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Simple chiral auxiliary-assisted resolution of 2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionic acid†

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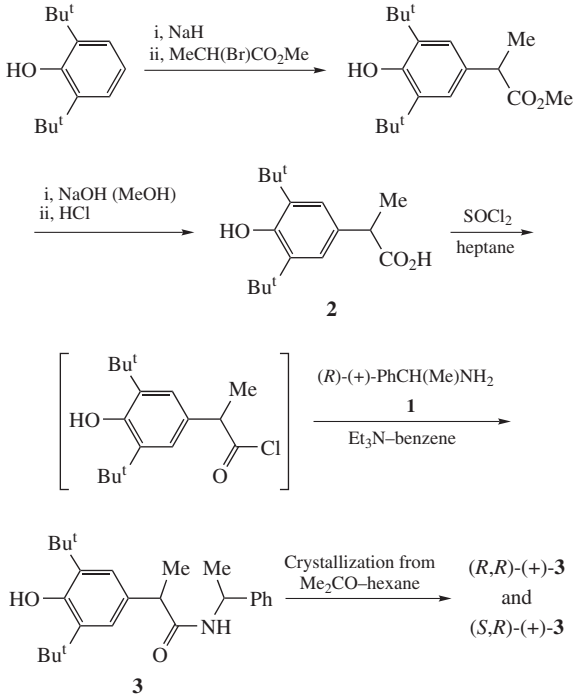
Chiroptical properties and X-ray diffraction were studied for both diastereomers of *N*-[(*R*)-1-phenylethyl]-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propanamide, whose acid moiety is a chiral antioxidant.

Synthesis and applications of achiral phenolic antioxidants (PAO) were broadly studied.[1] In the last decades, considerable attention was focused on the pharmaceutical chiral substances, including chiral PAO in racemic[2] and scalemic[3] forms. Several PAO-based chiral drugs of broad spectrum of action were devised, *e.g.*, Tazofelone[4] and its analogue[5] as well as recently reported antioxidant protector against cigarette smoke.[6] Investigations[7] dealing with mono-, di-, and three-isobornylphenols[7(a)] should be of special note. The works[8] on the phenomenon of 'mitochondria-targeted antioxidants more effective than untargeted one' are of particular interest. Studies of natural polyphenolic antioxidants discovered their antiinflammatory and antiinvasive activities.[9] Natural flavones and their synthetic analogues exhibited antiviral and antiinvasive activity against solid tumors.[9]

A key problem in obtaining chiral PAO is resolution of racemates into enantiomers. Here, this problem was solved through incorporation of enantiomerically pure moiety of amine **1** into the racemic PAO **2** followed by simple crystallization to resolve the diastereomers of amide **3** (Scheme 1).‡



Scheme 1

By three-fold crystallization of compound **3** from acetone, the well-shaped hexahedral plates were obtained; according to

† To the memory of Grigory Nikiforov, our long-time friend and colleague.

‡ *Methyl 2-(3,5-di*-tert-*butyl-4-hydroxyphenyl)propionate*. 2,6-Di-*tert*-butylphenol (20.6 g, 0.1 mol) was added to suspension of NaH (3 g, 0.1 mol) in dry 1,2-dimethoxyethane (200 ml) under argon stream. The mixture was stirred for 2.5 h at 40 °C, then cooled to 15–20 °C, methyl 2-bromopropionate (11.2 ml, 0.1 mol) was added under stirring. The mixture was stirred for 1 h at 80–85 °C, cooled to 20 °C, thereafter the solid residue was filtered off, and the mother liquor was evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 (100 ml), the solution was washed with 1% HCl, and the organic layer was separated and evaporated *in vacuo*. The residue was dissolved on heating in hexane (20 ml), then cooled to –5 °C, and the crystals were filtered off to give 20.3 g (69% yield) of the title ester, mp 84–85 °C. ^{1}H NMR (acetone-d_6) δ: 1.43 (s, 18H, 2Me$_3$C), 1.48 (d, 3H, Me, ^3J 6.7 Hz), 3.61 (s, 3H, MeO), 3.67 (q, 1H, C*H*Me, ^3J 6.7 Hz), 6.02 (s, 1H, OH), 7.11 (s, 2H, H_{Ar}).

2-(3,5-Di-tert-*butyl-4-hydroxyphenyl)propionic acid* **2**. The corresponding methyl ester (5.84 g, 20 mmol) was added to solution of NaOH (1 g, 25 mmol) in a mixture of MeOH and water (45 and 5 ml, respectively) under argon stream, and the mixture was boiled for 2 h. After cooling, 10% HCl was added to reach pH ≈ 5, and the mixture was diluted with equal amount of water. The residue was separated and washed with water and hexane to afford 5.7 g of the product, yield 98%, mp 200–201 °C. ^{1}H NMR ($CDCl_3$) δ: 1.43 (s, 18H, Bu^t), 1.48 (d, 3H, Me, ^3J 6.7 Hz), 3.65 (q, 1H, CH), 5.16 (s, 1H, OH), 7.12 (s, 2H, Ar).

Amide **3**. Thionyl chloride (1.2 ml, 17 mmol) was added to a suspension of acid **2** (2.78 g, 10 mmol) in heptane (30 ml), and the mixture was stirred for 3 h at 90–95 °C, cooled down and evaporated *in vacuo*. The chloroanhydride thus obtained (mp 40–42 °C) was dissolved in benzene (75 ml), and a solution of Et_3N (1.4 ml, 10 mmol) and (*R*)-(+)-PhCH(Me)NH$_2$ **1** (1.3 ml, 10 mmol) in benzene (10 ml) was added at 20 °C. The mixture was stirred for 0.5 h under argon stream, the precipitate of Et_3N·HCl was separated, and the filtrate was evaporated *in vacuo*. Crystallization of the residue from hexane gave 3.5 g of yellowish crystals of amide **3** (92% yield). Upon three-fold crystallization from acetone the diastereomer (*R*,*R*)-(+)-**3** was obtained, yield 92%, mp 188–189 °C, $[\alpha]_D^{20}$ +21.8 (*c* 0.49, MeOH). HRMS, *m/z*: 382.2763 [M$^+$] (calc. 381.5597). ^{1}H NMR (benzene-d_6) δ: 1.07 (d, 3H, *Me*CHAr, ^3J 6.9 Hz), 1.62 (d, 3H, *Me*CHN, ^3J 7.1 Hz), 1.35 (s, 18H, 2Me$_3$C), 3.33 (q, 1H, C*H*Ar, ^3J 6.9 Hz), 5.27 (dq, 1H, MeC*H*NH, ^3J 7.1 and 8.0 Hz), 5.02 (s, 1H, OH), 5.45 (d, 1H, NH, ^3J 8.0 Hz), 7.06 (m, 5H, Ph), 7.2 (s, 2H, H_{Ar}). Upon evaporation of mother liquor, three-fold crystallization of the residue from acetone–hexane mixture (1:9 v/v) gave the diastereomer (*S*,*R*)-(+)-**3**, yield 91%, mp 143–144 °C, $[\alpha]_D^{20}$ +57.4 (*c* 0.76, MeOH). ^{1}H NMR (benzene-d_6) δ: 1.06 (d, 3H, *Me*CHAr, ^3J 7.0 Hz), 1.38 (s, 18H, 2Me$_3$C), 1.58 (d, 3H, *Me*CHN, ^3J 7.1 Hz), 3.21 (q, 1H, C*H*Ar, ^3J 7.1 Hz), 5.25 (dq, 1H, MeC*H*NH).

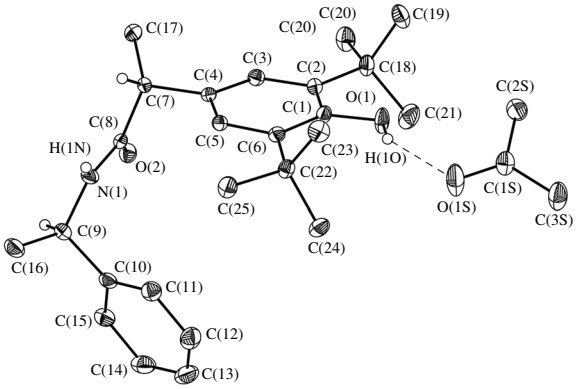


Figure 1 General view of the molecule of (*R*,*R*)-(+)-**3**.

results of X-ray diffraction they have the (*R*,*R*)-(+) configuration.§ This compound crystallizes as the solvate with acetone molecule that participates in the formation of hydrogen bond with hydroxy group [O(1)···O(1S) 2.826(2) Å]. In the crystal, the molecules are assembled into infinite chains by means of weak N–H···O hydrogen bonds [N···O 3.298(2) Å] (Figure 1).§ This diastereomer was characterized by the CD spectrum (Figure 2). Upon evaporation of the mother liquor, three-fold crystallization of the residue from acetone–hexane mixture (1:9 v/v) afforded fine needles of another diastereomer (*S*,*R*)-(+)-**3**.

To conclude, a simple and efficient method has been developed to synthesize (yields 69–92%) and resolve diastereomers of the described chiral PAO.

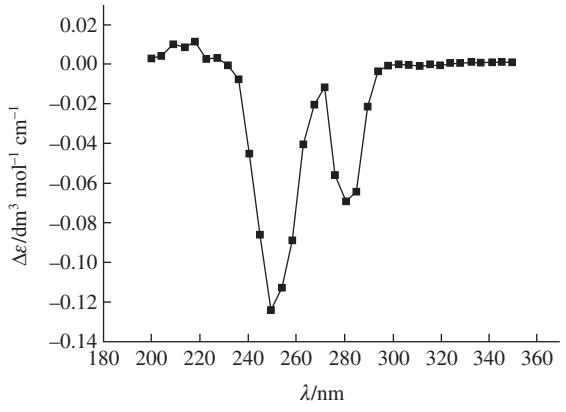


Figure 2 CD spectrum of (*R*,*R*)-(+)-**3**.

§ *Crystal data for* (*R*,*R*)-(+)-**3**. Crystals ($C_{25}H_{35}NO_2$, C_3H_6O, M = 439.62) are trigonal, space group $P3_22_1$, at 100 K: $a = b = 10.519(5)$ and $c = 40.33(4)$ Å, $V = 3865(4)$ Å^3, $Z = 6$ ($Z' = 1$), $d_{calc} = 1.133$ g cm^{-3}, μ(MoKα) = 0.72 cm^{-1}, $F(000) = 1440$. All measurements were performed with a Bruker SMART APEX2 CCD diffractometer [λ(MoKα) = 0.71073 Å, ω-scans]. 15781 reflections were measured ($2\theta < 58°$), from which 3950 are independent ($R_{int} = 0.0332$), $wR_2 = 0.1004$ and GOF = 1.062 for all independent reflections [$R_1 = 0.0407$ for 3626 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL-Plus 5.0.[10]

CCDC 791361 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2010.

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