Enantioselective Synthesis of β-Amino Alcohols: (−)-*erythro*-α-Methylepinephrine and (−)-*erythro*-α-Methylnorepinephrine

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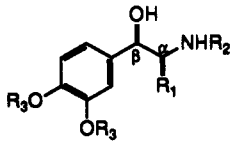
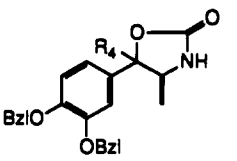
Both acyclic and cyclic β-amino alcohols constitute an important structural moiety as pharmacologically active compounds or as synthetically useful intermediates. Recently there has been considerable interest in developing the stereocontrolled synthesis of these amino alcohols.[2] In connection with our investigations of adrenergic agents, a large quantity of (−)-*erythro*-α-methylepinephrine (1), an intraneuronal metabolite of L-α-methyldopa, was required in enantiomerically pure form. Smith and coworker have previously resolved racemic 1 and assigned the absolute configuration of each enantiomer by comparison of the circular dichroism (CD) spectra with those of other catecholamine hydrochlorides of known absolute configuration.[3,4] Although the configurational assignment appears consistent with biological activity of (+)- and (−)-1,[5] no asymmetric synthesis has been recorded. Herein we report an enantioselective synthesis of (−)-1 and its prodrug (−)-3 as well as (−)-*erythro*-α-methylnorepinephrine (2).



1: R_1= CH_3, R_2= CH_3, R_3= H
2: R_1= CH_3, , R_2= H, R_3= H
3: R_1= CH_3, R_2= CH_3, R_3= tBuCO
13: R_1= H, R_2= CH_3, R_3= tBuCO

Results and Discussion

It occurred to us that a tandem use of the Evans aldol methodology and Hofmann-type rearrangement would provide a general method for the enantioselective synthesis of erytho β-amino alcohols. Treatment of 3,4-bis(benzyloxy)benzaldehyde with the boron enolate prepared from oxazolidinone 4 under Evans' standard conditions gave the aldol adduct 5 in 90% yield (>19:1 stereoselectivity).[6] Its *erythro* configuration is well-precedented and consistent with the small $H_{2,3}$ coupling constant, J = 4.2 Hz (Scheme I). Subsequent direct aminolysis (NH_3, MeOH or NH_4Cl–$AlMe_3$) of the chiral auxiliary was found to be sluggish, affording amide 6 in low yield.[7,8] The Hofmann-like rearrangement of 6 was then accomplished by action of iodobenzene bis(trifluoroacetate) in aqueous acetonitrile to afford oxazolidinone 7 in excellent (90–95%) yield.[9] The low overall yield for the introduction of the amino group was circumvented by using the well-established procedure of Shioiri.[10] Thus, the initial hydrolysis (LiOH, H_2O_2) of 5 furnished carboxylic acid 8 in 95% yield. Treatment of 8 with diphenylphosphorazidate in refluxing benzene for 20 min provided oxazolidinone 7 in 87% yield. For unequivocal confirmation of the correct stereochemistry, *threo* 9 was prepared by prolonged exposure under the rearrangement conditions: it shows a smaller coupling constant ($J_{2,3}$) of 5.2 Hz in comparison to $J_{2,3}$ of 7.9 Hz in 7.[11]



7: R_4= α-H
9: R_4= β-H

With a large quantity of 7 in hand, the requisite N-methylation was then achieved in 77% yield by LAH reduction to give β-amino alcohol 10. Subsequent debenzylation of the crude alcohol in ethanol containing a small amount of chloroform under Secrist's conditions[12] provided (−)-*erythro*-α-methylepinephrine hydrochloride [(−)-1·HCl], contaminated with a minor (~5%) amount of impurities. The use of the *N*-Cbz intermediate 11, however, provided the target compound (80% yield) in analytically and enantiomerically pure form (vide infra). Its spectroscopic data, optical rotation, and melting point were found to be comparable to literature values.[3,4] Thus, our synthesis confirms the absolute configuration of (−)-*erythro*-α-methylepinephrine to be αS,βR as shown in 1.

Similarly, amino alcohol 12 which was obtained in 62% yield by hydrolysis of 7 with potassium hydroxide in ethanol at refux was converted in 73% overall yield into (−)-*erythro*-α-methylnorepinephrine hydrochloride [(−)-2·HCl]. The spectroscopic data, optical rotation, and melting point of synthetic (−)-2·HCl were shown to be in agreement with literature values.[13]

The well-known utility of 1 and 2 in ocular therapeutics has been enhanced by the prodrug approach. For instance, dipivefrin (13) has led to a markedly improved ocular

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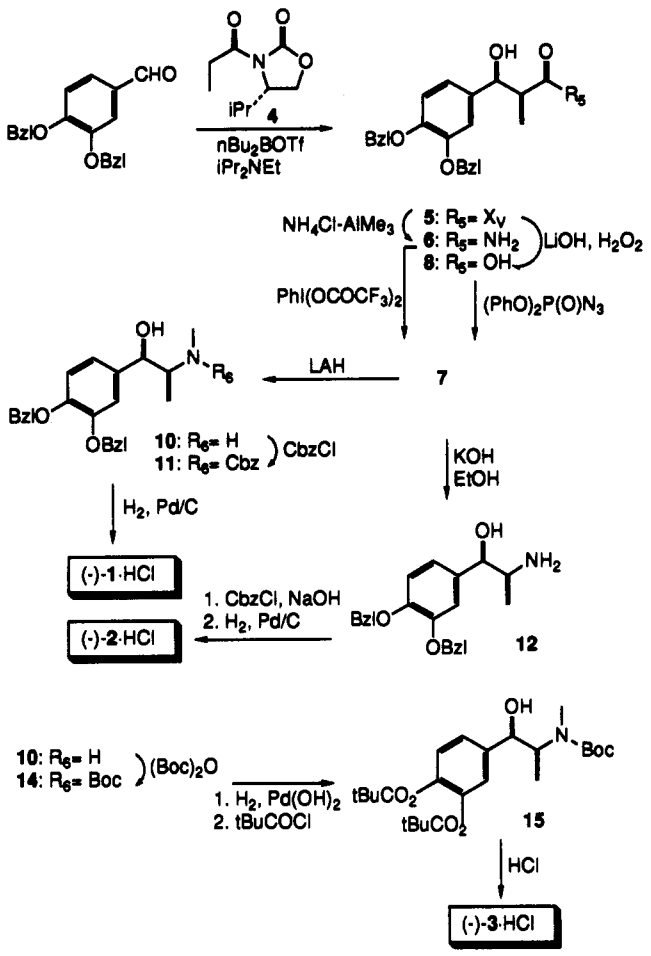
Scheme I



delivery of epinephrine.[14] Thus, we felt that it would be of interest to prepare the dipivalate ester prodrug **3** of **1** for biological evaluation. Amino alcohol **10** was first protected as the BOC derivative **14** (88% yield). Subsequent debenzylation (H_2, Pearlman's catalyst, 2.5 h) and pivaloylation (tBuCOCl, Et_3N) then provided dipivaloate **15** in 87% yield. Finally, treatment with 3 M HCl in EtOAc (room temperature, 30 min)[15] furnished the target prodrug as the hydrochloride salt [(-)-**3**·HCl] in 63% yield. Its enantiomeric purity was determined to be greater than 98% by HPLC analysis with a chiral stationary phase column (Chiralcell OD).[16]

In summary, we have developed an efficient route to our target β-amino alcohols **1–3** from a common intermediate, **7**. The synthetic methodology described herein embodies considerable flexibility for the construction of other amino alcohols.

Experimental Section

General. All reactions were conducted under an atmosphere of dry nitrogen and in oven-dried glassware, and concentrations were performed under reduced pressure with a Büchi rotary evaporator. All solvents were purified before use. Ether, tetrahydrofuran, and toluene were distilled from sodium benzophenone ketyl. Methylene chloride was distilled from CaH_2.

NMR spectra were measured on commercially available spectrometers: ^1H at 360 and ^{13}C at 90 MHz. For ^1H spectra tetramethylsilane was used as internal standard. ^{13}C NMR spectra were referenced with the δ 77.0 resonance of $CDCl_3$. Low and high resolution mass spectra were measured as EI or fast atom bombardment (FAB) spectra with 3-nitrobenzyl alcohol as the matrix solvent. Optical rotations were measured at room temperature.

Melting points are uncorrected. Analytical thin layer chromatography (TLC) was performed by using Merck 60 F_{254} glass plates precoated with a 0.25-mm thickness of silica gel. Column chromatography was performed on kieselgel 60 (70–230 mesh) silica gel. Unless otherwise noted, all compounds purified by chromatography are sufficiently pure (>95% by ^1H analysis) for use in subsequent reactions. Elemental analyses were performed by Atlantic Microlab, GA.

(+)-4(*S*)-3-[(2*S*,3*S*)-3-Hydroxy-2-methyl-1-oxo-3-(3′,4′-bis(phenylmethoxy)phenyl)propyl]-4-(1-methylethyl)-2-oxazolidinone (5). To a cold (0 °C), stirred solution of oxazolidinone **4** (2.50 g, 13.5 mmol) in CH_2Cl_2 (25 mL) under a nitrogen atmosphere were added sequentially 14.8 mL (14.8 mmol) of 1.0 M dibutylboron triflate solution in CH_2Cl_2 and diisopropylethylamine (3.1 mL, 17.6 mmol). The resulting mixture was stirred at 0 °C for 1 h and cooled to −78 °C. A solution of 3,4-bis(benzyloxy)benzaldehyde (14.73 g, 14.85 mmol) in CH_2Cl_2 (20 mL)–ether (6 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 1 h and quenched with addition of a pH 7 aqueous phosphate buffer. After the organic layer was separated, the aqueous layer was then extracted with ether (2 × 50 mL). The combined extracts were washed with brine (2 × 20 mL). After the solvents were removed on a rotary evaporator under vacuum, the residue was dissolved in methanol (50 mL). To the resulting solution was added at 0 °C 30% H_2O_2 (5 mL). After the mixture was stirred for additional 1 h, water (15 mL) was added, and methanol was removed on a rotary evaporator under vacuum. The aqueous layer was extracted with ether (3 × 35 mL). The combined organic layers were washed with 5% aqueous HCl (15 mL), 5% aqueous sodium bicarbonate (20 mL), and brine (15 mL), dried (Na_2SO_4), and evaporated in vacuo to give the crude aldol product as a yellow oil. Purification by flash column chromatography (3:1 hexane:EtOAc) gave 6.12 g (90%) of the pure aldol adduct **5** as a white powder: mp 106 °C; $[\alpha]^{25}_D$ = 49.0° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3580 (w), 1800 (s), 1710 (m), 1700 (m), 1525 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.86 (d, *J* = 6.9 Hz, 3 H), 0.90 (d, *J* = 6.9 Hz, 3 H), 1.16 (d, *J* = 7.0 Hz, 3 H), 2.31 (m, 1 H), 3.02 (br s, 1 H, O*H*), 4.05 (dq, *J* = 4.2 and 7.0 Hz, 1 H), 4.08–4.15 (m, 2 H), 4.30 (m, 1 H), 4.95 (d, *J* = 4.2 Hz, 1 H), 5.15 (s, 2 H), 5.17 (s, 2 H), 6.85 (d, *J* = 8.2 Hz, 1 H), 6.90 (d, *J* = 8.2 Hz, 1 H), 7.03 (s, 1 H), 7.29–7.47 (m, 10 H); ^{13}C NMR (90 MHz) δ 11.4, 14.6, 17.7, 28.3, 44.3, 58.2, 63.2, 70.9, 71.1, 73.3, 112.9, 114.6, 119.0, 127.1, 127.3, 127.6, 128.2 (3 C), 134.8, 137.1, 137.2, 148.0, 148.5, 153.3, 176.5; HRMS (M^+) calcd 503.2308 for $C_{30}H_{33}NO_6$, found 503.2312. Anal. Calcd for $C_{30}H_{33}NO_6$: C, 71.55; H, 6.60; N, 2.78. Found: C, 71.43; H, 6.64; N, 2.76.

(−)-(2*S*,3*S*)-3-Hydroxy-2-methyl-3-[3′,4′-bis(phenylmethoxy)phenyl]propanoic Acid (8). To a solution of the aldol adduct **5** (12 g, 23.86 mmol) in 3:1 THF-distilled water (80 mL) was added at 0 °C 30% aqueous hydrogen peroxide (13.5 mL, 0.12 mol), followed by 3 g (71.6 mmol) of lithium hydroxide. The reaction mixture was stirred at 0 °C for 3 h, and excess methyl sulfide (18 mL) was added. The mixture was then stirred at 0 °C for an additional 30 min. After the bulk of THF was removed on a rotary evaporator, the resulting mixture was washed with CH_2Cl_2 (2 × 50 mL). The aqueous layer was carefully acidified to pH 3 with 1 N hydrochloric acid at 0 °C. The aqueous phase was then saturated with NaCl and extracted with EtOAc (4 × 30 mL). The organic extracts were dried ($MgSO_4$) and evaporated in vacuo to give the crude product. The crude product was dissolved in ether (50 mL), washed with water (2 × 20 mL), and dried ($MgSO_4$). Evaporation of the solvent gave pure acid **8** (8.81 g, 95%) as a white solid: mp 115–118 °C; $[\alpha]^{25}_D$ = −17.6° (*c* 0.74, $CHCl_3$); IR ($CHCl_3$) 3000–3620, 1725, 1610 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.08 (d, *J* = 7.2 Hz, 3 H), 2.75 (dq, *J* = 4.2 and 7.2 Hz, 1 H), 5.02 (d, *J* = 4.2 Hz, 1 H), 5.15 (s, 2 H), 5.16 (s, 2 H), 6.84 (dd, *J* = 2.0 and 8.3 Hz, 1 H), 6.91 (d, *J* = 8.3 Hz, 1 H), 6.95 (d, *J* = 2.0 Hz, 1 H), 7.29–7.45 (m, 10 H), [CO_2H not shown]; ^{13}C NMR ($CDCl_3$, 90 MHz) δ 10.2, 46.3, 71.3, 73.1, 77.2, 113.2, 114.7, 118.9, 127.3, 127.4, 127.7, 128.4 (3 C), 134.4, 137.1, 137.2, 148.4, 148.6, 181.0; HRMS (M^+) calcd 392.1624 for $C_{24}H_{24}O_5$, found 392.1604.

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(16) Similarly, (+)-**3**·HCl was also obtained in good overall yield by employing the oxazolidinone chiral auxiliary derived from (1*S*,2*R*)-norephedrine hydrochloride.

(−)-(4*S*,5*R*)-4-Methyl-5-[3′,4′-bis(phenylmethoxy)phenyl]-2-oxazolidinone (7). To a solution of acid **8** (10 g, 27.8 mmol) in anhydrous benzene (100 mL) were added sequentially triethylamine (11 mL, 83.4 mmol) and diphenylphosphorazidate (1.4 g, 33.4 mmol). The reaction mixture was heated at 90 °C for 20 min and quenched with the addition of water. The mixture was extracted with EtOAc (3 × 20 mL), washed with brine (2 × 20 mL), dried ($MgSO_4$), and concentrated. The crude product was then dissolved in 10 mL of ether and kept overnight in a refrigerator. The crystals were collected by suction filtration to afford 8.6 g (87%) of **7** as a white solid: mp 148–150 °C; $[\alpha]^{25}_D$ = −61.5° (*c* 0.67, $CHCl_3$); IR ($CHCl_3$) 3480, 1770, 1610 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz), δ 0.69 (d, *J* = 6.5 Hz, 3 H), 4.07 (dq, *J* = 7.9 and 6.5 Hz, 1 H), 5.16 (s, 4 H), 5.45 (br s, 1 H), 5.59 (d, *J* = 7.9 Hz, 1 H), 6.79 (d, *J* = 8.2 Hz, 1 H), 6.88 (br s, 1 H), 6.93 (d, *J* = 8.2 Hz, 1 H), 7.29–7.45 (m, 10 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 17.3, 52.4, 71.3, 71.4, 80.8, 113.1, 114.7, 119.2, 127.3, 127.4, 127.9, 128.2, 128.5 (3C), 136.9, 137.0, 148.8, 149.2, 159.0; HRMS (M^+) calcd 389.1627 for $C_{24}H_{23}NO_4$, found 389.1604.

(−)-(α*R*,β*S*)-*N*-(Benzyloxycarbonyl)-3,4-bis(phenylmethoxy)-α-[1-(methylamino)ethyl]benzenemethanol (11). To a solution of oxazolidinone **7** (8.6 g, 24 mmol) in anhydrous THF (30 mL) was added $LiAlH_4$ (1.8 g, 36 mmol). The reaction mixture was heated at reflux overnight. The mixture was then quenched with the slow addition of water (2 mL), diluted with ether (30 mL), and filtered through Celite. The filtrate was concentrated under vacuum to give 6.45 g (77%) of **10** as a slightly yellow oil, which was used without further purification: ^1H NMR ($CDCl_3$, 360 MHz) δ 0.80 (d, *J* = 6.5 Hz, 3 H), 2.39 (s, 3 H), 2.68 (dq, *J* = 4.2 and 6.5 Hz, 1 H), 2.85 (br s, 2 H, exchangeable protons), 4.62 (d, *J* = 4.2 Hz, 1 H), 5.14 (s, 2 H), 5.16 (s, 2 H), 6.80 (dd, *J* = 1.9 and 8.2 Hz, 1 H), 6.91 (d, *J* = 8.2 Hz, 1 H), 6.97 (d, *J* = 1.9 Hz, 1 H), 7.29–7.46 (m, 10 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 14.2, 33.9, 60.4, 71.2, 71.4, 72.9, 113.4, 114.8, 119.2, 127.3, 127.4, 127.7, 128.4 (3C), 134.9, 137.3, 137.4, 148.1, 148.6.

To a solution of β-amino alcohol **10** (0.8 g, 2.3 mmol) in a 1:1 mixture of EtOAc–water were added sequentially $NaHCO_3$ (0.77 g, 9.2 mmol), NaCl (13 mg, 0.23 mmol), and benzyl chloroformate (0.43 mL, 3 mmol). The reaction mixture was stirred at room temperature for 6 h. The mixture was then diluted with EtOAc (40 mL), washed twice with brine, dried ($MgSO_4$), and concentrated. The resulting crude product was purified by flash column chromatography on silica gel using 2:1 hexane–EtOAc as eluent to give 890 mg (80%) of **11** as an off-white solid: mp 50–52 °C; $[\alpha]^{25}_D$ = −9.6° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3690, 1705, 1620 cm^{-1}; ^1H NMR for one conformer ($CDCl_3$, 360 MHz) δ 1.19 (d, *J* = 6.8 Hz, 3 H), 2.64 (br s, 3 H), 4.09 (br s, 1 H), 4.77 (br s, 1 H), 5.13 (br s, 4 H), 6.86–7.01 (m, 3 H), 7.28–7.45 (m, 15 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 12.3, 31.9, 59.0, 67.0, 71.1, 71.3, 77.2, 113.3, 114.7, 119.4, 127.3, 127.4, 127.8, 128.0, 128.3 (2 C), 128.4 (3 C), 135.2, 136.7, 137.3 (2 C), 148.4, 148.7, 157.1; HRMS (M^+) calcd 511.2359 for $C_{32}H_{33}NO_5$, found 511.2288.

(−)-(α*S*,β*R*)-*erythro*-α-Methylepinephrine Hydrochloride [(−)-1·HCl]. A solution of carbamate **11** (400 mg, 0.83 mmol) in ethanol (40 mL) containing 1 mL of chloroform was placed in a Parr hydrogenation apparatus with 10% Pd/C (40 mg). The hydrogenation was carried out under a 45 psi pressure of hydrogen for 30 h at room temperature. The catalyst was removed by filtration with the aid of additional ethanol. The filtrate and washings were concentrated under reduced pressure to give 150 mg (97%) of **1**·HCl as a white solid: mp 192–194 °C (lit.[4a] mp 196–198 °C; lit.[4b] mp for racemic **1**·HCl, 188–189 °C); $[\alpha]^{25}_D$ = −29.8° (*c* 0.4, 0.2 N HCl) [lit.[4a] $[\alpha]^{25}_D$ = −33° (*c* 0.4, 0.2 N HCl)]; ^1H NMR (D_2O, ref 4.67, 360 MHz) δ 1.05 (d, *J* = 6.8 Hz, 3 H), 2.63 (s, 3 H), 3.37 (dq, *J* = 3.8 and 6.8 Hz, 1 H), 4.85 (d, *J* = 3.8 Hz, 1 H), 6.72 (dd, *J* = 2.1 and 8.2 Hz, 1 H), 6.81 (d, *J* = 2.1 Hz, 1 H), 6.84 (d, *J* = 8.2 Hz, 1 H); ^{13}C NMR (D_2O, ref CH_3CH_2OH = 17.2, 90 MHz) δ 10.4, 31.1, 60.4, 71.8, 114.4, 116.6, 119.0, 131.3, 144.5, 144.7.

(−)-(α*R*,β*S*)-α-(1-Aminoethyl)-3,4-bis(phenylmethoxy)benzenemethanol (12). Oxazolidinone **7** (200 mg, 0.56 mmol) was dissolved in 4 mL of 0.7 N ethanolic potassium hydroxide. After the mixture was refluxed under nitrogen for 20 h, the bulk of ethanol was removed under reduced pressure. The residue was carefully acidified to pH 6 with 1 N hydrochloric acid at 0 °C and washed with ether. Aqueous 1 N sodium hydroxide solution was added until a pH of 13 was reached. The mixture was extracted 5 times with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to give 113 mg (62%) of **12** as a white solid: mp 50 °C; $[\alpha]^{25}_D$ = −17.2° (*c* 0.25, $CHCl_3$); ^1H NMR ($CDCl_3$, 360 MHz) δ 0.83 (d, *J* = 6.5 Hz, 3 H), 2.17 (br s, 3 H, exchangeable protons), 3.04 (dq, *J* = 4.7 and 6.5 Hz, 1 H), 4.38 (d, *J* = 4.7 Hz, 1 H), 5.06 (s, 2 H), 5.08 (s, 2 H), 6.73 (dd, *J* = 1.9 and 8.2 Hz, 1 H), 6.82 (d, *J* = 8.2 Hz, 1 H), 6.87 (d, *J* = 1.9 Hz, 1 H), 7.18–7.37 (m, 10 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 17.8, 52.0, 71.2, 71.3, 76.8, 113.7, 114.8, 119.6, 127.3, 127.4, 127.7, 127.8 (3 C), 134.5, 137.3, 137.3, 148.4, 148.6.

(−)-(α*S*,β*R*)-*erythro*-α-Methylnorepinephrine Hydrochloride [(−)-2·HCl]. To a solution of β-amino alcohol **12** (100 mg, 0.3 mmol) in a 1:1 mixture of EtOAc–water (10 mL) were added sequentially $NaHCO_3$ (96 mg, 1.2 mmol), NaCl (2 mg), and benzyl chloroformate (0.06 mL, 0.4 mmol). The reaction mixture was stirred at room temperature for 6 h. The mixture was then diluted with EtOAc (20 mL), washed twice with brine, dried ($MgSO_4$), and concentrated. The resulting crude product was purified by flash column chromatography on silica gel (2:1 hexane–EtOAc) to give 120 mg (85%) of the desired carbamate as a white solid: mp 123–125 °C; $[\alpha]^{25}_D$ = −39.4° (*c* 0.15, $CHCl_3$); IR ($CHCl_3$) 3720, 3620, 3470, 1730, 1620, 1510 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.84 (d, *J* = 6.9 Hz, 3 H), 2.55 (br s, 1 H, O*H*) 3.91 (m, 1 H), 4.70 (br s, 1 H, N*H*) 4.79 (br d, *J* = 8.0 Hz, 1 H), 5.04 (s, 2 H), 5.06 (s, 2 H), 5.07 (s, 2 H), 6.75 (br d, *J* = 8.2 Hz, 1 H), 6.82 (br d, *J* = 8.2 Hz, 1 H), 6.86 (br s, 1 H), 7.19–7.37 (m, 15 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 14.6, 52.3, 66.9, 71.2, 71.3, 76.0, 113.4, 114.8, 119.3, 127.3, 127.5, 127.8, 128.1, 128.2, 128.5 (3C), 128.6, 133.9, 136.4, 137.1, 137.3, 148.5, 148.7, 156.5; HRMS (M^+) calcd 497.2202 for $C_{31}H_{31}NO_5$, found 497.2212.

A solution of the carbamate thus obtained (110 mg, 0.24 mmol) in ethanol (20 mL) containing 0.5 mL of chloroform was placed in a Parr hydrogenation apparatus with 10% Pd/C (11 mg). The hydrogenation was carried out under a 45 psi pressure of hydrogen for 20 h at room temperature. The catalyst was removed by filtration with the aid of additional ethanol. The filtrate and washings were concentrated under reduced pressure to give 43 mg (86%) of **2**·HCl as a white solid: mp 205–207 °C (lit.[13] mp 207–209 °C); $[\alpha]^{25}_D$ = −23.3° (*c* 0.15, 0.2 N HCl) [lit.[13] $[\alpha]^{25}_D$ = −20.7° (*c* 0.5, 0.1 N HCl); −31.0° (*c* 0.5, 0.1 N HCl)]; ^1H NMR (D_2O, ref 4.67, 360 MHz) δ 1.11 (d, *J* = 6.8 Hz, 3 H), 3.50 (dq, *J* = 5.0 and 6.8 Hz, 1 H), 4.69 (d, *J* = 5.0 Hz, 1 H), 6.74 (dd, *J* = 1.9 and 8.2 Hz, 1 H), 6.82 (d, *J* = 1.9 Hz, 1 H), 6.85 (d, *J* = 8.2 Hz, 1 H); ^{13}C NMR (D_2O, ref CH_3CH_2OH = 17.2, 90 MHz) δ 13.3, 52.6, 73.2, 114.6, 116.7, 119.4, 131.4, 144.5, 144.6.

(−)-(α*S*,β*R*)-*erythro*-α-Methyl-3′,4′-dipivalolylepinephrine Hydrochloride [(−)-3·HCl]. To a solution of carbamate **15** (3.2 g, 7.37 mmol) in EtOAc (10 mL) was added 13 mL of 3 M HCl in EtOAc. After the reaction mixture was stirred at room temperature for 1.5 h, nitrogen was bubbled through in order to remove HCl. The solvent was then removed under reduced pressure to furnish the crude product. Trituration with a mixture of chloroform (1 mL), ether (4 mL), and pentane (10 mL) at 0 °C gave 2 g (63%) of **3**·HCl as a white solid: mp 162–164 °C; $[\alpha]^{25}_D$ = −13.3° (*c* 0.6, $CHCl_3$); IR ($CHCl_3$), 3700, 3370, 1780, 1620 cm^{-1}; ^1H NMR (D_2O, ref 4.67, 360 MHz) δ 1.04 (d, *J* = 6.8 Hz, 3 H), 1.25 (s, 18 H), 2.69 (s, 3 H), 3.45 (dq, *J* = 3.3 and 6.8 Hz, 1 H), 5.09 (d, *J* = 3.3 Hz, 1 H), 7.19 (d, *J* = 2.0 Hz, 1 H), 7.21 (d, *J* = 8.4 Hz, 1 H), 7.30 (dd, *J* = 2.0 and 8.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 8.3, 27.2 (6 C), 31.4, 39.1 (2 C), 61.2, 70.3, 121.0, 123.5, 123.8, 138.6, 141.9, 142.5, 175.9, 176.0; HRMS of **3** (M^+ + H) 365.2280 calcd for $C_{20}H_{32}NO_5$, found 365.2279. Anal. Calcd for $C_{20}H_{32}ClNO_5$: C, 59.77; H, 8.02; N, 3.48. Found: C, 59.71; H, 8.07; N, 3.43.

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Supplementary Material Available: Full experimental details for **12**, **14**, and **15** as well as ^1H and ^{13}C NMR spectra for selected compounds (24 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.