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Synthesis and configuration of (1*S*,3*R*)- and (1*R*,3*R*)-1-(3,4-dimethoxyphenyl)-1,3-dimethyl-1,3-dihydroisobenzofurans

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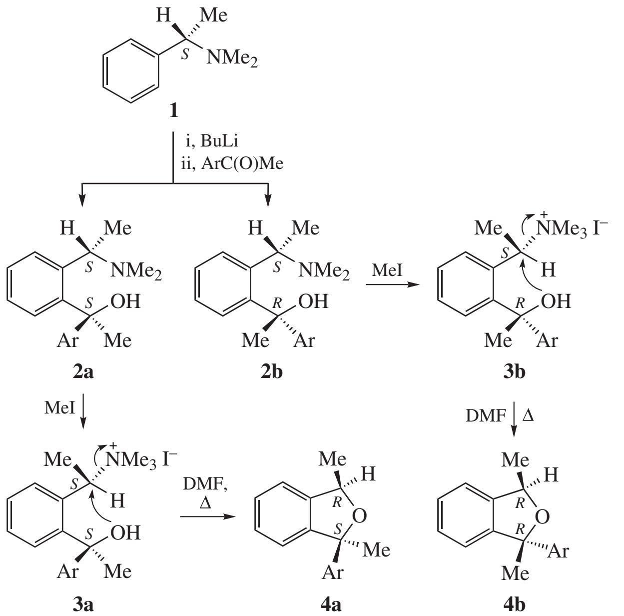
Cyclization of iodides of diastereomeric 1-(1-aryl-1-hydroxyethyl)-2-(1-trimethylammonioethyl)benzenes, derived from (*S*)-1-phenylethanamine, proceeds diastereospecifically to afford (1*S*,3*R*)- and (1*R*,3*R*)-1-aryl-1,3-dimethyl-1,3-dihydroisobenzofurans, the potent antidepressants.

1,3-Dihydroisobenzofurans (1,3-dihydro-2-benzofurans, phthalans) attract interest for their biological and pharmacological activities.[1–3] The first natural phthalan representative, pestacin, isolated from the microorganism *Pestalotiopsis microspora*, displays antifungal properties and antioxidant activity 11 times greater than vitamin E derivative – trolox.[4] Natural papulocandins containing dihydroisobensofuran linked with dicarbohydrate fragment, are antifungal drugs that were shown to be effective for treating AIDS-patients.[5]

Great attention is paid to 1-aryl-substituted phthalans as they possess antidepressant activity.[6,7] Among them, citalopram is a highly selective serotonin reuptake inhibitor without much cardiotoxic, anticholinergic and sedative effects. The high affinity and selectivity of citalopram for human serotonin exclusively resides in the (*S*)-enantiomer.[8] Its synthesis is patented[9] and now it is used as pure enantiomer (Escitalopram). However, limited data of chiral phthalans have been reported.[10,11]

Earlier we developed the synthesis of enantiopure 1,1-diaryl-3-methyl-substituted phthalans by cyclization of methoiodides of δ-aminoalcohols (aminotriarylcarbinols) obtained from *N*,*N*-dimethyl-(*S*)-1-phenylethanamine **1** *via* its *ortho*-lithiation followed by the reaction with substituted benzophenones.[12,13] In the extension, we studied the condensation with alkyl aryl ketones that would give rise to aminodiarylcarbinols. Methoxy-substituted ketones were studied first. The choice is due to the fact that methoxy group is present in many natural compounds. We think that methoxy-substituted phthalans as well as the intermediate amino alcohols may be of interest as potential biologically active compounds and as precursors for the hydroxy phthalans (pestacin analogues) which are not obtained non-racemic till now. The condensation of monomethoxyacetophenones with *ortho*-lithiated **1** proceeds without stereoselectivity as in the case of analogous benzophenones. However, 3,4-dimethoxybenzophenone reacted stereospecifically.[14] This can be explained by the influence of methoxy groups that reduced carbonyl activity and hence increased the stereoselectivity of the reaction. We expected the same effect on using 3,4-dimethoxyacetophenone (Scheme 1).[†]



Ar = 3,4-(MeO)$_2$C$_6$H$_3$

Scheme 1

Unfortunately, diastereoselectivity of the reaction was not high: the ratio of obtained diastereomeric aminoalcohols **2a**:**2b** was 3:1 (somewhat higher than in the condensation with acetophenone, *dr* 3:2). Using column chromatography on Kieselgel we managed to separate the diastereomers whose structure was confirmed by IR and ^{1}H NMR spectra. Both compounds reveal the

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[†] Amine **1** (10 mmol in 10 ml of hexane) was lithiated by treatment with 10 ml of Bu^{t}Li (1.3 M solution in hexane) and under dry argon atmosphere this solution was added dropwise to a solution of 12 mmol of 3,4-dimethoxyacetophenone in 15 ml of anhydrous diethyl ether. Reaction mixture was stirred for 30 min and after 24 h at room temperature was quenched with water. The water phase was extracted with diethyl ether (3×20 ml). The organic extracts were washed with water and then extracted with 6 M HCl. The aqueous layer was made alkaline with K$_2$CO$_3$ and the organics liberated were extracted with diethyl ether, dried over MgSO$_4$, concentrated under reduced pressure and unreacted amine **1** was distilled off *in vacuo*. The ratio of the resulting diastereomeric amino alcohols (**2a**:**2b**) was estimated as 3:1 from ^{1}H NMR spectrum of the crude mixture, yield 70%.

Diastereomers were separated by column chromatography (Kiesegel 60, gradient elution with benzene–acetone, 10:1 → 5:1).

Major diastereomer (S,S)-**2a**: mp 108 °C (EtOH), $[\alpha]_D$ –87.8 (*c* 1, EtOH). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 1.03 (d, 3H, Me, *J* 6.8 Hz), 1.80 (s, 3H, Me), 2.10 (s, 6H, NMe$_2$), 3.645 (q, 1H, CH, *J* 6.8 Hz), 3.82, 3.83 (2s, 2×3H, 2OMe), 6.50–7.75 (m, 7H, H$_{arom}$), 9.75 (s, 1H, OH). IR (ν/cm^{-1}): 2400–3100 (ν$_{OH}$).

broad band at 3100–2400 cm^{-1} in IR spectra and large shift of H-signal of the OH group (9.75 ppm for **2a** and ~7 ppm for **2b** as compared with 4.7 ppm for Ph$_2$CHOH). It is the evidence of the strong intramolecular H-bond. We observed such a phenomenon in our previous studies of 1-phenethylaminocarbinols.[14,15] The major diastereomer **2a** was obtained in crystalline form and (*S*)-configuration of the new chiral (carbinol) center was established by X-ray analysis on the basis of the known (*S*)-configuration of the chiral center of the parent amine **1** [Figure 1(*a*)].[‡]

Amino alcohols **2a**,**b** were converted to their methoiodides **3a**,**b**, which undergo cyclization to phthalans on warming in DMF in the presence of sodium acetate.[†] In amino alcohol methoiodide there are two points of possible attack by internal nucleophile: (i) benzylic carbon atom; its attack leads to the elimination of Me$_3$N and formation of 1,3-dihydroisobenzofuran; the reaction proceeds with the inversion of amine chiral center as we showed earlier;[13] (ii) methyl group at nitrogen; the result is the elimination of the methyl group and recovery of the initial amino alcohol, in this case the chiral center is not involved. Usually we isolate up to 10% of amino alcohol with the same optical purity as used initially.

The phthalan **4a** was obtained by cyclization of (1*S*,3*S*)-amino alcohol methoiodide **3a** and X-ray study showed that its chiral centers have different configurations [Figure 1(*b*)].[‡]

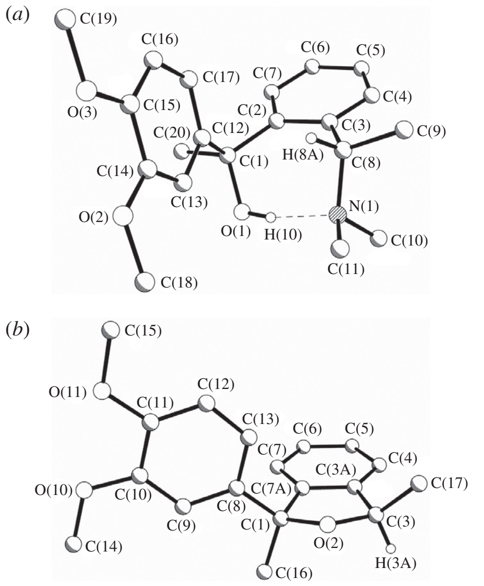

Figure 1 Molecular structure of (*a*) amino alcohol **2a** and (*b*) phthalan **4a**.

On the basis of previously established S$_N$2 mechanism of methoiodide cyclization[13] we assigned (1*S*,3*R*)-configuration to the chiral centers in the synthesized phthalan **4a**.

From the methoiodide of the second aminoalcohol (*S*,*R*)-**2b**, phthalan **4b** was obtained as an oil, and it should have (1*R*,3*R*)-configuration of its chiral centers.

In conclusion, chiral 1-(3,4-dimethoxyphenyl)-1,3-dimethyl-1,3-dihydroisobenzofurans (phthalans) were obtained using a new approach by cyclization of methoiodides of diastereomeric (*S*,*S*)- and (*S*,*R*)-δ-amino alcohols easily synthesized from (*S*)-1-phenylethanamine. The configuration of the new chiral centers in major amino alcohol **2a** and corresponding phthalan **4a** was established by X-ray analysis.

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Diastereomer (R,S)-**2b**: yellow oil, $[\alpha]_D$ 14.5 (*c* 1, EtOH). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 1.22 (d, 3H, CH*Me*, *J* 6.9 Hz), 1.89 (s, 3H, Me), 2.20 (s, 6H, NMe$_2$), 3.80, 3.84 (2s, 2×3H, 2OMe; q, 1H, C*H*Me), 6.75–7.30 (m, 7H, H$_{\text{arom}}$; 1H, OH). IR (ν/cm^{-1}): 2400–3100 (ν$_{\text{OH}}$).

Methoiodide **3a**: mp 207 °C (decomp.), $[\alpha]_D$ –44.4 (*c* 1, EtOH). ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ: 0.97 (d, 3H, CH*Me*, *J* 6.82 Hz), 2.09 (s, 3H, Me), 3.25 (s, 9H, NMe$_3$), 5.35–5.36 (q, 1H, C*H*Me, *J* 6.82 Hz), 3.81 (s, 6H, 2OMe), 5.1 (s, 1H, OH), 6.5–8.0 (m, 7H, H$_{\text{arom}}$). Found (%): C, 53.51; H, 6.41; N, 2.97. Calc. for C$_{21}$H$_{30}$INO$_3$ (%): C, 53.57; H, 6.42; N, 2.93.

Methoiodide **3b**: mp 200 °C (decomp.), $[\alpha]_D$ –96 (*c* 1, EtOH). ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ: 1.88 (d, 3H, CH*Me*, *J* 6.88 Hz), 2.17 (d, 3H, Me), 2.93 (s, 9H, NMe$_3$), 3.86 (2s, 2×3H, 2OMe), 4.0 (s, 1H, OH), 5.76 (q, 1H, C*H*Me, *J* 6.88 Hz), 6.5–7.5 (m, 7H, H$_{\text{arom}}$).

Phthalan (*S*,*R*)-**4a**. Methoiodide **3a** (5 mmol) and 0.5 g of anhydrous AcONa in 30 ml of freshly distilled DMF were refluxed for 8 h. DMF was distilled off under reduced pressure, water and Et$_2$O were added. The phases were separated, ether phase was washed with 6 M HCl and water phase was extracted with Et$_2$O, the ether extracts were washed with water and dried over MgSO$_4$. Et$_2$O was distilled off and the residue was crystallized from ethanol, yield 90%, mp 113 °C, $[\alpha]_D$ 39.5 (*c* 1, EtOH). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 1.60 (d, 3H, CH*Me*, *J* 6.6 Hz), 1.84 (s, 3H, Me), 5.47 (q, 1H, C*H*Me, *J* 6.6 Hz), 3.86, 3.88 (2s, 2×3H, 2OMe), 6.83–7.30 (m, 7H, H$_{\text{arom}}$). Found (%): C, 76.03; H, 7.09. Calc. for C$_{18}$H$_{20}$O$_3$ (%): C, 75.97; H, 7.13.

Phthalan (R,R)-**4b** was obtained by the same procedure from methoiodide **3b** as an oil, $[\alpha]_D$ 70 (*c* 1, EtOH). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 1.90 (d, 3H, CH*Me*, *J* 6.6 Hz), 1.90 (s, 3H, Me), 5.28 (q, 1H, C*H*Me, *J* 6.6 Hz), 3.83, 3.85 (2s, 2×3H, 2OMe), 6.70–8.00 (m, 7H, H$_{\text{arom}}$).

[‡] *Crystal data for amino alcohol* **2a**. Crystals (C$_{20}$H$_{27}$NO$_3$, M = 329.43) are orthorhombic, space group $P2_12_12_1$, at 296(2) K: a = 8.0818(7), b = 11.805(1) and c = 18.637(2) Å, V = 1778.0(3) Å^3, Z = 4, d_{calc} = 1.231 g cm^{-3}, μ(MoKα) = 0.082 mm^{-1}, F(000) = 712. 19486 reflections were measured (2θ < 60°), from which 5183 are independent (R_{int} = 0.0456), wR_2 = 0.1011 and GOF = 1.006 for all independent reflections [R_1 = 0.0424 for 4549 observed reflections with $I > 2\sigma(I)$].

Crystal data for phthalan **4a**. Crystals (C$_{18}$H$_{20}$O$_3$, M = 284.34) are orthorhombic, space group $P2_12_12_1$, at 100(2) K: a = 6.0313(5), b = 10.9807(9) and c = 22.334(2) Å, V = 1479.1(2) Å^3, Z = 4, d_{calc} = 1.277 g cm^{-3}, μ(MoKα) = 0.086 mm^{-1}, F(000) = 608. 15059 reflections were measured (2θ < 56°), from which 3560 are independent (R_{int} = 0.0453), wR_2 = 0.1113 and GOF = 1.001 for all independent reflections [R_1 = 0.0526 for 2974 observed reflections with $I > 2\sigma(I)$].

CCDC 985742 and 985743 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.