Pergamon

Tetrahedron 55 (1999) 7555–7562

TETRAHEDRON

Asymmetric Synthesis of 4-Amino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyrans

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Received 26 February 1999; accepted 23 April 1999

Abstract: Highly enantioselective reduction of 3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-ones **3 a-e** by BH_3 was achieved in the presence of catalytic amounts of Corey's oxazaborolidine **4** to afford the corresponding 3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-ols **2a-e** in quantitative yields. These benzopyran-4-ols **2a-e** were converted into the chiral 4-amino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyrans **1a-e** by mesylation, followed by introduction of an azide group by tetra-n-butyl-ammonium azide, and finally by reduction of the azide **6** with triphenylphosphine under very mild conditions without loss of stereo information. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Reduction; Enantiocontrol; Amines; Benzopyrans

Numerous 4-amino-benzopyrans and related compounds have attracted considerable interest in the last decade as modulators of potassium channels influencing the activity of the heart and blood pressure[1]. Asymmetric synthesis of chiral 4-amino-benzopyrans are receiving increasing interest. In this work we present the stereoselective synthesis of 4-amino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyrans **1 a-e** via the 3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-ols **2 a-e**. Compounds **2a-e** are accessible in both *R* and *S* forms from 3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-ones **3** using Corey's oxazaborolidine-catalyzed enantioselective reduction[2].

3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-ones **3a-e** were prepared from *o*-hydroxy acetophenones in the usual way[3].

The stereoselective reduction of the ketones **3a-e** was the first subject of our investigations. We examined the effect of the temperature, solvent, and stoichiometry on the stereoselective reduction of 3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-ones **3 a-e** by Corey's oxazaborolidine and BH_3 to the corresponding alcohols **2a-e**. 6-fluoro-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-one **3a** was used as a model compound (Scheme 1). The results are summarized in Table 1.

The best results were obtained in toluene. THF as solvent led to a decrease of optical yield (Table 1, entry 7). We were able to lower the amount of catalyst to 0.05eq. without loss of enantioselectivity (Table 1, entry 5 and 6). This was independently of the Borane-complex used. The other enantiomer [(*S*)-6-fluoro-3,4-dihydro-2,2-dimethyl-2*H*-1-benzo-pyran-4-ol] was synthesized (95% ee) using the (*R*)-oxazaborolidine (Table 1, entry 8).

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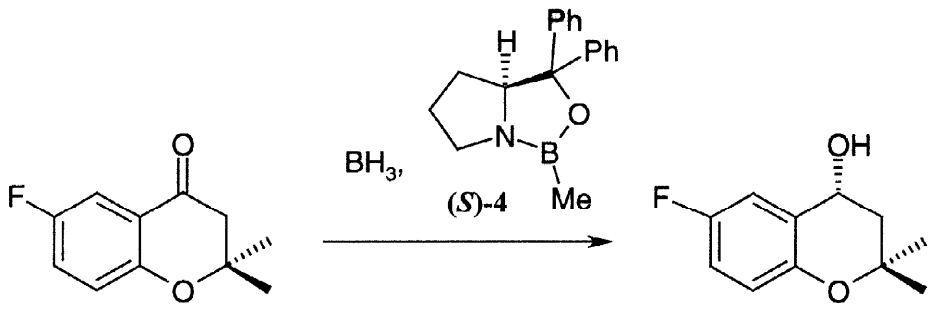
PII: S0040-4020(99)00376-2



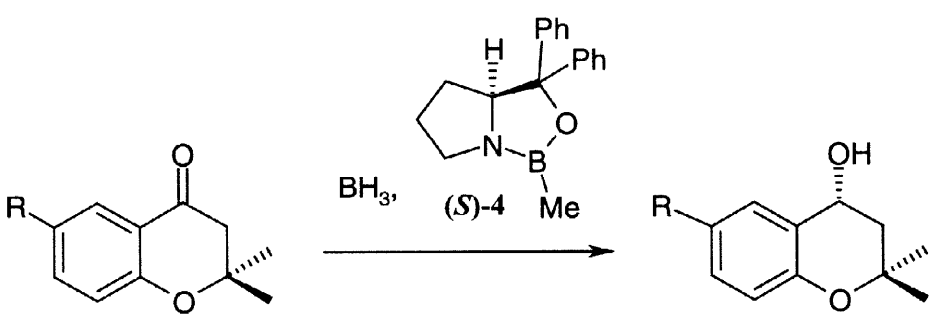
Scheme 1

Table 1. Enantioselective reduction of 6-fluoro-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4- one **3a** to 6-fluoro-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-ol **2a**

Entry	Ratio of reactants /ketone	Solvent	Temperature (°C)	Yield **2a** (%)[b]	(%ee)[a]
1	1eq (*S*)-**4** + 1eq BH_3-SMe_2	toluene	-20	>99	95 (*R*)
2	0.1eq (*S*)-**4** + 1eq BH_3-SMe_2	toluene	-20	>99	95 (*R*)
3	1eq (*S*)-**4**+ 1eq BH_3-SMe_2	toluene	20	>99	96 (*R*)
4	0.1eq (*S*)-**4**+ 1eq BH_3-SMe_2	toluene	20	>99	96 (*R*)
5	0.05eq (*S*)-**4**+ 1eq BH_3-SMe_2	toluene	20	>99	95 (*R*)
6	0.05eq (*S*)-**4**+ 1eq BH_3-THF	toluene	20	>99	96 (*R*)
7	0.05eq (*S*)-**4**+ 1eq BH_3-THF	THF	20	>99	91 (*R*)
8	0.1eq (*R*)-**4**+ 1eq BH_3-SMe_2	toluene	20	>99	95 (*S*)

[a] Enantiomeric excess was determined by chiral capillary GC, [b] isolated yield

Encouraged by the results with the fluoro derivative we extended our investigations to different 6-substituted 3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-ones **3b-e** (Scheme 2). The results are summarized in the following Table 2.



Scheme 2

Table 2. Enatioselective reduction of 6-substituted 3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-ones **3a-e** to 3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-ols **2a-e**

Entry	Alcohol	R	Yield (%)[d]	Optical Yield (%ee)[a]
1	**2a**	F	>99	96
2	**2b**	H	>99	94
3	**2c**	Me	96	94
4	**2d**	BnO	>99	94
5	**2e**	CN[b]	86	73
6	**2e**	CN[c]	76	57

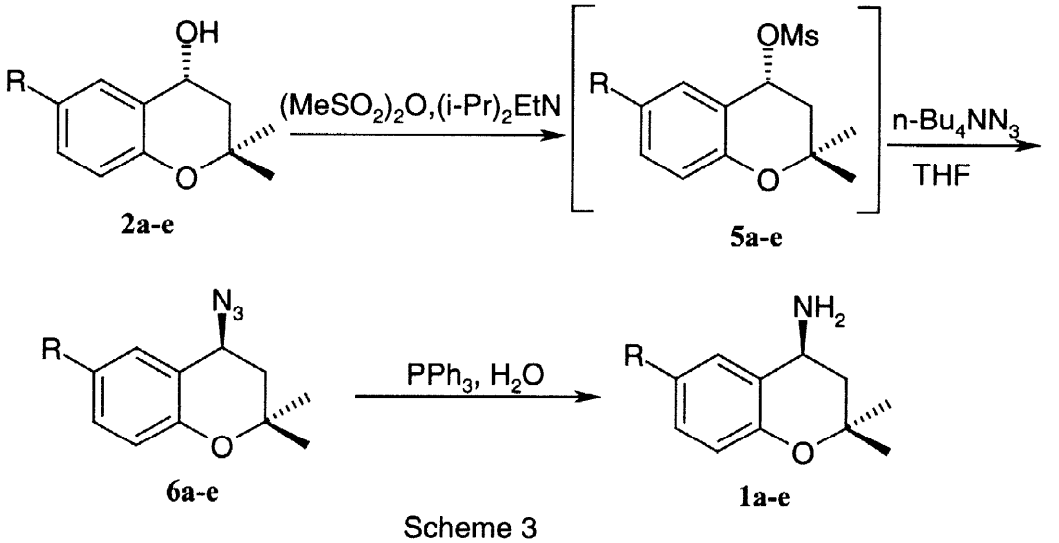
[a] Enantiomeric excess was determined by chiral capillary GC, [b] Initial reaction temperature -78°C → RT, [c] Initial reaction temperature RT, [d] Isolated yield

The good stereoselectivity found with the fluoro derivative could also be obtained with a variety of aromatic substituents (Table 2, entry 1-4). There is no difference in the stereochemical out-come with either small substituents (Table 2, entry 1-3) or bulkier ones (Table 2, entry 4). Also an electronic influence of the substituent was not seen, as fluoro, hydrogen, methyl and benzyloxy showed the same enantioselectivy. The only substituent, which did not give as high optical and chemical yields was the nitrile group. The nitrile group may interfere with the complexation necessary for the reduction of the keto group.

The conversion of the alcohols **2a-e** into the chiral amines **1a-e** was attempted under a variety of described conditions. We found that most conditions resulted in elimination to yield the corresponding chromene. Finally we found that treatment of the 3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-ols with methanesulphonicacid anhydride and diisopropylethylamine in tetrahydrofuran, at -60°C, gave the mesylates **5a-e**. Conversion of the intermediates **5a-e** to the 4-azido-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyrans **6a-e** could only be achieved with tetrabutyl ammonium azide in THF (Scheme 3)[6]. Reaction of the mesylates **5a-e** with sodium azide in different solvents such as DMSO or DMF produced exclusevely the coressponding chromene by elimination.

The 4-azido-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyrans **6a-e** was reduced via Staudinger reaction (triphenylphosphine/ water in tetrahydrofuran) into the 4-amino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyrans **1a-e** (Scheme 3, Table 3)[5]. Conversion **2a** to **1a** was achieved without loss of optical purity and good yield (Table 3, entry 1). The conversion of the other alcohols **2b-e** showed a slight loss in stereochemical information. The yields in these examples shown over three steps were moderate, but are unoptimized. Using methylenchloride as solvent has negative effects on chemical and optical yield (Table 3, entry 2).

(*S*)-4-Amino-6-fluoro-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran **(1a)** was converted into the hydrochloride **7**. The X-ray analysis of the 4-amino-6-fluoro-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran hydrochloride **(7)** proved the (*S*)-configuration of the major enantiomer[4].



Scheme 3

Table 3. Conversion of the 3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-ols **2a-e** into the chiral 4-amino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyrans **1a-e**

Entry	Amine	R	Yield (%)[a]	Optical yield (%ee)[b]
1	**1a**	F	80	94
2	**1a**	F[c]	60	59
3	**1b**	H	30	85
4	**1c**	Me	25	78
5	**1d**	BnO	35	74
6	**1e**	CN	30	90

[a] Isoltaed yield based on alcohol, [b] Enantiomeric excess was determined by chiral capillary GC, [c] Reaction was carried out in CH_2Cl_2

In conclusion, we describe a method for the preparation of enantiomerically enriched 4-amino-chromanes **1a-e** by stereoselective synthesis. One major point was the conversion of the stereoselectively synthesized 4-chromanols **2a-e** into the amino derivatives. This was only achieved by the incorporation of azide using tetrabutyl ammonium azide as reagent.

Experimental Section

Solvents and other reagents were used without further purification unless otherwise stated. Column chromatography was carried out on E. Merck silica gel 60 (0.04-0.063 mm). The NMR spectra were recorded on a Bruker AM 270. Chemical shifts are reported as δ values from an internal tetramethylsilane standard. Positive FAB mass spectra were obtained on a Kratos MS 902 in a 3-nitrobenzylic alcohol matrix using xenon as the target gas. DCI mass spectra were measured on a Kratos MS 80 RFA using isobutane as reagent gas. The chiral GC measurements were done with an Hewlett-Packard GC 5890 using hydrogen (1.0 bar) as eluent.

3,4-Dihydro-2,2-dimethyl-2H-1-benzopyran-4-ols 2a-e. General Procedure:

To a stirred solution of 0.5ml 2M borane-dimethyl sulfide/toluene (1mmol) and 0.1ml 1M (*S*)-2-methyl-CBS-oxazaborolidine/toluene **(4)** (0.1mmol) in toluene (10ml), was added dropwise at room temperature a solution of 3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-one **(3)** (1mmol) in 5ml toluene. After stirring for 3h the reaction was terminated by the addition of methanol. Ethyl acetate (100ml) was added and the mixture was washed with 2N aq. HCl (100ml), saturated. aq. $NaHCO_3$ (100ml). The organic layers were dried over Na_2SO_4, and concentrated to give the benzopyran-4-ol **2a-e**. Determination of the enantiomeric ratio was done with Chiraldex B-PH at an isocratic temperature of 150°C.

(R)-6-Fluoro-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-4-ol **(2a).** Yield: 100 %; mp 72°C; colorless crystals; $[\alpha]_D^{22}$ - 27.6 (c = 1, MeOH); enantiomeric excess (ee) 96%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.3 (s, 3H, CH_3), 1.4 (s, 3H, CH_3), 1.75 (bs, 1H, OH), 1.85 (dd, 1H, $J_{H\text{-}3a,\ H\text{-}3b}$ = 14,5 Hz, $J_{H\text{-}3a,\ H\text{-}4}$ = 9,5 Hz, H-3a), 2.19 (dd, 1H, $J_{H\text{-}3b,\ H\text{-}3a}$ = 14,5 Hz, $J_{H\text{-}3b,\ H\text{-}4}$ = 5,5 Hz, H-3b), 4.8 (dd, 1H, $J_{H\text{-}4,\ H\text{-}3a}$ = 9,5 Hz, $J_{H\text{-}4,\ H\text{-}3b}$ = 5,5 Hz, H-4), 6.7 (m, 1H, H-8), 6.85 (1H, H-7), 7.1 (m, 1H, H-5). - FAB-MS (pos.; NBA): m/z = 196.09070 calc. 196.08996 (100%).

(R)-3,4-Dihydro-2,2-dimethyl-2H-1-benzopyran-4-ol **(2b).** Yield: 100 %; mp 62°C; colorless crystals; $[\alpha]_D^{22}$ -26 (c = 1, MeOH); enantiomeric excess (ee) 94%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.3 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.7 (s, 1H, OH), 1.85 (dd, 1H, $J_{H\text{-}3a,\ H\text{-}3b}$ = 14,5 Hz, $J_{H\text{-}3a,\ H\text{-}4}$ = 9,5 Hz, H-3a), 2.19 (dd, 1H, $J_{H\text{-}3b,\ H\text{-}3a}$ = 14,5 Hz, $J_{H\text{-}3b,\ H\text{-}4}$ = 5,5 Hz, H-3b), 4.82 (dd, 1H, $J_{H\text{-}4,\ H\text{-}3a}$ = 9,5 Hz, $J_{H\text{-}4,\ H\text{-}3b}$ = 5,5 Hz, H-4), 6.8-7.4 (4m, 4H, H-5, H-6, H-7, H-8). - FAB-MS (pos.; NBA): m/z = 178.09896 calc. 178.09938 (100%).

(R)-6-Methyl-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-4-ol **(2c).** Yield: 96 %; amorphous; $[\alpha]_D^{22}$ -35 (c = 1, MeOH); enantiomeric excess (ee) 94%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.3 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.7 (bs, 1H, OH), 1.85 (dd, 1H, $J_{H\text{-}3a,\ H\text{-}3b}$ = 14,5 Hz, $J_{H\text{-}3a,\ H\text{-}4}$ = 9,5 Hz, H-3a), 2.18 (dd, 1H, $J_{H\text{-}3b,\ H\text{-}3a}$ = 14,5 Hz, $J_{H\text{-}3b,\ H\text{-}4}$ = 5,5 Hz, H-3b), 2.3 (s, 3H, 6-CH_3), 4.82 (dd, 1H, $J_{H\text{-}4,\ H\text{-}3a}$ = 9,5 Hz, $J_{H\text{-}4,\ H\text{-}3b}$ = 5,5 Hz, H-4), 6.7 (d, 1H, , $J_{H\text{-}8,\ H\text{-}7}$ = 9,5 Hz, H-8), 6.95 (dd, 1H, $J_{H\text{-}7,\ H\text{-}8}$ = 9,5 Hz, $J_{H\text{-}7,\ H\text{-}5}$ = 2,5 Hz, H-7), 7.1 (d, 1H, $J_{H\text{-}5,\ H\text{-}7}$ = 2,5 Hz, H-5). - FAB-MS (pos.; NBA): m/z = 192.11504 calc. 192.11503 (100%).

(R)-6-Benzyloxy-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-4-ol **(2d).** Yield: 100 %; mp 80°C; colorless crystals; $[\alpha]_D^{22}$ -29.5 (c = 1, MeOH); enantiomeric excess (ee) 94%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.3 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.6 (s, 1H, OH), 1.83 (dd, 1H, $J_{H\text{-}3a,\ H\text{-}3b}$ = 14,5 Hz, $J_{H\text{-}3a,\ H\text{-}4}$ = 9,5 Hz, H-3a), 2.18 (dd,

1H, $J_{H\text{-}3b,\ H\text{-}3a}$ = 14,5 Hz, $J_{H\text{-}3b,\ H\text{-}4}$ = 5,5 Hz, H-3b), 4.8 (dd, 1H, $J_{H\text{-}4,\ H\text{-}3a}$ = 9,5 Hz, $J_{H\text{-}4,\ H\text{-}3b}$ = 5,5 Hz, H-4), 5.0 (s, 2H, CH_2-benzyl), 6.7-7.4 (m, 8H, H-Ar). - FAB-MS (pos.; NBA): m/z = 284.14188 calc. 284.14124 (100%).

(R)-6-Cyano-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-4-ol **(2e).** Initial reaction temperature was -78°C instead of r.t.. Yield: 86 %; amorphous; $[\alpha]_D^{22}$ -36 (c = 1, MeOH); enantiomeric excess (ee) 73%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.3 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.85 (dd, 1H, $J_{H\text{-}3a,\ H\text{-}3b}$ = 14,5 Hz, $J_{H\text{-}3a,\ H\text{-}4}$ = 9,5 Hz, H-3a), 2.2 (dd, 1H, $J_{H\text{-}3b,\ H\text{-}3a}$ = 14,5 Hz, $J_{H\text{-}3b,\ H\text{-}4}$ = 5,5 Hz, H-3b), 4.82 (dd, 1H, $J_{H\text{-}4,\ H\text{-}3a}$ = 9,5 Hz, $J_{H\text{-}4,\ H\text{-}3b}$ = 5,5 Hz, H-4), 6.8 (d, 1H, $J_{H\text{-}8,\ H\text{-}7}$ = 9,5 Hz, H-8), 7.4 (dd, 1H, $J_{H\text{-}7,\ H\text{-}8}$ = 9,5 Hz, $J_{H\text{-}7,\ H\text{-}5}$ = 2,5 Hz, H-7), 7.8 (m, 1H, $J_{H\text{-}5,\ H\text{-}7}$ = 2,5 Hz, H-5). - FAB-MS (pos.; NBA): m/z = 204.10186 calc. 204.10245 ($M+H^+$,100%).

(S)-6-Fluoro-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-4-ol **(*S*-2a).** (*R*)-2-methyl-CBS-oxazaborolidine/toluene was used instead of (*S*)-2-methyl-CBS-oxazaborolidine/toluene; yield: 100 %; mp 64°C; colorless crystals; $[\alpha]_D^{22}$ + 27.5 (c = 1, MeOH); enantiomeric excess (ee) 95%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.3 (s, 3H, CH_3), 1.4 (s, 3H, CH_3), 1.75 (bs, 1H, OH), 1.85 (dd, 1H, $J_{H\text{-}3a,\ H\text{-}3b}$ = 14,5 Hz, $J_{H\text{-}3a,\ H\text{-}4}$ = 9,5 Hz, H-3a), 2.19 (dd, 1H, $J_{H\text{-}3b,\ H\text{-}3a}$ = 14,5 Hz, $J_{H\text{-}3b,\ H\text{-}4}$ = 5,5 Hz, H-3b), 4.8 (dd, 1H, $J_{H\text{-}4,\ H\text{-}3a}$ = 9,5 Hz, $J_{H\text{-}4,\ H\text{-}3b}$ = 5,5 Hz, H-4), 6.7 (m, 1H, H-8), 6.85 (1H, H-7), 7.1 (m, 1H, H-5). - FAB-MS (pos.; NBA): m/z = 196.09012 calc. 196.08996 (100%).

4-Amino-3,4-dihydro-2,2-dimethyl-2H-1-benzopyrans 1a-e. General Procedure:

To a solution of 3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-4-ol **2a-e** (1mmol) and diisopropylethylamine (1.5mmol; 0.27ml) in 5ml THF, was added dropwise a solution of methanesulfonicacid anhydride (2mmol; 348mg) in 5ml THF at -60°C. The mixture was allowed to warm up to -20°C. After stirring for 2h the mixture was cooled to -60°C and a solution of tetra-n-butylammonium azide (4mmol; 1.14g) in 5ml THF was added slowly. The reaction mixture was stirred overnight rising the reaction temperature to RT. The solvent was evaporated in vacuo. Methylene chloride was added and the resulting solution was filtered through silica gel, eluting with methylene chloride. The methylene chloride solution was evaporated in vacuo. The residue was dissolved in methanol (10ml), aq 1M sodium hydroxide (5ml) and methylene chloride (5ml). After stirring the mixture for 3h at RT the methylene chloride and the methanol were evaporated in vacuo. The residue was diluted with water (100ml) and extracted twice with methylene chloride (50ml). The organic layers were dried over Na_2SO_4, and the solvent evaporated in vacuo to obtain the azide **6**. The azide **6** was dissolved in THF (10ml). Triphenylphosphine (1.1mmol; 288.5mg) and water (0.5ml) was added and the mixture was stirred overnight at RT. The solvent was evaporated and the crude 4-amino-3,4-dihydro-2,2-dimethyl-2H-1-benzopyrans **1a-e** were purified by chromatography on silica gel (toluene/EtOAc, 8:1). Determination of the

enantiomeric ratio was done after derivatization of the amin with perfluoropropionicacid anhydrid on Chiraldex B-PH at an isocratic temperature of 120°C.

(S)-4-Amino-6-fluoro-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran **(1a).** Yield: 80 % (based on alcohol **2a**); amorphous; $[\alpha]_D^{22}$ + 19.25 (c = 2, MeOH); enantiomeric excess (ee) 94%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.63 (dd, 1H, $J_{H\text{-}3a,\ H\text{-}3b}$ = 14,5 Hz, $J_{H\text{-}3a,\ H\text{-}4}$ = 10,5 Hz, H-3a), 1.85 (s, 2H, NH_2), 2.19 (dd, 1H, $J_{H\text{-}3b,\ H\text{-}3a}$ = 14,5 Hz, $J_{H\text{-}3b,\ H\text{-}4}$ = 5,5 Hz, H-3b), 3.98 (dd, 1H, $J_{H\text{-}4,\ H\text{-}3a}$ = 10,5 Hz, $J_{H\text{-}4,\ H\text{-}3b}$ = 5,5 Hz, H-4), 6.7 (m, 1H, H-8), 6.85 (1H, H-7), 7.18 (m, 1H, H-5). - FAB-MS (pos.; NBA): m/z = 195.10632 calc. 195.10594 (100%).

(S)-4-Amino-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran **(1b).** Yield: 30 % (based on alcohol **2b**); amorphous; $[\alpha]_D^{22}$ + 15.15 (c = 2, MeOH); enantiomeric excess (ee) 85%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.3 (s, 3H, CH_3), 1.4 (s, 3H, CH_3), 1.64 (dd, 1H, $J_{H\text{-}3a,\ H\text{-}3b}$ = 14,5 Hz, $J_{H\text{-}3a,\ H\text{-}4}$ = 10,5 Hz, H-3a), 1.95 (bs, 2H, NH_2), 2.1 (dd, 1H, $J_{H\text{-}3b,\ H\text{-}3a}$ = 14,5 Hz, $J_{H\text{-}3b,\ H\text{-}4}$ = 5,5 Hz, H-3b), 4.0 (dd, 1H, $J_{H\text{-}4,\ H\text{-}3a}$ = 10,5 Hz, $J_{H\text{-}4,\ H\text{-}3b}$ = 5,5 Hz, H-4), 6.78-7.43 (4m, 4H, H-5, H-6, H-7, H-8). - FAB-MS (pos.; NBA): m/z = 176.10846 calc. 176.10754 ($M\text{-}H^+$, 100%).

(S)-4-Amino-6-methyl-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran **(1c).** Yield: 25 % (based on alcohol **2c**); amorphous; $[\alpha]_D^{22}$ + 46.13 (c = 1, MeOH); enantiomeric excess (ee) 78%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.3 (s, 3H, CH_3), 1.4 (s, 3H, CH_3), 1.65 (dd, 1H, $J_{H\text{-}3a,\ H\text{-}3b}$ = 14,5 Hz, $J_{H\text{-}3a,\ H\text{-}4}$ = 10,5 Hz, H-3a), 2.05 (dd, 1H, $J_{H\text{-}3b,\ H\text{-}3a}$ = 14,5 Hz, $J_{H\text{-}3b,\ H\text{-}4}$ = 5,5 Hz, H-3b), 2.2 (bs, 2H, NH_2), 4.0 (dd, 1H, $J_{H\text{-}4,\ H\text{-}3a}$ = 10,5 Hz, $J_{H\text{-}4,\ H\text{-}3b}$ = 5,5 Hz, H-4), 6.7 (d, 1H, , $J_{H\text{-}8,\ H\text{-}7}$ = 9,5 Hz, H-8), 6.95 (dd, 1H, $J_{H\text{-}7,\ H\text{-}8}$ = 9,5 Hz, $J_{H\text{-}7,\ H\text{-}5}$ = 2,5 Hz, H-7), 7.2 (d, 1H, $J_{H\text{-}5,\ H\text{-}7}$ = 2,5 Hz, H-5). - FAB-MS (pos.; NBA): m/z = 190.12344 calc. 190.12319 ($M\text{-}H^+$, 100%).

(S)-4-Amino-6-benzyloxy-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran **(1d).** Yield: 35 % (based on alcohol **2d**); amorphous; $[\alpha]_D^{22}$ + 23.97 (c = 2, MeOH); enantiomeric excess (ee) 74%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (s, 3H, CH_3), 1.4 (s, 3H, CH_3), 1.63 (dd, 1H, $J_{H\text{-}3a,\ H\text{-}3b}$ = 14,5 Hz, $J_{H\text{-}3a,\ H\text{-}4}$ = 10,5 Hz, H-3a), 1.9 (bs, 2H, NH_2), 2.1 (dd, 1H, $J_{H\text{-}3b,\ H\text{-}3a}$ = 14,5 Hz, $J_{H\text{-}3b,\ H\text{-}4}$ = 5,5 Hz, H-3b), 4.0 (dd, 1H, $J_{H\text{-}4,\ H\text{-}3a}$ = 10,5 Hz, $J_{H\text{-}4,\ H\text{-}3b}$ = 5,5 Hz, H-4), 5.0 (s, 2H, CH_2-benzyl), 6.7-7.42 (m, 8H, H-Ar). - FAB-MS (pos.; NBA): m/z = 283.15806 calc. 283.15723 (100%).

(S)-4-Amino-6-cyano-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran **(1e).** Yield: 30 % (based on alcohol **2e**); amorphous; $[\alpha]_D^{22}$ + 91.15 (c = 2, MeOH); enantiomeric excess (ee) 90%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25

(s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.6-1.8 (m, 3H, NH_2, H-3a), 2.1 (dd, 1H, $J_{H\text{-}3b,\ H\text{-}3a}$ = 14,5 Hz, $J_{H\text{-}3b,\ H\text{-}4}$ = 5,5 Hz, H-3b), 4.0 (dd, 1H, $J_{H\text{-}4,\ H\text{-}3a}$ = 10,5 Hz, $J_{H\text{-}4,\ H\text{-}3b}$ = 5,5 Hz, H-4), 6.8 (d, 1H, $J_{H\text{-}8,\ H\text{-}7}$ = 9,5 Hz, H-8), 7.4 (dd, 1H, $J_{H\text{-}7,\ H\text{-}8}$ = 9,5 Hz, $J_{H\text{-}7,\ H\text{-}5}$ = 2,5 Hz, H-7), 7.82 (m, H-5). - FAB-MS (pos.; NBA): m/z = 203.11798 calc. 203.11844 ($M+H^+$, 100%).

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