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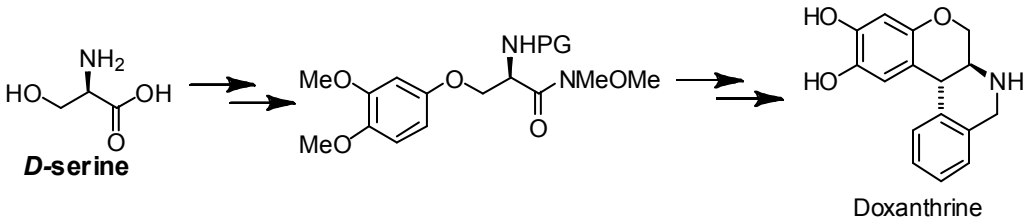

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Asymmetric synthesis towards doxanthrine, a dopamine D1 full agonist

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Asymmetric synthesis of *O*-methyl doxanthrine is accomplished with high diastereo- and enantioselectivity from β-aryloxyamino acid derived from *D*-serine.

Dopamine D1 full agonists are considered as potential therapeutic drugs for the treatment of Parkinson's disease.[1] Dihydrexidine **1** (Fig. 1) was introduced as the first high affinity bioavailable full dopamine D1 agonist with ten-fold higher affinity for D1-like receptors over D2 like receptors.[2] Initially it was examined for the treatment of Parkinson`s disease but due to intense hypotension upon intravenous administration the development work on this was halted. Recently an oxygen bioisostere of dihydrexidine, *trans*-2,3-dihydroxy-6a,7,8,12b-tetrahydro-6H-chromeno[3,4-c]isoquinoline namely doxanthrine **2** (Fig. 1), has been introduced. This showed >200 fold selectivity for D1-like receptors over D2 like receptors.[3] More importantly, these compounds are found to exhibit a high level of enantiospecificity

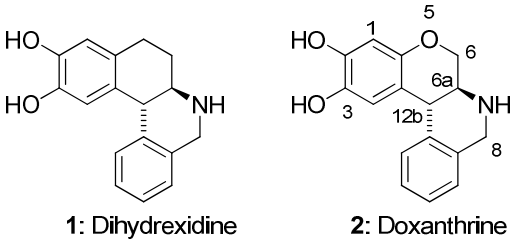
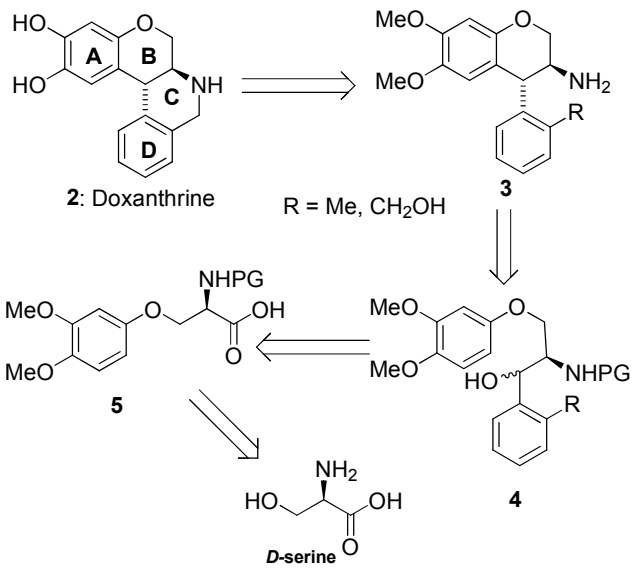


Figure 1 Structural difference in dihydrexidine **1** and doxanthrine **2**

in their interaction with the D1 receptor.[3b] Thus asymmetric synthesis of doxanthrine is in high demand. There are only two reports on synthesis of (±)-doxanthrine and both are by Nichols group,[3a,d] where non-racemic doxanthrine was obtained by resolution of *O*-protected doxanthrine via diastereomeric separation of amide of the later and *R*-(-)-*O*-methylmandeloyl chloride. First synthesis of (±)-**2** was done starting from 4-chromanon using Suzuki coupling, alkene nitration with tetranitromethane and chemoselective reduction of 4-aryl-3-nitro-2H-chromene as the key steps.[3a] Recently the same group reported an elegant and divergent approach for the racemic synthesis of **2** via 1,4-conjugate addition of *ortho*-lithiated aryloxazolines to 3-nitro-2H-chromene, which avoids the use of tetranitromethane and halogenated arenes.[3d] However, there is no report, to the best of our knowledge, on asymmetric synthesis of doxanthrine. Our continuous efforts[4,5] toward asymmetric synthesis of dopamine D1 agonists led us to investigate the synthesis of doxanthrine too. Here in, we report first asymmetric synthesis of *O*-methyl doxanthrine.

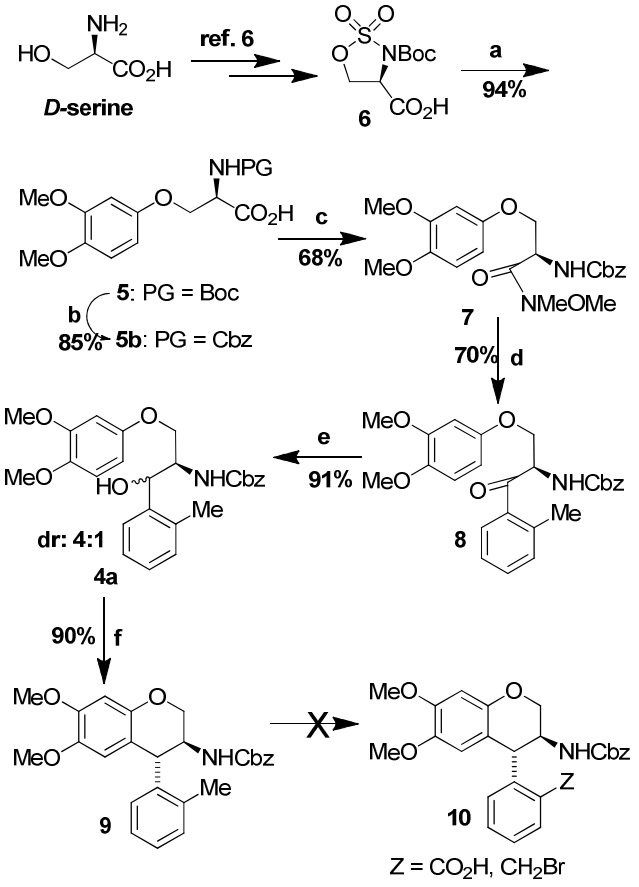
From our earlier study on hexahydrobenzophenanthrene compounds, it reveals that doxanthrine can be synthesized from aminochroman **3**, where tethered one-carbon *ortho*-substitution will be utilized for C-ring formation.[4,5] Aminochroman **3** can be obtained from 3-aryloxy-2-aminopropanol **4** via Friedel-Crafts type cyclization. In turn aminoalcohol **4** can be synthesized from β-aryloxyamino acid **5**, which can be obtained from *D*-serine (Scheme 1).



Scheme 1 Retrosynthetic approach of doxanthrine **2**

To begin the synthesis, *N*-Boc-β-aryloxyamino acid **5** was efficiently synthesized by regio-selective ring opening of sulfamidate carboxylic acid **6** derived from *D*-serine following our developed method (Scheme 2).[6] To avoid the difficulties in acid/Lewis acid mediated Friedel-Crafts cyclization,[4d] *N*-Boc protection of aryloxy acid **5** was changed to *N*-Cbz protected acid **5b**, which was transformed to Weinreb amide **7**. This amide **7** could be an important and advance precursor for the synthesis of a wide variety of chiral aminochromans and doxanthrine derivatives on reaction with different ArM (M = Li, MgX)

followed by Friedel-Crafts cyclization. Our earlier efforts towards syntheses of hexahydrobenzophenanthridine dopamine D1 agonists reveals that aminochroman must have a tethered *ortho*-substitution phenyl ring.[4d,5c] We planned for the reaction of the Weinreb amide **7** with *ortho*-lithiated toluene and also presumed that the tethered *ortho*-methyl group would be functionalized to construct the C-ring of doxanthrine. For this purpose, *ortho*-lithiated toluene generated from *ortho*-bromo toluene was reacted with the Weinreb amide **7** and produced ketone **8** in very good yield. $NaBH_4$ reduction of the ketone **8** afforded excellent yield of amino alcohol **4a** as a diastereomeric mixture (dr 4:1). We are delighted to report that amino alcohol **4a** smoothly underwent $Bi(OTf)_3$ catalyzed Friedel-Crafts reaction and afforded exclusively *trans*-*N*-Cbz protected amino chroman **9** (dr: 99:1) in good yield.[7] The *trans*-stereochemistry of aminochroman **9** was determined from the coupling constant of the bibenzylic proton (ArC*H*Ar′) appeared as a doublet at δ 4.03 (J = 8.4 Hz) and on correlation with *trans*-aminotetralin[4a,d] and with *cis*- and *trans*-tetrahydro chromenoisoquinolin.[3a] Functionalization of tethered



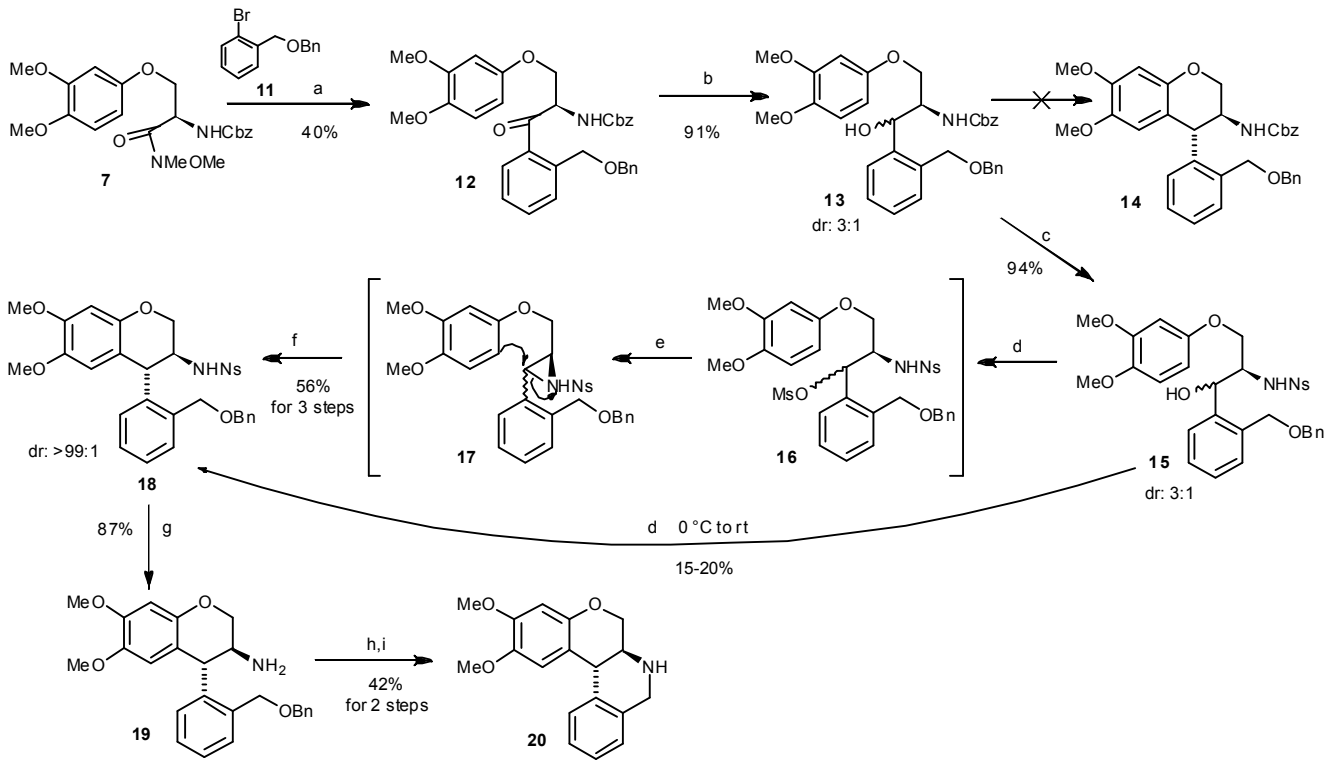
Reagents and conditions: a) 3,4-$(MeO)_2C_6H_3OH$ (0.8eq), NaH (3.2 equiv), THF, -15 to 0 °C; b) (i) TFA, CH_2Cl_2, 0 °C; (ii) Cbz-succinimide (1.0 equiv), Et_3N (4.0 equiv),), THF-H_2O (3:1), r.t., 12 h; c) NMe(OMe).HCl (1.5equiv), $ClCO_2Bu^i$ (1.2 equiv), NMM (2.2 equiv), CH_2Cl_2, -15 °C to rt, 5 h; d) 2-BrC_6H_4Me (3.2 equiv), *n*-BuLi (3.0 equiv), THF, -78 °C; e) $NaBH_4$ (1.0 equiv), EtOH; f) $Bi(OTf)_3$ (0.3eq), $MeNO_2$, 45 °C, 1 h.

Scheme 2 Synthesis of aminochroman **9**

ortho-methyl group and construction of C-ring can lead to doxanthrine moiety. However, our attempt to oxidize the methyl group of chroman **9** to carboxylic acid using $KMnO_4$ and SeO_2 was failed to give any desired acid and always led to a complex mixture of unidentified compounds. Peroxide as well as AIBN mediated benzylic bromonation with NBS was also unsuccessful, mostly provided (mono- and di-) bromoniation of electron-rich trioxyarene (ring A).

To avoid the difficulties in functionalization of *ortho*-methyl group, *O*-benzyl *ortho*-lithiated benzyl alcohol generated from 1-((benzyloxy)methyl)-2-bromobenzene **11** and *n*-BuLi was reacted with the Weinreb amid **7** and provided moderate yield of ketone **12** (Scheme 3). Reduction of ketone **12** with $NaBH_4$ gave diastereomeric mixture of alcohol **13** (dr: 3:1). Unlike alcohol **4**, $Bi(OTf)_3$ catalyzed Friedel-Crafts cyclization of alcohol **13** showed <10% of cyclised product chroman **14** in LC-MS analysis. A variety of acids and Lewis acids such as TFA, $MeSO_3H$, PTSA, PPA, $PhSO_3H$, $FeCl_3$, $Cu(OTf)_2$, $CuCl_2$ etc were tested for Friedel-Crafts cyclization of alcohol **13**. Most of the reactions showed a complex mixture of unidentified compounds, few cases did show desired mass in LC-MS, but as a minor product (5-10%). Poor yield of the Friedel-Crafts cyclization might be due to *ortho*-setric effect of tethered -CH_2OBn unit and its side reactions, indicated by the presence of mass (*m/z*) of debenzylated **13** in LC-MS of the above reaction mixtures.

Stereo- and regioselective aminoarylation towards synthesis of aminochromans could also be an alternative strategy.[5c] As a requirement, the *N*-Cbz amino alcohol **13** transformed to *N*-nosyl amino alcohol **15** via Pd/C hydrogenation and nosyl protection. Alcohol **15** on reaction with MsCl and Et_3N produced *O*-mesylated compound. Mesylate **16** was expected to undergo Friedel-Crafts cyclization providing desired aminochroman. When the mesylation reaction was continued at 0 °C and at rt, we did observe the formation of 15-20% of aminochroman **18** along with a mixture of unidentified compounds in LC-MS. However, prolonging the reaction at 0 °C and also at rt did not improve the yield of cyclised product rather it led to a complex mixture of unidentified compounds. This might be due to presence of three oxybenzyl units. It is thought that the mesylate **16** can be transformed to aziridine **17**, which would undergo aminoarylation (Friedel-Crafts cyclization) under mild condition. As the alcohol **15** is a mixture of diastereomers (dr: 3:1), the intermediate aziridine **17** is expected to be a mixture of diastereomers with same ratio (dr 3:1). It is well established in our previous study that *trans*-aziridine undergoes faster aminoarylation (Friedel-Crafts cyclization) via S_N2 type mechanism, where as *cis*-isomer is not reactive to S_N2 ring-opening and undergoes an S_N1 ring-opening mechanism followed by intramolecular Friedel–Crafts reaction to give the more stable *trans*-product.[8] Thus the *cis*-isomer needs little harsh conditions compare to *trans*-aziridine, but both provide exclusively *trans*-cyclized product. Accordingly the mesylate of **16**, without any purification, was treated with NaH and heated at 50 °C. We are delighted to report that it gave directly aminochroman **18** along with minor amount of an intermediate azidirine **17** as a non-separable mixture. The crude mixture in $ClCH_2CH_2Cl$ was treated with catalytic amount of $Cu(OTf)_2$ and it fully transformed to *trans*-amino chroman **18**



Reaction conditions and reagents: a) ArBr **11** (3.2 equiv), *n*-BuLi (3.0 equiv), THF, -78 °C; b) $NaBH_4$ (1.0 equiv), EtOH; c) (i) H_2 (1 atm), 10% Pd/C, MeOH, rt, 1 h; (ii) NsCl (1.1 equiv), Et_3N (3.0 equiv), CH_2Cl_2, 0 °C to rt; d) MsCl (1.7 equiv), Et_3N (3.0 equiv), CH_2Cl_2 e) NaH (1.0 equiv), THF, 50 °C, 4h; f) $Cu(OTf)_2$, $ClCH_2CH_2Cl$, 70 °C, 2h, 56%; g) 4-$MeOC_6H_4SH$ (3.0 equiv), K_2CO_3 (5.0 equiv), CH_3CN : DMSO (49:1), rt, 5 h; h) H_2 (1atm), 10% Pd/C, AcOH, rt, 8h; i) (i) HCl, 1,4-dioxane, reflux, 2 h; (ii) K_2CO_3 (40.0 equiv), 1,4-dioxane, 80 °C, 1 h.

Scheme 3 Asymmetric synthesis of *O*-methyl doxanthrine

with excellent diastereoselectivity (dr: >99:1) in 56% of yield over three steps from amino alcohol **15**. *trans*-Stereochemistry of aminochroman **18** was assigned from the coupling constant of ArC*H*Ar′ appeared as a doublet at δ 3.94 with coupling constant of 10.4 Hz, and comparing with that of *trans*-aminotetralin[4a,d] and with *cis*- and *trans*- tetrahydro chromenoisoquinolin.[3a] Thus confirms the absolute stereochemistry of compound **18** as 3*S*, 4*R*. *N*-Nosyl group of chroman **18** was removed on treatment with 4-methoxythiophenol and K_2CO_3 and afforded aminochroman **19** in 87% of yield. For the construction of C-ring, debenzylation of compound **19** by hydrogenation in the presence of Pd/C produced amino alcohol. Without any purification it was heated with HCl in dioxane followed by treatment with K_2CO_3 accomplished the synthesis of *O*-methyl doxanthrine **20** as an off-white solid in 42% of yield over two steps. Bibenzylic proton (ArC*H*Ar′) of compound **20** appeared as a doublet at δ 3.94 (J = 10.9 Hz), which was compared with literature data, where the ArC*H*Ar′ of methylenedioxy doxanthrine showed at δ 4.03 (d, J = 11.4) and the corresponding *cis*-isomer at δ 3.89 (d, J = 6.0 Hz).[3a] Thus it determines the *trans*-stereochemistry of *O*-methyl doxanthrine and in turn confirms the absolute stereochemistry of compound **20** as 6a*S*,12b*R*. Optical rotation of the *O*-methyl doxanthrine **20** was found to be +76.2 (c 1.0, CH_2Cl_2). Demethylation of compound **20** would accomplish the synthesis of doxanthrine **2**.

O-Methyl doxanthrine **20** was treated with BBr_3 under ice-cold conditions. It showed the formation of desired demethylated product along with a mixture of uncharacterized compounds, but the doxanthrine **2** could not be isolated as a pure form. HBr, HI and $AlCl_3$ instead of BBr_3 gave a complex mixture of identified compounds and there was no reaction with BCl_3 and Py.HCl under different reaction conditions.

In conclusion, we have achieved first asymmetric synthesis of *O*-methyl doxanthrine from β-aryloxy amino acid derived from *D*-serine using metaloarene addition to Weinreb amide and Friedel-Crafts cyclization as the key steps. Accomplishment to the total synthesis of doxanthrine via demethylation was not successful. It may need milder condition for the demethylation or instead of methoxy group some other stable, but easily removable phenolic protection group. The developed protocol provides an easy avenue for the asymmetric synthesis of a variety of aminochromans and tetrahydrochromeno-isoquinolines by varying the phenols in regioselective opening of serine sulfamidate and in metaloarenes addition to Weinreb amide.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [^{1}H- and ^{13}C NMR spectra and LC-MS for all the compounds **4-9, 12, 13, 15, 18-20**]. See DOI: 10.1039/b000000x/

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