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Resolution of 2,3-dihydro-benzofuran-3-ols

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Abstract. A new method for the preparation of enantiopure 2,2-disubstituted 2,3-dihydro-benzofuran-3-ols is described. A short synthesis is designed for obtaining various 2,2-disubstitued benzofuran-3-ols as racemic mixtures of the two possible *syn* and *anti* diastereoisomers, which can be separated after silylation. The major racemic *anti* isomers were transesterified using (R)-pentolactone, allowing separation of the pure enantiomers.

Keywords. benzofuran-3-ol; resolution; pentolactone.

1. Introduction

Dibenzofuranone is a moiety, found in many biologically significant natural products,[1] such as the rocaglamide **1** insecticide or the synthetic PPARα agonist **2**,[2] the receptor α-2 antagonist Efaroxan **3**[3] and the vasinfectins **4**[4] (figure 1). These compounds may be mono- or disubstituted in position 2, generating a stereogenic centre requiring asymmetric synthesis. Although many methods have been described for enantioselective preparation of 2,3-dihydro-benzofuran,[2,4–7] direct preparation of enantiopure 2,3-dihydrobenzofuran-3-ols is still a challenging, especially when a 2,2 disubstituted derivative is needed. Involved in the preparation of biologically active molecules **5** based on benzofuran-3-ones,[8] we studied a possible practical preparation of the two enantiomers of 2,2-disubstitued benzofuran-3-ols **6** to obtain enantiopure compounds **5** (figure 1). We focused more specifically on a methodology designed to prepare structures **6** where the R group could be modulated, and also allowing further modifications at any synthetic stage. The R′ group should preferably be a carbonyl function used to prepare the butadiene chain found in compound **5**. Clive described the use of the Enders'[9] method with the SAMP hydrazine for the conversion of indanones to the corresponding SAMP hydrazone. Despite the possible access to the other enantiomer with the RAMP hydrazine, this work showed that methylation followed by carbonylation gave a poor final diastereoisomeric excess.[10] Some recycling methods[11] found in the literature can mitigate the inadequateness of such costly methods. Recently, a synthesis of 2,2-disubstituted indan-3-ols and benzofuran-3-ols was described utilizing HPLC-based separation for the indanols, while a Jacobsen's asymmetric synthesis was used for the preparation of the benzofuranols due to impossible HPLC separation of the stereoisomers.[12] In the case of 2,3-dihydrobenzofurane, a resolution-based method was described,[13] prompting us to develop an equivalent method for the resolution of 2,3-dihydrobenzofuran-3-ols that should give both enantiomers in a standard sequence. Our strategy is focused on the access to alcohols **6** from diversely substituted salicylaldehydes, with subsequent transformations to obtain a possible resolution.

2. Experimental

Abbreviations used: PE: petroleum ether, EtOAc: ethyl acetate, THF: tetrahydrofuran, EDC: 1-[3(dimethylamino)propyl]-3-ethyl-carbodiimide hydrochloride, DMAP: dimethylaminopyridine.

2.1 *4-Dimethylamino-2-hydroxy-benzaldehyde* **8a**

Phosphorus oxychloride (63.7 g, 38.7 ml) was added drop-wise to ice cold DMF (93 ml). After 30 min. of stirring at ambient temperature, N,N-dimethylaminophenol (50 g, 0.336 mol) in DMF (minimum) was added, and the resulting solution heated on a water bath for 1 h. After cooling, the solution was hydrolysed with NaOH 1N and stirred overnight. The final solution was

*For correspondence

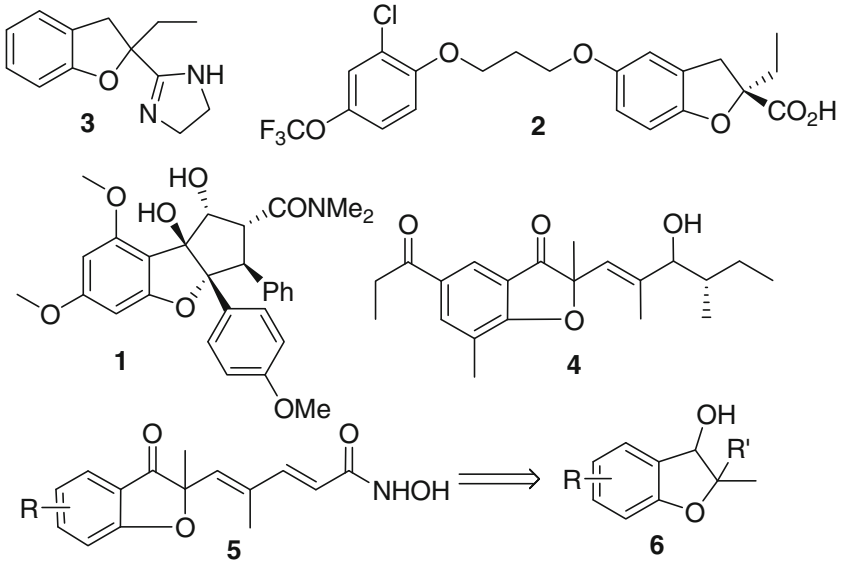


Figure 1. Benzofuran-based bioactive compounds.

extracted with ether to give **7a** as a brown solid (65%), which was further used without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 11.6 (s, 1H), 9.5 (s, 1H), 7.29 (d, 1H, J = 8.7 Hz), 6.32 (dd, 1H, J = 8.7, 2.5 Hz), 6.08 (d, 1H, J = 2.5 Hz), 3.0 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 192.3, 163.9, 156.1, 135.1, 111.6, 104.6, 97.0, 39.9.

2.2 *4-Chloro-2-hydroxy-benzaldehyde* **7b**

To a solution of 3-chlorophenol **8b** (2.57 g, 20 mmol) in CH_3CN (100 ml) were added: $MgCl_2$ (30 mmol), NEt_3 (75 mmol) and paraformaldehyde (135 mmol). The mixture was refluxed for 3 h and after cooling to room temperature, HCl 6N (50 ml) was added. The resulting mixture was extracted with Et_2O (3 × 100 ml) dried over $MgSO_4$ and concentrated. Purification (flash chromatography on silica, PE:EtOAc 97:3) gave the phenol **7b** as a solid (1.88 g, 60%) along with regioisomer **9** (0.38 g, 12%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 11.2 (s, 1H), 9.9 (s, 1H), 7.5 (d, 1H, J = 7.8 Hz), 7.0 (m, 1H).

2.3 *6-Dimethylamino-3-hydroxy-2-methyl-2,3-dihydro-benzofuran-2-carboxylic acid methyl ester* **6a**

To a solution of phenol **7a** (5 g, 0.019 mol) in DMF (100 ml) were added: K_2CO_3 (5.4 g, 0.038 mol) and 2-bromopropionate methyl ester (2.2 ml, 0.019 mol). The solution was heated at 125°C for 3 h. After cooling, water was added (100 ml) and the mixture was extracted with Et_2O (5 × 100 ml). The combined organic layers were washed with water (100 ml), dried over $MgSO_4$, and concentrated. Purification (flash chromatography, silica, PE:EtOAc 80:20) gave 2.25 g of **6a** as the single anti isomer (47%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.17 (d, 1H, J = 8.2 Hz), 6.3 (m, 2H), 6.1 (m, 1H), 5.17 (d, 1H), 3.70 (s, 3H), 2.90 (s, 6H), 2.43 (s, 1H), 1.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 173.7, 160.8, 153.4, 126.0, 114.8, 106.2, 94.0, 91.4, 76.0, 52.8, 40.5, 18.0.

2.4 *6-Chloro-3-hydroxy-2-methyl-2,3-dihydro-benzofuran-2-carboxylic acid methyl ester* **6b** *(anti + syn diastereoisomers)*

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.23 (d, 1H, J = 8.2 Hz), 6.85 (m, 2H), 6.1 (m, 1H), 5.25 (s, 0.8H), 4.90 (s, 0.2H), 3.72 (s, 0.6H), 3.70 (s, 2.4H), 2.43 (s, 0.8H), 1.66 (s, 0.6H), 1.64 (s, 2.4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 171.3, 170.3, 159.6, 159.5, 136.2, 135.9, 126.7, 126.6, 126.2, 125.1, 121.7, 121.6, 111.4, 111.0, 92.6, 91.6, 78.5, 75.0, 52.7, 52.4, 17.3, 17.0.

2.5 *5-Bromo-3-hydroxy-2-methyl-2,3-dihydro-benzofuran-2-carboxylic methyl ester* **6c**

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.50 (d, 1H, J = 2.2 Hz), 7.38 (dd, 1H, J = 8.6, 2.2 Hz), 6.81 (d, 1H, J = 8.6 Hz), 5.35 (d, 0.9H), 4.90 (d, 0.1H), 3.85 (s, 0.3H), 3.75 (s, 2.7H), 2.0 (s, 0.9H), 1.66 (s, 0.3H), 1.64 (s, 2.7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm (anti

only): 173.5, 158.3, 134.1, 129.8, 129.3, 113.7, 112.7, 91.7, 76.0, 53.4, 17.9.

2.6 *6-Dimethylamino-3-ter-butyltrimethylsilyloxy-2-methyl-2,3-dihydro-benzofuran-2-carboxylic acid methyl ester* **11a** *(anti only)*

Imidazole (0.81 g) was added to a solution of **6a** (2 g, 7.96 mmol) in DMF (20 ml). After 15 min. of stirring under nitrogen atmosphere, TBDMS-Cl (1.79 g, 8 mmol) was added. The solution was stirred overnight at room temperature and then diluted with water (20 ml). The resulting mixture was extracted with Et_2O (3 × 50 ml) and the combined organic layers washed with water (50 ml), dried over $MgSO_4$ and concentrated. Purification (flash chromatography, silica, PE:EtOAc 97:3) gave 2.24 g of **11a** as an oil (87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.08 (d, 1H, J = 8.1 Hz), 6.30 (m, 2H), 6.1 (m, 1H), 5.31 (s, 1H), 3.72 (s, 3H), 2.91 (s, 6H), 1.6 (s, 3H), 0.91 (s, 9H), 0.19 (s, 3H), 0.17 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ ppm: 174.2, 160.5, 152.8, 125.8, 115.4, 105.9, 94.1, 91.5, 76.3, 52.7, 40.6, 25.8, 18.7, 18.2, −44.1,−4.6.

2.7 *6-Chloro-3-ter-butyltrimethylsilyloxy-2-methyl-2,3-dihydro-benzofuran-2-carboxylic acid methyl-ester* **11b**

Obtained as **11a** as oil with a yield of 73%. Anti isomer ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 6.90 (d, 1H, J = 8.0 Hz), 6.70 (m, 2H), 5.15 (s, 1H), 3.62 (s, 3H), 1.6 (s, 3H), 0.91 (s, 9H), 0.19 (s, 3H), 0.17 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ ppm: 173.3, 159.6, 135.8, 126.7, 126.3, 111.4, 91.9, 75.9, 52.9, 25.8, 21.1, 18.4, −4.0, −4.4.

Syn isomer ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 6.94 (d, 1H, J = 8.0 Hz), 6.70 (m, 2H), 4.88 (s, 1H), 3.65 (s, 3H), 1.6 (s, 3H), 0.91 (s, 9H), 0.19 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm : 170.1, 157.8, 136.0, 126.4, 126.0, 111.8, 92.8, 79.9, 52.3, 25.7, 22.2, 18.2, −4.1, −4.4.

2.8 *5-Bromo-3-ter-butyltrimethylsilyloxy-2-methyl-2,3-dihydro-benzofuran-2-carboxylic acid methyl ester* **11c**. *Obtained as* **11a** *as oil with a yield of 84%*

Anti isomer. ^{1}H NMR (300 MHz; $CDCl_3$) δ ppm: 7.3 (m, 2H), 6.81 (d, 1H, J = 8.6 Hz), 5.37 (s, 1H), 3.75 (s, 3H), 1.61 (s, 3H), 0.91 (s, 9H), 0.20 (s, 6H); ^{13}C NMR (75 MHz; $CDCl_3$) δ ppm: 173.1, 157.7, 133.1, 130.1, 128.5, 112.9, 112.3, 91.5, 76.1, 52.8, 25.7, 18.2, 18.0, −4.2, −4.6.

Syn isomer ^{1}H NMR (300 MHz; $CDCl_3$) δ ppm: 7.3 (m, 2H), 6.81 (d, 1H, J = 8.59 Hz), 5.0 (s, 1H), 3.76 (s, 3H), 1.59 (s, 3H), 0.85 (s, 9H), 0.15 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 169.9, 158.0, 133.2, 129.5, 128.5, 112.7, 112.6, 92.2, 80.0, 52.3, 25.5, 22.1, 17.9, −4.1, −4,6.

2.9 *General procedure for hydrolysis of esters* **11** *to acid* **12**. *To a solution of ester* **11** *(3 mmol) in THF*

MeOH (5 : 1, 12 ml) an aqueous solution of LiOH (2.5 M, 2 ml) was added. After stirring overnight at ambient temperature, the mixture was acidified to pH 1 with HCl (6N). The mixture was then diluted with H_2O (50 ml) and saturated with NaCl and extracted with EtOAc (6 × 50 ml) until no more acid was found in the aqueous layer. The combined organic layers were dried ($MgSO_4$) and concentrated to give the crude acid. Minimum CH_2Cl_2 was then added to dissolve the acid, and 100 ml of PE was added to obtain the acid as a white precipitate. After removal of the supernatant liquid, the acid was obtained as a white solid. This purification was repeated twice to have the acid pure enough for the next step, and in nearly quantitative yields.

2.10 *6-Diméthylamino-3-ter-butyltrimethylsilyloxy-2-methyl-2,3-dihydro-benzofuran-2-carboxylic acid pentolactone ester*

To a solution of acid **12a** (6 g, 25.5 mmol) in CH_2Cl_2 (65 ml) EDC (3.4 g), (*R*)-pentolactone (6.05 g, 45 mmol) and DMAP (350 mg) were added. The solution was stirred overnight, hydrolysed with water (100 ml) and extracted with CH_2Cl_2 (2 × 100 ml). The combined organic layers were dried over $MgSO_4$ and concentrated. Purification (flash chromatography, silica, PE:EtOAc 30:70) gave 3.8 g (32%) of the less polar isomer as an yellow solid and 3.3 g (28%) of the more polar isomer as an yellow solid.

Less polar isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7,08 (d, 1H, J = 8.1 Hz), 6.28 (m, 2H), 5.37 (s, 1H), 5.31 (s, 1H), 4.0 (m, 2H), 2.93 (s, 6H), 1.70 (s, 3H), 1.16 (s, 3H), 1.01(s, 3H), 0.92 (s, 9H), 0,17 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 172.2, 171.5, 160.7, 153.0, 125.9, 115.5, 106.0, 94.1, 91.4, 76.3, 76.2, 75.8, 40.7, 40.1, 25.9, 23.1, 19.9, 18.4, 18.3, −4.1, −4.4.

More polar isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7,0 (d, 1H, J = 8.1 Hz), 6.28 (m, 2H), 5.39 (s,

1H), 5.30 (s, 1H), 4.03 (d, 1H, $J = 9.0$ Hz), 3.99 (d, 1H, $J = 9.0$ Hz), 2.90 (s, 6H), 1.70 (s, 3H), 1.12 (s, 3H), 1.03 (s, 3H), 0.9 (s, 9H), 0.17 (s, 3H), 0.16(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 172.6, 171.8, 160.9, 153.1, 126.1, 115.3, 106.2, 94.1, 91.3, 76.4, 76.2, 75.6, 40.7, 40.3, 25.9, 23.0, 19.9, 18.5, 18.3, −4.1, −4.4.

2.11 *6-Chloro-3-ter-butyltrimethylsilyloxy-2-méthyl-2,3-dihydro-benzofuran-2-carboxylic acid pentolactone ester* **13b**. *Prepared and isolated as* **13a** *in 77% overall yield as a 1:1 ratio*

Less polar isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.2 (d, 1H, $J = 8.7$ Hz), 6.8 (m, 2H), 5.43 (s, 1H), 5.30 (s, 1H), 4.0 (d, 1H, $J = 9.0$ Hz), 4.0 (d, 1H, $J = 9.0$ Hz), 1.70 (s, 3 H), 1.17 (s, 3H), 0.93 (s, 3H), 0.90 (s, 9H), 0.20 (s, 3H), 0.19 (s, 3H).

More polar isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.2 (d, 1H, $J = 8.7$ Hz), 6.9 (m, 2H), 5.43 (s, 1H), 5.33 (s, 1H), 4.05 (d, 1H, $J = 9.0$ Hz), 4.01 (d, 1H, $J = 9.0$ Hz), 1.70 (s, 3H), 1.14 (s, 3H), 1.04 (s, 3H), 0.90 (s, 9H), 0.20 (s, 3H), 0.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 171.6, 171.6, 159.9, 135.9, 126.6, 126.5, 121.8, 111.2, 91.6, 76.1, 75.8, 75.8, 53.5, 40.1, 25.7, 22.7, 19.8, 18.1, 17.9, −4.2, −4.6.

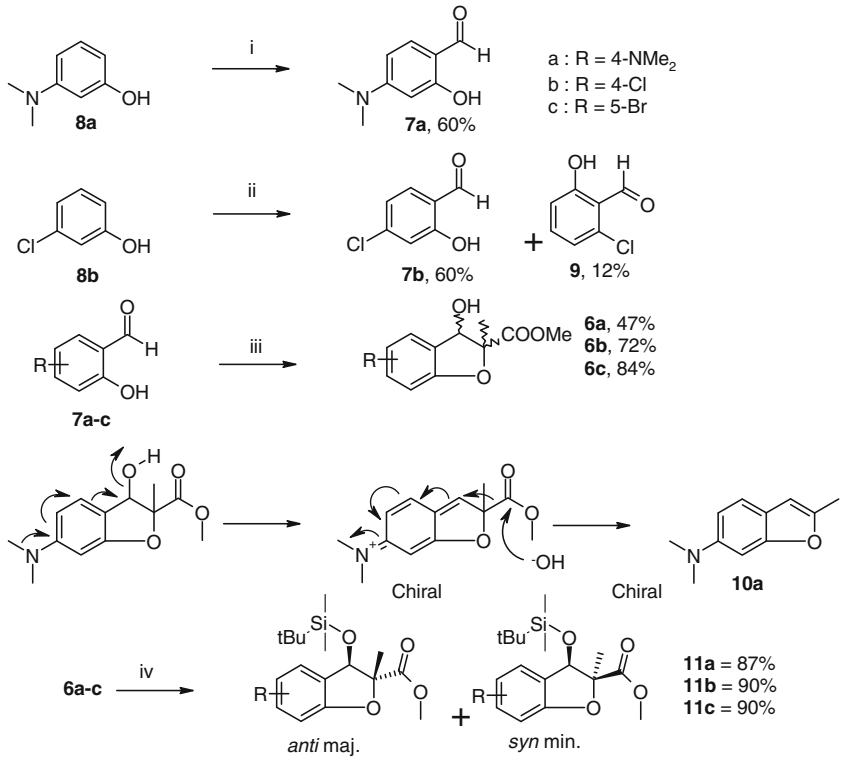
2.12 *5-Bromo-3-ter-butyltrimethylsilyloxy-2-méthyl-2,3-dihydro-benzofuran-2-carboxylic acid pentolactone ester* **13c**. *Prepared and isolated as* **13a** *in 80% overall yields as a 1:1 ratio*

Less polar isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.34 (m, 2H), 6.78 (d, 1H, $J = 8.9$ Hz), 5.46 (s, 1H), 5.30 (s, 1H), 4.00 (s, 2H), 1.68 (s, 3H), 1.16 (s, 3H), 0.94 (s, 3H), 0.92 (s, 9H), 0.20 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 171.4, 158.0, 133.1, 130.3, 128.6, 113.0, 112.0, 91.3, 76.1, 76.0, 75.9, 39.9, 25.7, 22.9, 19.8, 18.1, 17.7, −4.2, −4.5.

More polar isomer: ^{1}H (300 MHz, $CDCl_3$) δ ppm: 7.4 (m, 2H), 6.81 (d, 1H, $J = 8.9$ Hz), 5.44 (s, 1H), 5.33 (s, 1H), 4.04 (d, 1H, $J = 8.9$ Hz), 3.95 (d, 1H, $J = 8.9$ Hz), 1.71 (s, 3H), 1.14 (s, 3H), 1.04 (s, 3H), 0.92 (s, 9H), 0.20 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 171.6, 171.5, 158.1, 133.3, 130.0, 128.7, 113.1, 112.2, 91.2, 76.1, 76.0, 75.8, 40.1, 25.7, 22.8, 19.8, 18.0, 17.9, −4.2, −4.6.

3. Results and discussion

Salicylaldehyde **7a** is a known compound prepared by Vilsmeier–Haack formylation of 3-aminophenol **8a**,



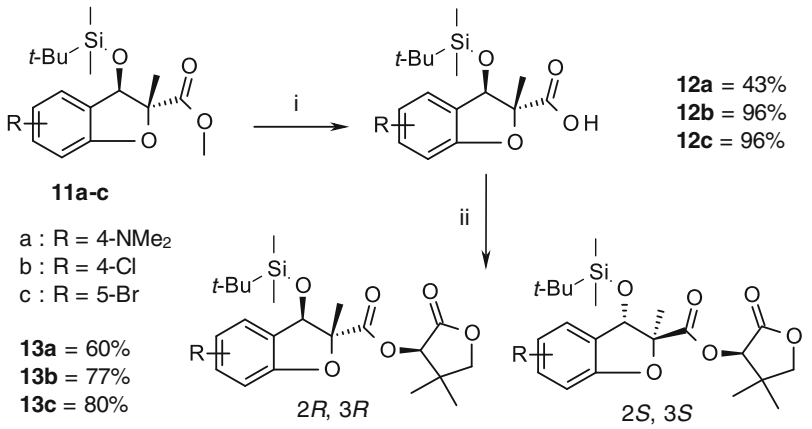
Scheme 1. **i**) $POCl_3$ DMF reflux; **ii**) $(CH_2O)n$ $MgCl_2$, NEt_3, CH_3CN; **iii**) CH_3–CHBr–COOMe, K_2CO_3, DMF, 140°C 1 h; **iv**) TBDMSCl, imidazole, DMF, chromatographic separation.

Table 1. Determination of the *anti-syn* ratios of compounds **6** and **11** by ^{1}H NMR and $H_{benzylic}$ chemical shifts.

R	*anti* 6 ratio $H_{benzylic}$(δ ppm)	*syn* 6 ratio $H_{benzylic}$(δ ppm)
H	74 5.35	26 5.02
4-NMe_2	50 5.17	Not detected
4-Cl	79.6 5.25	20.4 4.90
4-Br	90 5.35	10 4.90
	Anti **10**	*Syn* **10**
	Ha (δ ppm)	Ha (δ ppm)
4-NMe_2	5.31	-
4-Cl	5.15	4.88
4-Br	5.37	5.00

while formylation of the chlorinated homologue **8b** was obtained by Skattebol's method, using paraformaldehyde as the formyl source and $MgCl_2$ as a catalyst[14] (scheme 1). Interestingly, the Skattebol's method does not work with the aminophenol, while the Vilsmeier–Haack method was not convenient for **8b**. Aldehydes **7a–c** were then reacted with 2-bromopropanoic acid methyl ester in the presence of K_2CO_3 in precisely controlled DMF reflux to directly afford the corresponding 2,3-dihydrobenzofuran-3-ol **6** as a mixture of diastereoisomers. The control of the reaction time and the temperature was critical, to avoid the formation of the corresponding benzofurans. In the particular case of compound **6a**, only the *anti* isomer was detected, with concomitant formation of the corresponding benzofuran **10a**, whose formation could not be avoided. As only the *anti* isomer **6a** was obtained with the benzofuran **10a**, the formation of the latter from the *syn* isomer could not be determined. Unexpectedly, the brominated compound **6c** was obtained with a very high diastereoselectivity, with an *anti–syn* ratio of 90:10, compared to the chlorinated counterpart with an *anti–syn* ratio of 79:21 (table 1), and the known unsubstituted analogue with a 74:26 ratio. For the brominated derivative **6c**, an easy separation of the *anti* and *syn* isomers could be achieved by precipitation, a result already observed for unsubstituted benzofuran-3-ols.[12] This practical separation was not possible for compound **6b**. At this stage, prior to the replacement of the methyl ester by a chiral alcohol to achieve resolution, a protection of the 3-hydroxyl group was found necessary. We also expected this protection to favour the general separation of esters **6** by the use of a bulk protecting group.

The mixtures of *anti–syn* alcohols **6a–c** were thus protected as *ter*-butyldimethylsilyl ethers **11**, and we observed an easy chromatographic separation of the isomers of derivatives **6b, c**. The *anti–syn* ratios for compounds **11** were determined by ^{1}H NMR analysis (table 1). The benzylic proton of the *anti* and *syn* diastereoisomers of compounds **11** appeared to be around 5.3 and 5.0 ppm respectively. This 0.3 ppm shift was attributed to the effect of the adjacent carboxyl



Scheme 2. (**i**) LiOH 2.5 M, MeOH, THF; (**ii**) (R)-pentolactone, EDC, DMAP, CH_2Cl_2, chromatographic separation.

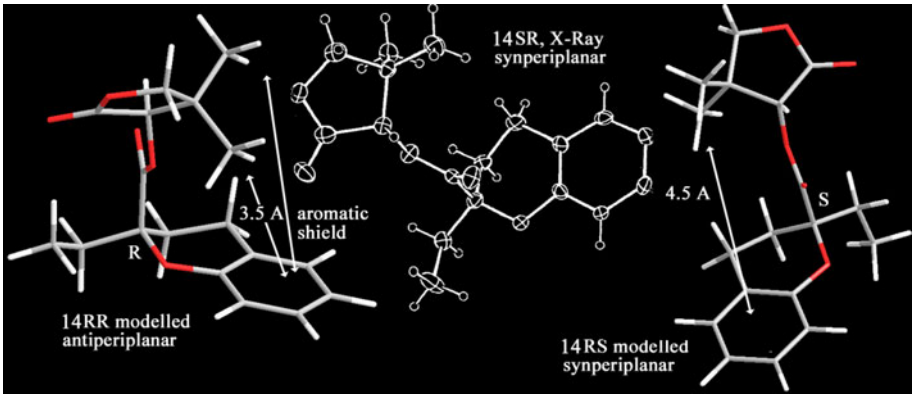


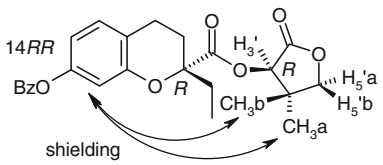
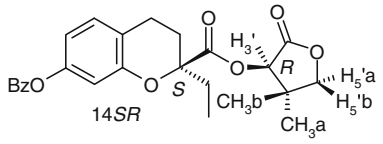
Figure 2. Modelled and X-Ray structure of pentolactone esters **13** and **14**.

group in the *anti* isomers. Analysis of the diastereisomeric mixture **6** before the separation showed the same differences in *anti* and *syn* chemical shifts, confirming the initial ratio for compounds **6** and the fact that silylation did not modify the composition.

The resolution of the major *anti* isomers was then investigated with (*R*)-pentolactone. Hydrolysis of esters **11** afforded the corresponding acids **12** (scheme 2). Compound **11a** once more gave the degradation product **10a**, accounting for the moderate yield. These acids were esterified with (*R*)-pentolactone under EDC coupling conditions to afford esters **13a–c**. In all cases, a 1:1 ratio of esters **13a–c** was obtained and the two enantiomers were separated using chromatography. At this stage, X-ray analysis was unfortunately not possible, all isomers being obtained as deliquescent solids.

In order to determine the possible absolute stereochemistry of the isolated isomers, we compared our ^{1}H NMR results with literature data. Koyoma *et al*. prepared the diastereoisomeric ***R***- and ***S***-(*R*)-pentolactone esters **14** of a chroman derivative (figure 2).[15] In the following text the second letter in **14*RR*** and **14*SR*** referred to the pentolactone chirality. In the case of the **14*RR*** isomer a transesterification with (*S*)-pentolactone gave the **14*RS*** isomer suitable for X-ray analysis, and allowing the determination of the absolute configurations. ^{1}H NMR chemical shift analysis showed significant differences for the methyl groups of the lactone moiety. One methyl group was shielded in the **14*RR*** isomer (1.03 and 0.87 ppm, table 2, entry 1), compared to the **14*SR*** isomer (1.2 and 1.03 ppm, table 2, entry 2). The negative values indicated a shielding effect that must be due to the neighbour aromatic ring. The ***14RR***

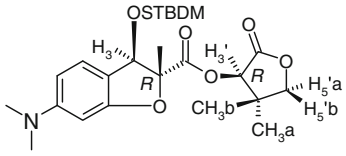
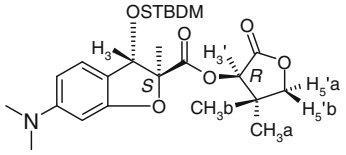
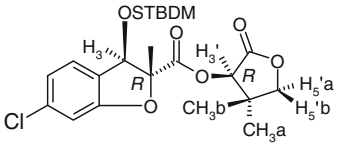
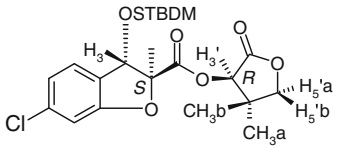
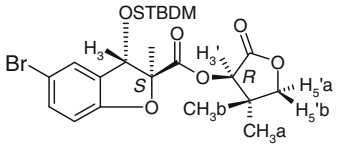
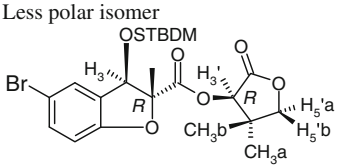
Table 2. ^{1}H NMR comparison for reference compounds **14**.

Entry		δH_3	$\delta H_{3'}$	$\delta H_{5'a}$	$\delta H_{5'b}$	δCH_{3a}	δCH_{3b}
							
1	antiperiplanar		5.35	4.0	4.0	1.03	0.87
							
2	synperiplanar		5.35	4.0	4.0	1.20	1.03
3	$\Delta\delta$ 14*RR*−14*SR*		0.0			−0.17	−0.16

isomer corresponded to an antiperiplanar angle (130–140°) while the ***14SR*** isomer gave a synperiplanar angle around the O=C–C–O bonds (15–30°). Modelled isomers **14** gave stable anti- and synperiplanar conformers. The stable modelled **14*RS*** conformer (figure 2) was found identical to the crystallographic structure obtained for the **14*SR*** antipode. In this conformer, the lactone ring is 4.5 Å away from the aromatic ring and the shielding effect is probably low. A stable **14*RR*** isomer was found with an antiperiplanar angle giving a 3.5 Å distance between one lactone methyl group and the phenyl ring. The observed ^{1}H NMR chemical shifts are in agreement with a synperiplanar **14*SR*** conformer (identical to the X-Ray structure) and an antiperiplanar **14*RR*** conformer. The chemical shifts found for compounds **14** confirmed that the shielding effect must be distance-dependant.

The differences in chemical shifts for selected hydrogen atoms in compounds **13*SR*** and **13*RR*** were then calculated (table 3) and compared to **14*SR*** and **14*RR*** (table 2). For the halogenated compounds **13b, c**, only one lactone methyl group (CH_{3b}) appeared to be significantly shielded (0.1 ppm). The lower values observed for compounds **13** compared to compounds **14** may be due to the five-membered rings that did not have real equatorial and axial positions, as can be found in

Table 3. ^{1}H NMR comparison for compounds **13**.

Entry		δH_3	$\delta H_{3'}$	$\delta H_{5'a}$	$\delta H_{5'b}$	δCH_{3a}	δCH_{3b}
							
1	Less polar isomer	5.37	5.31	4.0	4.0	1.16	1.01
							
2	More polar isomer	5.39	5.30	4.03	3.99	1.12	1.03
3	Dd 13a*RR*-13a*SR*	−0.02	0.01	−0.03	0.01	0.04	−0.02
							
4		5.43	5.30	4.0	4.0	1.17	0.93
							
5		5.43	5.33	4.05	4.01	1.14	1.04
6	Dd 13b*RR*-13b*SR*	0.0	−0.03	−0.05	0.01	0.03	−0.11
							
7		5.46	5.30	4.0	4.0	1.16	0.94
	Less polar isomer 						
8	More polar isomer	5.44	5.33	4.04	3.95	1.14	1.04
9	Dd 13c*RR*-13c*SR*	0.02	−0.03	−0.04	0.05	0.02	−0.10

six-membered rings. Although we were not able to obtain X-ray data to confirm our proposal, we suggested the absolute configuration for compounds **13** as depicted in table 3, in accordance with the results observed for compounds **14,** and the fact that this shielding effect can probably be used in other circumstances.

4. Conclusion

A synthesis of 2,2-disubstituted-dihydro 2,2-disubstituted benzofuran-3-ols was investigated as an intermediate access to a wide range of structures. We showed that the initial introduction of a dialkylamino group was not convenient, giving an easier dehydration to the furan **10**. Replacement by halogen atoms opened the way for potential modifications, with particular high *anti* diastereoselectivity for the bromide derivative. Derivatisation as *ter*-butyldimethylsilyl ethers provided a convenient and apparently general way to separate the *syn* and *anti* diastereoisomers **11** by chromatography. Their relative stereochemistry can be determined by ^{1}H NMR analysis and the enantiodifferentiation of the *anti* isomers has been achieved by transesterification with a resolving agent: (*R*)-pentolactone. Due to the impossibility of obtaining the *syn* isomers **6a** or the lower *syn* isomers yields for **6b, c**, this resolution protocol was not validated for the *syn* isomer. A method was proposed for the determination of the absolute configuration of esters **13** and was found efficient with the halogenated compounds. Work is currently in progress towards accessing enantiopure compounds **5** and assessing the importance of the stereogenic centre for the inhibitory activities of these compounds.

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