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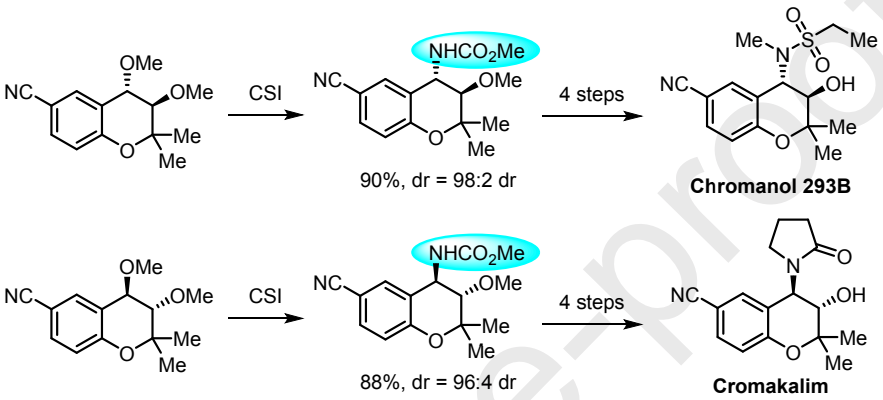

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ABSTRACT

Stereoselective benzylic amination reaction is important for their further application as pharmaceuticals and agrochemicals, and other chemical entities. Herein, we describe the diastereoselective amination of 1,2-*anti*-dialkoxychromane on chromane framework using chlorosulfonyl isocyanate. Notably, the utility of this protocol is highlighted by the total synthesis of chromanol 293B and cromakalim.

1. Introduction

Bicyclic molecules with amine functionality at the benzylic position are attractive from the perspectives of medicinal chemistry and drug discovery due to their remarkable therapeutic potential.[1] In particular, 4-amino-3-chromanols are privileged heterocyclic units that are found in a number of pharmaceuticals for the treatment of arrhythmia, hypertension, migraine, and cystic fibrosis (Figure 1).[2] Conventional route for 4-amino-3-chromanol scaffold is the asymmetric epoxidation of chromenes followed by regioselective ring-opening reaction using various amine nucleophiles. For example, chromanol 293B[2a] as a selective I_{Ks}-channel blocker and cromakalim[2b] as a selective K^+-channel opener were synthesized by the stereoselective amination of chiral expoxides for the formation of *anti*-amino alcohol moiety. Recently, our group has developed the regioselective and stereoselective amination of allylic and benzylic ethers using chlorosulfonyl isocyanate (CSI).[3] Notably, this method provided a facile route for the total synthesis of carbocyclic bioactive molecules such as (+)-sertraline,[4a] (+)-indatraline,[4b] and (+)-neplanocin A.[4c] In connection with our previous works on the stereoselective amination of chiral benzylic ethers using CSI, we herein report the stereoselective amination of 1,2-*anti*-dialkoxychromane on chromane framework and its application to the total synthesis of chromanol 293B and cromakalim.

2. Results and discussion

Our study started from the efficient construction of chiral 1,2-*anti*-dialkoxychromane as key precursors for the synthesis of chromanol 293B (Scheme 1). Initially, (2*H*)-chromene **1** was smoothly reacted with *m*-CPBA in the presence of (*R*,*R*)-Jacobsen catalyst and *N*-methylmorpholine-*N*-oxide (NMO) to afford the chiral epoxide **2** in 99% yield.[5] Regioselective hydrolysis of chiral epoxide **3** was subjected with $Ti(O^iPr)_4$ and H_2O to give 1,2-*anti*-diol adduct **3**, which was coupled with BnBr or MeI, furnishing 1,2-*anti*-dibenzyloxychromane **4** and 1,2-*anti*-dimethoxychromane **5**, respectively.

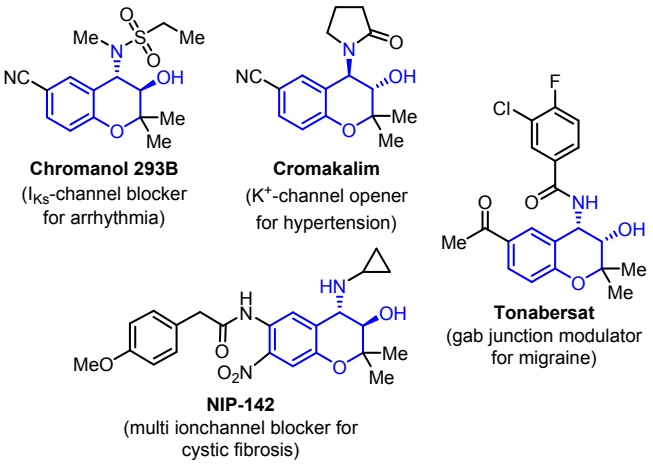

Figure 1. Structure of bioactive 4-amino-3-chromanol compounds.

Subsequently, the diastereoselectivity of the reaction of **4** with CSI was evaluated under various reaction conditions, and

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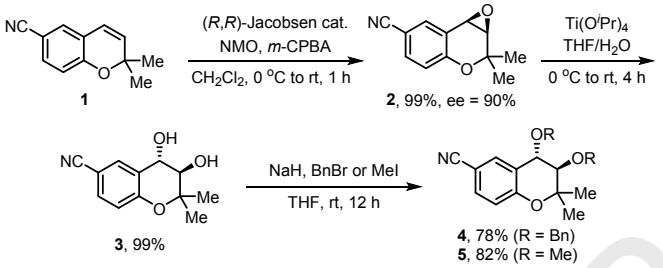
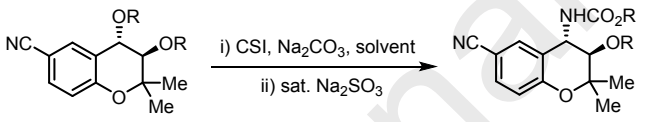
1,2-*anti*-dibenzyloxychromane **4** with CSI in CH_2Cl_2 solvent at 0 °C afforded benzyl carbamate **6** in 60% yield with 80:20 of diastereomeric ratio (Table 1, entry 1). Next, screening of solvents revealed that toluene is more effective than CH_2Cl_2, and *n*-hexane, but both chemical yield and diastereoselectivity still displayed unsatisfactory results (Table 1, entries 2–4). Thus, we further screened the reactivity and diastereoselectivity of the reaction of 1,2-*anti*-dimethoxychromane **5**. To our delight, a high yield (90%) and an excellent diastereoselectivity (98:2) on product **7** were observed in toluene solvent at –20 °C under otherwise identical reaction conditions (Table 1, entry 9). These results suggested that the methyl group is very crucial for the diastereoselectivity as well as yield. The observed stereochemistry can be rationalized by the competition between the S_Ni mechanism leading to retention of stereochemistry and the S_N1 mechanism inducing racemization through carbocation intermediate.[4a] Notably, a toluene solvent at low temperature might mainly affect the S_Ni mechanism through tight ion pair intermediate in a four-centered transition state. It has been reported that the reaction proceeds in the same S_Ni manner in the case of the benzylic alkoxy compound without homobenzylic alkoxy group under the above reaction conditions.[4a]



Scheme 1. Synthesis of chiral 1,2-*anti*-dibenzyl ethers.

Table 1. Optimization for the reaction of **4** and **5** with CSI[a]



Entry	Ethers	Solvent	Temp (°C)	Yield[b] (%)	dr[c]
1	**4**	CH_2Cl_2	0	60	80:20
2	**4**	*n*-hexane	0	20	67:33
3	**4**	toluene	rt	68	80:20
4	**4**	toluene	0	65	83:17
5	**4**	toluene	–20	53	83:17
6	**5**	CH_2Cl_2	0	85	94:6
7	**5**	toluene	rt	83	92:8
8	**5**	toluene	0	88	96:4
9	**5**	toluene	–20	90	98:2
10	**5**	toluene	–78	50	93:7

[a] *Reaction conditions*: i) Chlorosulfonyl isocyanate (20 equiv.), Na_2CO_3 (20 equiv.), solvent (0.15 M) at indicated temperature for 72 h; ii) saturated Na_2SO_3 solution at rt for 12 h.

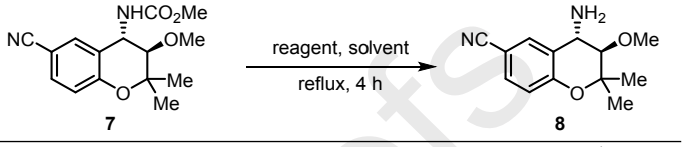
[b] Isolated yield by column chromatography.

[c] Diastereomeric ratio was determined by ^{1}H NMR analysis of a crude reaction mixture.

Next, the deprotection of a carbamate group of **7** was performed, as shown in Table 2. Basic hydrolysis conditions were found to be unsuccessful in this transformation (Table 2, entries 1 and 2). Surprisingly, TBAF could be readily used to **8** in a high yield (82%), as shown in entry 3.[6]

To complete the synthesis of chromanol 293B, compound **8** was reacted with $EtSO_2Cl$ to afford sulfonamide **9**, which was further methylated with MeI, generating **10** in 96% yield (Scheme 2). Finally, demethylation of **10** with BBr_3 gave chromanol 293B in 87% yield. The spectroscopic data and specific rotation value of synthesized chromanol 293B were in full agreement with the reported literatures.[2a]

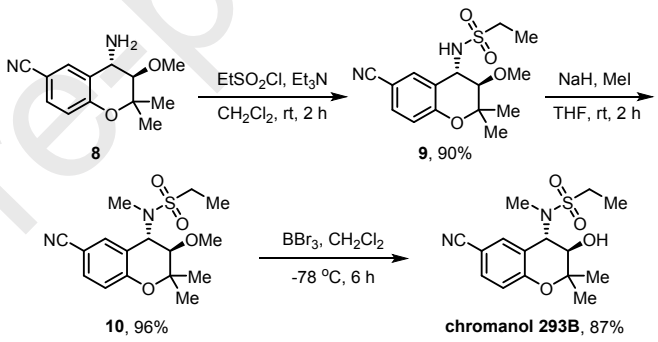
Table 2. Deprotection of carbamate group[a]



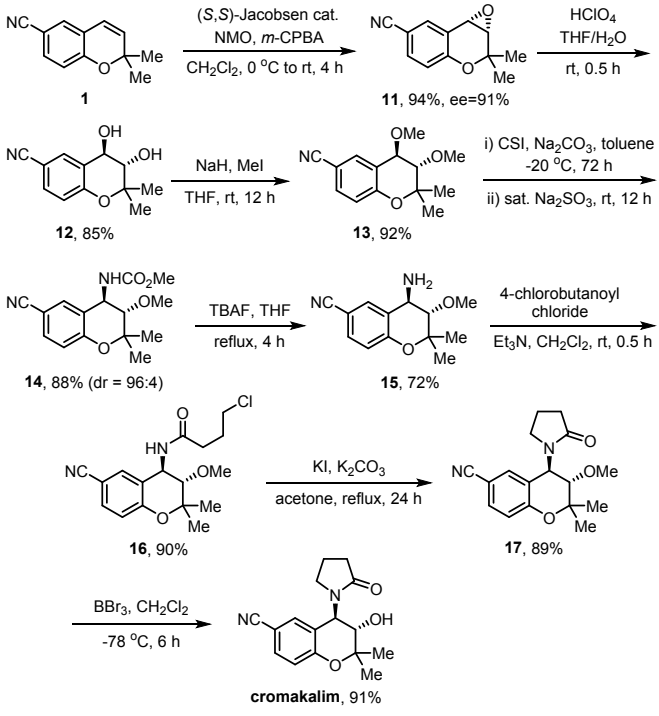
Entry	Reagent	Solvent	Yield[b] (%)
1	LiOH·H_2O	1,4-dioxane/H_2O (3:1)	12
2	LiOH·H_2O	EtOH/H_2O (95:5)	5
3	TBAF	THF	82

[a] *Reaction conditions*: reagent (5 equiv.), solvent (0.48 M) at reflux for 4 h.

[b] Isolated yield by column chromatography.



Scheme 2. Total synthesis of chromanol 293B



Scheme 3. Total synthesis of cromakalim.

Inspired by the above results, we further examined the total synthesis of cromakalim as an enantiomeric analogue of chromanol 293B (Scheme 3). Compound **1** was readily converted

into asymmetric epoxidation, $HClO_4$-mediated hydrolysis,[7] and *O*-methylation. The reaction of **13** with CSI under the optimized reaction conditions afforded 1,2-*anti*-amino alcohol adduct **14** in 88% yield with a diastereoselectivity of 96:4. Exchange of amido group was performed with a treatment of TBAF and subsequent 4-chlorobutanoyl chloride to furnish **16**, which underwent intramolecular cyclization to give **17** in 89% yield. Finally, cromakalim was formed in 91% by demethylation reaction using BBr_3.

3. Conclusion

In conclusion, we have described the diastereoselective amination of 1,2-*anti*-dialkoxychromane on chromane framework using chlorosulfonyl isocyanate. Notably, the reaction of 1,2-*anti*-dialkoxychromane with chlorosulfonyl isocyanate in toluene solvent afforded exclusively the *anti*-1,2-amino alcohols in high yield with excellent level of diastereoselectivities. These observations can be explained by S_Ni mechanism leading to retention of stereochemistry of methyl ethers at the benzylic position. Therefore, we believe that this synthetic strategy can be readily applied to the preparation of heterocyclic molecules with amine functionality at the benzylic position.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data (experimental and spectroscopic data for all compounds) associated with this article can be found in the online version, at http://

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References and notes

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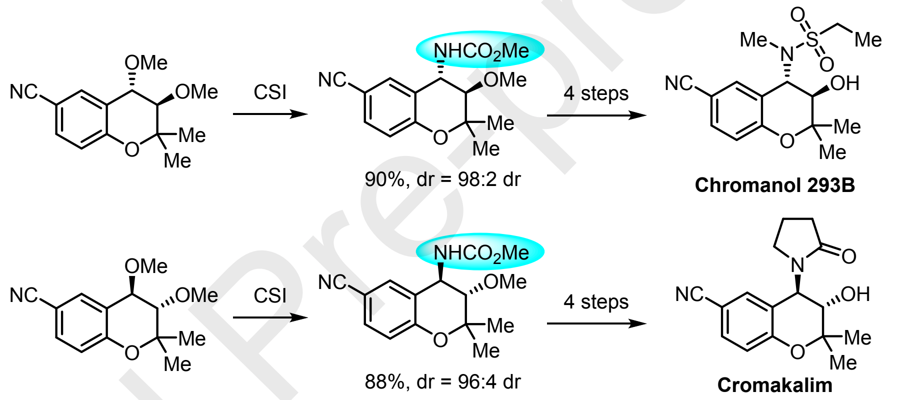

8.

Highlights

- Total synthesis of chromanol 293B and cromakalim
- Stereoselective amination of chiral benzylic ethers using chlorosulfonyl isocyanate
- S_Ni mechanism leading to retention of stereochemistry

9.