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# Syntheses of (*S*,*S*)-Reboxetine via a Catalytic Stereospecific Rearrangement of *β*-Amino Alcohols

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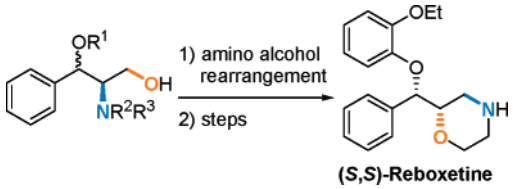
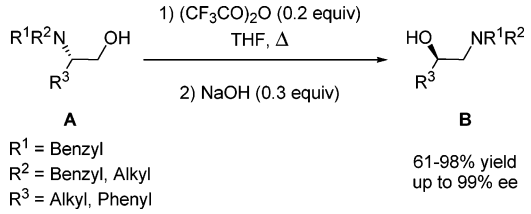



The formal total synthesis of (*S*,*S*)-reboxetine has been realized by two different approaches using a stereospecific rearrangement of *β*-amino alcohols catalyzed by $(CF_3CO)_2O$.

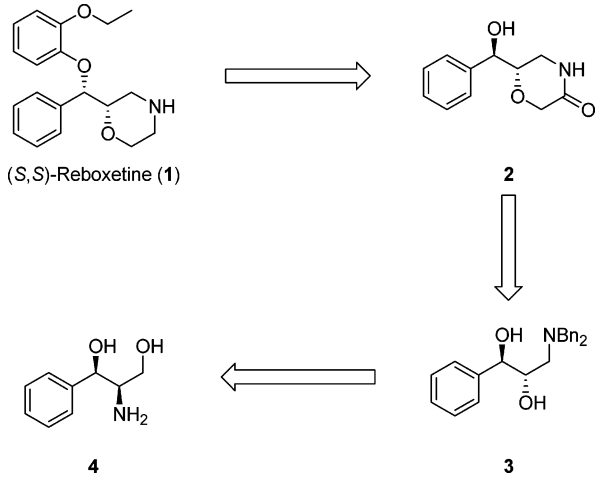
Recently, we have shown that *N*,*N*-dialkyl-*β*-amino alcohols of type **A** can be rearranged stereospecifically by using a catalytic amount of $(CF_3CO)_2O$ followed by saponification with NaOH to produce *β*-amino alcohols of type **B** (Scheme 1).[1]

Herein, we would like to report the application of this rearrangement to the synthesis of (*S*,*S*)-reboxetine. Reboxetine is a selective norepinephrine reuptake inhibitor (NRI) which has been widely studied for its pharmacological properties.[2] Commercially available under the name Edronax, Prolift, Vestra, and Norebox, reboxetine is indicated in the treatment of depressive disorder and is marketed as a racemic mixture of the (*R*,*R*)- and (*S*,*S*)-enantiomers. However, the latter enantiomer has a greater affinity and selectivity for the norepinephrine transporter (NET).[3] So far, the methods reported to isolate the (*S*,*S*)-enantiomer of reboxetine and analogues include chemical resolution,[4] capillary electrophoresis,[5] and chiral HPLC.[6] Asymmetric syntheses via a chiral starting material[4a,7] and by Sharpless epoxidation[8] or dihydroxylation[9] have also been reported.

**SCHEME 1**




**SCHEME 2**




The synthesis of (*S*,*S*)-reboxetine **1** was envisaged from morpholinone **2** that would arise from the *β*-amino alcohol **3**. The latter compound would be issued from the rearrangement of a *N*,*N*-dibenzylated amino alcohol obtained from the commercially available (−)-(1*R*,2*R*)-2-amino-1-phenyl-1,3-propanediol **4** (Scheme 2).

The synthesis of (*S*,*S*)-reboxetine started with the transformation of the commercially available (−)-(1*R*,2*R*)-2-amino-1-phenyl-1,3-propanediol **4** to the corresponding tertiary amine **5** by *N*,*N*-dibenzylation in 98% yield. When **5** was treated with $(CF_3CO)_2O$ (0.4 equiv) in refluxing toluene for 5 h followed by a NaOH treatment, the rearranged amino alcohol **3**[1] was isolated in 78% yield with an ee of 99%.[10] Whereas in these

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(2) (a) Melloni, P.; Carniel, G.; Della Torre, A.; Bonsignori, A.; Buonamici, A.; Pozzi, O.; Ricciardi, S.; Rossi, A. C. *Eur. J. Med. Chem.* **1984**, *19*, 235−242. (b) Hajós, M.; Fleishaker, J. C.; Filipiak-Reisner, J. K.; Brown, M. T.; Wong, E. H. F. *CNS Drug Rev.* **2004**, *10*, 23−44.

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(4) (a) Melloni, P.; Della Torre, A.; Lazzari, E.; Mazzini, G.; Meroni, M. *Tetrahedron* **1985**, *41*, 1393−1399. (b) Prabhakaran, J.; Majo, V. J.; Mann, J. J.; Kumar, J. S. D. *Chirality* **2004**, *16*, 168−173.

(5) Raggi, M. A.; Mandrioli, R.; Sabbioni, C.; Parenti, C.; Cannazza, G.; Fanali, S. *Electrophoresis* **2002**, *23*, 1870−1877.

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(7) Brenner, E.; Baldwin, R. M.; Tamagnan, G. *Org. Lett.* **2005**, *7*, 937−939.

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(10) Determined by SFC using a Daicel chiralcel OD-H column.

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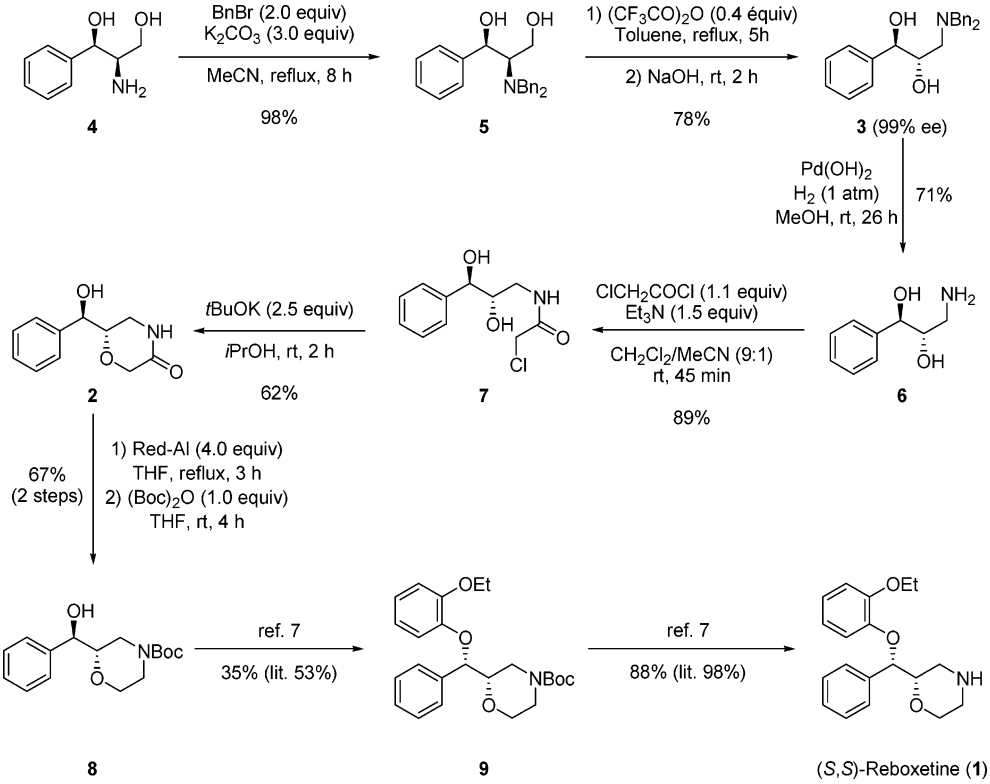
**SCHEME 3**



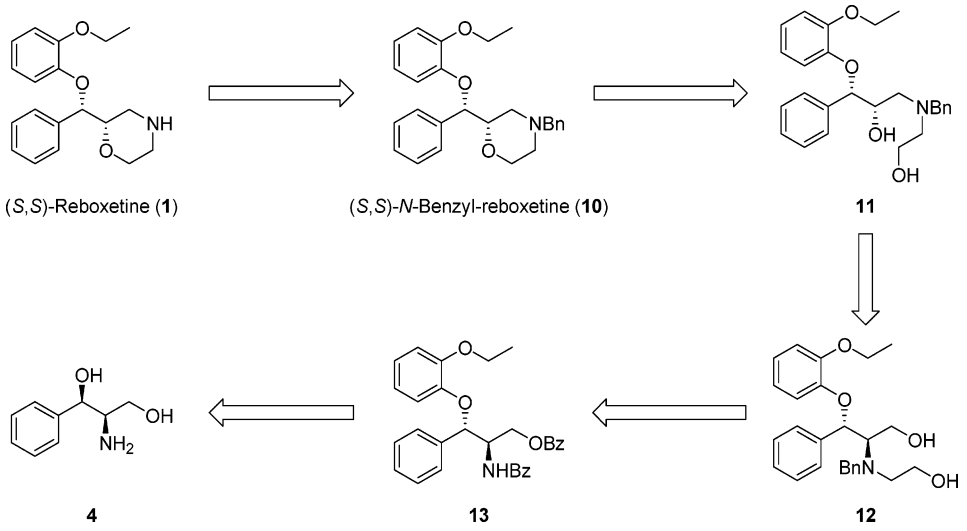

conditions the yield was slightly lower than in the previously reported conditions [$(CF_3CO)_2O$ (0.2 equiv), THF, 100 °C, 18 h, microwaves irradiation, 83%)],[1b] using 0.4 equiv of $(CF_3CO)_2O$ in refluxing toluene allowed us to reduce the reaction time, to perform the rearrangement on a bigger scale, and to avoid the use of the microwave apparatus. Removing the benzyl groups of the *N*,*N*-dibenzylamino alcohol **3** was initially attempted by hydrogenolysis under 1 or 4 atm of $H_2$ in the presence of Pd/C with and without formic acid, but under these conditions, the debenzylation did not go to completion and a mixture of the mono- and didebenzylated products was obtained. Additionally, using ammonium formate as a hydrogen source in the presence of Pd/C in refluxing MeOH or in MeOH under microwave irradiation[11] did not improve the conversion toward the didebenzylated amino alcohol **6**. However, the hydrogenolysis of **3** under 1 atm of $H_2$ in the presence of $Pd(OH)_2$ in MeOH at room temperature for 26 h led to the primary amine **6** with a yield of 71%. As the construction of the morpholine ring was conceived to be achievable by an intramolecular substitution of a chloroamide by an alkoxide, compound **6** was treated with chloroacetyl chloride, and chloroacetamide **7** was isolated in 89% yield. The latter compound was then transformed into morpholinone **2** in 62% yield by treatment with *t*BuOK (2.5 equiv) in *i*PrOH at room temperature for 2 h. As the stereogenic center at the benzylic position in morpholinone **2** has to be inverted, a Mitsunobu reaction[12] was applied directly on substrate **2**. As the introduction of the 2-ethoxyphenoxy group failed under these conditions, probably related to the presence of the secondary amide in **2**, it was decided to first reduce the morpholinone ring and then to protect the resulting secondary amine as a *tert*-butylcarbamate. Therefore morpholinone **2** was reduced with Red-Al (4.0 equiv) in refluxing THF for 3 h, and the resulting secondary amine was directly transformed into *tert*-butylcarbamate **8** in 67% yield over two steps. The physical and spectroscopic data of **8** were in full agreement with the literature data, and the synthesis of (*S*,*S*)-reboxetine was completed as described by Tamagnan et al.[7] The protected morpholine **8** was treated under Mitsunobu conditions [$PPh_3$ (2.0 equiv), 2-ethoxyphenol (2.0 equiv), DIAD (2.0 equiv), THF, rt, 22 h] to produce the desired compound **9** in modest yield (35%, lit. 53%). Deprotection of morpholine **9** using TFA (15 equiv, $CH_2Cl_2$, rt, 16 h then NaOH) afforded (*S*,*S*)-reboxetine in 88% yield (Scheme 3). Using this strategy, (*S*,*S*)-reboxetine was obtained in nine steps with an overall yield of 6.2%.

A second approach of (*S*,*S*)-reboxetine was envisioned from the (*S*,*S*)-*N*-benzylreboxetine **10**, as this compound had been previously transformed to (*S*,*S*)-reboxetine in 88% yield by treatment with 1-chloroethylchloroformate (5.0 equiv) and *i*$Pr_2$NEt (5.0 equiv) in refluxing $CH_2Cl_2$.[9a] In order to shorten the reaction sequence, the construction of the morpholine ring present in **10** was planned by an intramolecular cyclization of the aminodiol **11** already possessing a hydroxyethyl chain on the nitrogen atom. The aminodiol **11** would arise from the rearrangement of aminodiol **12** which could be obtained from the dibenzoylated amino alcohol **13**. The latter would be prepared from the commercially available (−)-(1*R*,2*R*)-2-amino-1-phenyl-1,3-propanediol **4** (Scheme 4).

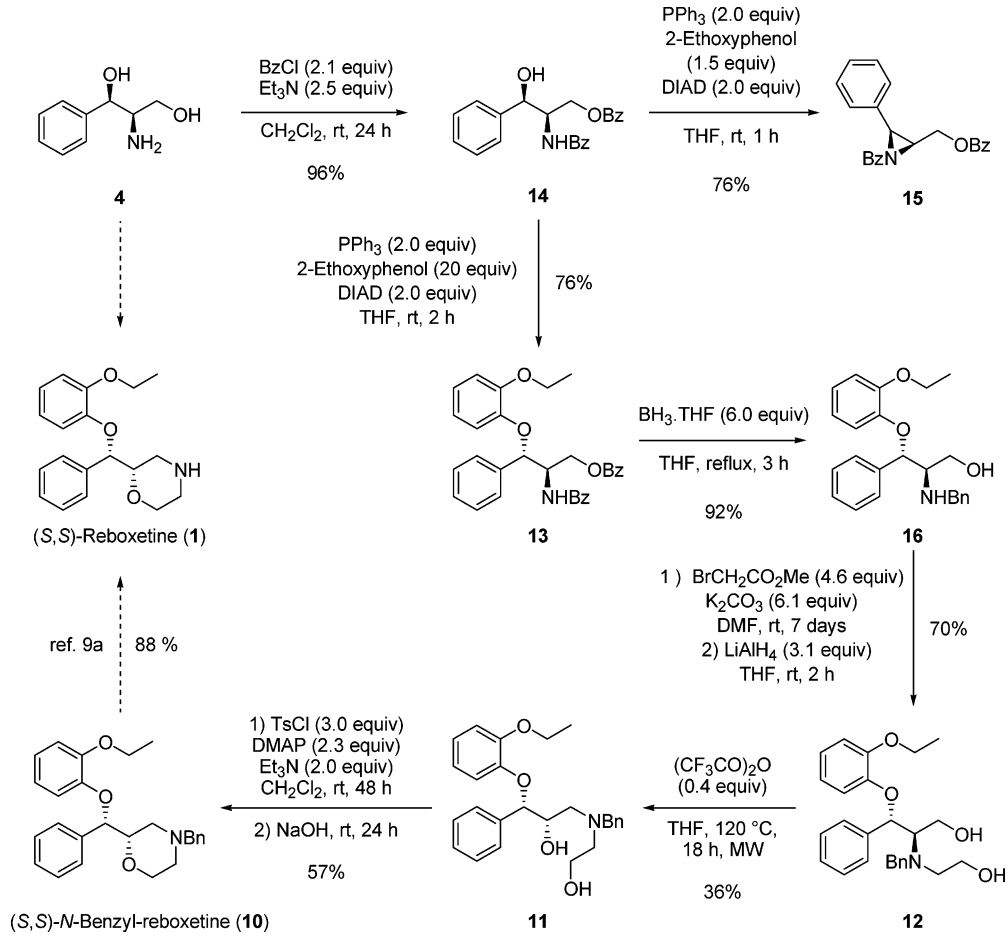
In order to perform a Mitsunobu reaction on the benzylic alcohol present in **4**, the primary amino and hydroxyl groups were benzoylated to provide compound **14** with a yield of 96%. After treatment of **14** with 2-ethoxyphenol (1.5 equiv), $PPh_3$ (2.0 equiv), and DIAD (2.0 equiv) in THF at room temperature for 1 h, compound **13** was not isolated, but aziridine **15** was

(11) Banik, B. K.; Barakat, K. J.; Wagle, D. R.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1999**, *64*, 5746−5753.
(12) Mitsunobu, O. *Synthesis* **1981**, 1−28.

**SCHEME 4**




**SCHEME 5**




obtained in 76% yield, resulting from the substitution of the benzylic position by the amide group. In order to avoid the formation of **15**, a large excess of 2-ethoxyphenol (20 equiv), $PPh_3$ (2.0 equiv), and DIAD (2.0 equiv) was stirred in THF during 30 min at room temperature before the addition of compound **14** (1.0 equiv) in one portion. The desired benzylic ether **13** was obtained as the major compound in 76% yield. The latter was then reduced by treatment with $BH_3$·THF (6.0 equiv) in refluxing THF for 3 h to afford *N*-benzylamino alcohol **16** in 92% yield. Diol **12**, which will be the substrate used for the rearrangement, was obtained in 70% yield (two steps from **16**) by *N*-alkylation using methyl bromoacetate (4.6 equiv) followed by reduction of the crude material by $LiAlH_4$. The *N*,*N*-dialkylamino alcohol **12** was then submitted to the rearrangement by treatment with $(CF_3CO)_2O$ (0.4 equiv, THF, 120 °C, 18 h under microwave irradiation), and the rearranged aminodiol **11** was isolated in a modest yield of 36%, probably because of the sensitivity of the ether functionality in acidic

conditions. We have to point out that, when the rearrangement was performed with 1.1 equiv of $(CF_3CO)_2O$ in the presence of $Et_3N$ (2.0 equiv) in THF at 120 °C during 27 h under microwave irradiation,[1a] the rearranged amino alcohol **11** could not be separated from byproducts. In order to obtain the morpholine ring, a solution of amino alcohol **11**, $Et_3N$ (2.0 equiv), and DMAP (2.3 equiv) in $CH_2Cl_2$ was treated with TsCl (3.0 equiv) which was added in small portions until complete disappearance of aminodiol **11**. The reaction mixture was then treated under basic conditions (NaOH) to produce (*S*,*S*)-*N*-benzylreboxetine **10** in 57% yield (Scheme 5). As this product was previously transformed to (*S*,*S*)-reboxetine in 88% yield,[9a] we have achieved a formal synthesis of (*S*,*S*)-reboxetine in eight steps from **4** with an overall yield of 8.5%. Even though the rearrangement of **12** to **11** proceeded with a modest yield, this strategy is better than the previous one considering the overall yield.

We have shown that the stereospecific rearrangement of *N*,*N*-dialkyl-*β*-amino alcohols in the presence of a catalytic amount of $(CF_3CO)_2O$ could be successfully applied in total synthesis as we performed two different syntheses of the (*S*,*S*)-reboxetine using the rearrangement as a key step. The first approach allowed us to complete a total synthesis of (*S*,*S*)-reboxetine in nine steps with an overall yield of 6.2%, and in the second approach, a formal synthesis of (*S*,*S*)-reboxetine was achieved in eight steps with an improved overall yield of 8.5%.

## Experimental Section

**(−)-(1*R*,2*S*)-3-*N*,*N*-Dibenzylamino-1-phenylpropan-1,2-diol (3).**[1] To a solution of the *N*,*N*-dibenzylamino alcohol **5** (4.23 g, 12.2 mmol, 1.0 equiv) in freshly distilled toluene (50 mL) at room temperature was added $(CF_3CO)_2O$ (689 $\mu$L, 4.9 mmol, 0.4 equiv), and the solution was heated at reflux for 5 h. After addition at room temperature of an aqueous 3.75 M NaOH solution (15 mL), the mixture was stirred for 2 h, extracted with EtOAc (2 × 50 mL), and the combined organic extract was dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (silica gel, $CH_2Cl_2$/MeOH 99/1) afforded 3.3 g (9.5 mmol, 78%) of **3** as a yellow oil: $C_{23}H_{25}NO_2$; MW = 347.45 g·mol$^{-1}$; $[\alpha]^{20}_D = -84.0$ (*c* 0.3, $CHCl_3$); IR (neat) 3387, 3028, 2839, 1494, 1452, 1064, 1027, 733, 697 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.35−7.23 (15H), 4.62 (d, $J$ = 5.6 Hz, 1H), 3.82−3.75 (2H), 3.61 (d, $J$ = 13.2 Hz, 2H), 3.56 (d, $J$ = 13.2 Hz, 2H), 2.73 (dd, $J$ = 12.8, 8.0 Hz, 1H), 2.46 (dd, $J$ = 12.9, 5.8 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 140.1 (s), 137.9 (s), 129.3 (d), 128.6 (d), 128.4 (d), 127.7 (d), 127.5 (d), 126.4 (d), 76.3 (d), 70.1 (d), 58.9 (t), 53.7 (t); 99% ee (SFC, Daicel chiralcel OD-H, 100 bar of $CO_2$, 20% MeOH, 5 mL/min, $\lambda$ = 220 nm, $t_R$ (major) = 2.7 min, $t_R$ (minor) = 3.4 min); HRMS ($CI^+$, $CH_4$) calcd for $C_{23}H_{26}NO_2$ ($M + H^+$) 348.1964, found 348.1966.

**(+)-(2*S*,3*S*)-1-[Benzyl-(2-hydroxyethyl)amino]-3-(2-ethoxyphenoxy)-3-phenylpropan-2-ol (11).** To a solution of **12** (141 mg, 0.33 mmol, 1.0 equiv) in THF (2 mL) was added $(CF_3CO)_2O$ (19 $\mu$L, 0.13 mmol, 0.4 equiv). After being stirred for 18 h at 120 °C under microwave irradiation, the reaction was quenched with a 3.75 M NaOH solution (2 mL) at room temperature and stirred for 2 h. The aqueous phase was extracted with AcOEt (2 × 25 mL), and the combined organic extract was dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (silica gel, $CH_2Cl_2$/MeOH 90/10) afforded 51 mg (0.12 mmol, 36%) of **11** as a colorless oil: $C_{26}H_{31}NO_4$; MW = 421.53 g·mol$^{-1}$; $[\alpha]^{20}_D = +38.0$ (*c* 0.55, $CHCl_3$); IR (neat) 3600−3100, 3050−2700, 1735, 1594, 1499, 1453, 1252, 1213, 1123, 1042, 742, 701 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.35−7.28 (5H), 7.24−7.18 (3H), 7.17−7.14 (2H), 6.90 (m, 1H), 6.85 (ddd, $J$ = 8.1, 8.1, 1.4 Hz, 1H), 6.66 (ddd, $J$ = 8.0, 8.0, 1.6 Hz, 1H), 6.59 (dd, $J$ = 8.0, 1.4 Hz, 1H), 4.65 (d, $J$ = 7.5 Hz, 1H), 4.13−4.04 (3H), 3.66 (d, $J$ = 13.7 Hz, 1H), 3.59 (d, $J$ = 13.7 Hz, 1H), 3.56−3.44 (4H), 2.74 (m, 1H), 2.61−2.54 (2H), 2.45 (dd, $J$ = 13.8, 2.9 Hz, 1H), 1.46 (t, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 150.0 (s), 148.0 (s), 138.6 (s), 129.0 (d), 128.6 (d), 128.4 (d), 128.3 (d), 127.4 (d), 127.0 (d), 123.2 (d), 120.9 (d), 119.2 (d), 113.2 (d), 87.1 (d), 73.8 (d), 64.4 (t), 59.7 (t), 59.5 (t), 56.4 (t), 55.3 (t), 14.9 (q); HRMS (ESI) calcd for $C_{26}H_{32}NO_4$ ($M + H^+$) 422.2326, found 422.2317.

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**Supporting Information Available:** Experimental procedures and characterization data of compounds **1**−**3** and **5**−**16**. This material is available free of charge via the Internet http://pubs.acs.org.

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