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Stereoselective synthesis of (2*S*,3*S*)-3-hydroxy-2-phenylpiperidine from D-mannitol

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ABSTRACT

A novel stereoselective synthesis of *N*-Boc-(2*S*,3*S*)-3-hydroxy-2-phenylpiperidine was achieved from D-mannitol involving the highly stereoselective addition of phenyl Grignard to an allyl imine (de >98%) and ring-closing metathesis (RCM) in the key steps.

1. Introduction

Functionalized piperidines are useful as biologically active agents, and several methods have been developed for the synthesis of substituted piperidines in a diastreo- and enantioselective manner.[1] *N*-Boc-(2*S*,3*S*)-3-Hydroxy-2-phenylpiperidine **1** is an important intermediate from which non-peptidic neurokinin NK1 receptor antagonists **2**[2] and **3**[3] have been prepared (Fig. 1). These non-peptidic ligands **2** and **3** are known to exhibit a variety of biological activities including neurogenic inflammation,[4] pain transmission and regulation of the immune response.[5] They have also been implicated in a variety of disorders including migraine,[6] rheumatoid arthritis[7] and pain.[8] Considering their pharmacological importance,[9] various methods have been developed to access compound **1**.[10] These include the introduction of stereogenic centres via Sharpless epoxidations and one-pot aza Witting reactions,[10a] Sharpless asymmetric dihydroxylations of silyl enol ethers,[10b] Sharpless asymmetric aminohydroxylations[10c] or Jacobson's asymmetric epoxidations followed by ring expansions.[10d] Although these methods are fairly efficient (ee 94–99%, yields 65–75%), they require expensive chiral ligands to induce chirality or highly toxic Osmium complexes. Other strategies involve intermediates derived from amino acids such as L-phenylglycine[10e–g] and L-glutamic acid.[10h,10i] However, these methods produce the key chiral intermediate in either low yield (58%) or with low diastereoselectivity (90%). Herein, we report a far simpler, novel stereoselective synthesis of *N*-Boc-(2*S*,3*S*)-3-hydroxy-2-phenylpiperidine **1** starting with naturally occurring, easily available D-mannitol possessing the required stereochemistry. Most steps are straightforward and are high yielding (overall yield 24% from **4** in 10 steps). The required chiral intermediate **11** is obtained as a single *syn*-diasteromer in the key step through stereoselective chelation controlled Grignard addition reaction on a chiral imine.

2. Results and discussion

The synthesis of *N*-Boc-(2*S*,3*S*)-3-hydroxy-2-phenylpiperidine **1** (shown in Scheme 2) commenced from alcohol **4**, which was prepared from D-mannitol[11] in 50% overall yield. Compound **4** was converted to allylic alcohol **6**[12] in two steps, involving the formation of chloride **5** with triphenyl phosphine (TPP) in CCl_4 (92%) followed by Na-mediated elimination to furnish allylic alcohol **6** (85%). The resulting secondary hydroxyl group was protected as its benzyl ether **7,** and then the acetonide group was removed using 90% TFA to afford the corresponding diol **8**, in 80% yield, which was cleaved with $NaIO_4$ to give aldehyde **9**, in 90% yield. This aldehyde was converted to imine **10**, in 85% yield using allylamine in the presence of anhydrous $MgSO_4$, and was subsequently reacted with phenylmagnesium bromide in diethylether under ice cold conditions. This Grignard reaction proceeded with excellent stereoselectivity and afforded the corresponding amine **11**, in 78% yield as a single diastereomer. In the ^1H NMR spectrum, the C_2–H resonates as triplet at 3.82 ppm (J = 7.9 Hz) and the C_1–H as a doublet at 3.69 ppm (J = 8.12 Hz). No other peaks corresponding to other diastereomers were observed in the 3.5–4.0 ppm region. The *syn*-configuration of the amino alcohol derivative **11** was confirmed from the stereochemistry of the final product. Our results are in agreement with those observed by Cativiela et al.[13] who have reported high stereoselectivity during the Grignard reaction of *N*-benzylimine derived from 2-*O*-benzyl-D-glyceraldehyde and phenyl and methyl magnesium bromide under similar conditions. The formation of the *syn*-product can be explained on the basis of a chelation-controlled Cram model[14] involving coordination of the *O*-benzyl lone pair with the metal ion prior to nucleophilic attack (Scheme 1).

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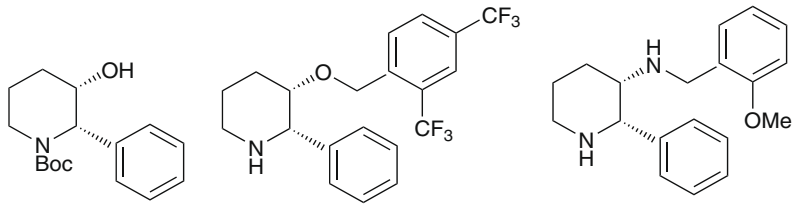
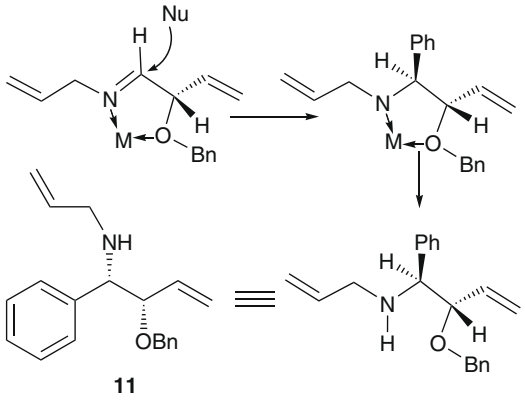


1 **2**: (+)-(2*S*,3*S*)-CP-99,994 **3**: (+)-(2*S*,3*S*)-L-733,060

Figure 1.

Protection of amine **11** with $(Boc)_2O$ to give **12** followed by ring-closing metathesis (RCM)[15] of **12** using Grubbs's first generation catalyst, $Cl_2Ru(=CHPh)(PCy_3)_2$ (5 mol %), in DCM at RT proceeded to give **13** in 92% yield. Saturation of the double bond and debenzylation were carried out with H_2/Pd–C in EtOH to furnish the target molecule **1**, in 93% yield. The physical and spectroscopic data of **1** were in full agreement with those reported in the literature.[10f]



11

Scheme 1.

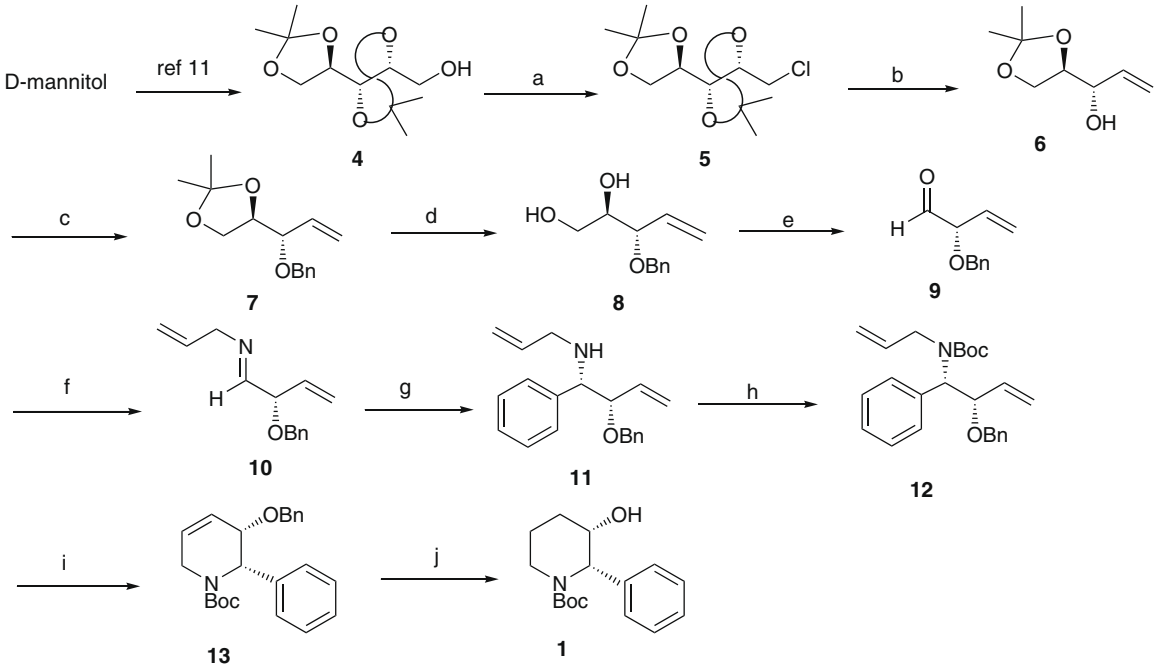
3. Conclusion

In conclusion, we have carried out a highly stereoselective synthesis of *N*-Boc-(2*S*,3*S*)-3-hydroxy-2-phenylpiperidine starting with D-mannitol. Naturally occurring mannitol provides one stereocentre while the stereoselective addition of phenyl Grignard to an allyl imine derivative provides the second stereocentre with very high diastereoselectivity. This strategy can be used for making analogues by changing the Grignard reagent. Finally, ring-closing metathesis (RCM) provides the required appropriately substituted piperidine ring.

4. Experimental

4.1. General experimental

All reagents were purchased from Aldrich. IR spectra were recorded on a Perkin–Elmer RX-1 FT-IR system. ^{1}H NMR (200 MHz) spectra were recorded on a Varian Gemini-200 MHz spectrometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded



4 **5** **6** **7** **8** **9** **10** **11** **12** **13** **1**

Scheme 2. Reagents and conditions: (a) CCl_4, TPP, $NaHCO_3$, reflux 1 h, 92%; (b) Na, dry E_2O, 0 °C to rt, 12 h, 85%; (c) NaH, BnBr, dry DMF, 0 °C to rt, 1 h, 84%; (d) 90% CF_3COOH in water, 0 °C, 4 h, 80%; (e) $NaIO_4$, 60% CH_3CN, 0 °C to rt, 1 h, 90%; (f) allylamine, anhydrous $MgSO_4$, dry ether, 0 °C to rt, 2 h, 85%; (g) phenyl magnesium bromide, dry ether, 0 °C to rt, 6 h, 78%; (h) Boc_2O, Et_3N, DCM, rt,1 h, 90%; (i) Grubbs, I, DCM, rt, 12 h, 92%; (j) H_2/Pd–C, EtOH, 4 h, 93%.

on Bruker Avance-300 MHz spectrometer. Optical rotations were measured with Horiba-SEPA-300 digital polarimeter. Mass measurement was performed on Q STAR mass spectrometer (Applied Biosystems, USA).

4.2. 1,2:3,4-Di-*O*-isopropylidene-(2*R*,3*R*,4*S*)-5-chloropentane-1,2,3,4-tetraol 5

Compound **4** (8 g, 34.5 mmol) was dissolved in CCl_4 (15 mL). Triphenyl phosphine (13.6 g, 51.7 mmol) and $NaHCO_3$ (5.8 g, 69 mmol) were added with stirring and the reaction mixture was refluxed at 80 °C for 1 h. The contents were then cooled to room temperature and extracted with $CHCl_3$ (2 × 100 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (ethyl acetate/hexane) (5:95) to afford pure **5** (7.94 g, 92%) as a pale yellow oil. $[\alpha]_D^{25} = +13.2$ (c 1, CHCl3); IR (neat, cm^{-1}): ν_{max} 3446, 2988, 2935, 2882, 1373, 1218, 1155, 1069, 841; ^1H NMR (300 MHz, CDCl3): δ 1.34 (s, 3H), 1.39 (s, 3H), 1.42 (s, 3H), 1.44 (s, 3H), 3.65 (dd, *J* = 5.28, 12.08 Hz, 1H), 3.76 (t, *J* = 7.55 Hz, 1H), 3.80–3.85 (m, 1H), 3.93–4.06 (m, 2H), 4.09–4.16 (m, 2H); ^{13}C NMR (75 MHz, CDCl3): δ 25.04, 26.60, 26.90, 27.04, 44.62, 67.54, 76.82, 78.16, 79.73, 109.65, 109.91; EI-MS: m/z = 273.5 [M+Na]+.

4.3. (1*S*)-1-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-propen-1-ol 6

Compound **5** (6 g, 24 mmol) was dissolved in dry ether (50 mL) at 0 °C and shining Na pieces (1.66 g, 72 mmol) were added under a nitrogen atmosphere. After stirring at room temperature for 12 h, the reaction mixture was quenched with methanol (10 mL) and filtered. The residue was washed with diethyl ether and the combined filtrate was concentrated in vacuo. The oily residue was dissolved in EtOAc (50 mL) and the organic layer was washed with brine, and dried over anhydrous Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by column chromatography (ethyl acetate/hexane) (15:85) to afford pure **6** (3.22 g, 85%) as a pale yellow oil. $[\alpha]_D^{25} = +2.8$ (*c* 1, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3449, 2923, 2854, 1648, 1022, 754; ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 (s, 3H), 1.44 (s, 3H), 2.07 (d, *J* = 3.02 Hz, 1H), 3.83–3.95 (m, 2H), 4.07 (q, *J* = 4.53, 6.79 Hz, 1H), 4.24 (m, 1H), 5.21–5.42 (m, 2H), 5.76–5.87 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.03, 26.33, 64.79, 71.87, 78.05, 109.34, 116.72, 136.24; EI-MS: *m*/*z* = 181 $[M+Na]^+$.

4.4. (4*R*)-4-[(1*S*)-1-(Benzyloxy)-2-propenyl]-2,2-dimethyl-1,3-dioxolane 7

To a stirred suspension of NaH (0.91 g, 38 mmol) in dry DMF (20 mL) was added a solution of **6** (3 g, 19 mmol) in dry DMF (10 mL) dropwise at 0 °C under a nitrogen atmosphere. After stirring at room temperature for 15 min, benzyl bromide (2.20 mL, 19 mmol) was added and the reaction mixture was stirred overnight. The reaction was quenched with saturated aq NH_4Cl at 0 °C and extracted with ether (2 × 100 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (ethyl acetate/hexane) (5:95) to afford pure **7** (3.95 g, 84%) as a yellow oil. $[\alpha]_D^{25} = +49.2$ (*c* 1, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3403, 2926, 2876, 1719, 1643, 1454, 1394, 1277, 1211, 1066, 933, 699; ^1H NMR (200 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.41 (s, 3H), 3.74 (t, *J* = 5.85, 7.31 Hz, 1H), 3.84–3.93 (m, 1H), 4.02–4.17 (m, 2H), 4.36–4.68 (m, 2H), 5.30–5.43 (m, 3H), 5.74–5.92 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.16, 26.40, 66.6 70.37, 77.67, 80.82, 109.51, 119.39, 127.45, 127.65, 128.18, 135.08, 138.00; EI-MS: *m*/*z* = 271.2 $[M+Na]^+$.

4.5. (2*R*,3*S*)-3-(Benzyloxy)-4-pentene-1,2-diol 8

Compound **7** (2 g, 8 mmol) was dissolved in 90% aq CF_3COOH (15 mL) at 0 °C and the mixture was stirred at the same temperature for 4 h. The reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL). The collected organic layers were combined, washed with 10% $NaHCO_3$, water and brine, dried over Na_2SO_4 and concentrated in vacuo. The residual oil was purified by silica gel column chromatography using ethyl acetate/ hexane (1:3) to give **8** (1.34 g, 80%) as a syrup. $[\alpha]_D^{25} = +55.0$ (*c* 1, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3410, 2966, 2931, 2877, 1713, 1455, 1274, 1070, 1024, 701; ^1H NMR (200 MHz, $CDCl_3$): δ 2.15–2.23 (br s, 1H), 2.57–2.64 (br s, 1H), 3.51–3.74 (m, 3H), 3.85–3.95 (m, 1H), 4.32–4.65 (m, 2H), 5.27–5.45 (m, 2H), 5.70–5.92 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 63.14, 70.47, 73.30, 81.71, 119.80, 127.59, 127.69, 128.28, 134.90, 137.82; EI-MS: *m*/*z* = 231.0 $[M+Na]^+$.

4.6. *N*-Allyl-*N*-[(1*S*,2*S*)-2-(benzyloxy)-phenyl-3-butenyl] amine 11

To a solution of **8** (1 g, 4.8 mmol) in 60% aq CH_3CN (20 mL) was added $NaIO_4$ (2.14 g, 10 mmol) in one portion. The mixture was stirred at room temperature for 1 h and filtered. Acetonitrile was evaporated on a rotavaporator and the residue was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give aldehyde **9** (0.762 g, 90%) as a colourless oil. The crude aldehyde **9** (0.762 g, 4.32 mmol) was dissolved in dry diethyl ether (15 mL), and anhydrous $MgSO_4$ (2 g) followed by allylamine (0.34 mL, 4.33 mmol) was added at 0 °C with vigorous stirring. After 30 min, the cooling bath was removed and stirring was continued at room temperature for 2 h. After completion of the reaction, the solution was filtered and the filtrate was concentrated in vacuo to give imine **10** (0.8 g, 85%) as a yellow syrup. This was dissolved in dry diethyl ether (10 mL) and was added dropwise over 30 min to a stirred solution of phenyl magnesium bromide (0.5 M in diethyl ether, 18.4 mL, 9.2 mmol) at 0 °C under nitrogen atmosphere. After being stirred for 6 h at room temperature, the reaction mixture was poured into saturated aqueous NH_4Cl (20 mL), the organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography using ethyl acetate/hexane (1:9) to give **11** (0.84 g, 78%) as a yellow oil. $[\alpha]_D^{25} = +51.0$ (*c* 1, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3435, 3060, 3028, 2924, 2856, 1641, 1452, 1064, 923, 769, 699; ^1H NMR (300 MHz, $CDCl_3$): δ 1.67–1.92 (br s, 1H), 2.85–3.13 (m, 2H), 3.69 (d, *J* = 8.12 Hz, 1H), 3.82 (t, *J* = 7.9 Hz, 1H), 4.3–4.6 (m, 2H), 4.92–5.15 (m, 5H), 5.47–5.64 (m, 1H), 5.73–5.9 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.9, 49.8, 66.8, 70.9, 85.2, 115.7, 119.1, 127.5, 127.9, 128.1, 128.4, 128.8, 135.6, 137.0, 138.4, 140.3; EI-MS: *m*/*z* = 294.2 $[M+1]^+$. HRMS (EI): *m*/*z* calcd for $C_{20}H_{24}NO$: 294.1857; found: 294.1856.

4.7. *tert*-Butyl *N*-allyl-*N*-[(1*S*,2*S*)-2-(benzyloxy)-1-phenyl-3-butenyl] carbamate 12

To compound **11** (0.3 g, 1.02 mmol) in dry DCM (10 mL), Et_3N (0.14 ml, 1.02 mmol) followed by Boc_2O (0.59 mL, 2.56 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was then washed with saturated NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The collected organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified through silica gel column chromatography using ethyl acetate/

hexane (2:98) to give **11** (0.362 g, 90%) as a syrup. $[\alpha]_D^{25} = +46.0$ (*c* 1, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3448, 3067, 2975, 2927, 1691, 1451, 1396, 1363, 1248, 1172, 923, 769, 699; ^1H NMR (300 MHz, $CDCl_3$): δ 1.44 (s,9H), 3.67 (d, *J* = 5.3 Hz, 2H), 4.29–4.69 (m, 3H), 4.76–4.98 (m, 2H), 5.1 (d, *J* = 7.55 Hz, 1H), 5.16–5.33 (m, 2H), 5.44–5.60 (m, 1H), 5.61–5.75 (m, 1H), 7.15–7.42 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.4, 29.6, 47.7, 62.4, 69.9, 79.5, 115.2, 119.4, 127.3, 127.4, 127.5, 127.8, 128.1, 129.3, 135.9, 138.2,138.8, 140.5, 156.4; EI-MS: *m*/*z* = 416.0 $[M+Na]^+$. HRMS (EI): *m*/*z* calcd for $C_{25}H_{31}NO_3Na$: 416.2201; found: 416.2217.

4.8. *tert*-Butyl (2*S*,3*S*)-3-(benzyloxy)-2-phenyl 1,2,3,6-tetrahydro-1-pyridine carboxylate 13

Diene **12** (0.25 g, 0.64 mmol) was dissolved in dry CH_2Cl_2 (25 mL). Grubbs's first generation catalyst (52 mg, 0.064 mmol, 0.1 equiv) was added and the resulting purple solution turned brown after 10 min. The reaction mixture was stirred at room temperature for 12 h, then concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate/hexane) (3:97) and the title compound **13** (0.21 g) was obtained as a colourless oil. Yield: 92%; $[\alpha]_D^{25} = +44.0$ (*c* 1, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3445, 2975, 2924, 2852, 1694, 1402, 1167,1089, 750, 698; ^1H NMR (300 MHz, $CDCl_3$): δ 1.48 (s, 9H), 3.24 (dd, *J* = 3.02, 18.88 Hz, 1H), 3.99–4.22 (m, 1H), 4.4–4.5 (m, 1H), 4.51–4.63 (m, 2H), 5.58–5.72 (m, 2H), 5.97 (d, *J* = 9.82 Hz, 1H), 7.1–7.58 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.4, 29.6, 40.6, 70.7, 73.0, 80.3, 124.4, 127.0, 127.2, 127.5, 127.7, 127.86, 128.3, 129.1, 137.1, 137.9, 154.6; EI-MS: *m*/*z* = 388.8 $[M+Na]^+$. HRMS (EI): *m*/*z* calcd for $C_{23}H_{27}NO_3Na$: 388.1888; found: 388.1892.

4.9. (2*S*,3*S*)-3-Hydroxy-2-phenyl-piperidine-1-carboxylic acid *tert*-butyl ester 1

To a solution of **13** (0.2 g) in ethanol (10 mL) was added 20 mg of 10% Pd/C and mixture was stirred under a hydrogen atmosphere for 6 h. After completion of reaction, the solution was filtered and the filtrate was concentrated. The crude product was purified on silica gel column using ethyl acetate/hexane (3:7) as eluent to give **1** (0.141 g, 93%) as a viscous liquid. $[\alpha]_D^{25} = +39.0$ (*c* 1, $CHCl_3$) {lit.[10e] +38.3 (*c* 1.92, $CHCl_3$)}. IR (neat, cm^{-1}): ν_{max} 3441, 2924, 1666, 1415, 1365,1254, 1172; ^1H NMR (200 MHz, $CDCl_3$): δ 1.37 (s, 9H), 1.60–1.93 (m, 5H), 2.98 (ddd, *J* = 4.4,11.5,13.2 Hz, 1H), 3.84–4.18 (m, 2H), 5.26 (d, *J* = 5.8 Hz, 1H), 7.20–7.49 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.19, 27.65, 28.30, 39.41, 59.17, 70.08, 79.85, 127.10, 128.28, 128.36, 138.40, 155.35; EI-MS: *m*/*z* = 300.7 $[M+Na]^+$. HRMS (EI): *m*/*z* calcd for $C_{16}H_{23}NO_3Na$: 300.1575; found: 300.1589.

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References

1. (a) Reddy, M. S.; Narender, M.; Rao, K. R. *Tetrahedron* **2007**, *63*, 331–336; (b) Radha Krisha, P.; Dayaker, G. *Tetrahedron Lett.* **2007**, *48*, 7279–7282; (c) Yokoyama, K.; Ejiri, H.; Miyajawa, M.; Yamaguchi, S.; Hirai, Y. *Tetrahedron: Asymmetry* **2007**, *18*, 852–856; (d) Zhu, S.; Meng, L.; Zhang, Q.; Wei, L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1854–1858; (e) Kandula, S. R. V.; Kumar, P. *Tetrahedron: Asymmetry* **2005**, *16*, 3268–3274; (f) Bates, R. W.; Sa-Ei, K. *Tetrahedron* **2002**, *58*, 5957–5978; (g) Wilkinson, T. J.; Stehla, N. W.; Beak, P. *Org. Lett.* **2000**, *2*, 155–158; (h) Lasschat, S.; Dickner, T. *Synthesis* **2000**, *13*, 1781–1813. and references cited therein.
2. (a) Baker, R.; Harrison, T.; Hollingworth, G. J.; Swain, C. J.; Williams, B. J. EP 528,495 A1, 1993.; (b) Harrison, T.; Williams, B. J.; Swain, C. J.; Ball, R. G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2545–2550.
3. Desai, M. C.; Lefkowitz, S. L.; Thadeio, P. F.; Longo, K. P.; Snider, R. M. *J. Med. Chem.* **1992**, *35*, 4911–4913.
4. Lotz, M.; Vaughan, J. H.; Carson, D. A. *Science* **1988**, *241*, 1218–1221.
5. Perianan, A.; Snyderman, R.; Malfroy, B. *Biochem. Biophys. Res. Commun.* **1989**, *161*, 520–524.
6. Moskowitz, M. A. *Trends Pharmacol. Sci.* **1992**, *13*, 307–311.
7. Lotz, M.; Vaughan, J. H.; Carson, D. A. *Science* **1987**, *235*, 893–895.
8. Otsuka, M.; Yanagisawa, M. *J. Physiol. (London)* **1988**, *395*, 255–270.
9. (a) Giardina, G. A. M.; Raveglia, L. F.; Grugni, M. *Drugs Future* **1997**, *22*, 1235–1257; (b) Chandrasekhar, S.; Mohanty, P. K. *Tetrahedron Lett.* **1999**, *40*, 5071–5072.
10. (a) Cherian, S. K.; Kumar, P. *Tetrahedron: Asymmetry* **2007**, *18*, 982–987; (b) Stadler, H.; Bos, M. *Heterocycles* **1999**, *51*, 1067–1071; (c) Kandula, S. R. V.; Kumar, P. *Tetrahedron: Asymmetry.* **2005**, *16*, 3579–3583; (d) Lee, J.; Hoang, T.; Lewis, S.; Weissman, S. A.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **2001**, *42*, 6223–6225; (e) Yoon, Y.-J.; Joo, J. E.; Lee, K.-Y.; Kim, Y.-H.; Oh, C.-Y.; Ham, W.-H. *Tetrahedron Lett.* **2005**, *46*, 739–741; (f) Bhaskar, G.; Rao, B. V. *Tetrahedron Lett.* **2003**, *44*, 915–917; (g) Bodas Mandar, S.; Upadhyay Puspesh, K.; Kumar, P. *Tetrahedron Lett.* **2004**, *45*, 987–988; (h) Huang, P.-Q.; Liu, L.-X.; Wei, B.-G.; Ruan, Y.-P. *Org. Lett.* **2003**, *5*, 1927–1929; (i) Calvez, O.; Langlois, N. *Tetrahedron Lett.* **1999**, *40*, 7099–7100.
11. Reddy, J. S.; Kumar, A. R.; Rao, B. V. *Tetrahedron: Asymmetry* **2005**, *16*, 3154–3159.
12. Lu, W.; Zheng, G.; Cai, J. *Synlett* **1998**, 737–738.
13. (a) Badorrey, R.; Cativiela, C.; Diaz-de-villegas Marie, D.; Galvez Jose, A. *Tetrahedron* **1997**, *53*, 1411–1416; (b) Cativiela, C.; Diaz-de-villegas, M. D.; Galvez, J. A. *Tetrahedron: Asymmetry* **1996**, *7*, 529–536.
14. (a) Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828–5835; (b) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748–2755.
15. For syntheses of piperidine moieties using ring-closing metathesis, see: (a) Cossy, J.; Willis, C.; Bellosta, V.; BouzBouz, S. *J. Org. Chem.* **2002**, *67*, 1982–1992; (b) Ginesta, X.; Pericas, M. A.; Riera, A. *Tetrahedron Lett.* **2002**, *43*, 779–782; (c) Davies, S. G.; Iwamoto, K.; Smethurst, C. A. P.; Smith, A. D.; Rodriguez-Solla, H. *Synlett* **2002**, 1146–1148; (d) Felpin, F.; Girard, S.; Vo-Thanh, G.; Robins, R. J.; Villieras, J.; Lebreton, J. *J. Org. Chem.* **2001**, *66*, 6305–6312; (e) Banba, Y.; Abe, C.; Nemoto, H.; Kato, A.; Adachi, I.; Takahata, H. *Tetrahedron: Asymmetry* **2001**, *12*, 817–819; (f) Pernerstorfer, J.; Schuster, M.; Blechert, S. *Synthesis* **1999**, 138–144; (g) Zumpe, F. L.; Kazmaier, U. *Synthesis* **1999**, 1785–1791.