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Expedient asymmetric synthesis of (2*S*,3*S*)-Boc-phenylalanine epoxide, a key intermediate for the synthesis of biologically active compounds

Ramón Badorrey, María D. Díaz-de-Villegas *, José A. Gálvez *

Departamento de Química Orgánica, Instituto de Ciencia de Materiales de Aragón, Instituto Universitario de Catálisis Homogénea, Universidad de Zaragoza-CSIC, E-50009 Zaragoza, Spain

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ABSTRACT

The asymmetric synthesis of (2*S*,3*S*)-3-(*tert*-butoxycarbonyl)amino-1,2-epoxy-4-phenylbutane [(2*S*,3*S*)-Boc-phenylalanine epoxide] has been achieved in six steps and in 55% overall yield from the *N*-benzylimine derived from (*R*)-2,3-*O*-isopropylidene-glyceraldehyde. The required *vic*-aminodiol intermediate was obtained through a highly diastereoselective addition of benzylmagnesium chloride to the *N*-benzylimine in the presence of $BF_3{\cdot}OEt_2$ as an imine precomplexing agent.

1. Introduction

1-Aminoalkyl epoxides are versatile intermediates for the synthesis of a variety of densely functionalised compounds with biological activities. In particular, (2*S*,3*S*)-3-(*tert*-butoxycarbonyl)-amino-1,2-epoxy-4-phenylbutane **1** [(2*S*,3*S*)-Boc-phenylalanine epoxide] is an essential building block for the synthesis of approved HIV protease inhibitors Saquinavir[1] and Amprenavir,[2] hydroxyethylpiperazine derivatives with antimalarial activity,[3] hydroxyethylamines (HEAs) with improved β-secretase inhibitory properties[4] and novel dual inhibitors of acetylcholine esterase (AChE) and β-secretase (BACE-1) to be evaluated as multi-target-directed agents,[5] among others.

The current main approaches to the synthesis of epoxide **1** have recently been reviewed[6] and these include epoxidation of (*S*)-2-(*tert*-butoxycarbonyl)amino-3-phenylpropanal **I** with a sulfoxonium ylide, cyclisation of (2*S*,3*S*)-3-(*tert*-butoxycarbonyl)amino-1-chloro-4-phenylbutan-2-ol **II**—obtained by *anti*-selective reduction of (*S*)-3-(*tert*-butoxycarbonyl)amino-1-chloro-4-phenylbutan-2-one **III**—and cyclisation of *syn* or *anti* (3*S*)-3-(*tert*-butoxycarbonyl)-amino-4-phenylbutane-1,2-diols **IV** using the appropriate reaction sequence[7] (Fig. 1).

A synthetic protocol to obtain this useful intermediate starting from a cheap and readily available precursor would be of interest. In this context, we previously reported[8] the preparation of epoxide **1** in six steps and in 26% overall yield, with the key step being the *syn* diastereoselective addition of benzylmagnesium chloride to the chiral *N*-benzylimine derived from (*S*)-2,3-di-*O*-benzylglyceraldehyde, which was in turn obtained from L-mannonic acid γ-lactone. We report herein a more efficient and economical way to obtain epoxide **1** from the chiral *N*-benzylimine derived from (*R*)-2,3-*O*-isopropylideneglyceraldehyde.

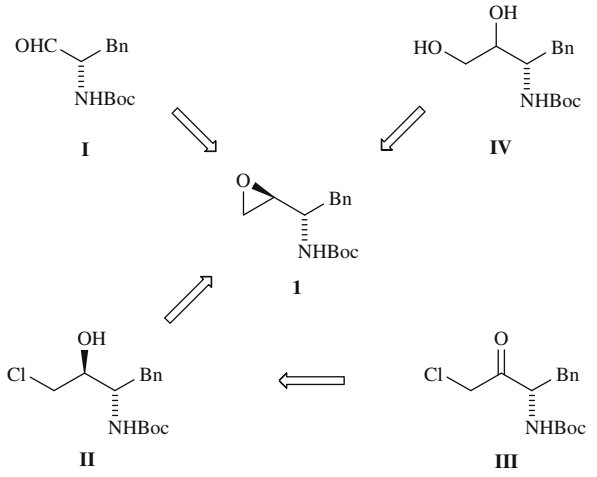

Figure 1. Immediate epoxide precursors.

2. Results and discussion

The synthesis of epoxide **1** (Scheme 1) started from the *N*-benzylimine **2** derived from (*R*)-2,3-*O*-isopropylideneglyceraldehyde, which is easily available on a gram scale from the inexpensive precursor D-mannitol.[9] The first step in the proposed route involved the nucleophilic addition of a benzyl organometallic reagent to obtain the corresponding 3-amino-4-phenylbutane-1,2-diol derivative. The product of this reaction must have the *S* configuration

* Corresponding authors. Tel.: +34 976762274; fax: +34 976761202 (M.D.D.); tel.: +34 976762273; fax: +34 976761202 (J.A.G.).
E-mail addresses: loladiaz@unizar.es (M.D. Díaz-de-Villegas), jagl@unizar.es (J.A. Gálvez).

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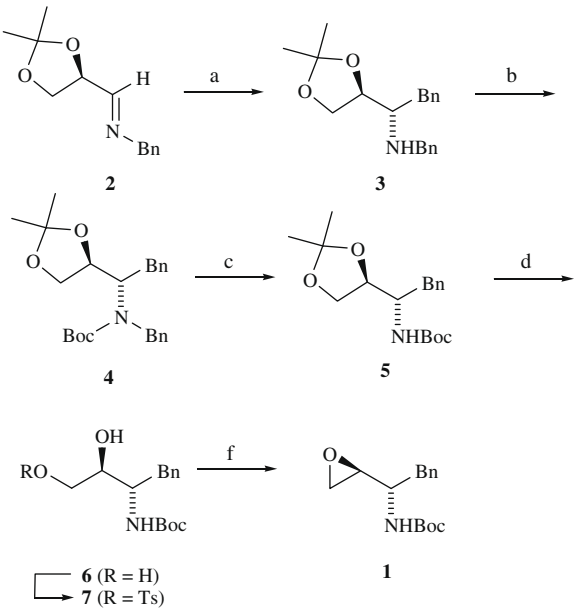

Scheme 1. Reaction conditions: (a) BnMgCl, $BF_3{\cdot}OEt_2$, Et_2O, −20 °C (72%); (b) Boc_2O, CH_3OH/Et_3N, 45 °C (96%); (c) Li/NH_3, Et_2O, −50 °C (96%); (d) TFA, CH_3OH/H_2O (3:1), rt (90%); (e) K_2CO_3, CH_3OH, 0 °C (98%); and (f) n-Bu_2SnO, Et_3N, TsCl, CH_2Cl_2, rt (93%).

at the newly formed stereogenic carbon, which implies the diastereoselective formation of the *anti* β-aminodiol derivative **3**. Addition of benzylmagnesium chloride to imine **2** under usual conditions[8] provided the corresponding *syn* β-aminodiol derivative with almost total diastereoselectivity. However, this compound did not have the appropriate configuration at C_3. In order to obtain epoxide **1** from imine **2** the stereochemical course of the reaction had to be reversed.

Recently,[10] we observed that the *syn*/*anti* diastereoselectivity of the addition of 3-(*tert*-butyldimethylsilyloxy)propyn-1-yllithium to *N*-benzylimines derived from (*R*)-2,3-*O*-isopropylideneglyceraldehyde can be controlled and reversed by the appropriate use of Lewis acids as imine precomplexing agents. In the presence of $EtAlCl_2$, aminodiol derivatives of *syn* configuration are obtained preferentially, whereas in the presence of $BF_3{\cdot}OEt_2$ aminodiol derivatives of *anti* configuration are the major products. The addition of benzylmagnesium chloride to imine **1** in the presence of $BF_3{\cdot}OEt_2$ provided the desired β-aminodiol derivative **3** of *anti* configuration with a high diastereoselectivity (*anti*/*syn* = 90/10). Diastereomerically pure compound **3** was isolated by column chromatography in 72% yield.

Compound **3** was converted to *N*-Boc derivative **5** in two steps, which involved the formation of *N*-Boc-*N*-benzyl derivative **4** by treatment with di-*tert*-butyl dicarbonate in the presence of Et_3N in methanol (96%) followed by N-debenzylation at −50 °C using lithium/liquid ammonia (96%). All attempts to perform this transformation directly from **3** by hydrogenolysis in the presence of di-*tert*-butyl dicarbonate at atmospheric pressure using $Pd(OH)_2/C$ as the catalyst led to a ca. 1/2 mixture of **4** and **5**. This mixture did not evolve even upon heating. On the other hand, compound **4** was inert to N-debenzylation by hydrogenation. *N*-Boc aminodiol **6** was subsequently obtained in 90% yield from compound **5** by selective removal of the acetonide group using TFA.

Conversion of diol **6** into epoxide **1** has previously been performed by intramolecular Mitsunobu reaction using PPh_3 and DEAD in refluxing $CHCl_3$[7a,c,d] to give variable yields (61–95% yield) or by conversion of the diol into the corresponding chloroacetate by treatment with 1-(chlorocarbonyl)-1-methylethyl acetate and subsequent NaOMe-promoted cyclisation[7b] (58% yield, two steps). In our hands the intramolecular Mitsunobu reaction, using PPh_3 and the more readily available DIAD in refluxing $CHCl_3$, resulted in a crude product that was extremely difficult to purify. Epoxide **1** was finally obtained from **6** in 91% overall yield in a two-step procedure that involved tosylation of the primary alcohol by treatment with di-*n*-butyltin oxide, triethylamine and *p*-toluenesulfonyl chloride followed by cyclisation promoted by potassium carbonate.

3. Conclusion

In conclusion, we have developed an efficient synthesis of (2*S*,3*S*)-Boc-phenylalanine epoxide **1** starting from the *N*-benzylimine derived from (*R*)-2,3-*O*-isopropylidene-glyceraldehyde, which is easily available from renewable sources, that is, the inexpensive D-mannitol. The starting imine provides the C2 stereogenic carbon and the C3 stereogenic carbon is created in a highly diastereoselective manner by the addition of benzylmagnesium chloride in the presence of an appropriate precomplexing agent, $BF_3{\cdot}OEt_2$. The overall yield of the six-step sequence is 55% and most of the steps are operationally simple and high yielding.

4. Experimental

4.1. General experimental

All reagents for reactions were of analytical grade and were used as obtained from commercial sources. All manipulations with air-sensitive reagents were carried out under a dry argon atmosphere using standard Schlenk techniques. Anhydrous solvents were used with the exception of methanol. Whenever possible the reactions were monitored by TLC. TLC was performed on precoated silica gel polyester plates and products were visualised using UV light (254 nm) and ninhydrin or phosphomolybdic acid visualising agents followed by heating. Column chromatography was performed using silica gel (60 Å, 35–70 μm). *N*-[[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methylydene]benzylamine **2** was prepared as previously described in the literature.[10]

Melting points were determined in open capillary tubes using a Gallenkamp capillary melting point apparatus and were not corrected. FT-IR spectra of oils were recorded as thin films on NaCl plates and FT-IR spectra of solids were recorded as KBr pellets, using a Thermo Nicolet Avatar 360 FT-IR spectrometer; ν_{max} values expressed in cm^{-1} were given for the main absorption bands. Optical rotations were measured on a Jasco P-1020 polarimeter at λ 589 nm and 25 °C in a cell with 10 cm path length, $[\alpha]_D$ values were given in 10^{-1} deg cm^2 g^{-1} and concentrations are given in g/100 mL. ^1H NMR and ^{13}C NMR spectra were acquired on Bruker AV-300, AV-400 or AV-500 instruments operating at 300, 400 or 500 MHz for ^1H NMR and 75, 100 or 125 MHz for ^{13}C NMR using a 5-mm probe. The chemical shifts (δ) were reported in parts per million and were referenced to the residual solvent peak. Coupling constants (J) were quoted in hertz. The following abbreviations were used: s, singlet; d, doublet; m, multiplet; dd, doublet of doublets; and br s, broad signal. High resolution mass spectra were recorded using a Bruker Daltonics MicroToF-Q instrument from methanolic solutions using the positive electrospray ionisation mode (ESI+). Microanalyses were performed using a Perkin–Elmer 200 CHNS elemental analyser.

4.2. (*S*)-*N*-Benzyl-1-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-phenylethanamine 3

To a solution of imine **2** (5.00 g, 22.8 mmol) in dry Et_2O (150 mL) at −20 °C under argon was added dropwise $BF_3{\cdot}OEt_2$

(2.89 mL, 22.8 mmol) and stirring was continued for 10 min at the same temperature. A 1 M solution of BnMgCl (45.6 mL, 45.6 mmol) in ether was added and the reaction mixture was stirred for 5 h at −20 °C. The reaction mixture was treated at 0 °C with saturated aqueous $NaHCO_3$ (25 mL) and water (25 mL). The mixture was filtered through a Celite® pad, which was washed with Et_2O (2 × 30 mL). The organic phase was separated and the aqueous layer was extracted with Et_2O (2 × 60 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated to give **3** as a 90/10 *anti*/*syn* mixture of diastereoisomers. Purification of the crude product by column chromatography (1st eluent: Et_2O/hexanes 1:3, 2nd eluent: Et_2O/hexanes 1:1) afforded 5.10 g (72%) of diastereomerically pure **3** with the *anti* configuration as a pale yellow oil. $[\alpha]_D^{25} = +18.1$ (*c* 0.64, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3335; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 3H), 1.36 (s, 3H), 2.70 (dd, *J* = 14.0, 6.8 Hz, 1H), 2.79 (dd, *J* = 14.0, 4.8 Hz, 1H), 2.84–2.90 (m, 1H), 3.63 (d, *J* = 13.2, 1H), 3.68 (d, *J* = 13.2, 1H), 3.79–3.86 (m, 2H), 3.88–3.95 (m, 1H), 7.15–7.27 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 26.5, 36.2, 51.5, 59.6, 66.7, 77.0, 108.5, 126.0, 126.6, 127.7, 128.0, 128.2, 129.3, 137.9, 140.2; HRMS (ESI+): *m/z* [M+H$^+$] calcd for $C_{20}H_{26}NO_2$ (MH^+) 312.1958, found 312.1946.

4.3. (*S*)-*N*-Benzyl-*N*-*tert*-butoxycarbonyl-1-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-phenylethanamine 4

To a solution of compound **3** (1.52 g, 4.9 mmol) in a solution of 10% Et_3N in MeOH (30 mL) was added Boc_2O (2.13 g, 9.8 mmol) and the mixture was stirred for 90 min at 45 °C. Then an additional portion of Boc_2O (2.13 g, 9.8 mmol) was added and stirring was continued for 90 min at 45 °C. After completion of the reaction, the solution was concentrated in vacuo. Purification of the crude product by column chromatography (1st eluent: Et_2O/hexanes 1:8, 2nd eluent: Et_2O/hexanes 1:4) afforded 1.93 g (96%) of compound **4** as a colourless oil. $[\alpha]_D^{25} = -26.1$ (*c* 1.00, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 1695; ^1H NMR (300 MHz, C_6D_6, 353 K) δ 1.34 (s, 3H), 1.42 (s, 9H), 1.46 (s, 3H), 3.12–3.27 (m, 1H), 3.36 (dd, *J* = 14.1, 3.9 Hz, 1H), 3.67–3.79 (m, 1H), 3.80–3.84 (m, 1H), 4.30–4.50 (m, 4H), 7.10–7.30 (m, 10H); ^{13}C NMR (125 MHz, C_6D_6, 353 K) δ 25.7, 27.1, 28.4, 36.2, 50.8, 62.4, 68.0, 78.2, 79.8, 109.6, 126.4, 127.3, 127.9, 128.1, 128.3, 128.5, 129.7, 137.9, 155.9; HRMS (ESI+): *m/z* [M+Na$^+$] calcd for $C_{25}H_{33}NNaO_4$ (MNa^+) 434.2302, found 434.2290.

4.4. (*S*)-*N*-*tert*-Butoxycarbonyl-1-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-phenylethanamine 5

To a solution of compound **4** (1.15 g, 2.8 mmol) in dry Et_2O (25 mL) and liquid ammonia (25 mL) at −50 °C was added lithium in small portions until the colour of the solution remained blue. The reaction mixture was treated with saturated aqueous NH_4Cl (15 mL) and the ammonia was evaporated. The reaction mixture was diluted with water (15 mL). The aqueous phase was extracted with Et_2O (3 × 30 mL), the combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo. Purification of the crude product by column chromatography (eluent: Et_2O/hexanes 1:2) afforded 860 mg (96%) of compound **5** as a white solid. Mp = 125–126 °C; $[\alpha]_D^{25} = -1.0$ (*c* 1.00, $CHCl_3$); IR (KBr, cm^{-1}): ν_{max} 3358, 1686; ^1H NMR (500 MHz, $CDCl_3$, 333 K) δ 1.39 (s, 3H), 1.39 (s, 9H), 1.50 (s, 3H), 2.84 (dd, *J* = 8.4, 4.5 Hz, 1H), 3.01 (dd, *J* = 8.4, 2.7 Hz, 1H), 3.84–3.89 (m, 1H), 3.90–3.96 (m, 1H), 3.98–4.05 (m, 2H), 4.38 (br s, 1H), 7.15–7.35 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, 333 K) δ 25.3, 26.6, 28.3, 37.2, 54.1, 67.1, 77.2, 79.5, 109.6, 126.4, 128.4, 129.5, 137.6, 155.3. Elemental Anal. Calcd for $C_{18}H_{27}NO_4$: C, 67.3; H, 8.5; N, 4.4. Found: C, 67.4; H, 8.5; N, 4.3; HRMS (ESI+): *m/z* [M+Na$^+$] calcd for $C_{18}H_{27}NNaO_4$ (MNa^+) 344.1832, found 344.1824.

4.5. (2*S*,3*S*)-3-(*tert*-Butoxycarbonyl)amino-4-phenyl-1,2-butanediol 6

A solution of compound **5** (850 mg, 2.65 mmol) in 3:1 MeOH/H_2O (20 mL) was treated with TFA (19 μL, 0.26 mmol) and stirred for 24 h at room temperature. Then an additional portion of TFA (19 μL, 0.26 mmol) was added and stirring was continued for 24 h at room temperature. Saturated aqueous $NaHCO_3$ was added until the pH was basic and the solution was concentrated in vacuo. The concentrate was diluted with water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo. Purification of the crude product by column chromatography (1st eluent: Et_2O/hexanes 1:1, 2nd eluent: EtOAc) afforded 670 mg (90%) of compound **6** as a white solid. Mp = 124–125 °C (lit.[7c] mp = 118–125 °C); $[\alpha]_D^{25} = +12.6$ (*c* 1.00, $CHCl_3$) [lit.[7c] $[\alpha]_D^{25} = +8.6$ (*c* 0.62, $CHCl_3$)]; IR (KBr, cm^{-1}): ν_{max} 3356, 1688; ^1H NMR (500 MHz, $CDCl_3$, 333 K) δ 1.38 (s, 9H), 2.86 (dd, *J* = 14.0, 8.5 Hz, 1H), 3.05 (d, *J* = 8.0 Hz, 1H), 3.07 (dd, *J* = 14.0, 4.5 Hz, 1H), 3.14 (br s, 1H), 3.44–3.48 (m, 1H), 3.66–3.71 (m, 2H), 3.83–3.90 (m, 1H), 4.64 (br d, 1H), 7.20–7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, 333 K) δ 28.2, 36.4, 52.4, 63.0, 73.1, 80.2, 126.5, 128.5, 129.4, 137.4, 156.9. Elemental Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.0; H, 8.2; N, 5.0. Found: C, 64.0; H, 8.1; N, 5.10; HRMS (ESI+): *m/z* [M+Na$^+$] calcd for $C_{15}H_{23}NNaO_4$ (MNa^+) 304.1519, found 304.1512.

4.6. (2*S*,3*S*)-3-(*tert*-Butoxycarbonyl)amino-4-phenyl-1-tosyloxy-2-butanol 7

To a solution of compound **6** (290 mg, 1.03 mmol) in dry CH_2Cl_2 (4 mL) at room temperature were added successively *n*-Bu_2SnO (8 mg, 0.03 mmol), a solution of Et_3N (171 μL, 1.24 mmol) in dry CH_2Cl_2 (4 mL) and TsCl (236 mg, 1.24 mmol) and the reaction mixture was stirred for 6 h at room temperature. The reaction mixture was treated with saturated aqueous NaCl (5 mL). The organic phase separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo. Purification of the crude product by column chromatography (1st eluent: Et_2O/hexanes 1:1, 2nd eluent: Et_2O) afforded 416 mg (93%) of compound **7** as a white solid. Mp = 118–119 °C; $[\alpha]_D^{25} = +6.8$ (*c* 1.00, $CHCl_3$); IR (KBr, cm^{-1}): ν_{max} 3384, 1686, 1361; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 9H), 2.46 (s, 3H), 2.83–2.94 (m, 2H), 3.82–3.90 (m, 2H), 4.01 (dd, *J* = 10.2, 6.3 Hz, 1H), 4.11 (dd, *J* = 10.2, 3.6 Hz, 1H), 4.64 (d, *J* = 8.0 Hz, 1H), 7.15–7.31 (m, 2H), 7.34–7.37 (m, 2H), 7.78–7.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 28.1, 35.7, 53.8, 71.2, 71.5, 80.0, 126.6, 128.0, 128.5, 129.3, 129.9, 132.3, 137.1, 145.1, 156.1. Elemental Anal. Calcd for $C_{22}H_{29}NO_6S$: C, 60.7; H, 6.7; N, 3.2; S, 7.4. Found: C, 60.7; H, 6.6; N, 3.4; S, 7.5; HRMS (ESI+): *m/z* [M+Na$^+$] calcd for $C_{22}H_{29}NNaO_6S$ (MNa^+) 458.1608, found 458.1601.

4.7. (2*S*,3*S*)-3-(*tert*-Butoxycarbonyl)amino-1,2-epoxy-4-phenylbutane 1

To a solution of compound **7** (391 mg, 0.90 mmol) in dry MeOH (10 mL) at 0 °C was added anhydrous K_2CO_3 (149 mg, 1.08 mmol) and the mixture was stirred for 2 h at room temperature. The reaction mixture was treated with saturated aqueous NH_4Cl (5 mL) and water (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo. Purification of the crude product by column chromatography (eluent: Et_2O/hexanes 1:2) afforded 232 mg (98%) of compound **1** as a white solid. Mp = 124–125 °C (lit.[11] mp = 122–124.5 °C); $[\alpha]_D^{25} = +8.0$ (*c* 1.00, $CHCl_3$) [lit.[11] $[\alpha]_D^{25} = +6.9$ (*c* 0.62, $CHCl_3$)]; IR (KBr, cm^{-1}): ν_{max} 3377, 1680; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (s, 9H), 2.65–2.69 (m, 1H), 2.71 (dd,

J = 4.8, 3.0 Hz, 1H), 2.78 (dd, J = 14.0, 7.6 Hz, 1H), 2.82–2.86 (m, 1H), 2.89 (dd, J = 14.0, 3.9 Hz, 1H), 3.61–3.63 (m, 1H), 4.43 (br d, 1H), 7.10–7.28 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 37.5, 46.8, 52.5, 53.2, 79.5, 126.6, 128.5, 129.4, 136.7, 155.2. Elemental Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.4; H, 8.0; N, 5.3. Found: C, 68.5; H, 7.9; N, 5.5; HRMS (ESI+): m/z [M+Na$^+$] calcd for $C_{15}H_{21}NNaO_3$ (MNa^+) 286.1414. Found 286.1402.

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