Concise Synthesis of (2*S*,3*R*)-3-Hydroxy-2-phenylpiperidine: An Advanced Key Intermediate of Human Non-Peptide NK-1 Receptor Antagonists

Benoît Hélal, Franck Ferreira,* Candice Botuha, Fabrice Chemla,* Alejandro Pérez-Luna

UPMC–Univ Paris 06, CNRS UMR 7201, Institut Parisien de Chimie Moléculaire (FR 2769), Case 183, 4 Place Jussieu, 75005 Paris, France

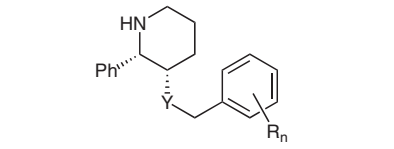
Fax +33(1)44277567; E-mail: franck.ferreira@upmc.fr; E-mail: fabrice.chemla@upmc.fr

Received 24 July 2009

Abstract: The rapid, high-yielding synthesis of (2*S*,3*R*)-3-hydroxy-2-phenylpiperidine, a known advanced key intermediate of some non-peptide human NK-1 receptor antagonists such as (+)-CP-99,994, (+)-CP-122,721 and (+)-LP-733,060, is reported. This synthesis involves the stereoselective addition of racemic 3-(methoxymethoxy)allenylzinc bromide to enantiopure (R_S,*E*)-*N*-2-benzylidene-2-methylpropane-2-sulfinamide and a ring-closing metathesis reaction as the key steps. Following this procedure, (2*S*,3*R*)-3-hydroxy-2-phenylpiperidine is obtained in seven steps in 56.2% overall yield.

Key words: metathesis, piperidines, ring-closure, stereoselective synthesis, zinc

The neuropeptide substance P is an undecapeptide belonging to the tachykinin family that binds preferentially to the endogenous neurokinin-1 (NK-1) receptor.[1] Substance P is involved in complex mechanisms related to the transmission of pain information in the central nervous system. It is associated with the regulation of mood disorders, anxiety, stress,[2] reinforcement,[3] neurogenesis,[4] respiratory rhythm,[5] neurotoxicity, nausea/emesis,[6] migraine,[7] neurogenic inflammation,[8] pain and nociception.[9] Due to the various activities in which substance P is implicated, the search for non-peptide NK-1 receptor antagonists has been investigated in recent years.[10]



Y = NH, R = 2-MeO (+)-CP-99,994
Y = NH, R = 2-MeO, 3-OCF_3 (+)-CP-122,721
Y = O, R = 3,5-CF_3 (+)-LP-733,060

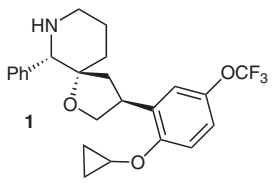
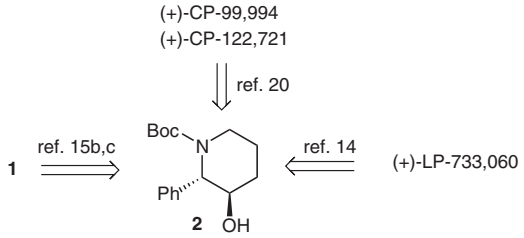


Figure 1 Some non-peptide human NK-1 receptor antagonists

Thus, in 1992, (+)-CP-99,994 (Figure 1) was shown to exhibit high affinity for human NK-1 receptors[11] and to possess potent anti-emetic activity.[12] Since the discovery of (+)-CP-99,994, other 3-amino- and 3-alkoxy-2-phenylpiperidine derivatives, such as (+)-CP-122,721,[13] (+)-LP-733,060[14] and the oxaazaspirodecane **1**,[15] have been demonstrated to be of potential therapeutic value (Figure 1). All the biological studies on these compounds have established that both the cis-relationship between the two substituents on the piperidine ring and the (2*S*,3*S*)-configuration are crucial for high bioactivity.[16]

Amongst the various approaches reported for the preparation of such 3-hydroxy-2-phenylpiperidine derivatives,[17,18] some involve the formation of (2*S*,3*R*)-*N*-*tert*-butyl 3-hydroxy-2-phenylpiperidine-1-carboxylate (**2**),[19] which can be regarded as an advanced versatile and valuable precursor of (+)-CP-99,994,[20] (+)-CP-122,721,[20] (+)-LP-733,060[14] and **1**[15b,c] (Scheme 1).

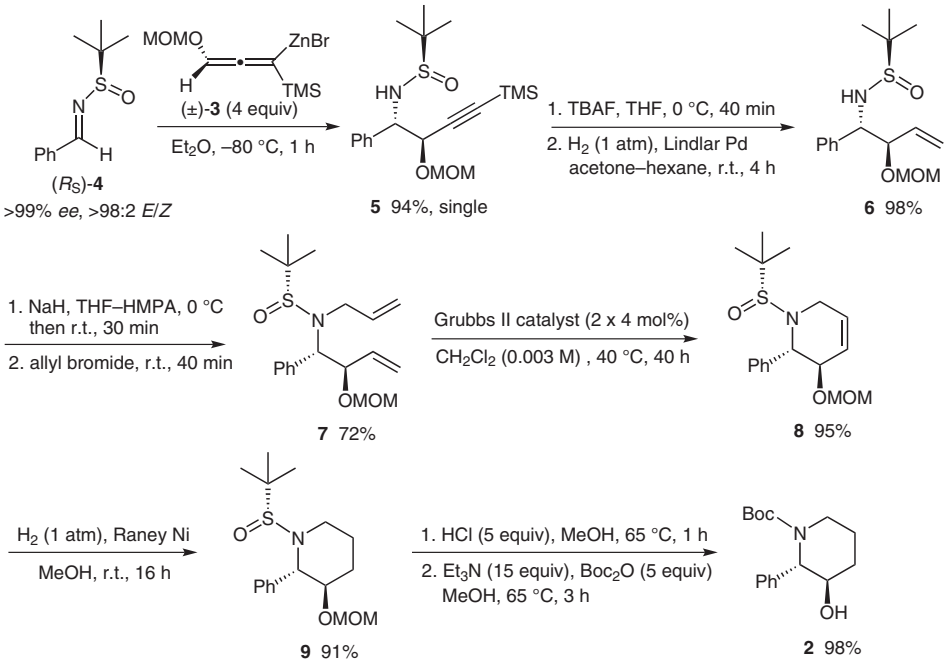


Scheme 1 Advanced key intermediate **2** for the synthesis of (+)-CP-99,994, (+)-CP-122,721, (+)-LP-733,060 and **1**

In the course of our studies on the synthesis of biologically active compounds, we were interested in preparing **2** using a reaction developed in our group (i.e. the stereoselective addition of a racemic allenylzinc to an enantiopure *N*-*tert*-butylsulfinyl imine[21]) and a ring-closing metathesis as two key steps. Analogous allylsulfone addition to (*S*)-*p*-toluenesulfinylimine and ring-closing metathesis has been described before as an entry into optically active 2-arylpiperidines.[22]

Our synthesis then began with the reaction between racemic allenylzinc (±)-**3** and *N*-*tert*-butylsulfinyl imine (R_S)-**4**, which is easily prepared in diastereo- and enantiomerically pure form from commercially or readily synthetically available (R_S)-*tert*-butylsulfinyl amide.[23] Addition of (R_S)-**4** to (±)-**3** (4 equiv) allowed a high dynamic kinetic resolution to take place; the (a*R*)-enantiomer of **3** reacted

SYNLETT 2009, No. 19, pp 3115–3118
Advanced online publication: 23.10.2009
DOI: 10.1055/s-0029-1218308; Art ID: G25109ST



Scheme 2 Synthesis of (2*S*,3*R*)-3-hydroxy-2-phenylpiperidine derivative **2**

with (R_S)-**4** faster [(a*R*)-**3**·(R_S)-**4** matched pair] than the (a*S*)-antipode [(a*S*)-**3**·(R_S)-**4** mismatched pair]. After acidic workup, the desired acetylenic *anti*-(2*S*,3*R*)-sulfinylamidoalkyl ether **5** was isolated as a single isomer in 94% yield (Scheme 2).[24]

Treatment of **5** with TBAF (1.05 equiv) in THF resulted in the clean protodesilylation of the acetylenic position within 40 minutes at 0 °C. The resulting crude product was subjected to semihydrogenation (1 atm H_2) for four hours in the presence of Lindlar palladium catalyst (20 wt% of Pd) and 3,5-dithia-1,2-octanediol (4 wt%) in acetone–hexane (5%).[21b] Compound **6** was thus obtained in 98% isolated yield over the two steps (Scheme 2).

Continuing the synthesis, intermediate **6** was added to NaH (4 equiv) in a mixture of THF–HMPA (85:15) at 0 °C, and the resulting suspension was stirred at room temperature for 30 minutes. The formed sodium sulfinyl amide was subsequently treated with allyl bromide (10 equiv) for 40 minutes at room temperature. After the usual workup, the expected allyl *N*-*tert*-butylsulfinyl amine **7** was obtained in 72% yield (Scheme 2).

At this stage, we expected to construct the piperidine ring system of the target molecule by subjecting **7** to ring-closing metathesis with Grubbs II catalyst. Indeed, performing the reaction with 8 mol% of ruthenium catalyst (added as two portions each of 4 mol% separated by a period of 20 h) in CH_2Cl_2 (0.003 M solution) at 40 °C for 40 hours, resulted in the formation of the desired compound **8**[25] in 95% yield (Scheme 2).

In order to obtain the piperidine derivative **9**, we undertook the hydrogenation of the C–C double bond. While carrying out the hydrogenation (1 atm) in the presence of Pd/C failed to produce **9** (starting material **8** being quantitatively recovered), the desired product **9**[26] was obtained in 91% yield within 16 hours at room temperature in the presence of Raney nickel in MeOH (Scheme 2).

Finally, acid-mediated removal of the *tert*-butylsulfinyl auxiliary and MOM-ether deprotection were concomitantly accomplished by treatment with anhydrous HCl (4 M in 1,4-dioxane, 5 equiv) at 65 °C in MeOH for one hour. Successive addition of Et_3N (15 equiv) and Boc_2O (5 equiv) to the reaction mixture, followed by additional heating at 65 °C for three hours afforded the target molecule **2** in 98% yield after usual work-up, intensive extraction with EtOAc and silica gel flash chromatography (Scheme 2). It is worth noting that compound **2**, thus obtained, exhibited spectroscopic data {$[\alpha]_D^{22}$ +64.1 (*c* 0.96, $CHCl_3$)} in excellent agreement with those reported for the (2*R*,3*S*)-antipode[19c] {$[\alpha]_D^{20}$ –66.1 (*c* 0.9, $CHCl_3$)}, presumably indicating its optical purity.

In conclusion, (2*S*,3*R*)-*N*-*tert*-butyl 3-hydroxy-2-phenylpiperidine-1-carboxylate, a known advanced key intermediate of several non-petide human NK-1 receptor antagonists, has been obtained in seven steps and 56.2% overall yield. This concise and high-yielding synthesis, which involves the stereoselective addition of a racemic 3-alkoxy allenylzinc to an enantiopure (R_S)-*N*-*tert*-butylsulfinyl imine and a ring-closing metathesis reaction as the key steps, represents a competitive alternative to previously reported approaches.

References and Notes

(1) (a) Chang, M. M.; Leeman, S. E. *J. Biol. Chem.* **1970**, *245*, 4784. (b) von Euler, U. S.; Gaddum, J. H. *J. Physiol.* **1931**, *72*, 74. (c) Nicoll, R. A.; Schenker, C.; Leeman, S. E. *Ann. Rev. Neurosci.* **1980**, *3*, 227.
(2) Ebner, K.; Singewald, N. *Amino Acids* **2006**, *31*, 251.

(3) Huston, J. P.; Hasenöhrl, R. U.; Boix, F.; Gerhardt, P.; Schwarting, R. K. *Psychopharmacology* **1993**, *112*, 147.
(4) Park, S. W.; Yan, Y. P.; Satriotomo, I.; Vemuganti, R.; Dempsey, R. J. *J. Neurosurgery* **2007**, *107*, 593.
(5) (a) Bonham, A. C. *Respir. Physiol.* **1995**, *101*, 219. (b) Payan, D. G. *Ann. Rev. Med.* **1989**, *40*, 341.
(6) Hesketh, P. J. *Supportive Care Cancer* **2001**, *9*, 350.
(7) Moskowitz, M. A. *Trends Pharmacol. Sci.* **1992**, *13*, 307.
(8) Mantyh, C. R.; Gates, T. S.; Zimmerman, R. P.; Welton, M. L.; Passaro, E. P. Jr.; Vigna, S. R.; Maggio, J. E.; Kruger, L.; Mantyh, P. W. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 3235.
(9) (a) Zubrzycka, M.; Janecka, A. *Endocr. Regul.* **2000**, *34*, 195. (b) Cuello, A. C. *Neuropharmacology* **1987**, *26*, 971.
(10) (a) Armour, D. R.; Chung, K. M. L.; Congreve, M.; Evans, B.; Guntrip, S.; Hubbard, T.; Kay, C.; Middlemiss, D.; Mordaunt, J. E.; Pegg, N. A.; Vinader, M. V.; Ward, P.; Watson, S. P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1015. (b) Guard, S.; Wtason, S. P. *Neurochem. Int.* **1991**, *18*, 149.
(11) Desai, M. C.; Lefkowitz, S. L.; Thadeio, P. F.; Longo, K. P.; Snider, R. M. *J. Med. Chem.* **1992**, *35*, 4911.
(12) Zaman, S.; Woods, A. J.; Watson, J. W.; Reynolds, D. J. M.; Andrews, P. L. *Neuropharmacology* **2000**, *39*, 316.
(13) McLean, S.; Ganong, A.; Seymour, P. A.; Bryce, D. K.; Crawford, R. T.; Morrone, J.; Reynolds, L. S.; Schmidt, A. W.; Zorn, S.; Watson, J.; Fossa, A.; DePasquale, M.; Rosen, T.; Nagahisa, A.; Tsuchiya, M.; Heym, J. *J. Pharmacol. Exp. Ther.* **1996**, *277*, 900.
(14) Harrison, T.; Williams, B. J.; Swain, C. J.; Ball, R. G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2545.
(15) (a) Kulagowski, J. J.; Curtis, N. R.; Swain, C. J.; Williams, B. J. *Org. Lett.* **2001**, *3*, 667. (b) Baker, R.; Curtis, N. R.; Elliott, J. M.; Harrisson, T.; Hollingworth, G. J.; Jackson, P. S.; Kulagowski, J. J.; Rupniak, N. M.; Seward, E. M.; Swain, C. J.; Williams, B. J. Use of NK-1 receptor antagonists for treating major depressive disorders with anxiety; WO 98,24,441, **1998**. (c) Baker, R.; Curtis, N. R.; Elliott, J. M.; Harrisson, T.; Hollingworth, G. J.; Jackson, P. S. Spiro-piperidine derivatives and their use as therapeutic agents; WO 97,49,710, **1997**.
(16) (a) Ward, P.; Armour, D. C.; Bays, D. E.; Evans, B.; Giblin, G. M. P.; Heron, N.; Hubbard, T.; Liang, K.; Middlemiss, D.; Mordaunt, J.; Naylor, A.; Pegg, N. A.; Vinader, M. V.; Watson, S. P.; Bountra, C.; Evans, D. C. *J. Med. Chem.* **1995**, *38*, 4985. (b) Boks, G. J.; Tollenaere, J. P.; Kroon, J. *Bioorg. Med. Chem.* **1997**, *5*, 535.
(17) For selected syntheses of (+)-CP-99,994, see: (a) Liu, R.-H.; Fang, K.; Wang, B.; Xu, M.-H.; Lin, G.-Q. *J. Org. Chem.* **2008**, *73*, 3307. (b) Davis, F. A.; Zhang, Y.; Li, D. *Tetrahedron Lett.* **2007**, *48*, 7838. (c) Huang, P.-Q.; Liu, L.-X.; Wei, B.-G.; Ruan, Y.-P. *Org. Lett.* **2003**, *5*, 1927. (d) Tsuritani, N.; Yamada, K.; Yoshikawa, N.; Shibasaki, M. *Chem. Lett.* **2002**, 276. (e) Chandrasekhar, S.; Mohanty, P. K. *Tetrahedron Lett.* **1999**, *40*, 5071. (f) Rosen, T.; Seeger, T. F.; McLean, S.; Desai, M. C.; G uarino, K. J.; Bryce, D.; Pratt, K.; Heym, J.; Chalabi, P. M.; Windels, J. H.; Roth, R. W. *J. Med. Chem.* **1993**, *36*, 3197.
(18) For selected syntheses of (+)-LP-733,060, see: (a) Davis, F. A.; Ramachandar, T. *Tetrahedron Lett.* **2008**, *49*, 870. (b) Cherian, S. K.; Kumar, P. *Tetrahedron: Asymmetry* **2007**, *18*, 982. (c) Kandula, S. R. V.; Kumar, P. *Tetrahedron: Asymmetry* **2005**, *15*, 3579. (d) Yoon, Y.-J.; Joo, J. E.; Lee, K.-Y.; Kim, Y.-H.; Oh, C.-Y.; Ham, W.-H. *Tetrahedron Lett.* **2005**, *46*, 739. (e) Bhaskar, G.; Rao, B. V. *Tetrahedron Lett.* **2003**, *44*, 915.
(19) For previous syntheses of **2** and its antipode, see: (a) Cochi, A.; Burger, B.; Navarro, C.; Gomez Pardo, D.; Cossy, J.; Zhao, Y.; Cohen, T. *Synlett* **2009**, 2157. (b) Takahashi, K.; Nakano, H.; Fujita, R. *Tetrahedron Lett.* **2005**, *46*, 8927. (c) Liu, L.-X.; Ruan, Y.-P.; Guo, Z.-Q.; Huang, P.-Q. *J. Org. Chem.* **2004**, *69*, 6001. (d) Calvez, O.; Langlois, N. *Tetrahedron Lett.* **1999**, *40*, 7099.
(20) Yamazaki, N.; Atobe, M.; Kibayashi, C. *Tetrahedron Lett.* **2002**, *43*, 7979.
(21) (a) Séguin, C.; Ferreira, F.; Botuha, C.; Chemla, F.; Pérez-Luna, A. *J. Org. Chem.* **2009**, *74*, 6986. (b) Ferreira, F.; Botuha, C.; Chemla, F.; Pérez-Luna, A. *J. Org. Chem.* **2009**, *74*, 2238. (c) Voituriez, A.; Pérez-Luna, A.; Ferreira, F.; Botuha, C.; Chemla, F. *Org. Lett.* **2009**, *11*, 931. (d) Roy, B.; Pérez-Luna, A.; Ferreira, F.; Botuha, C.; Chemla, F. *Tetrahedron Lett.* **2008**, *49*, 1534. (e) Voituriez, A.; Ferreira, F.; Chemla, F. *J. Org. Chem.* **2007**, *72*, 5358. (f) Voituriez, A.; Ferreira, F.; Pérez-Luna, A.; Chemla, F. *Org. Lett.* **2007**, *9*, 4705. (g) Botuha, C.; Chemla, F.; Ferreira, F.; Pérez-Luna, A.; Roy, B. *New J. Chem.* **2007**, *31*, 1552. (h) Chemla, F.; Ferreira, F.; Gaucher, X.; Palais, L. *Synthesis* **2007**, 1235. (i) Chemla, F.; Ferreira, F. *Synlett* **2006**, 2613. (j) Palais, L.; Chemla, F.; Ferreira, F. *Synlett* **2006**, 1039. (k) Ferreira, F.; Audouin, M.; Chemla, F. *Chem. Eur. J.* **2005**, *11*, 5269. (l) Chemla, F.; Ferreira, F. *J. Org. Chem.* **2004**, *69*, 8244. (m) Ferreira, F.; Denichoux, A.; Chemla, F.; Bejjani, J. *Synlett* **2004**, 2051. (n) Chemla, F.; Ferreira, F. *Synlett* **2004**, 983. (o) Ferreira, F.; Herse, C.; Riguet, E.; Normant, J. F. *Tetrahedron Lett.* **2000**, *41*, 1733.
(22) (a) Balasubramanian, T.; Hassner, A. *Tetrahedron: Asymmetry* **1998**, *9*, 2201. (b) Kumareswaran, R.; Hassner, A. *Tetrahedron: Asymmetry* **2001**, *12*, 2269.
(23) For leading references on *N*-*tert*-butylsulfinyl imines, see: (a) Ferreira, F.; Botuha, C.; Chemla, F.; Pérez-Luna, A. *Chem. Soc. Rev.* **2009**, *38*, 1162. (b) Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869. (c) Weix, D. J.; Ellman, J. A. *Org. Synth.* **2005**, *82*, 157. (d) Ellman, J. A. *Pure Appl. Chem.* **2003**, *75*, 39. (e) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (f) Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 268. (g) Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011. (h) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913.
(24) **Procedure for the formation of 5:** Under a nitrogen atmosphere, to a stirred solution of 3-[(methoxymethoxy)-prop-1-ynyl]trimethylsilane (8.40 mL, 48.00 mmol) and TMEDA (0.66 mL, 4.80 mmol) in anhydrous Et_2O (400 mL) at –80 °C, was added dropwise *s*-BuLi (1.3 M in cyclohexane–hexane, 92:8, 36.90 mL, 48.00 mmol). The resulting clear orange mixture was stirred for 1 h at –80 °C and then a solution of $ZnBr_2$ (1 M in Et_2O, 48.00 mL, 48.00 mmol) was added. The resulting white slurry of allenylzinc (±)-**3** was stirred at –80 °C for an additional 20 min before imine **4** (2.51 g, 12.00 mmol) in anhydrous Et_2O (48 mL) was added dropwise. The mixture was stirred for 1 h at –80 °C, then HCl (1 M, 200 mL) was added and the mixture was warmed to room temperature. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 200 mL). The combined organic layers were washed with sat. $NaHCO_3$ (60 mL), water (2 × 120 mL) and brine (120 mL), dried over $MgSO_4$ and concentrated in vacuo. The residual oil was purified by flash chromatography on silica gel (EtOAc–cyclohexane, 20→50%) to produce the desired compound **5** (4.32 g, 94%) as a pale-yellow solid. The physical and spectroscopic data of **5** were in good agreement with those previously reported for its antipode.[21h]

(25) **Procedure for the formation of 8:** Under an argon atmosphere, to a stirred solution of **7** (1.12 g, 3.20 mmol) in anhydrous CH_2Cl_2 (1 L), was added Grubbs II catalyst (109 mg, 0.128 mmol). After 20 h stirring at 40 °C, additional Grubbs II catalyst (109 mg, 0.128 mmol) was added. The mixture was stirred for an additional 20 h and then cooled to room temperature. Removal of the solvent in vacuo gave a dark oil, which was purified by flash chromatography on silica gel (EtOAc–cyclohexane, 30→50%) to yield **8** (984 mg, 95%) as a brown oil; $[\alpha]_D^{20}$ +13.4 (*c* 1.11, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.26 (m, 5 H), 6.11–6.02 (m, 2 H), 4.78 (AB system, *J* = 7.0 Hz, 1 H), 4.74 (AB system, *J* = 7.0 Hz, 1 H), 4.62 (d, *J* = 3.3 Hz, 1 H), 4.51–4.47 (m, 1 H), 3.77–3.60 (m, 2 H), 3.36 (s, 3 H), 1.18 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.7, 129.4, 129.3, 128.4, 128.2, 127.8, 125.3, 95.0, 71.3, 63.8, 59.3, 55.51, 55.50, 40.1, 23.2. IR (ATR diamond): 3033, 2948, 2887, 1657, 1601, 1028, 699 cm^{-1}. HRMS (ESI): *m*/*z* [M + H^+] calcd for $C_{17}H_{26}NO_3S$: 324.1628; found: 326.1620.

(26) **Procedure for the formation of 9**: To a solution of **8** (1.35 g, 4.18 mmol) in absolute MeOH (100 mL), Raney Ni (5 spatulas) was added. The flask was flushed with H_2 (3×). After 16 h stirring at room temperature under 1 atm of H_2, the reaction mixture was filtered through a short pad of flash silica gel (EtOAc–cyclohexane, 30%). The solvents were removed and the residue was filtered through a short pad of flash silica gel eluting with EtOAc. Removal of the solvent gave **9** (1.23 g, 91%) as a colorless viscous oil; $[\alpha]_D^{20}$ +105.3 (*c* 0.82, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 8.0 Hz, 2 H), 7.40 (t, *J* = 8.0 Hz, 2 H), 7.31–7.26 (m, 1 H), 4.63 (AB system, *J* = 6.8 Hz, 1 H), 4.57 (AB system, *J* = 6.8 Hz, 1 H), 4.39 (d, *J* = 5.0 Hz, 1 H), 4.14–4.09 (m, 1 H), 3.43 (ddd, *J* = 13.1, 9.4, 3.5 Hz, 1 H), 3.31–3.22 (m, 1 H), 3.27 (s, 3 H), 2.02–1.91 (m, 1 H), 1.86–1.77 (m, 1 H), 1.76–1.65 (m, 1 H), 1.61–1.51 (m, 1 H), 1.18 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.1, 128.6, 128.1, 127.3, 94.6, 74.6, 64.6, 59.6, 55.4, 41.1, 27.2, 23.4, 21.3. IR (ATR diamond): 3059, 3028, 2927, 2862, 1601, 1032, 914 cm^{-1}. HRMS (ESI): *m*/*z* [M + H^+] calcd for $C_{17}H_{28}NO_3S$: 326.1784; found: 326.1768.