Synthesis of 2-*N,N*-Dimethylaminomethyl-2,3,3a,12b-tetrahydrodibenzo-*[b,f]*furo[2,3-*d*]oxepin Derivatives as Potential Anxiolytic Agents

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New synthesis approaches that have led to a series of novel tetrahydrodibenzo[*b,f*]furo[2,3-*d*]oxepin derivatives are described. According to preliminary data these novel tetracycles can be useful intermediates for the preparation of potential new therapeutic agents.

Key words anxiolytic; tetrahydrofuran; dibenzoxepin; heterocyclic compound

We have recently described the synthesis of two new series of 2-(aminomethyl)-2,3,3a,8-tetrahydrodibenzo[*c,f*]isoxazolo[2,3-*a*]azepine derivatives (I) and 2-(aminomethyl)-3,3a,8,12b-tetrahydrodibenzo[3,4:6,7]cyclohepta[1,2-*b*]furan derivatives (II) as novel 5-HT_{2A/2C} receptor blockers (Fig. 1).^{1–5} Some of those tetracyclic isoxazolidines/tetrahydrofurans were potent mCPP (*m*-chlorophenylpiperazine) antagonists as shown in our *in vivo* mCPP challenge test,^{3–5} and therefore could be considered as potential anxiolytic/antidepressants.^{6–12} One enantiomer within this isoxazolidine series, R107500, was selected for clinical evaluation as an anxiolytic agent.

Following our research program on modifications of these tetracyclic structures, we now report the synthesis of the corresponding dibenzoxepine (III) analogues. The described synthetic pathway allowed us to synthesize the four different diastereoisomers of the THF core.

Results and Discussion

trans-Fused analogues were prepared following a similar methodology to that used for the synthesis of 2-(aminomethyl)-3,3a,8,12b-tetrahydrodibenzo[3,4:6,7]cyclohepta[1,2-*b*]furan derivatives (II).^{4,5,13,14} Thus, epoxidation of dibenzo[*b,f*]oxepine (1)¹⁵ with *meta*-chloroperbenzoic acid (MCPBA) gave dibenzo[*b,f*]oxepin-10,11-epoxide (2) in 79% yield (Chart 1). Epoxide ring opening with allylmagnesium bromide resulted in the desired *trans*-type β -allylic alcohol 3. The cyclization of 3 to form the tetrahydrofuran ring was carried out under the reaction conditions shown in Table 1. Bromine or pyridinium bromide perbromate in chloroform afforded with good yield (80% and 78% respectively) and diastereoselectivity (95 : 5) the *trans*-fused diastereoisomer 4b. When the cyclization step was performed with I₂ under basic reaction conditions the expected tetrahydrofuran derivatives

4a and 5a were obtained in satisfactory yield (80%), although the diastereoselectivity outcome of the cyclization was somewhat lower (4a : 5a; 90 : 10). The use of IPy₂BF₄ (bis(pyridine)iodonium(I) tetrafluoroborate; Barluenga's reagent)¹⁶ or MCPBA resulted in slightly increased yields (92% for 4c, 5c and 99% for 4a, 5a) but not diastereoselectivity at all. Remarkable is the fact that the cyclization reaction with Barluenga's reagent reached completion in two minutes affording the expected products in nearly quantitative

Reagents and conditions:

(i) MCPBA, CH₂Cl₂, reflux, 6h; (ii) allylmagnesium bromide, THF, rt, 3 h. (iii) see Table 1.

Chart 1

Table 1. Reagents and Reaction Conditions for the Cyclization of the *trans*- β -Allylic Alcohol 3

Cyclization conditions	X	4 : 5 ^{a)}	Yield (%)
Br ₂ , CHCl ₃ 1.5 h, rt	Br	95 : 5	80
PyHBr ₃ , CHCl ₃ 2.5 h, rt	Br	95 : 5	78
I ₂ , NaHCO ₃ , CH ₃ CN/H ₂ O 3 h, 0 °C to rt	I	90 : 10	80
IPy ₂ BF ₄ , CH ₂ Cl ₂ 2 min, rt	I	50 : 50	99 ^{b)}
MCPBA, CH ₂ Cl ₂ 8 h, rt	OH	50 : 50	92

^{a)} 4 : 5 ratio was determined in the ¹H-NMR spectra of the reaction crude. ^{b)} The reaction was carried out under N₂ atmosphere.

Fig. 1

Reagents and conditions:

(i) TosCl, NEt₃, CH₂Cl₂, 0 °C to rt, 12 h. (ii) NHMe₂, THF, 120 °C, 8 h.

Chart 2

Reagents and conditions:

(i) NaH, THF, 0 °C, 2 h then allylbromide, rt, 6 h; (ii) NaBH₄, THF/MeOH, 0 °C, 3 h; (iii) MCPBA, CH₂Cl₂, rt, 12 h.

Chart 3

tive yield. Due to our interest to obtain all possible isomers, and an easier chromatographic separation of diastereoisomers, we decided the use MCPBA in CH₂Cl₂ as the cyclization agent.

Finally, transformation of pure **4c** and **5c** into the target compounds **6** and **7** was carried out by reaction of the alcohol group with tosyl chloride in dichloromethane and subsequent thermal displacement of the tosyl group by dimethylamine in THF at 120 °C (Chart 2). The stereochemistry of the final compounds was determined by two dimensional nuclear Overhauser effect spectroscopy (2D-NOESY) experiments; double arrows in Chart 2 stand for the observed cross peaks in the NOESY spectra.

The synthetic scheme followed for the synthesis of *cis*-fused analogues is shown in Chart 3. Firstly, the reaction of 11*H*-dibenzo[*b,f*]oxepin-10-one (**8**)¹⁷ with sodium hydride, followed by addition of allyl bromide afforded the α-allylated ketone **9** with moderate yield (73%) due to competition with the double allylation reaction.¹⁸

Then, the reduction of **9** with sodium borohydride at 0 °C, gave the expected *cis*-alcohol **10** with high diastereoselectivity (90% de) and excellent yield.¹⁹ The cyclization of the *cis* β-allylic alcohol with MCPBA occurred with almost no selectivity, affording a 3 : 2 mixture of diastereoisomers **11**—**12**

Reagents and conditions:

(i) TosCl, NEt₃, CH₂Cl₂, 0 °C to rt, 12 h. (ii) NHMe₂, THF, 120 °C, 8 h.

Chart 4

that were easily separated by column chromatography. The double arrows in Chart 3 indicate the cross peaks in the 2D-NOESY spectra, of compounds **11** and **12**, used for the assignment of the relative stereochemistry. Finally, an identical reaction sequence to those shown in Chart 2 (reaction with tosyl chloride and displacement of the tosyl group with NHMe₂) yielded the *cis*-fused analogues **13** and **14** (Chart 4).

In conclusion, we have reported an straightforward synthesis of a novel class of tetracycles that, according to preliminary data,²⁰ could be considered as potential therapeutic agents for the treatment of anxiety/depression. We are continuing research along this line and it will be communicated in due course.

Experimental

General All reactions involving organometallic species were carried out under a nitrogen atmosphere in oven dried glassware. 1D- and 2D-NMR spectra (δ ppm, *J* in Hz) were run on a Bruker AM-400 Spectrometer with tetramethylsilane (TMS) as internal standard. Low resolution mass measurements were performed on a Platform series II single quadrupole from Micromass Ltd. High resolution (HR) mass measurements were performed with an LCT mass spectrometer, with Lockmass probe, from Micromass Ltd.; Leucine encephaline was used as calibration reference.

Dibenzo[*b,f*]oxepin-10,11-epoxide (2) 3-Chloroperbenzoic acid (621 mg, 3.6 mmol) was added to a solution of dibenzo[*b,f*]oxepine (**1**) (583 mg, 3 mmol) in dry CH₂Cl₂ (60 ml) at room temperature (rt). The solution was heated under reflux for 6 h. The solution was cooled on an ice bath and washed with sodium bicarbonate and water. Evaporation of the volatiles under reduced pressure gave a residue that was recrystallised from methanol to yield 498 mg of **2** (79%). Compound **2**: White solid. mp: 111–112 °C.²¹

trans-10,11-Dihydro-11-(2-propenyl)-dibenzo[*b,f*]oxepin-10-ol (3) Allylmagnesium bromide (2 ml of 2.0 M in THF, 4 mmol) was added dropwise over 15 min to epoxide **2** (483 mg, 2.3 mmol) in dry THF (50 ml) at 0 °C. The reaction mixture was allowed to warm to rt. After being stirred at rt for 3 h the mixture was partitioned between saturated aqueous NH₄Cl and ethyl acetate. The combined organic extract was dried (Na₂SO₄) and concentrated. The residue was flash chromatographed on silica gel (heptane/ethyl acetate 100 : 0—75 : 25) to give 435 mg of **3** (75%). Compound **3**: Colorless oil. *R*_f=0.26 heptane/ethyl acetate (v/v 9 : 1). ¹H-NMR (CDCl₃) δ : 7.30–7.05 (8H, m), 5.75 (1H, m), 5.00 (1H, dq, *J*=9.3, 0.8 Hz), 4.97 (1H, dq, *J*=17.0, 1.4 Hz), 4.92 (1H, dd, *J*=8.7, 5.6 Hz), 3.30 (1H, ddd, *J*=7.5, 5.8, 5.6 Hz), 2.58 (1H, m), 2.42 (1H, m), 1.98 (1H, d, *J*=8.7 Hz). MS *m/z* 253 (*M*⁺+H). HR-MS Calcd C₁₇H₁₇O₂ (*M*⁺+H): 253.1229, Found 253.1233.

11-(2-Propenyl)-dibenzo[*b,f*]oxepin-10(11*H*)one (9) To a suspension of sodium hydride (84 mg, 3.5 mmol) in dry THF (40 ml) at 0 °C was added 11*H*-dibenzo[*b,f*]oxepin-10-one (**8**) (630 mg, 3 mmol) in dry THF (20 ml). The reaction mixture was stirred until hydrogen evolution had ceased and the solution was homogeneous (ca. 2 h). Addition of allyl bromide was followed by stirring of the reaction mixture for 6 h at rt. An aqueous ammo-

nium chloride saturated solution was added, and the resulting mixture was extracted with diethyl ether. The combined organic extracts were washed with water and dried over sodium sulfate. After evaporation of the solvent, the residue was chromatographed on a silica gel column (heptane) to give 548 mg of **9** (73%). Compound **9**: Pale green oil. $R_f=0.61$ heptane. $^1\text{H-NMR}$ (CDCl_3) δ : 8.03 (1H, dd, $J=7.9, 1.8$ Hz), 7.53 (1H, ddd, $J=8.5, 7.4, 2.0$ Hz), 7.37 (1H, dd, $J=8.2, 1.2$ Hz), 7.30–7.11 (5H, m), 5.92–5.72 (1H, m), 5.10 (1H, dq, $J=17.2, 1.6$ Hz), 5.02 (1H, dq, $J=10.5, 1.6$ Hz), 4.29 (1H, t, $J=7.5$ Hz), 3.13–2.96 (1H, m), 2.85–2.70 (1H, m). $^{13}\text{C-NMR}$ (CDCl_3) δ : 191.5 (q), 159.4 (q), 156.6 (q), 135.3 (s), 134.6 (s), 130.5 (s), 128.7 (q), 128.2 (s), 127.7 (s), 126.2 (s), 126.0 (q), 123.5 (s), 121.1 (s), 120.6 (s), 117.1 (s), 54.7 (s), 30.7 (d). MS m/z 251 ($\text{M}^+ + \text{H}$). HR-MS Calcd $\text{C}_{17}\text{H}_{15}\text{O}_2$ ($\text{M}^+ + \text{H}$): 251.1072, Found 251.1077.

cis-10,11-Dihydro-11-(2-propenyl)-dibenzo[b,f]oxepin-10-ol (10) To an ethanol/THF (1:1 30 ml) solution of **9** (501 mg, 2 mmol) was added NaBH_4 (113 mg, 3 mmol) at 0 °C, and the mixture was stirred for 3 h. Then 2 N HCl was added, and the organic materials were extracted twice with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4), concentrated, and chromatographed on silica gel to give the *cis*- β -allyl alcohol **10** (469 mg, 93%). Compound **10**: Colorless oil. $R_f=0.23$ heptane/ethyl acetate (v/v 9:1). $^1\text{H-NMR}$ (CDCl_3) δ : 7.30–7.10 (8H, m), 5.88 (1H, m), 5.16 (1H, dq, $J=17.0, 1.5$ Hz), 5.10 (1H, dq, $J=10.2, 0.9$ Hz), 5.02 (1H, dd, $J=9.7, 2.0$ Hz), 3.68 (1H, ddd, $J=8.5, 7.5, 2.0$ Hz), 2.70 (1H, m), 2.58 (1H, m), 1.60 (1H, d, $J=9.70$ Hz). MS m/z 253 ($\text{M}^+ + \text{H}$). HR-MS Calcd $\text{C}_{17}\text{H}_{17}\text{O}_2$ ($\text{M}^+ + \text{H}$): 253.1229, Found 253.1233.

General Procedure for Preparation of Compounds 4c, 5c, 11, 12. 3-Chloroperbenzoic acid (414 mg, 2.4 mmol) was added to a solution of the corresponding β -allyl alcohol **3** or **10** (504 mg, 2 mmol) in dry CH_2Cl_2 (20 ml) at rt. After stirring at rt for the appropriate time, the mixture was portioned between saturated aqueous NH_4Cl and CH_2Cl_2 . The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was purified by HPLC chromatography on silica gel affording the corresponding pure diastereoisomers **4c**, **5c**, or **10**, **11**.

(2*SR*,3*aRS*,12*bSR*)-2-Hydroxymethyl-2,3,3*a*,12*b*-tetrahydrodibenzo[b,f]furo[2,3-*d*]oxepin (**4c**): Colorless oil. $R_f=0.23$ heptane/ethyl acetate (v/v 95:5). $^1\text{H-NMR}$ (CDCl_3) δ : 7.25–7.05 (8H, m), 5.06 (1H, d, $J=10.8$ Hz), 4.55–4.43 (1H, m), 3.92–3.80 (1H, m), 3.75–3.65 (1H, m), 3.55–3.45 (1H, m), 2.61 (1H, ddd, $J=11.8, 6.4, 5.6$ Hz), 2.18 (1H, ddd, $J=11.8, 9.7, 9.5$ Hz), 2.02 (1H, t, $J=6.4$ Hz). MS m/z 269 ($\text{M}^+ + \text{H}$). HR-MS Calcd $\text{C}_{17}\text{H}_{17}\text{O}_3$ ($\text{M}^+ + \text{H}$): 269.1178, Found 269.1173.

(2*RS*,3*aRS*,12*bSR*)-2-Hydroxymethyl-2,3,3*a*,12*b*-tetrahydrodibenzo[b,f]furo[2,3-*d*]oxepin (**5c**): Colorless oil. $R_f=0.22$ heptane/ethyl acetate (v/v 95:5). $^1\text{H-NMR}$ (CDCl_3) δ : 7.30–7.09 (8H, m), 5.01 (1H, d, $J=10.6$ Hz), 4.55–4.40 (1H, m), 3.90–3.80 (1H, m), 3.75–3.65 (1H, m), 3.42 (1H, ddd, $J=11.4, 10.6, 8.9$ Hz), 2.65–2.55 (1H, m), 2.25–2.15 (1H, m), 1.90 (1H, t, $J=6.9$ Hz). MS m/z 269 ($\text{M}^+ + \text{H}$). HR-MS Calcd $\text{C}_{17}\text{H}_{17}\text{O}_3$ ($\text{M}^+ + \text{H}$): 269.1178, Found 269.1169.

(2*SR*,3*aRS*,12*bRS*)-2-Hydroxymethyl-2,3,3*a*,12*b*-tetrahydrodibenzo[b,f]furo[2,3-*d*]oxepin (**11**): Colorless oil. $R_f=0.17$ heptane/ethyl acetate (v/v 95:5). $^1\text{H-NMR}$ (CDCl_3) δ : 7.30–7.07 (8H, m), 5.64 (1H, d, $J=7.46$ Hz), 4.45–4.39 (1H, m), 3.90–3.78 (2H, m), 3.67 (1H, dd, $J=11.6, 5.4$ Hz), 2.42–2.36 (1H, m), 2.18 (1H, br dd, $J=10.8, 10.4$ Hz), 2.05 (1H, br s). MS m/z 269 ($\text{M}^+ + \text{H}$). HR-MS Calcd $\text{C}_{17}\text{H}_{17}\text{O}_3$ ($\text{M}^+ + \text{H}$): 269.1178, Found 269.1177.

(2*RS*,3*aRS*,12*bRS*)-2-Hydroxymethyl-2,3,3*a*,12*b*-tetrahydrodibenzo[b,f]furo[2,3-*d*]oxepin (**12**): Colorless oil. $R_f=0.23$ heptane/ethyl acetate (v/v 95:5). $^1\text{H-NMR}$ (CDCl_3) δ : 7.25–7.05 (8H, m), 5.36 (1H, d, $J=8.7$ Hz), 4.31–4.23 (1H, m), 3.92–3.77 (2H, m), 3.62 (1H, q, $J=5.9$ Hz), 2.47–2.40 (1H, m), 2.17 (1H, ddd, $J=12.0, 11.2, 10.4$ Hz), 1.9 (1H, t, $J=6.2$ Hz). MS m/z 296 ($\text{M}^+ + \text{H}$). HR-MS Calcd $\text{C}_{17}\text{H}_{17}\text{O}_3$ ($\text{M}^+ + \text{H}$): 269.1178, Found 269.1176.

General Procedure for Preparation of Compounds 6, 7, 13, 14 Under N_2 atmosphere, triethylamine (0.92 ml, 6.6 mmol) and *p*-toluenesulfonyl chloride (629 mg, 3.3 mmol) were added to a stirred solution of the corresponding alcohol (**4c**, **5c**, **11**, **12**) (590 mg, 2.2 mmol) in dry dichloromethane (30 ml) at 0 °C. The reaction mixture was allowed to warm to rt. After being stirred for an additionally 12 h the reaction mixture was partitioned with an aqueous saturated solution of NaHCO_3 and the mixture was extracted with CHCl_3 . The combined organic extract was dried (Na_2SO_4) and vacuum concentrated affording a residue that was not further purified. This residue was taken up in 20 ml of THF and 4 ml of a 2 M solution of dimethylamine in THF were added at rt. The resulting solution was heated at 120 °C (oil bath temperature) into a pressure reactor vessel for 8 h. After cooling to rt the mixture was washed with Na_2CO_3 and water. The or-

ganic extract was dried (Na_2SO_4) and vacuum concentrated affording a residue that was purified by flash column chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}(\text{NH}_3)$ 98:2–95:5) yielding the corresponding compound **6**, **7**, **13**, **14**.

(2*SR*,3*aRS*,12*bSR*)-2-*N,N*-dimethylaminomethyl-2,3,3*a*,12*b*-tetrahydrodibenzo[b,f]furo[2,3-*d*]oxepin (**6**): Colorless oil. $R_f=0.23$ $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (v/v 95:5). $^1\text{H-NMR}$ (CDCl_3) δ : 7.43–7.05 (8H, m), 4.92 (1H, d, $J=10.8$ Hz), 4.47–4.38 (1H, m), 3.37–3.26 (3H, m), 2.75–2.65 (1H, m), 2.23 (6H, s), 1.94 (1H, ddd, $J=11.6, 10.5, 9.7$ Hz). MS m/z 296 ($\text{M}^+ + \text{H}$). HR-MS Calcd $\text{C}_{19}\text{H}_{22}\text{NO}_2$ ($\text{M}^+ + \text{H}$): 296.1651, Found 296.1654.

(2*RS*,3*aRS*,12*bSR*)-2-*N,N*-dimethylaminomethyl-2,3,3*a*,12*b*-tetrahydrodibenzo[b,f]furo[2,3-*d*]oxepin (**7**): Colorless oil. $R_f=0.23$ $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (v/v 95:5). $^1\text{H-NMR}$ (CDCl_3) δ : 7.30–7.05 (8H, m), 4.87 (1H, d, $J=10.8$ Hz), 4.39 (1H, m), 3.27 (1H, ddd, $J=11.2, 10.8, 7.9$ Hz), 2.42 (2H, d, $J=6.2$ Hz), 2.42–2.30 (2H, m), 2.23 (6H, s), 1.95 (1H, m). MS m/z 296 ($\text{M}^+ + \text{H}$). HR-MS Calcd $\text{C}_{19}\text{H}_{22}\text{NO}_2$ ($\text{M}^+ + \text{H}$): 296.1651, Found 296.1643.

(2*SR*,3*aRS*,12*bRS*)-2-*N,N*-dimethylaminomethyl-2,3,3*a*,12*b*-tetrahydrodibenzo[b,f]furo[2,3-*d*]oxepin (**13**): Colorless oil. $R_f=0.21$ $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (v/v 95:5). $^1\text{H-NMR}$ (CDCl_3) δ : 7.23–7.05 (8H, m), 5.52 (1H, d, $J=8.7$ Hz), 4.30 (1H, m), 3.88 (1H, m), 2.62 (1H, dd, $J=12.6, 7.3$ Hz), 2.53 (1H, ddd, $J=12.0, 6.8, 5.0$ Hz), 2.48 (1H, dd, $J=12.6, 4.5$ Hz), 2.34 (6H, s), 1.83 (1H, ddd, $J=12.0, 10.6, 9.0$ Hz); $^{13}\text{C-NMR}$ (CDCl_3) δ : 157.4 (q), 157.2 (q), 132.3 (q), 131.8 (q), 130.8 (s), 130.7 (s), 129.1 (s), 128.0 (s), 124.9 (s), 124.8 (s), 121.4 (s), 120.9 (s), 78.7 (s), 76.3 (s), 63.8 (d), 45.9 (2 $\times$ s), 45.2 (s), 38.2 (d). MS m/z 296 ($\text{M}^+ + \text{H}$). HR-MS Calcd $\text{C}_{19}\text{H}_{22}\text{NO}_2$ ($\text{M}^+ + \text{H}$): 296.1651, Found 296.1647.

(2*RS*,3*aRS*,12*bRS*)-2-*N,N*-dimethylaminomethyl-2,3,3*a*,12*b*-tetrahydrodibenzo[b,f]furo[2,3-*d*]oxepin (**14**): Colorless oil. $R_f=0.20$ $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (v/v 95:5). $^1\text{H-NMR}$ (CDCl_3) δ : 7.25–7.05 (8H, m), 5.63 (1H, d, $J=7.2$ Hz), 4.44 (1H, m), 3.82 (1H, ddd, $J=9.7, 8.1, 7.2$ Hz), 2.61 (1H, dd, $J=12.4, 7.5$ Hz), 2.39 (1H, dd, $J=12.4, 5.2$ Hz), 2.34 (6H, s), 2.53 (1H, ddd, $J=12.4, 8.1, 4.1$ Hz), 2.18 (1H, ddd, $J=12.4, 9.7, 8.3$ Hz). MS m/z 296 ($\text{M}^+ + \text{H}$). HR-MS Calcd $\text{C}_{19}\text{H}_{22}\text{NO}_2$ ($\text{M}^+ + \text{H}$): 296.1651, Found 296.1644.

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- 18) The double C-allylation product was isolated from the reaction crude in 17% yield; the *O*-allylated product was detected by ¹H-NMR spectroscopy of the crude reaction (<5%), although it was not isolated.
- 19) Both diastereoisomers were separated by HPLC chromatography. The relative configuration between the allyl and alcohol groups was determined by 2D-NOESY experiments on the major diastereoisomer **10**.
- 20) **13**: Binding affinity K_i (nM): 5-HT_{2A} 92.63, 5-HT_{2C} 182.7. Further pharmacological results will be published elsewhere.
- 21) The melting point of compound **2** corresponds to that described in reference 13.