Tetrahedron: *Asymmetry* 22 (2011) 1542–1547

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Novel stereoselective synthesis of 2,3-dihydro-1*H*-benzo[*f*]chromen-3-amine derivatives through a one-pot three-component reaction

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ARTICLE INFO

Article history:
Received 18 July 2011
Accepted 9 August 2011
Available online 15 September 2011

ABSTRACT

A short and stereoselective novel synthesis of benzo[*f*]chromen-3-amine derivatives in good yields, through a three-component aromatic Betti type reaction under solvent free conditions is reported. The spontaneous reaction occurs in the absence of acid catalysts. The use of chiral 1-phenylethylamine or α,β-unsaturated aldehydes allowed us to prepare enantiopure benzo[*f*]chromen-3-amine derivatives with good stereoselectivity. Conformational analysis compared with the ^{1}H NMR data of the products obtained, allowed us to the determine the absolute configuration, which was also confirmed by X-ray analysis.

1. Introduction

New methods for the stereoselective aminoalkylation of electron-rich aromatic compounds are of great interest. The Mannich reaction is one of the most important multi-component reactions of aminoalkylation in organic synthesis.[1–3] At the beginning of the 20th century, Betti reported the synthesis of 1-aminoalkyl-2-naphthols, a reaction that is very important because a C–C bond is formed under mild experimental conditions.[4–9] Although a variety of methods for the aminoalkylation of electron-rich aromatic compounds are available,[10,11] new, mild and direct approaches that are stereoselective enough to allow the preparation of single diastereoisomers are of increasing interest. We have found that a straightforward and stereoselective synthesis of aminoalkyl naphthols can be performed by a Betti reaction using enantiopure amines and other inexpensive reagents.[12,13] The aminoalkyl naphthols obtained with this methodology, in typically good yield and high enantiomeric purity, are effective catalysts in the enantioselective alkylation of aldehydes.[12–17] With the aim of exploring the synthetic possibilities of this reaction we have studied a condensation that makes use of α,β-unsaturated aldehydes.

In the literature, there are examples in which the 2-naphthol promotes conjugate addition to α,β-unsaturated electrophilic molecules such as unsaturated ketoesters or dicyanoolefins.[18,19] Some synthetic approaches reported in the literature were found to be most closely related to the present investigation.[20–23] The reaction of 2-naphthol with *trans*-cinnamaldehyde, affords 1-phenyl-1*H*-naphtho[2,1-*b*]pyran as the main product rather than 1-phenyl-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyran-3-ol. This can be used to obtain amino derivatives by reaction with amines in the absence of a catalyst.[24]

However, to the best of our knowledge, the previously reported synthetic procedures were generally complicated and did not give satisfactory yields, also we were unable to find a report on the asymmetric synthesis of 2,3-dihydro-1*H*-benzo[*f*]chromen-3-amine derivatives.

2. Results and discussion

Herein we report the results of the diastereoselective synthesis of 2,3-dihydro-1*H*-benzo[*f*]chromen-3-amine **3a**–**g** through a three-component Betti type one-pot reaction from β-naphthol, α,β-unsaturated aldehydes **1** and amines **2** under solvent free conditions (Table 1). On the basis of our previous experience and of literature reports,[16,17] only electron-rich naphthols and phenols can take part in this spontaneous reaction to afford the desired adduct without the use of an acid catalyst. We limited our research to 2-naphthol for practical reasons.

The reaction was performed at 70 °C for 12–72 h under solvent free conditions and under an argon atmosphere. The reaction mixture showed an increasing viscosity over time while the water produced by the condensation was separated. The use of Lewis acid catalysts ($LiClO_4$, $BF_3{\cdot}OEt_2$) did not give better results. The major stereoisomers **3** can be obtained in enantiomerically pure form, by flash chromatography and are stable for a long time with no epimerisation being observed.

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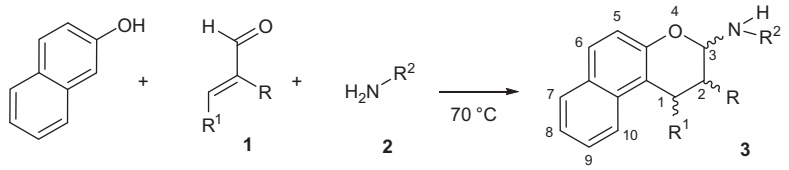
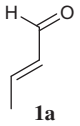
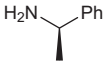
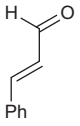
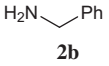
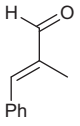
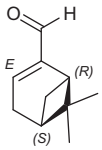
doi:10.1016/j.tetasy.2011.08.007

Table 1
Stereoselective synthesis of 2,3-dihydro-1*H*-benzo[*f*]chromen-3-amine **3a**–**g** through a three-component Betti type reaction



	1	2	1,3-*trans*-**3**, yield[a] (%)	dr[b]
1	 **1a**	 **2a**	(1*S*,3*R*)-**3a**, 47	—
2	 **1b**	 **2b**	(*R**,*R**)-**3b**, 42	76/24
3	**1b**	**2a**	(1*R*,3*R*)-**3c**, 43	81/19
4	**1b**	**2a**	(1*S*,3*S*)-**3c**, 10	
5	 **1c**	**2b**	(1*R**,2*S**,3*R**)-**3d**, 51	82/18
6	**1c**	**2a**	(1*R*,2*S*,3*R*)-**3e**, 51	84/16
7	 **1d**	**2b**	(1*R*,2*R*,3*S*)-**3f**, 48	68/23
8	**1d**	**2a**	(1*R*,2*R*,3*S*)-**3g**, 42	59/41

[a] Yield of the pure isolated diastereomers.
[b] The dr values (1,3-*trans*/*cis*-**3b**,**d**,**f** and enantiopure 1,3-*trans*-**3c**,**e**,**g** major stereoisomers) were determined by ^{1}H NMR of the crude reaction mixture.

3. Configuration attribution

Conformational analysis of the ^{1}H NMR data of the products obtained, allowed us to determine the relative and absolute configurations, which were confirmed by X-ray analysis. With the help of molecular modelling the most stable conformations of all possible stereoisomers were found. Conformational analysis on all of the possible diastereomers of products **3**, through a preliminary conformational search, was carried out using a systematic search with the MMFF molecular mechanics force field. All of the conformations within a 3 kcal/mol window were then optimized using DFT at the B3LYP/6-31G* level.[25] On the basis of ^3J values measured by ^{1}H NMR (reported in Table 2 for protons H-1, H-2 and H-3 and the dihedral angle for these protons) as observed on the stable conformations, it was possible to assign the configuration of benzochromenes **3**, isolated as the main products and reported in Table 2.

For all the examples in Table 1, the 1,3-*trans*-**3a**–**g** diastereomers reported, are thermodynamically more stable and prevail quantitatively over the 1,3-*cis*-**3b**,**d**,**f** or 1,3-*trans*-**3a**,**c**,**e**,**g** diastereomers. In enantiopure compounds 1,3-*trans*-**3a**,**c**,**e**, the prevailing stereoisomer had an (*R*)-configuration at the C-3 carbon atom. The cyclization of intermediate **C** takes place onto the *Re*-face of the imine carbon atom, leading to the formation of the thermodynamically more stable benzochromenes **3** (Scheme 1). However, for benzochromenes **3f**,**g**, the cyclization of the respective intermediate **C** preferentially takes place on the *Si*-face of the imine carbon atom, due to the asymmetric induction from the (1*R*,5*S*)-6.6-dimethylbicyclo[3.1.1]heptane system of the starting (1*R*)-(−)-myrtenal **1d** to form enantiopure (1*R*,2*R*,3*S*)-**3f** and (1*R*,2*R*,3*S*)-**3g** as the main products. The cyclization occurs from the *exo* side of the bicyclic system, as it is sterically less cumbersome.

The (1*R*,2*S*,3*R*)-configuration was determined by ^{1}H NMR for the major stereoisomer of the benzochromene **3e** and confirmed by X-ray analysis[26] (see Fig. 1). The molecular modelling structure calculated for (1*R*,2*S*,3*R*)-**3e** was almost identical to that of the X-ray structure. The dihedral angles (78.13° and 58.61°) measured for the solid compound in the crystalline form, were in agreement with the estimated values made on the basis of the ^3J coupling constants measured by ^{1}H NMR spectroscopy in $CDCl_3$ solution (2.9 and 1.8 Hz, respectively).

A mechanistic hypothesis is depicted in Scheme 1. Mixing aldehydes **1** and amines **2** caused an immediate exothermic reaction to take place, which afforded the corresponding imine, as evidenced by the formation of drops of water in the reaction flask.[27,28] After the addition of naphthol, it was assumed that an aldimonium type complex **A** was formed through protonation of the imine nitrogen by 2-naphthol, in which the reactivity of both the electrophilic imonium carbon atom and the nucleophilic carbon atom at the 1-position of 2-naphthol are activated.

Table 2
The ^{1}H NMR chemical shift, the multiplicity and ^{3}J (in brackets) are reported

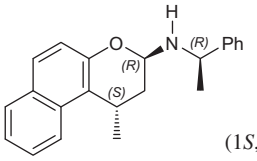
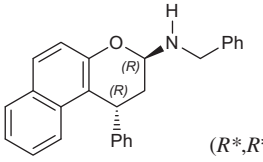
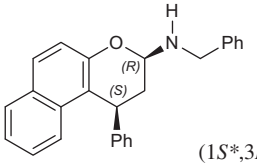
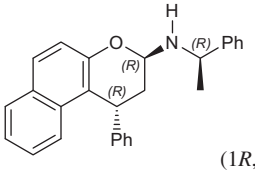
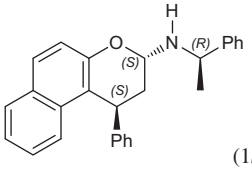
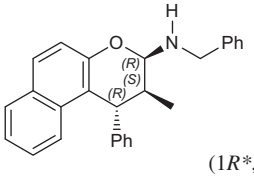
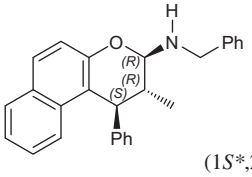
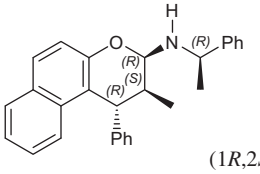
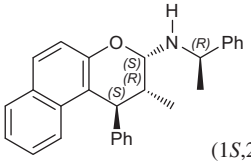
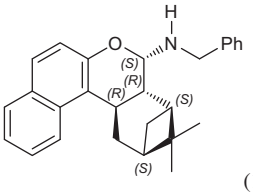
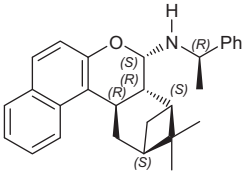
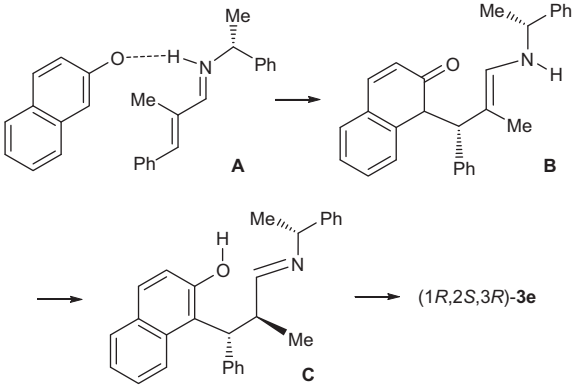
	3[a]	H-1	H-2	H-3
1	 (1*S*,3*R*)-**3a**	4.64, m	3.48–3.71, m	4.75, dd (6.6, 1.5)
2	 (*R**,*R**)-**3b**	4.16, dd (4.2, 3.5)	2.02, ddd (15.3, 4.8, 2.1) 2.50, ddd (15.3, 10.9, 3.5)	4.65, dd (10.9, 2.0)
3	 (1*S**,3*R**)-**3b**	3.78, dd (9.2, 3.5)	2.02, dt (15.3, 3.2) 2.35 dt (15.3, 9.8)	4.87, dd (10.2, 3.1)
4	 (1*R*,3*R*)-**3c**	4.72, dd (4.8, 3.7)	2.10–2.40, m	4.66, dd (8.4, 3.6)
5	 (1*S*,3*S*)-**3c**	4.72, dd (3.7, 2.0)	2.22, ddd (13.2, 10.0, 4.2) 2.31, dt (13.2, 2.0)	4.98, dd (9.7, 2.0)
6	 (1*R**,2*S**,3*R**)-**3d**	4.43, d (2.2)	2.40, qt (7.0, 2.1)	4.85, d (2.0)
7	 (1*S**,2*R**,3*R**)-**3d**	4.25, d (6.8)	2.34, sext (7.0)	4.58, d (7.0)
8	 (1*R*,2*S*,3*R*)-**3e**	4.28, d (2.9)	2.16, qdd (7.0, 2.9, 1.8)	4.54, d (1.8)
9	 (1*S*,2*R*,3*S*)-**3e**	4.45, d (2.0)	2.39, qt (7.0, 1.7)	5.01, d (1.6)

Table 2 (*continued*)

	3[a]	H-1	H-2	H-3
10	 (1*R*,2*R*,3*S*)-**3f**	3.78, td (10.1, 1.8)	–	4.77, d (0.8)
11	 (1*R*,2*R*,3*S*)-**3g**	3.88, t (9.7)	–	4.28, d (2.9)

[a] The configurations was determined on the basis of the ^{3}J values observed for the H-1, H-2, H-3 protons of the isolated 2,3-dihydro-1*H*-benzo[*f*]chromen-3-amine **3**.



Scheme 1. The mechanistic hypothesis for the Mannich type diastereoselective aminoalkylation.

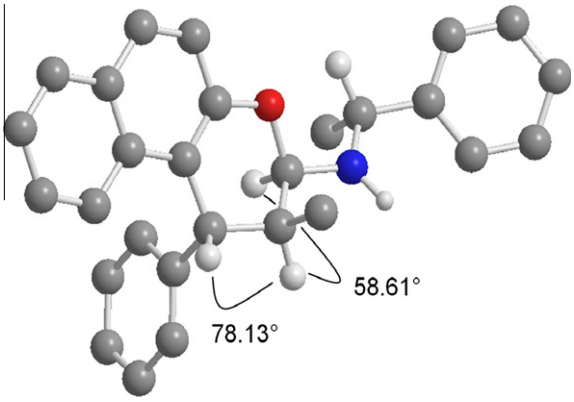


Figure 1. X-ray structure of the benzo[*f*]chromen-3-amine (1*R*,2*S*,3*R*)-**3e** major diastereomer.

Next, the conjugate addition of 2-naphthol to the β-carbon atom of the α,β-unsaturated imonium ion took place.[18,19] When (*R*)-1-phenylethylamine was used, the immonium ion intermediate derived from α-methyl-*trans*-cinnamaldehyde, took the shape as shown in Figure 2 where the LUMO molecular orbital is more developed on the imonium- and β-carbon atoms. The chiral group on the nitrogen atom induces the stereoselective attack of the *Re*-face of the β-naphthol onto the *Si*-face of the β-carbon atom of the

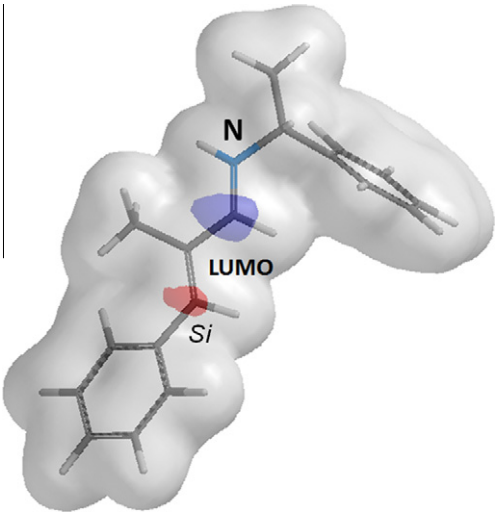


Figure 2. A more stable conformation for the aldimonium ion **A** resulting from the condensation of α-methyl-*trans*-cinnamaldehyde **1c** and (*R*)-1-phenylethylamine **2a**, with the LUMO, more developed on the imonium- and β-carbon atoms and exceeding the isodensity surface.

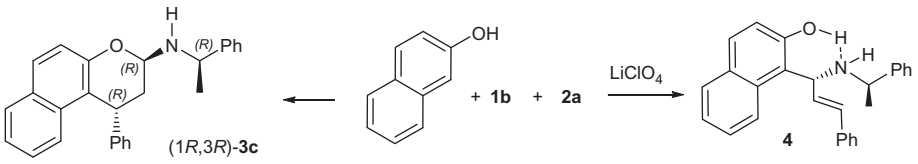
α,β-unsaturated imonium ion, which is sterically less hindered, to form the intermediate **B**. This intermediate isomerizes to the thermodinamically more stable intermediate **C**, which then cyclizes to (1*R*,2*S*,3*R*)-**3e**.

In the literature there has already been reported an example in which *trans*-cinnamaldehyde is placed to react with 2-naphthol and (*R*)-1-phenylethylamine (mediated by lithium perchlorate) to form compound **4** (Scheme 2). That is the result of a Mannich reaction on the imino carbon atom (a description of the spectroscopic data of this compound is not reported).[29]

This is in contrast to our results, where the formation of compound **3c**, resulting from conjugate addition and then successive cyclization, was observed.

4. Conclusion

In conclusion, we have reported on a short and stereoselective synthesis of benzo[*f*]chromen-3-amine derivatives obtained in good yields, through a three-component aromatic Betti type reaction under solvent free conditions. The use of chiral 1-phenylethylamine or α,β-unsaturated aldehydes [(1*R*)-(−)-myrtenal] allows to



Scheme 2.

prepare enantiopure benzo[*f*]chromen-3-amine derivatives, with good stereoselectivity. Conformational analysis compared with ^{1}H NMR data of the products obtained, allows the attribution of the absolute configuration, also confirmed by X-ray analysis.

5. Experimental

5.1. General methods

^{1}H and ^{13}C NMR spectra were recorded at 200 or 400 MHz and 50 or 100 MHz, respectively. Chemical shifts are given in ppm downfield from Me_4Si in a $CDCl_3$ solution. Coupling constants are given in Hertz. IR spectra were recorded using a FTIR apparatus. Optical rotations were measured in a 1 dm cell at 20 °C. All melting points are uncorrected. In cases where only the major diastereomer was obtained in its pure form, the ^{1}H NMR signals for the minor diastereomer were deduced from the spectra of the crude reaction mixture or from enriched chromatographic fractions.

5.2. General procedure for the preparation of 2,3-dihydro-1*H*-benzo[*f*]chromen-3-amine derivatives 3a–g

Amine **2a**–**d** (5.0 mmol) was added to aldehyde **1a**–**d** (5.0 mmol) at 0 °C and the resultant mixture stirred for 30 min. The oil was dissolved in DCM and the resulting solution dried ($MgSO_4$). After filtration, the solvent was removed under reduced pressure. To the resulting oil was added 2-naphthol (0.72 g, 5.0 mmol) and the mixture was stirred and left to stand, under argon, under solvent free conditions at 70 °C for the time required (12–72 h, monitored by TLC). Analogous yields were obtained when a mixture of 2-naphthol (0.72 g, 5.0 mmol), aldehyde **1a**–**d** (5.0 mmol) and amine **2a**–**d** (5.0 mmol) was stirred and left to stand, under argon, under solvent free conditions at 70 °C for the time required (12–72 h, without the elimination of condensation water). Aminoalkylnaphthols **3a**–**g** were separated and purified by flash chromatography (on silica gel, hexane–ethyl acetate, 95:5 to 70:30, v/v) directly from the reaction mixture, without any work-up.

5.2.1. (1*S*,3*R*)-2,3-Dihydro-1-methyl-*N*-((*R*)-1-phenylethyl)-1*H*-benzo[f]chromen-3-amine (1*S*,3*R*)-3a

Oil, $[\alpha]_D^{20} = +54.5$ (*c* 2.41, $CHCl_3$); IR (neat) ν_{max} 3338, 1622, 1599, 1397, 1139 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.32 (d, 3H, *J* = 7.0 Hz), 1.48 (d, 3H, *J* = 6.2 Hz), 2.10 (br s, 1H), 3.48–3.71 (m, 2H, H-2), 4.56 (q, 1H, *J* = 6.2 Hz), 4.64 (m, 1H, H-1), 4.75 (dd, 1H, *J* = 6.6, 1.5 Hz, H-3), 6.98–8.02 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 27.1, 35.8, 52.8, 53.3, 80.9, 119.3, 122.3, 123.0, 123.4, 126.4, 126.9, 127.2, 127.3, 128.6, 128.8, 129.2, 129.3, 132.1, 132.4. Anal. Calcd for $C_{22}H_{23}NO$ (317.42): C, 83.24; H, 7.30; N, 4.41. Found: C, 83.46; H, 7.49; N, 4.22.

5.2.1.1. (*R**,*R**)-N-benzyl-2,3-dihydro-1-phenyl-1*H*-benzo[*f*]-chromen-3-amine (*R**,*R**)-3b.

Oil; IR (neat) ν_{max} 3227, 3061, 2923, 2848, 1621, 1453, 1269 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.74 (br s, 1H), 2.02 (ddd, 1H, *J* = 15.3, 4.8, 2.1 Hz, H-2a), 2.50 (ddd, 1H, *J* = 15.3, 10.9, 3.5 Hz, H-2b), 3.55 (d, 1H, *J* = 12.8 Hz), 3.82 (d, 1H, *J* = 12.8 Hz), 4.16 (dd, 1H, *J* = 4.2, 3.5 Hz, H-1), 4.65 (dd, 1H, *J* = 10.9, 2.0 Hz, H-3), 7.00–7.85 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.2, 52.1, 55.3, 61.2, 115.1, 120.0, 120.6, 126.4, 126.9, 127.3, 127.6, 128.3, 128.7, 128.8, 129.0, 129.1, 129.2, 132.2, 138.7, 139.9, 142.1, 156.9. Anal. Calcd for $C_{26}H_{23}NO$ (365.47): C, 85.45; H, 6.34; N, 3.83. Found: C, 85.53; H, 6.49; N, 3.56.

5.2.1.2. (1*S**,3*R**)-*N*-Benzyl-2,3-dihydro-1-phenyl-1*H*-benzo[*f*]chromen-3-amine (1*S**,3*R**)-3b.

^{1}H NMR (200 MHz, $CDCl_3$) δ 1.74 (br s, 1H), 2.02 (dt, 1H, *J* = 15.3, 3.2 Hz, H-2a), 2.35 (dt, 1H, *J* = 15.3, 9.8 Hz, H-2b), 3.54 (d, 1H, *J* = 12.9 Hz), 3.65 (d, 1H, *J* = 12.9 Hz), 3.78 (dd, 1H, *J* = 9.2, 3.5 Hz, H-1), 4.87 (dd, 1H, *J* = 10.2, 3.1 Hz, H-3), 7.00–7.85 (m, 16H).

5.2.2. (1*R*,3*R*)-2,3-Dihydro-1-phenyl-*N*-((*R*)-1-phenylethyl)-1*H*-benzo[*f*]chromen-3-amine (1*R*,3*R*)-3c

Oil; $[\alpha]_D^{20} = +178.0$ (*c* 0.31, $CHCl_3$); IR (neat) ν_{max} 3225, 2921, 1621, 1498, 1134, 841 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (d, 3H, *J* = 6.4 Hz), 2.05 (br s, 1H), 2.10–2.40 (m, 2H, H-2a,b), 4.56 (q, 1H, *J* = 6.4 Hz), 4.66 (dd, 1H, *J* = 8.4, 3.6 Hz, H-3), 4.72 (dd, 1H, *J* = 4.8, 3.7 Hz, H-1), 6.96–7.80 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 37.6, 38.9, 53.6, 81.4, 119.4, 123.1, 123.4, 126.3, 126.6, 126.9, 127.0, 127.3, 127.6, 128.2, 128.5, 128.7, 128.8, 129.2, 129.3, 132.9, 138.6, 145.8. Anal. Calcd for $C_{27}H_{25}NO$ (379.49): C, 85.45; H, 6.64; N, 3.69. Found: C, 85.68; H, 6.51; N, 3.47.

5.2.3. (1*S*,3*S*)-2,3-Dihydro-1-phenyl-*N*-((*R*)-1-phenylethyl)-1*H*-benzo[*f*]chromen-3-amine (1*S*,3*S*)-3c

Crystals mp 158–160 (hexane); $[\alpha]_D^{20} = -67.8$ (*c* 0.42, $CHCl_3$); IR (neat) ν_{max} 3203, 2925, 1618, 1498, 1133, 837 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (d, 3H, *J* = 6.4 Hz), 2.15 (br s, 1H), 2.22 (ddd, 1H, *J* = 13.2, 10.0, 4.2 Hz, H-2a), 2.31 (dt, 1H, *J* = 13.2, 2.0 Hz, H-2b), 4.49 (q, 1H, *J* = 6.4 Hz), 4.72 (dd, 1H, *J* = 3.7, 2.0 Hz, H-1), 4.98 (dd, 1H, *J* = 9.7, 2.0 Hz, H-3), 6.96–7.80 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 37.3, 39.0, 52.9, 81.0, 113.9, 119.4, 123.2, 123.5, 126.6, 126.7, 126.9, 127.3, 128.5, 128.6, 128.7, 128.8, 129.3, 129.5, 133.0, 146.0, 146.8, 153.5. Anal. Calcd for $C_{27}H_{25}NO$ (379.49): C, 85.45; H, 6.64; N, 3.69. Found: C, 85.62; H, 6.54; N, 3.52.

5.2.3.1. (1*R**,2*S**,3*R**)-*N*-Benzyl-2,3-dihydro-2-methyl-1-phenyl-1*H*-benzo[*f*]chromen-3-amine (1*R**,2*S**,3*R**)-3d.

Crystals mp 183–186 °C (hexane); IR (Nujol) ν_{max} 1598, 1508, 1229, 1215 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.14 (d, 3H, *J* = 7.0 Hz), 2.20 (br s, 1H), 2.40 (qt, 1H, *J* = 7.0, 2.1 Hz), 3.90 (d, 1H, *J* = 12.8 Hz), 4.35 (d, 1H, *J* = 12.8 Hz), 4.43 (d, 1H, *J* = 2.2 Hz), 4.85 (d, 1H, *J* = 2.0 Hz), 7.05–7.83 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 39.6, 47.4, 50.5, 85.1, 112.8, 119.1, 119.6, 123.3, 123.6, 124.1, 126.6, 126.61, 128.50, 128.55, 128.66, 128.70, 128.7, 129.3, 129.8, 133.5, 146.0, 152.8. Anal. Calcd for $C_{27}H_{25}NO$ (379.494): C, 85.45; H, 6.64; N, 3.69. Found: C, 85.63; H, 6.79; N, 3.46.

5.2.3.2. (1*S**,2*R**,3*R**)-*N*-Benzyl-2,3-dihydro-2-methyl-1-phenyl-1*H*-benzo[*f*]chromen-3-amine (1*S**,2*R**,3*R**)-3d.

^{1}H NMR (200 MHz, $CDCl_3$) δ 1.28 (d, 3H, *J* = 7.0 Hz), 2.20 (br s, 1H), 2.34 (sext, 1H, *J* = 7.0 Hz), 4.03 (d, 1H, *J* = 13.5 Hz), 4.19 (d, 1H,

J = 13.5 Hz), 4.25 (d, 1H, *J* = 6.8 Hz), 4. 58 (d, 1H, *J* = 7.0 Hz), 7.05–7.83 (m, 16H).

5.2.3.3. (1*R*,2*S*,3*R*)-2,3-Dihydro-2-methyl-1-phenyl-*N*-((*R*)-1-phenylethyl)-1*H*-benzo[*f*]chromen-3-amine (1*R*,2*S*,3*R*)-3e. Crystals mp 158–160 °C (hexane); $[\alpha]_D^{20} = +126.4$ (*c* 0.41, $CHCl_3$); IR (Nujol) ν_{max} 1610, 1623, 1599, 851, 831 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.11 (d, 3H, *J* = 7.0 Hz), 1.37 (d, 3H, *J* = 6.6 Hz), 2.16 (qdd, 1H, *J* = 7.0, 2.9, 1.8 Hz, H-2), 2.20 (br s, 1H), 4.28 (d, 1H, *J* = 2.9 Hz, H-1), 4.37 (q, 1H, *J* = 6.6 Hz), 4.54 (d, 1H, *J* = 1.8 Hz, H-3), 6.80–7.80 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 25.3, 39.9, 47.3, 54.0, 83.3, 113.2, 119.2, 123.1, 123.6, 126.3, 126.4, 126.9, 128.3, 128.4, 128.5, 128.6, 129.1, 130.3, 133.5, 144.3, 145.3, 150.1, 153.1. Anal. Calcd for $C_{28}H_{27}NO$ (393.520): C, 85.46; H, 6.92; N, 3.56. Found: C, 85.59; H, 7.09; N, 3.42.

5.2.3.4. (1*S*,2*R*,3*S*)-2,3-Dihydro-2-methyl-1-phenyl-*N*-((*R*)-1-phenylethyl)-1*H*-benzo[*f*]chromen-3-amine (1*S*,2*R*,3*S*)-3e. ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (d, 3H, *J* = 6.8 Hz), 1.33 (d, 3H, *J* = 6.4 Hz), 2.25 (br s, 1H), 2.39 (qt, 1H, *J* = 7.0, 1.7 Hz, H-2), 4.43 (q, 1H, *J* = 6.4 Hz), 4.45 (d, 1H, *J* = 2.0 Hz, H-1), 5.01 (d, 1H, *J* = 1.6 Hz, H-3), 6.80–7.80 (m, 16H).

5.2.4. (1*R*,2*R*,3*S*)-3f

Crystals mp 121–124 °C (hexane); $[\alpha]_D^{20} = +31.2$ (*c* 1.4, $CHCl_3$); IR (Nujol) ν_{max} 3059, 1758, 1686, 1257, 1226 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.03 (s, 3H), 1.28 (s, 3H), 1.40–1.49 (m, 1H), 1.77–1.99 (m, 2H), 2.06–2.50 (m, 3H), 2.78 (d, 2H, *J* = 9.9 Hz), 3.72 (d, 1H, *J* = 13.2 Hz), 3.78 (td, 1H, *J* = 10.1, 1.8 Hz), 3.80 (d, 1H, *J* = 13.2 Hz); 4.77 (d, 1H, *J* = 0.8 Hz), 7.90–7.10 (m, 11H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.8, 22.4, 25.0, 26.2, 35.9, 39.6, 40.4, 40.5, 47.0, 48.8, 90.8, 120.8, 123.6, 123.8, 126.2, 127.2 127.6, 128.4, 128.5, 128.6, 129.1, 130.7, 132.1, 139.6, 147.7. Anal. Calcd for $C_{27}H_{29}NO$ (383.53): C, 84.55; H, 7.62; N, 3.65. Found: C, 84.34; H, 7.76; N, 3.48.

5.2.5. (1*R*,2*R*,3*S*)-3g

Oil; $[\alpha]_D^{20} = +38.3$ (*c* 1.6, $CHCl_3$); IR (liquid film) ν_{max} 3361, 3258, 1622, 1542, 969 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 3H), 1.37 (s, 3H), 1.51 (d, 3H, *J* = 6.6 Hz), 1.81–1.97 (m, 2H), 2.16–2.39 (m, 3H), 2.46 (br s, 1H), 2.64–2.86 (m, 2H), 3.88 (t, 1H, *J* = 9.7 Hz), 4.28 (d, 1H, *J* = 2.9 Hz), 4.57 (q, 1H, *J* = 6.6 Hz), 7.02–7.90 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 22.3, 25.3, 26.1, 26.3, 27.6, 36.4, 39.6, 40.5, 40.7, 53.8, 89.4, 119.3, 123.4, 123.9, 126.1, 126.2, 126.8, 127.3, 127.5, 128.6, 129.0, 130.5, 132.3, 145.0, 152.7. Anal. Calcd for $C_{28}H_{31}NO$ (397.55): C, 84.59; H, 7.86; N, 3.52. Found: C, 84.43; H, 7.66; N, 3.34.

Acknowledgements

The financial support of this research by a grant from the University of Camerino and from MIUR is gratefully acknowledged.

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