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Synthesis of desymmetrized, enantiopure dihydro-methano-diarylazocines: topologically interesting eyeteaser molecules☆

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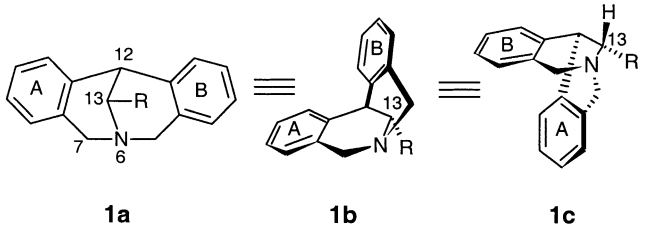
Abstract—Friedel–Crafts double cyclizations of enantiopure *N*,*N*-dibenzyl α-amino aldehydes derived from the corresponding α-amino acids leads to topologically unique, bridged tetrahydroisoquinolines in one step.

1. Introduction

The dihydro-methano-diarylazocines represented by the generic structure **1** (7,12-dihydro-5*H*-6,12-methano-dibenzo-[*c*,*f*]-azocine) are a class of topologically interesting and readily available bridged tetrahydroisoquinolines[1] (Fig. 1). They are potentially versatile intermediates for the synthesis of alkaloids such as argemonine,[2] thalidine,[3] and related structural types, particularly as phenolic ethers.[4] The pharmacological properties of dibenzoazocines in the central nervous system have been the subject of interest for some time.[5]

Viewed in a 3-dimensional perspective, dihydro-methano-dibenzoazocines portray interesting topology, whereby the aryl rings adopt a mutually orthogonal relationship comprising two tetrahydroisoquinoline motifs with a common nitrogen atom as shown in Fig. 1. The introduction of an appendage at C-13 as illustrated in the perspective structures



1a **1b** **1c**

7,12-Dihydro-5H-6,12-methano-dibenzo[c,f]azocine

Figure 1. Perspective drawings of dihydro-methano-dibenzo-azocines: **1b**, R=pseudoaxial; **1c**, R=pseudoequatorial.

1a–c, effectively desymmetrizes the original motif **1** (R=H), thus adding a functional vector with the potential for diversification. Should the aryl rings A and B be differentiated by introduction of substituents, then the spatial orientation of the R substituent will depend on which of the tetrahydroisoquinolines A or B is taken as reference point. To the best of our knowledge, a general synthesis of enantiopure C-13 substituted dihydro-methano-dibenzoazocines has not been previously reported.

Traditionally, the synthesis of symmetrical dihydro-methano-dibenzoazocines has relied on the intramolecular acid-catalyzed carbocyclization of *N*,*N*-dibenzyl amino-acetaldehyde dimethylacetals.[6] The first chiral non-racemic dihydro-5*H*-6,12-methano-dibenzo[*c*,*f*]azocine harboring different ether groups on each aryl ring was obtained by optical resolution.[7]

2. Results and discussion

In a recent paper,[8] we described a method for the synthesis of enantiopure 3- and 3,4-disubstituted tetrahydroisoquinoline-2-ones via the intramolecular Friedel–Crafts condensation of β-aryl isocyanates. We now show that *N*,*N*-dibenzyl α-aminoalkyl aldehydes **3**, readily available from the corresponding α-amino acids,[9] undergo facile double intramolecular Friedel–Crafts cyclizations leading to the corresponding desymmetrized dihydro-methano-dibenzo-azocines bearing a chiral appendage at C-13 as shown in Scheme 1.[10] In the presence of $AlCl_3$ as Lewis acid, and conducting the reaction at −45°C in CH_2Cl_2, the initial cyclization product corresponds to the tetrahydroisoquinoline **4** which can be isolated as a mixture of diastereoisomers or as a single isomer. Subsequent reaction at 0°C, or a direct double cyclization from **3** generates the corresponding dihydro-methano-dibenzoazocine. In this manner, a series of C-13 branched enantiopure analogs **5–9** were prepared in good to excellent yields.

☆ *Supporting information available*: ^1H and ^{13}C NMR spectra for the synthesis of **5**, **7–9**, **11–13**, **17**, **20–22** can be obtained from the author.

Keywords: Friedel–Crafts; amino acid; tetrahydroisoquinoline.

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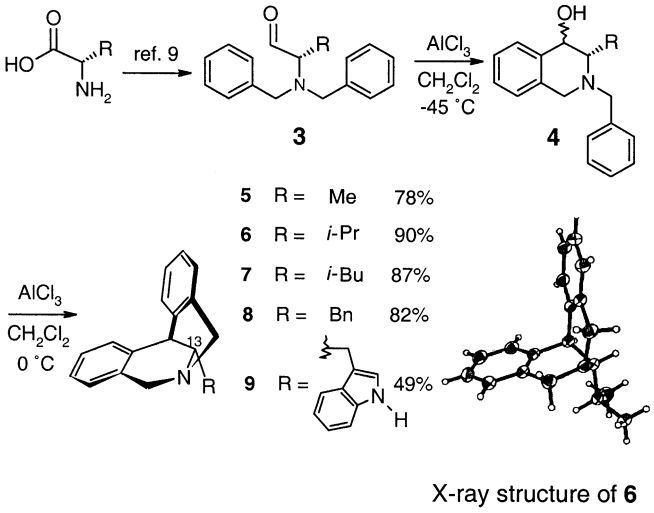
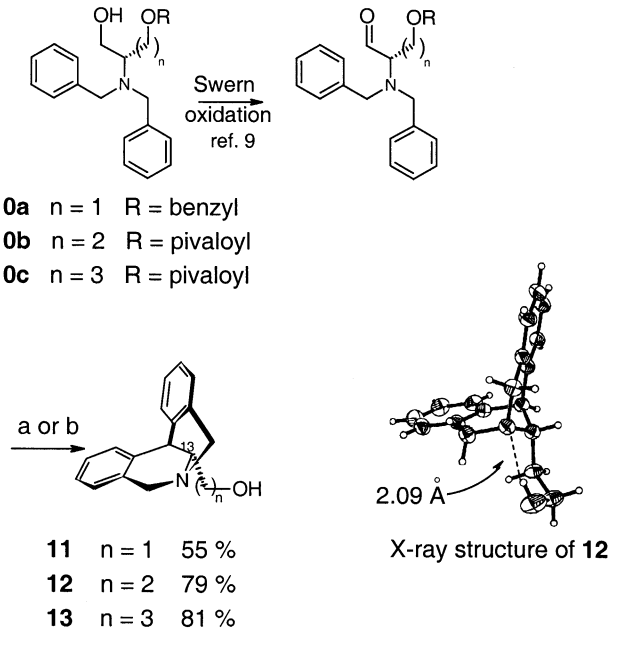


Scheme 1. X-Ray structure of **6**.

We were also successful in the synthesis of 13-ω-hydroxymethyl and related dihydro-methano-dibenzoazocines from the corresponding α-amino alcohol derivatives **10a–c**. The presence of the hydroxymethyl group necessitated a protective group that would be compatible with the conditions of the Friedel–Crafts reaction. To this end, the use of $AlCl_3$ and a pivaloate ester proved to be highly effective.[8,11] Alternatively, a benzyl ether could also be used, and cleaved during the reaction without affecting the double cyclization. Scheme 2 shows the general synthesis of C-13 ω-hydroxymethyl, ω-hydroxyethyl, and ω-hydroxypropyl dihydro-methano-dibenzoazocines **11–13**, prepared individually from L-serine, L-homoserine and L-bis-homoserine, respectively. Detailed ^{19}F NMR analysis of the Mosher esters derived from **12** as a representative alcohol, and comparison with the corresponding racemic ester, ascertained the enantiopurity of the original product. The X-ray crystal structure[12] of **12** is shown in Scheme 2, where the orthogonality of the 6,12-phenyl ring with regard to the plane of the tetrahydroisoquinoline unit can be seen as in the case of the C-13 isopropyl analog **7** (Scheme 1). An added structural element in the case of **12** reveals an intramolecular H-bond between the hydroxyethyl group and the tertiary nitrogen (2.09 Å).



Scheme 2. (a) Where R=pivaloyl: (i) $AlCl_3$ 3 equiv., CH_2Cl_2, rt, 12 h; and (ii) DIBAL-H 2.5 equiv., toluene, −78°C, 1 h. (b) Where R=benzyl: $AlCl_3$ 10 equiv., CH_2Cl_2, rt, 12 h.

A cursory look at the perspective structures **1a–c** is misleading, since the rigid topology does not truly reflect the enantiotopic pathways of ring closure from the initially formed *N*-benzyl 4-hydroxy tetrahydroisoquinoline. Fig. 2 portrays two possible *ortho*-cyclization modes arising from the attack of rapidly equilibrating *N*-benzyl invertomers. The putative compound **14** representing the '*anti*' benzyl group relative to R, effectively cyclizes to produce the 13*S* isomer shown as **1b**. If the '*syn*' invertomer **15** were to cyclize, it would also lead to the same 13*S* product **1b** (Fig. 2). This topological eyeteaser can be better appreciated by numbering (or color-coding) the phenyl rings. Based on this tenet, one would intuitively conclude that the steric encumberment in the '*syn*' isomer **15** should favor the closure of the '*anti*' isomer **14** with an unimpeded trajectory of attack on the incipient benzylic carbocation. Although such a trend may indeed be operative, it is not possible to validate it in the case of the unsubstituted dihydro-methano-dibenzoazocines, because both pathways of cyclization lead to the same product.

In order to resolve this issue, we carried out the ring closure from a dissymmetric *N*-benzyl tetrahydroisoquinoline with a 'small' (methyl), and a 'large' (isopropyl) side-chain (Scheme 3). Reaction of *N*-3,5-dimethoxybenzyl-*N'*-3,5-difluorobenzyl 2-amino L-propionaldehyde **16** with $AlCl_3$ at −45°C led, as expected to the corresponding 3,5-dimethoxy *N'*-3,5-difluorobenzyl tetrahydroisoquinoline **17**. Upon ring-closure at rt, we obtained a mixture of inseparable products assumed to consist of **20** and **21** (R=Me) in a ratio of 2:1 as estimated by NMR. However, when the bulk of the C-13 side-chain was increased to an isopropyl group as in **18**, the quasi-exclusive product arising from the

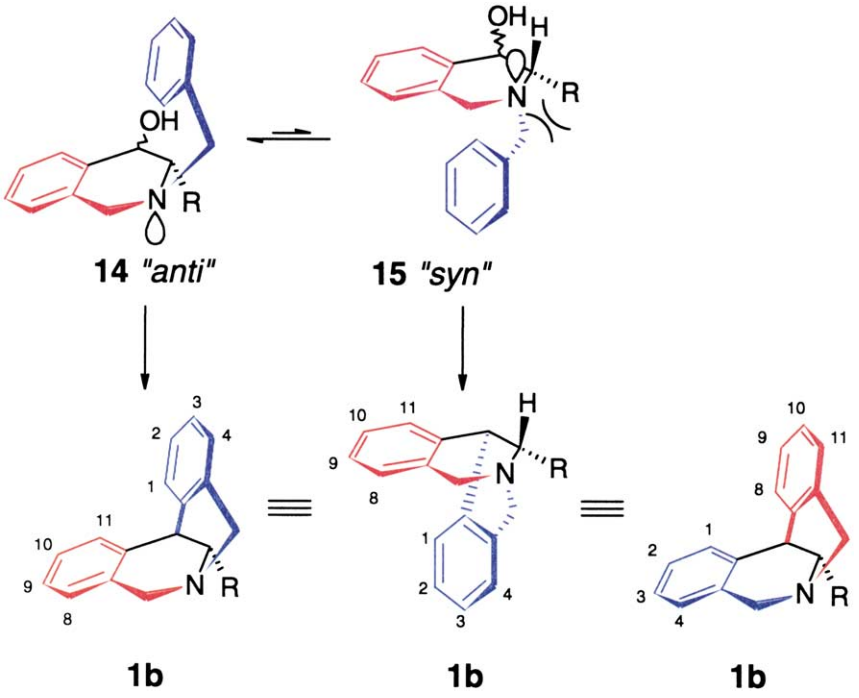
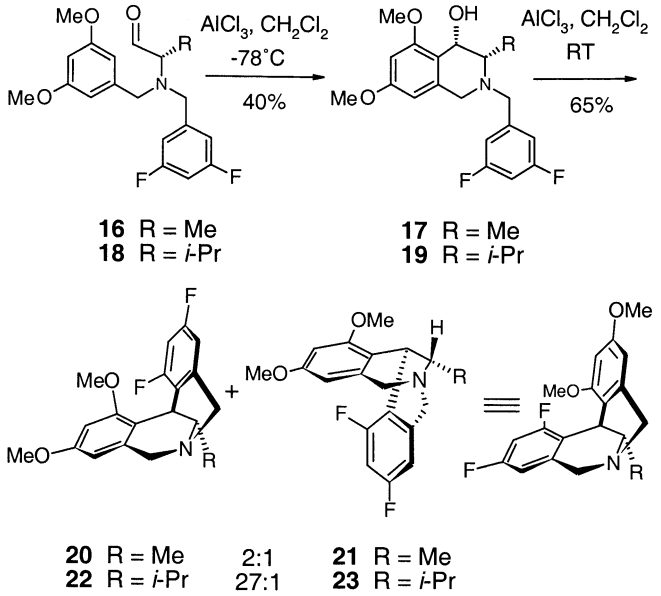


Figure 2. '*anti*' and '*syn*' modes of cyclization.

cyclization of the intermediate **19** which was obtained as a single diastereomer, was found to be **22**. This would result from an '*anti*' attack of the *N*′-3,5-difluorobenzyl group on the incipient carbocation at C-4 of the 3,5-dimethoxy tetrahydroisoquinoline from the side opposite to the bulky isopropyl group. In this manner, we could show indirectly the influence of the C-3 substituent (tetrahydroisoquinoline numbering) on the mode of cyclization, which also leads to differentially functionalized aryl rings in this series.

3. Conclusion

We have developed a highly stereoselective synthesis of 13-substituted dihydro-methano-diarylazocines, which are interesting examples of desymmetrized bridged tetrahydroisoquinolines. Variations in the starting amino acid, and the substituents on the *N*,*N*′-dibenzyl groups lead to functionally diverse double cyclization products in which the aromatic rings and the C-13 appendage are voluntarily modified. Desymmetrized dihydro-methano-dibenzoazocines of the type reported here undergo a highly diastereoselective Stevens rearrangement to afford enantiopure isopavine alkaloids with morphine-like activity on human opioid receptors.[13] Further studies involving these topologically interesting molecules capitalizing on the functionalized appendages with applications in ligand design and catalysis will be reported in due course.



Scheme 3. Desymmetrization of dihydro-methano-dibenzo-azocines.

4. Experimental

4.1. Generalities

^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. Optical rotations were recorded at 20°C. Chromatographic purifications were performed on a column with 230–400 mesh silica gel (Merck 9385) using the indicated solvent system. Dichloromethane was distilled from calcium hydride. Toluene, diethyl ether and THF were distilled from sodium metal/benzophenone ketyl. Methanol was distilled from magnesium. All non-aqueous reactions were performed under an argon atmosphere using oven-dried glassware. FAB signifies fast atom bombardment and MAB refers to metastable atom bombardment.[14]

4.2. Synthesis of azocines (5, 7–9)

4.2.1. Friedel–Crafts reaction of α-*N*,*N*-dibenzylamino aldehydes. *General procedure*. To a suspension of $AlCl_3$ (400 mg, 3 mmol, 3 equiv.) in dry dichloromethane (10 mL) at 0°C was added via cannula the crude aldehyde prepared according to Reetz[9] obtained from the corresponding alcohol (1 mmol, 1 equiv.) in dry dichloromethane (10 mL). The mixture was stirred for 15 min at 0°C. The red-colored reaction mixture was diluted with dichloromethane (20 mL), and quenched with saturated aqueous sodium hydrogen carbonate solution. After the pH became basic (pH 8), the layers were separated and the aqueous phase was extracted with dichloromethane. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by chromatography (indicated solvent system) to give the desired azocine.

4.2.2. (13*S*)-13-Methyl-7,12-dihydro-5*H*-6,12-methano-dibenzo[*c*,*f*]azocine (5). Using the general procedure, **5** (183 mg, white foamy solid) was obtained in 78% overall yield. Chromatography: hexane/ethyl acetate 1/1 to 0/100; $[\alpha]_D$=+36.8 (*c* 1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.22 (3H, d, *J*=6.9 Hz), 3.53 (1H, d, *J*=6.9), 3.60 (1H, broad s), 3.85 (1H, d, *J*=18.4 Hz), 4.02 (1H, d, *J*=17.7 Hz), 4.54 (1H, d, *J*=18.4 Hz), 4.64 (1H, d, *J*=17.7 Hz), 6.98 (2H, m), 7.08 (4H, m), 7.22 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 17.5, 41.6, 52.1, 52.4, 59.7, 125.6, 125.8, 125.9, 126.0, 126.1, 126.2, 127.5, 128.3, 133.4, 133.7, 138.2, 141.6; mass (EI): *m*/*z* 236 (M^++1), 220, 191, 178, 154, 136, 107, 91, 77; $[\alpha]_D^{20}$=+36.8 (*c* 1, $CHCl_3$); HRMS (FAB), calcd for $C_{17}H_{18}N$ (M^++1): 236.1439; found: 236.1429.

4.2.3. (13*S*)-13-Isopropyl-7,12-dihydro-5*H*-6,12-methano-dibenzo[*c*,*f*]azocine (6). Using the general procedure, **6** (66 mg, white solid) was obtained in 90% overall yield. Chromatography: hexane/ethyl acetate 95/5 to 90/10, mp 78°; $[\alpha]_D^{20}$=+47.3°, (*c* 1.2, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.96 (d, *J*=6.6 Hz, 3H), 1.14 (d, *J*=6.5 Hz, 3H), 1.56 (m, 1H), 2.82 (dd, *J*=10.6, 1.5 Hz, 1H), 3.84 (d, *J*=18.5 Hz, 1H), 3.86 (s, 1H), 4.06 (d, *J*=17.6 Hz, 1H), 4.46 (d, *J*=18.5 Hz, 1H), 4.60 (d, *J*=17.6 Hz, 1H), 7.01 (m, 2H) 7.10 (m, 4H), 7.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 19.8, 20.2, 27.5, 38.5, 52.6, 60.5, 63.8, 125.5, 125.8, 125.9, 125.9, 126.0, 126.1, 127.8, 127.9, 134.4, 134.6, 138.5, 141.5; mass (EI): *m*/*z* 279 (M^++1), 220, 154, 136, 77; HRMS (MAB), calcd for $C_{19}H_{22}N$ (M^++1): 265.1752; found: 264.1757.

4.2.4. (13*S*)-13-Isobutyl-7,12-dihydro-5*H*-6,12-methano-dibenzo[*c*,*f*]azocine (7). Using the general procedure, **7** (241 mg, colorless oil) was obtained in 87% overall yield. Chromatography: hexane/ethyl acetate 90/10 to 75/25; $[\alpha]_D$=+31.6 (*c* 2.2, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.95 (3H, d, *J*=6.5 Hz), 0.97 (3H, d, *J*=6.6 Hz), 1.27 (1H, m), 1.49 (1H, m), 1.88 (1H, m), 3.44 (1H, dd, *J*=6.7, 8.2 Hz), 3.63 (1H, s), 3.86 (1H, d, *J*=18.4 Hz), 4.05 (1H, d, *J*=17.7 Hz), 4.49 (1H, d, *J*=18.4 Hz), 4.66 (1H, d, *J*=17.7 Hz), 7.03 (2H, m), 7.10 (4H, m), 7.26 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 22.6, 23.0, 24.9, 40.2, 40.7, 52.6, 54.7, 60.0, 125.6, 125.8, 125.9, 126.0, 126.1, 126.2, 127.6, 128.1, 134.0, 134.2, 138.6, 141.8; mass (EI): *m*/*z* 278 (M^++1), 234, 220, 192, 154, 136, 120, 107, 91; HRMS (FAB), calcd for $C_{20}H_{24}N$ (M^++1): 278.1909; found: 278.1917.

4.2.5. (13*S*)-13-Benzyl-7,12-dihydro-5*H*-6,12-methano-dibenzo[*c*,*f*]azocine (8). Using the general procedure, **8** (255 mg, colorless oil) was obtained in 82% overall yield. Chromatography: hexane/ethyl acetate 75/25 to 50/50; $[\alpha]_D$=+43.8 (*c* 2, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.68 (1H, dd, *J*=13.4, 9.7 Hz), 2.98 (1H, dd, *J*=13.4, 5.6 Hz), 3.58 (1H, s), 3.63 (1H, m), 3.94 (1H, d, *J*=18.4 Hz), 4.05 (1H, d, *J*=17.6 Hz), 4.63 (1H, d, *J*=18.4 Hz), 4.67 (1H, d, *J*=17.6 Hz), 6.94–7.39 (13H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 37.8, 38.7, 52.9, 58.5, 60.1, 125.7, 125.9, 126.0, 126.1, 126.1, 126.2, 126.5, 127.8, 128.2, 128.3, 128.3, 129.0, 129.1, 133.6, 133.7, 138.1, 139.1, 141.1; mass (EI): *m*/*z* 312 (M^++1), 286, 220, 191, 178, 154, 136, 107, 91; HRMS (MAB), calcd for $C_{23}H_{21}N$ (M^+): 311.1674; found: 311.1675.

4.2.6. (13*S*)-13-(1*H*-indol-3-yl-methyl)-7,12-dihydro-5*H*-6,12-methano-dibenzo[*c*,*f*]azocine (9). Using the general procedure, **9** (171.0 mg, amorphous yellow foam) was obtained in 49% overall yield. Chromatography: hexane/ethyl acetate 1/1 to 0/100; $[\alpha]_D$=+13.5 (*c* 2.6, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.89 (1H, dd, *J*=14.2, 9.8 Hz), 3.13 (1H, dd, *J*=14.2, 5.4 Hz), 3.66 (1H, s), 3.78 (1H, m), 3.97 (1H, d, *J*=18.4 Hz), 4.08 (1H, d, *J*=17.8 Hz), 4.71 (2H, 2d, *J*=18.4, 17.8 Hz), 6.95–7.55 (13H, m), 8.18 (1H, broad s); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 27.4, 39.0, 52.8, 57.5, 60.1, 111.0, 113.0, 118.8, 119.1, 121.8, 122.3, 125.7, 125.8, 125.9 (2C), 126.0, 126.3, 127.5, 127.8, 128.4, 133.7, 133.8, 136.2, 138.3, 141.3; mass (EI): *m*/*z* 350 (M^+), 293, 234, 192, 102; HRMS (MAB), calcd for $C_{25}H_{22}N_2$ (M^+): 350.1783; found: 350.1769.

4.3. Synthesis of azocines 11–13

4.3.1. (13*R*)-(7,12-Dihydro-5*H*-6,12-methano-dibenzo[*c*,*f*]-azocin-13-yl)-methanol (11). To a suspension of $AlCl_3$ (2.80 g, 28.5 mmol, 10 equiv.) in dry dichloromethane

(30 mL) at 0°C was added via cannula the crude aldehyde obtained from **10a**[9] (1.9 g, 2.85 mmol, 1 equiv.) in dry dichloromethane (10 mL). The mixture was stirred for 4 h at rt. After the usual work-up, the crude product was purified by chromatography (ethyl acetate/methanol 93/7) to give the desired azocine **11** (1.18 g, 55% overall yield) as a white foam; $[\alpha]_D$=+43.0 (*c* 1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.33 (1H, broad s), 3.59 (3H, m), 3.70 (1H, s), 3.85 (1H, d, *J*=18.5 Hz), 4.05 (1H, d, *J*=17.6 Hz), 4.49 (1H, d, *J*=18.5 Hz), 4.60 (1H, d, *J*=17.6 Hz), 6.90–7.15 (6H, m), 7.23 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 38.1, 52.2, 58.8, 59.8, 61.4, 125.7, 126.0, 126.1, 126.2, 126.4, 126.5, 127.6, 127.7, 133.1, 133.6, 137.8, 140.7; mass (EI): *m/z* 251 (M^+), 234; HRMS (MAB), calcd for $C_{17}H_{17}NO$ (M^+): 251.1310; found: 251.1319.

4.3.2. (13*S*)-2-(7,12-Dihydro-5*H*-6,12-methano-dibenzo-[*c*,*f*]azocin-13-yl)-ethanol (12). To a suspension of $AlCl_3$ (6.52 g, 49.2 mmol, 3 equiv.) in dry dichloromethane (200 mL) at 0°C was added via cannula the crude aldehyde obtained from the alcohol **10b**[9] (16.4 mmol, 1 equiv.) in dry dichloromethane (30 mL). The mixture was stirred for 12 h at rt then $AlCl_3$ (3.26 g, 24.6 mmol, 1.5 equiv.) was added to complete the reaction after 2 h stirring. After the usual work-up, the crude product was dissolved in dry toluene (110 mL) and a DIBAL-H solution 1 M in toluene (41 mL, 41 mmol, 2.5 equiv.) was added at −78°C. The mixture was stirred for 1 h at −78°C and then methanol (24 mL) was added and the mixture was warmed to rt. A saturated solution of potassium and sodium tartrate tetrahydrate was added and the mixture was stirred for 30 min. The layers were separated and the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by chromatography (methanol/ethyl acetate 7/93) to give the desired azocine **12** (3.43 g, 79% yield) as a white solid.

Mp 129°C (AcOEt); $[\alpha]_D$=+83.0 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.48 (1H, m), 1.82 (1H, m), 3.55 (2H, m), 3.82–4.00 (4H, m), 4.65 (1H, d, *J*=17.4 Hz), 4.68 (1H, d, *J*=18.4 Hz), 6.98 (2H, m), 7.15 (4H, m), 7.20 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 32.1, 41.7, 52.9, 58.9, 60.3, 63.9, 126.2, 126.7 (2C), 126.8, 126.9 (2C), 128.2, 128.3, 133.6 (2C), 138.5, 141.3; mass (EI): *m/z* 265 (M^+); HRMS (MAB), calcd for $C_{18}H_{19}NO$ (M^+): 265.1466; found: 265.1467.

4.3.3. (13*S*)-3-(7,12-Dihydro-5*H*-6,12-methano-dibenzo-[*c*,*f*]azocin-13-yl)-propan-1-ol (13). Using the same procedure described for **12**, and starting from **10c**[9] the desired azocine **13** was isolated (81% yield) as a yellow foamy solid; $[\alpha]_D$=+37.5 (*c* 1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.52 (1H, m), 1.60–1.73 (3H, m), 3.30 (1H, dd, *J*=3.3, 5.1 Hz), 3.56 (1H, dt, *J*=3.2, 8.9 Hz), 3.6 (1H, s), 3.73 (1H, dt, *J*=4.4, 8.9 Hz), 3.90 (1H, d, *J*=18.5 Hz), 4.0 (1H, d, *J*=17.6 Hz), 4.50 (1H, d, *J*=18.5 Hz), 4.60 (1H, d, *J*=17.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 30.6, 31.7, 41.8, 52.0, 57.5, 59.4, 63.0, 125.6, 126.1, 126.15, 126.2, 126.4, 126.5, 127.6, 127.8, 132.5, 132.6, 138.0, 140.9; mass (EI): *m/z* 279 (M^+); HRMS (MAB), calcd for $C_{19}H_{21}NO$ (M^+): 279.1623; found: 279.1625.

4.4. Synthesis of desymmetrized azocines

4.4.1. (3*S*,4*S*)-2-(3,5-Difluoro-benzyl)-3-isopropyl-5,7-dimethoxy-1,2,3,4-tetrahydro-isoquinolin-4-ol (19). To a suspension of $AlCl_3$ (400 mg, 3 mmol, 3 equiv.) in dry dichloromethane (10 mL) at −78°C was added via cannula the crude aldehyde **18** obtained from the corresponding alcohol (379 mg, 1 mmol, 1 equiv.)[9] in dry dichloromethane (10 mL). The mixture was stirred for 2.5 h at −78°C. After the usual work-up, the crude product was purified by chromatography (hexane/ethyl acetate 8/2) to give the desired tetrahydroisoquinolinol **19** as a single diastereomer (150 mg, 40% overall yield) as a colorless oil; $[\alpha]_D$=−34.7 (*c* 1.65, $CHCl_3$).

^{1}H NMR (400 MHz, C_6D_6): δ (ppm) 1.24 (6H, 2d, *J*=6.6 Hz), 2.40 (1H, dd, *J*=3.4, 10.5 Hz), 2.54 (2H, m), 3.19 (3H, s), 3.37 (3H, s), 3.67 (1H, d, *J*=16.9 Hz), 3.77 (1H, d, *J*=16.9 Hz), 3.83 (1H, d, *J*=16.0 Hz), 4.15 (1H, d, *J*=16.0 Hz), 4.94 (1H, d, *J*=3.3 Hz), 5.97 (1H, d, *J*=2.2 Hz), 6.35 (1H, d, *J*=2.2 Hz), 6.54 (2H, tt, *J*=2.3, 8.9 Hz), 6.97 (1H, dd, *J*=2.3, 8.9 Hz); ^{13}C NMR (100 MHz, C_6D_6): δ (ppm) 17.5, 18.0, 23.2, 48.0, 51.7, 51.9, 52.1, 57.6, 66.0, 94.7, 99.1 (1C, t, *J*=25.6 Hz), 99.6, 107.9 (2C, d, *J*=25 Hz), 116.8, 133.4, 144.2 (1C, t, *J*=8.3 Hz), 156.3, 158.0, 160.9 (2C, dd, *J*=248.0, 13.0 Hz); mass (EI): *m/z* 377 (M^+), 334, 231, 198, 180, 164; HRMS (MAB), calcd for $C_{21}H_{25}NO_3F_2$ (M^+): 377.1802; found: 377.1795.

4.4.2. (12*S*,13*S*)-1,3-Difluoro-13-isopropyl-9,11-dimethoxy-7,12-dihydro-5*H*-6,12-methano-dibenzo[*c*,*f*]azocine (22). To a suspension of $AlCl_3$ (60 mg, 0.45 mmol, 3 equiv.) in dry dichloromethane (5 mL) at 0°C was added via cannula **19** (57 mg, 0.15 mmol, 1 equiv.) in dry dichloromethane (5 mL). The mixture was stirred for 2 h at rt. After the usual work-up, the crude product consisting of a mixture of **22** and **23** (27:1) was purified by chromatography (hexane/ethyl acetate 8/2) to give **22** (35 mg, 65% overall yield) as a colorless oil.

22: ^{1}H NMR (400 MHz, C_6D_6): δ (ppm) 0.83 (3H, d, *J*=6.6 Hz), 1.05 (3H, d, *J*=6.6 Hz), 1.48 (1H, m), 2.32 (1H, dd, *J*=1.9, 10.4 Hz), 3.31 (3H, s), 3.41 (3H, s), 3.45 (1H, d, *J*=18.5 Hz), 3.57 (1H, d, *J*=17.9 Hz), 4.09 (1H, d, *J*=17.9 Hz), 4.21 (1H, d, *J*=18.5 Hz), 4.73 (1H, d, *J*=1.7 Hz), 6.00 (1H, d, *J*=2.3 Hz), 6.16 (1H, dd, *J*=2.3, 8.3 Hz), 6.23 (1H, d, *J*=2.3 Hz), 6.40 (1H, td, *J*=2.3, 8.3 Hz); ^{13}C NMR (100 MHz, C_6D_6): δ (ppm) 16.9, 17.6, 20.2, 25.3, 50.4, 52.0, 52.3, 57.9, 61.5, 94.1, 98.6 (1C, t, *J*=25.6 Hz), 98.9, 105.4 (1C, d, *J*=25 Hz), 116.9, 122.8 (1C, d, *J*=25 Hz), 125.1, 134.7, 136.8 (1C, t, *J*=8.3 Hz), 155.4, 156.4, 158.0 (1C, dd, *J*=249, 13 Hz); mass (EI): *m/z* 359 (M^+), 316, 273, 219, 205, 163, 147, 84; HRMS (MAB), calcd for $C_{21}H_{23}NO_2F_2$ (M^+): 359.1697; found: 359.1680.

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10. Crystal data for **6**: $C_{19}H_{21}N$, monocyclic, $P2_1$, a=7.383(2), b=13.3127(3), c=7.6507(2) Å, β=100.311(2)°, V=739.83(3) Å^3, Z=2, ρ_{calcd}=1.1823 Mg m^{-3}, $F(000)$=284, θ=5.88–73.03°, 8936 measured reflections, 2822 (R(int)=0.0258) independent reflections, $R(F)(F>1\sigma(F))$=0.0418, wR (all data)=0.1105, GOF=1.025.
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