040.

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