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Sulfoxide-Directed Stereocontrolled Access to 2*H*-Chromans: Total Synthesis of the (*S*,*R*,*R*,*R*)-Enantiomer of the Antihypertensive Drug Nebivolol

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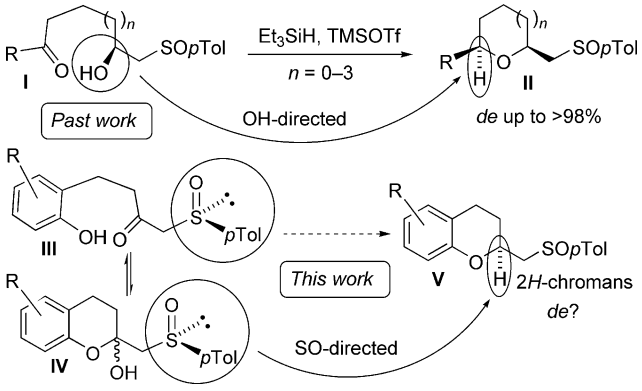
A homochiral sulfoxide-directed reductive deoxygenation of 2-(*p*-tolylsulfinyl)methyl-2-chromanols allows the stereoselective formation of 2*H*-chromans with up to 95:5 diastereoisomeric ratio. This new methodology was applied in a short and convergent enantioselective synthesis of the (*S*,*R*,*R*,*R*)-enantiomer of the antihypertensive drug Nebivolol.

Introduction

Sulfoxides have been extensively used in asymmetric synthesis due to the excellent asymmetric inductions they provide in a wide range of reactions.[1] Among them, the diastereodivergent reduction of β-keto sulfoxides has been one of the most exploited in synthetic applications. We recently reported[2] an enantioselective access to different sized *cis*-α,ω-disubstituted cyclic ethers (**II**, Scheme 1) based on the combination of the stereocontrolled reduction of a β-keto sulfoxide and the reductive cyclization of the resulting β-hydroxysulfinyl ketone **I**, in which the stereogenic hydroxylic center was controlling the stereochemical course of the reaction. Seeking for a short stereoselective approach to the 2*H*-chroman unit, a structural component of several natural products and pharmaceuticals, we thought about the direct transformation of enantiopure 4-(2-hydroxyphenyl)-1-(*p*-tolylsulfinyl)-2-butanone **III** into sulfinyl-substituted 2*H*-chroman **V**, in which the homochiral sulfoxide would be solely responsible for the diastereoselectivity of the reaction. Although important advances in the formation of the C-2 stereocenter in such systems have been achieved,[3] to the best of our knowledge, sulfoxides have never been used as asymmetric inductors to directly generate the 2*H*-chroman moiety from a phenol in a single step.



Scheme 1. Seeking the sulfoxide-directed stereocontrolled access to 2*H*-chromans.

Herein we describe a novel enantioselective access to the hydrobenzopyran moiety with a defined stereochemistry at the C-2 stereogenic center, starting from easily accessible δ-(*o*-hydroxyphenyl)-substituted β-keto sulfoxides **III**, on the basis of the stereoselective Et_3SiH/TMSOTf-promoted deoxygenation of the corresponding lactols **IV**, in equilibrium with the former. An additional advantage of our method is the presence of the sulfoxide in the resulting 2*H*-chromans, allowing further synthetic exploitation. We illustrate the efficiency of our approach with a short and convergent synthesis of (*S*,*R*,*R*,*R*)-Nebivolol, a known antihypertensive drug currently in clinical use, which has potent and selective β_1-adrenergic antagonist activity.[4]

Results and Discussion

The synthesis of β-keto sulfoxide (*R*)-**3a**, chosen as a model, was achieved from reaction of hydrocoumarin **1a** with the LDA-generated lithium anion of (*R*)-methyl *p*-tolyl

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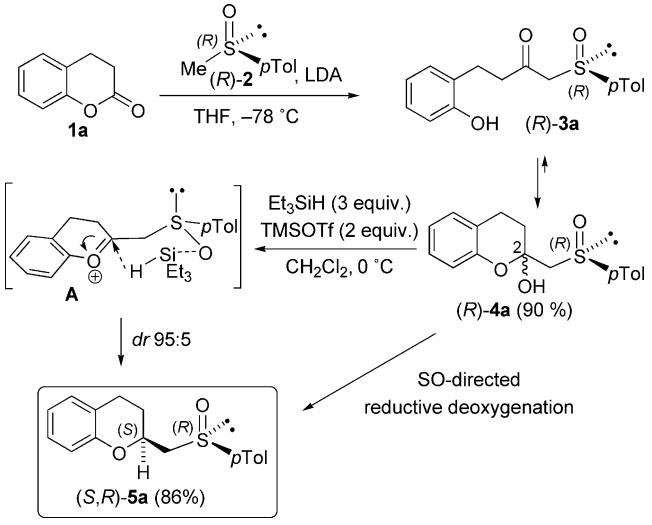
sulfoxide [(*R*)-**2**][5] (Scheme 2). Under these conditions, **3a** was isolated as an equilibrium mixture with cyclic hemiketal (*R*)-**4a** (mixture of C-2 epimers), in 90% yield. When this mixture was sequentially treated with Et_3SiH and TMSOTf at 0 °C, a stereoselective reductive deoxygenation process took place affording, in 86% yield, 2*H*-chroman (*S*,*R*)-**5a**[6] in an excellent 95:5 diastereoisomeric ratio. A mechanistic pathway explaining this result involves the initial formation of an oxocarbenium intermediate such as **A**, after ionic cleavage of the C–OH bond of (*R*)-**4a** by activation with TMSOTf. After coordination of the silane to the sulfinyl oxygen of **A**, the attack of the hydride mainly occurred from the lower face of the dihydrobenzopyran unit in the preferred six-membered chair-like transition state represented in Scheme 2, showing the most favorable equatorial disposition of the bulky *p*-tolyl substituent of the sulfoxide.

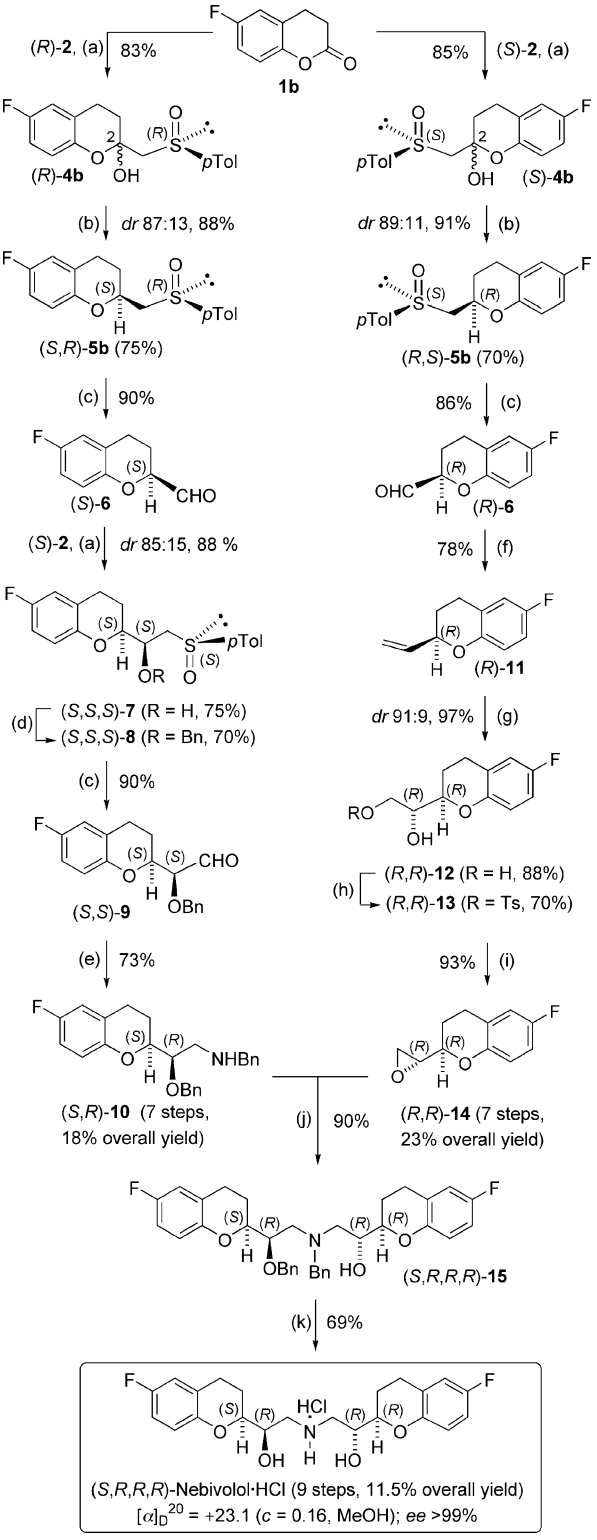


Scheme 2. Highly diastereoselective two-step synthesis of 2*H*-chroman (*S*,*R*)-**5a**.

With this result in hand, we turned our attention to the total synthesis of the antihypertensive agent (*S*,*R*,*R*,*R*)-Nebivolol. Although racemic Nebivolol has been prepared by a number of groups, including several patents,[7] only a few syntheses of the (*S*,*R*,*R*,*R*)-enantiomer have been addressed mainly by using nonstereoselective approaches or multistep processes.[8] The main challenging and non-well resolved task has been the efficient generation of the C-2 stereocenters at the 2*H*-chroman units.

We initiated the synthesis of the left fragment of (*S*,*R*,*R*,*R*)-Nebivolol, (*S*,*R*)-**10**, with the addition of the lithium anion of (*R*)-**2** to 6-fluorochroman-2-one (**1b**)[9] to obtain, in 83% yield, lactol (*R*)-**4b**, as a mixture of C-2 epimers (Scheme 3). The treatment of **4b** with Et_3SiH/TMSOTf, following the protocol previously established for **4a**, afforded, in 75% yield, enantiopure 2*H*-chroman (*S*,*R*)-**5b**, after separation of the initially formed 87:13 mixture of diastereoisomers.

The stereoselective formation of the second chiral carbinol present on the left fragment of (*S*,*R*,*R*,*R*)-Nebivolol, was achieved after transformation of sulfoxide (*S*,*R*)-**5b** into



Scheme 3. Convergent total synthesis of the (*S*,*R*,*R*,*R*)-enantiomer of the antihypertensive drug Nebivolol hydrochloride starting from lactone **1b**. Reagents and conditions: (a) LDA, THF, –78 °C; (b) Et_3SiH (10 equiv.), TMSOTf (2 equiv.), CH_2Cl_2, 0 °C; (c) (i) 2,4,6-collidine, TFAA, CH_3CN, 0 °C; (ii) $CuCl_2$, H_2O, room temp.; (d) NaH, BnBr, nBu_4NI, THF, room temp.; (e) $BnNH_2$, $NaBH(OAc)_3$, 1,2-dichloroethane, room temp.; (f) Ph_3PCH_3Br, *n*BuLi, THF, –78 °C to room temp.; (g) AD-mix-α, *t*BuOH/H_2O, 0 °C; (h) TsCl, pyridine, 0 °C; (i) NaH, THF, room temp.; (j) EtOH, reflux; (k) (i) H_2, Pd/C, EtOH, room temp. (ii) HCl (g), room temp.

aldehyde (*S*)-**6** through a Pummerer reaction[10] (90% yield, Scheme 3), followed by addition of the lithium anion derived from (*S*)-methyl *p*-tolyl sulfoxide [(*S*)-**2**][5] to aldehyde (*S*)-**6**. Under these conditions, compound (*S*,*S*,*S*)-**7**[6] could be isolated pure in 75% yield, after chromatographic separation of the initially formed 85:15 mixture of epimeric β-hydroxy sulfoxides. The high diastereoselectivity achieved can be attributed to the matched double asymmetric induction process occurring between aldehyde (*S*)-**6** and the nucleophile derived from sulfoxide (*S*)-**2**.[11]

With compound **7** in hand, we undertook the transformation of the sulfoxide into the required amine present in the advanced intermediate (*S*,*R*)-**10**. Protection of carbinol **7** (NaH/BnBr/nBu$_4$NI) furnished the *O*-benzyl derivative (*S*,*S*,*S*)-**8**, in 70% yield. Transformation of sulfoxide **8** into aldehyde (*S*,*S*)-**9** was again performed through a Pummerer reaction, in 83% yield. Finally, the reductive amination of aldehyde **9** by using BnNH$_2$ and NaBH(OAc)$_3$ gave dibenzyl-protected amino alcohol (*S*,*R*)-**10**, in 73% yield. Thus, we have achieved the stereoselective synthesis of the left fragment of (*S*,*R*,*R*,*R*)-Nebivolol, (*S*,*R*)-**10**, from known lactone **1b**, in seven steps and 18% overall yield.

The stereoselective preparation of the right fragment of (*S*,*R*,*R*,*R*)-Nebivolol, (*R*,*R*)-**14**, started with the formation of sulfinyl lactol (*S*)-**4b** (mixture of C-2 epimers) from the reaction of lactone **1b** and sulfoxide (*S*)-**2** (Scheme 3). The reductive deoxygenation process (Et$_3$SiH/TMSOTf) of **4b** gave rise to a 89:11 mixture of epimers, from which (*R*,*S*)-**5b** was isolated pure, in 70% yield. This result demonstrated that it was possible to obtain both enantiomers of the 2*H*-chroman moiety by simply changing the absolute configuration at sulfur of the starting sulfinyl lactol. Sulfoxide **5b** was then transformed into vinyl derivative (*R*)-**11**, after Pummerer reaction (86% yield) followed by Wittig reaction (78% yield) on the initially formed aldehyde (*R*)-**6**. Epoxide (*R*,*R*)-**14** was finally obtained from vinyl chroman (*R*)-**11** in a three-step stereoselective sequence. Thus, the Sharpless asymmetric dihydroxylation of the double bond of (*R*)-**11** with AD-mix-α gave rise, in 97% yield, to a 91:9 mixture of the corresponding diastereoisomeric diols, from which major (*R*,*R*)-**12**[12] could be isolated pure in 88% yield. Selective tosylation of the primary OH of **12** (TsCl/Py) afforded carbinol (*R*,*R*)-**13** (70% yield), which, after treatment with NaH in THF, led to epoxy chroman (*R*,*R*)-**14** in 93% yield. Thus, the stereoselective synthesis of the right fragment of (*S*,*R*,*R*,*R*)-Nebivolol, (*R*,*R*)-**14**, was achieved in seven steps and 23% overall yield, starting from known lactone **1b**.

The assembly of benzylamine (*S*,*R*)-**10** and epoxide (*R*,*R*)-**14** (Scheme 3), was simply effected by heating the mixture at reflux in EtOH to furnish, in 90% yield, *O*,*N*-dibenzylated Nebivolol (*S*,*R*,*R*,*R*)-**15** after epoxide aminolysis. Removal of the two benzyl protecting groups by hydrogenolysis followed by acidic treatment led to (*S*,*R*,*R*,*R*)-Nebivolol hydrochloride, with 69% yield for the two last reactions. The synthetic material proved identical with an authentic sample of racemic Nebivolol hydrochloride.[13] The value of the optical rotation,[14] $[\alpha]_D^{20}$ = +23.1 (c = 0.16, MeOH), corresponded to an optical purity >99%, measured by chiral HPLC. Thus, the (*S*,*R*,*R*,*R*)-enantiomer of the antihypertensive drug Nebivolol was prepared in nine steps for the longest linear sequence, with 11.5% overall yield.

Conclusions

The stereoselective reductive deoxygenation of 2-(*p*-tolylsulfinyl)methyl-2-chromanols was shown to provide an efficient entry into the challenging generation of the stereogenic center at C-2 of the 2*H*-chroman unit, thus expanding the known ability of homochiral sulfoxides in asymmetric synthesis. We have applied such methodology in a new stereoselective synthesis of (*S*,*R*,*R*,*R*)-Nebivolol by using both sulfinyl lactols (*R*)-**4b** and (*S*)-**4b** for the key construction of the left and right 2*H*-chroman moieties and by using the known 6-fluorochroman-2-one (**1b**) as the common starting material.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data, NMR spectra, and HPLC data.

Acknowledgments

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