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An enantioselective approach to (−)-aphanorphine featuring a stereoselective oxidative amidation†

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A formal enantioselective synthesis of (−)-aphanorphine (91% ee), that culminates with the preparation of (+)-*O*-methyl aphanorphine, was achieved. The methodology involves the diastereoselective synthesis of a key 3,5-disubstituted pyrrolidinone intermediate by the intramolecular oxidative amidation of a suitably functionalized α-hydroxy pentenoic acid derivative. A late-stage *N*-formyl protection, which functions as a latent *N*-methyl group, is utilized as a simple alternative to a protecting group switch and subsequent *N*-methylation strategy implemented in all other syntheses of aphanorphine related to the present approach.

Aphanorphine (**1**)[1] is an alkaloid that shares structural features with the analgesic benzomorphan alkaloids eptazocine (**3**), pentazocine (**4**) and morphine (**5**, Fig. 1). This structural resemblance and the synthetically intriguing 3-benzazepine ring system and quaternary stereocenter have all contributed to significant interest in the synthesis of aphanorphine,[2–4] which continues to be a popular target for showcasing new methodology leading to the benzazepine motif. We describe here a synthesis of (+)-*O*-methyl aphanorphine (**2**), an immediate synthetic precursor of (−)-aphanorphine.

Our interest in aphanorphine stems from our studies on the enantioselective synthesis and applications of α-alkyl α-hydroxy acid derivatives as intermediates to biologically relevant motifs and natural products.[5] We therefore envisaged an α-hydroxy acid based route to aphanorphine as detailed in Scheme 1. The strategy utilizes a stereoselective, intramolecular C–N bond formation as a pivotal step in the synthesis of a key pyrrolidine intermediate. A cyclative Friedel–Crafts alkylation in this pyrrolidine is used, as in previous aphanorphine syntheses,[2a,3a,4f] for constructing the bridged benzazepine motif in aphanorphine. The precursor of the pyrrolidine is obtained by a cross metathesis reaction of an enantiomerically enriched α-hydroxy pentenoic acid derivative which, in turn, is obtained by asymmetric allylation of a chiral pyruvate (Scheme 1).

Initially, we chose to explore the synthesis of a suitably substituted *N*-methyl pyrrolidinone as a precursor to the functionalized pyrrolidine motif in aphanorphine. The motivation for this approach was twofold: 1) several substituted *N*-methyl pyrrolidinones are natural products[6] or motifs in bioactive molecules,[7] and the present study could potentially provide methodology for their synthesis as well; and 2) the starting material for the pyrrolidinone based approach, the α-hydroxy *N*-methyl amide (*R*)-**8**[5f] (Scheme 2) is directly obtained by our asymmetric allylation protocol[5f] employing an ephedrine-derived chiral pyruvamide. Furthermore, the intramolecular Friedel–Crafts alkylation (Scheme 1) of the *N*-methyl pyrrolidine, obtained from the pyrrolidinone, could potentially provide the aphanorphine framework. Our studies therefore commenced with (*R*)-**8** (92% ee) which was prepared by the asymmetric allylation of an ephedrine and pyruvic acid-derived morpholinone **6** as shown in Scheme 2.[5f]

We reasoned that a simple halolactamization of **8** would provide the functionalized pyrrolidinone **9** (Scheme 3) which could be elaborated further to provide the target benzazepine motif. Towards this goal, the halolactamization of **8** was examined under a variety of conditions that are reported to

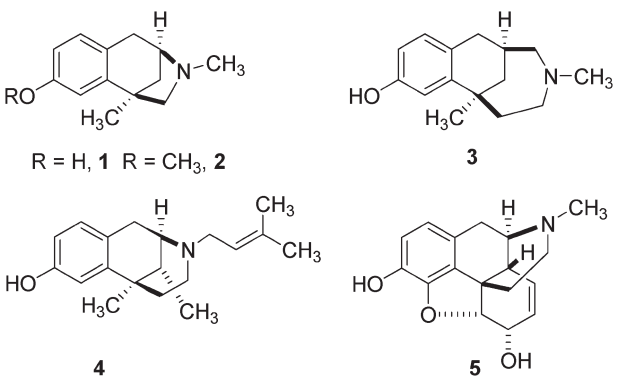

Fig. 1 (−)-Aphanorphine (**1**), (+)-*O*-methylaphanorphine (**2**), (−)-eptazocine (**3**), (−)-pentazocine (**4**) and (−)-morphine (**5**).

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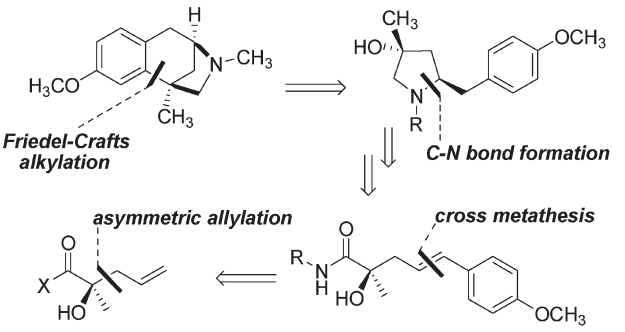
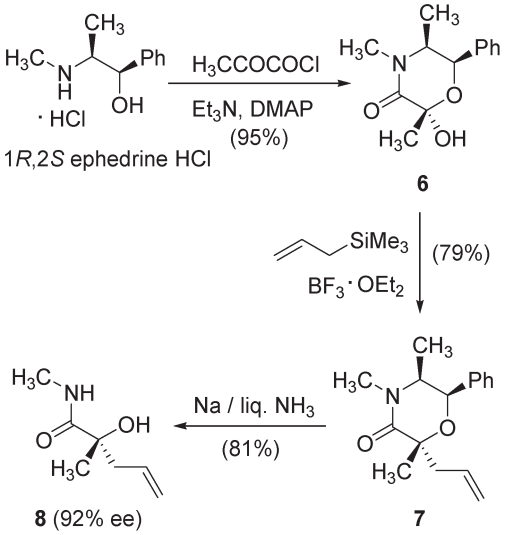


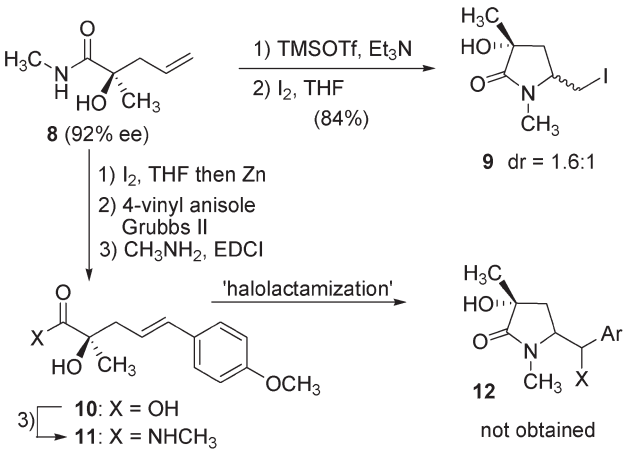
Scheme 1

promote lactamization of secondary amides (I_2/$NaHCO_3$,[8a] NIS/NaOH,[8b] ICl,[8c] NBS,[8d] BuLi/I_2,[8e] and bromonium bis(collidine)perchlorate[8f]). None of these attempts provided any halolactam. This may be due, in part, to competing halolactonization as evidenced by the formation of small amounts of the halolactone. In addition, the halohydrin resulting from halolactone hydrolysis was also observed in some of these reactions. Similarly, intramolecular amidomercuration/halogenation[9] protocols ($Hg(OAc)_2$, KI, I_2 or $Hg(OAc)_2$, KBr) were also unsuccessful. Nonetheless, iodolactamization[10] of **8** employing the conditions of Knapp[10h] (treatment of **8** with TMSOTf, which presumably forms the *O*-silylimidate, followed by addition of iodine) provided **9** in good yield (84%) but with poor diastereoselectivity (dr = 1.6 : 1, Scheme 3).

It is noteworthy that the direct halolactamization of 5-aryl-4-pentenamides is not reported, and the iodolactamization of the corresponding thioimidates follows the 5-*exo* mode.[11] We were therefore curious about the direct iodolactamization of **11** (Scheme 3). To examine this possibility, **8** was converted to the acid[12] which was subjected to a Grubbs II catalyst mediated cross-metathesis[13] with 4-vinyl anisole to provide



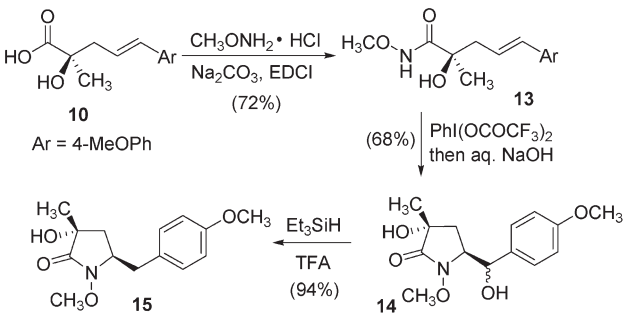
Scheme 2



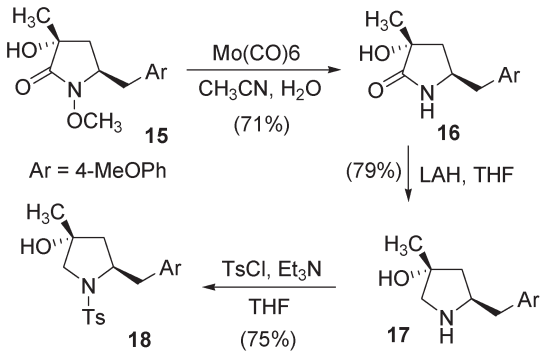
Scheme 3

the *trans* pentenoic acid **10**. Amidation of **10** with methylamine provided **11**. However, reactions of **11** under a variety of halolactamization conditions, including the Knapp procedure, lead to complex mixtures which rarely contained a trace of the required lactam **12** (Scheme 3). Consequently, the direct halolactamization of **8** or **11** as a route to an advanced, pyrrolidine precursor to aphanorphine was not pursued further.

Clearly, an alternative to halolactamization was necessary. We decided to explore the possibility of a nitrenium ion mediated construction of the key pyrrolidine intermediate[14] and chose to use a *N*-methoxy amide for this purpose.[15] Towards this end, conventional amidation of the acid **10** with methoxyamine provided the corresponding *N*-methoxyamide **13** (Scheme 4). Oxidative ring closure of the crude *N*-methoxyamide employing bis(trifluoroacetoxy)iodobenzene[16] and *in situ* hydrolysis of the resulting benzylic trifluoroacetate[15] generated the hydroxypyrrolidinone **14** as a 5 : 1 mixture of diastereomers. At this stage, it was unclear if the diastereomers of **14** were a consequence of indiscriminate C–N bond formation or due to unselective capture of the intermediate benzylic cation by trifluoroacetate. However, subsequent reduction of **14** with triethylsilane yielded the pyrrolidinone **15** as a single diastereomer. This indicated that



Scheme 4

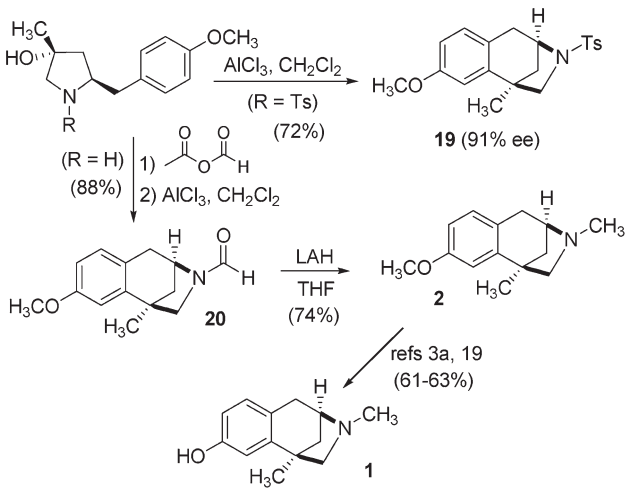


Scheme 5

the crucial C–N bond formation step was highly stereoselective.[17] The high diastereoselectivity for the formation of **15** contrasts the modest diastereoselectivity (1.8 : 1) observed for the iodine(III) mediated intramolecular amidohydroxylation of *N-para*-methoxyphenyl-2-benzyl-4-pentenamides.[18] While it is reasonable to assume that the stereocenter in **13** plays some role in the stereoselective C–N bond formation, the exact reasons for this significant difference in stereoselectivity are unclear at present.

With the pyrrolidinone **15** in hand, the synthesis of the target was in sight. Reduction of the N–O bond in **15** with $Mo(CO)_6$[15] provided lactam **16** (Scheme 5) which was reduced with LAH to provide the key pyrrolidine **17**. *N*-Tosylation of **17** provided **18**.

The stereochemistry of the oxamidation step, and hence the absolute configuration of the pyrrolidinone **15**, was first established by conversion of the tosylamide **18** to the benzomorphan derivative (−)-**19** (91% ee, Scheme 6) which has previously been converted to (−)-aphanorphine. Comparison of the optical rotation of **19** ($[\alpha]_D^{25}$ −18.9 (*c* 0.9, $CHCl_3$)) with the reported[2b] value for (1*R*,4*S*)-**19** ($[\alpha]_D^{25}$ −16.9 (*c* 0.89, $CHCl_3$)) confirmed the shown absolute stereochemistry



Scheme 6

for **19**. This also confirmed the absolute configuration of **15**, and hence that of **17**, to be as shown. We now proceeded to complete the synthesis of (+)-*O*-methyl aphanorphine from **17**. Treatment of **17** with acetic formic anhydride provided the *N*-formyl derivative, an intramolecular Friedel–Crafts cyclization ($AlCl_3$, Scheme 6) of which efficiently provided the benzomorphan **20**. Reduction of the formamide in **20** with LAH provided (+)-*O*-methyl aphanorphine (**2**). The conversion of **2** to (−)-aphanorphine (**1**) by *O*-demethylation with BBr_3 is known,[3a,19] so the present synthesis of **2** also constitutes a formal synthesis of **1**.

In conclusion, a synthesis of (+)-*O*-methyl aphanorphine (91% ee) was achieved from the readily available α-hydroxy acid derivative **8** in 10 steps and 7.1% overall yield. This constitutes a formal synthesis of (−)-aphanorphine (91% ee). A highly stereoselective intramolecular oxamidation was employed to construct the key pyrrolidine precursor to the benzazepine framework of the target. Notably, a *N*-formyl protecting group serves as a *N*-methyl surrogate in this synthesis. This avoids the more conventional approach employed in related aphanorphine syntheses that rely on *N*-deprotection, after the intramolecular Friedel Crafts cyclization, followed by *N*-methylation. Since the *N*-deprotection step usually requires forcing conditions (detosylation[3a,4f] (Red-Al in refluxing xylene) or debenzoylation[2a,4l] (50% aq. NaOH or KOH, ethanol, reflux, 24 h), the *N*-formylation approach provides a convenient alternative that eliminates a late-stage step in the synthesis. We are currently investigating applications of the methodology described here in the synthesis of other, pyrrolidinone- and pyrrolidine-containing, natural products.

Experimental section

General experimental methods

All commercially available reagents were used without purification. All reactions requiring anhydrous conditions were performed under an atmosphere of dry nitrogen using oven dried glassware. Dichloromethane and tetrahydrofuran were distilled from CaH_2 and sodium/benzophenone respectively. Commercial precoated silica gel plates were used for TLC. Silica gel for column chromatography was 230–400 mesh. All melting points are uncorrected. Optical rotations were measured at the sodium D line on a digital polarimeter at ambient temperature.

(*R*)-2-Hydroxy-*N*,2-dimethylpent-4-enamide (8)[5f]

This was prepared according to the literature procedure.[5f] Reaction of 1*R*,2*S* ephedrine hydrochloride with pyruvoyl chloride provided the morpholinone **6**[5f] which was allylated to provide **7**.[5f] Dissolving metal reduction of **7** provided **8**.[5f] Spectroscopic data for **6**, **7** and **8** (IR, ^{1}H NMR, ^{13}C NMR) is in agreement with reported data.[5f] The enantiomeric excess of **8** (92%) was determined by chiral HPLC analysis; Chiralpak AS-H, hexanes–2-propanol 93 : 7, 254 nm, t_1 = 12.4 min (minor), t_2

= 14.6 min (major), Ee: 92%. In repeated preparations, **8** was obtained in 92–96% ee.

(3*R*)-3-Hydroxy-5-(iodomethyl)-1,3-dimethylpyrrolidin-2-one (9)

To a solution of *R*-**8** (92% ee, 0.27 g, 1.91 mmol) in CH_2Cl_2 (6 mL) at 0 °C, was added freshly distilled triethylamine (0.58 mL, 4.21 mmol) and freshly distilled trimethylsilyltriflate (0.78 mL, 4.21 mmol). The resulting brown solution was warmed to room temperature and stirred for 45 min. The mixture was cooled to 0 °C and a solution of iodine (1.07g, 4.21 mmol) in CH_2Cl_2 (19 mL) was added. The mixture was stirred at room temperature for 20 h and a saturated solution of sodium bicarbonate (25 mL) was added. The mixture was stirred for 30 min and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL), the combined organic phases were washed with saturated, aqueous sodium thiosulfate (15 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc–hexanes, 8 : 2) to provide the iodolactam **9** (light brown solid, 430 mg, 84%) as a 1.6 : 1 mixture of diastereomers.

IR (neat): 3316, 2361, 1682, 1254 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): Major diastereomer: δ 3.48–3.35 (m, 2H), 3.33–3.27 (m, 1H), 2.84 (s, 3H), 2.36–2.32 (dd, 1H, J = 7.7, 14.0), 1.83–1.79 (dd, 1H, J = 5.5, 14.0), 1.51 (s, 3H); minor diastereomer: δ 3.48–3.35 (m, 2H), 3.33–3.27 (m, 1H), 2.87 (s, 3H), 2.29–2.25 (dd, 1H, J = 7.0, 13.3), 2.02–1.98 (dd, 1H, J = 6.1, 13.3), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): Major diastereomer: δ 177.1, 73.8, 56.6, 40.9, 28.0, 25.2, 8.6; minor diastereomer: δ 175.1, 73.9, 56.1, 40.2, 27.8, 20.7, 10.6; MS (APCI, pos.): m/z 270.0 (M + 1); HRMS: m/z 268.9915 (268.9913 calculated for $C_7H_{12}INO_2$ (M^+)).

(*R*)-*E*-2-Hydroxy-5-(4-methoxyphenyl)-2-methylpent-4-enoic acid (10)

To a solution of the amide **8** (405 mg, 2.83 mmol) in THF–water (1 : 1, 14 mL) at ambient temperature was added iodine (1.69 g, 6.60 mmol) and the solution was stirred in the dark for 12 h. The solution was then extracted with ethyl acetate (3 × 20 mL), the combined extracts were washed with saturated aqueous sodium thiosulfate solution, dried (Na_2SO_4) and concentrated under reduced pressure to provide 610 mg of a yellow gum. This was dissolved in THF–water (1 : 1, 12 mL) and zinc (480 mg, 7.4 mmol) was added. The vigorously stirred mixture was heated at 50 °C for 4 h, cooled to room temperature and the THF was removed under reduced pressure. The residue was cooled to 0 °C, aqueous HCl (4N, 10 mL) was added and the mixture was stirred until all of the solids dissolved. The resulting acidic solution was extracted with EtOAc (3 × 50 mL) and the combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was dissolved in EtOAc (10 mL) and the solution was extracted with saturated aqueous $NaHCO_3$ (2 × 10 mL). The combined aqueous extracts were cooled to 0 °C, acidified with concentrated aqueous HCl and the resulting clear solution was extracted with EtOAc (3 × 30 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was dissolved in EtOAc and the solution was filtered through a pad of silica gel to provide 220 mg (60%) of (*R*)-2-hydroxy-2-methyl-4-pentenoic acid (**8a**)[12] as a pale yellow gum. This was used in the next step without further purification.

IR (neat): 3362, 2980, 1719, 1635, 1227, 1163, 919 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.85–5.74 (m, 1H, C*H*), 5.22 (br s, 1H, CH=CH_2), 5.18–5.17 (br d, 1H, J = 5.0, CH=CH_2), 2.64–2.57 (dd, 1H, J = 7.1, 13.8, CH_2CH), 2.48–2.40 (dd, 1H, J = 7.5, 13.8, CH_2CH), 1.50 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.6 (*C*=O), 131.8 (*C*H=CH_2), 120.0 (CH=*C*H_2), 74.4 (*C*-CO_2H), 44.4 (*C*H_2CH), 25.4 (*C*H_3); MS (APCI, neg.): m/z 128.9 (M-1) (APCI, neg.): m/z 128.9 (M-1); $[\alpha]_D^{25}$ −11.1 (*c* 1, EtOH); lit.[12] $[\alpha]_D^{25}$ −5.2 (*c* 1, EtOH) for material with 42% ee).

To a solution of the above acid (300 mg, 2.30 mmol) in CH_2Cl_2 (4 mL) under nitrogen was added a solution of the Grubbs second generation catalyst (39.0 mg, 0.046 mmol) in CH_2Cl_2 (4 mL) followed by the addition of 4-vinyl anisole (0.6 mL, 4.60 mmol). The solution was heated to reflux 7 h, cooled to ambient temperature and the solvent was evaporated under reduced pressure to obtain a brown solid. This was dissolved in EtOAc (5 mL) and the solution was extracted with saturated, aqueous $NaHCO_3$ (2 × 5 mL). The combined bicarbonate extracts were cooled and acidified to pH 2 with conc. HCl. The acidic solution was extracted with EtOAc (3 × 15 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to provide 380 mg (70%) of **10** as a white solid. This was pure by ^1H NMR and was used without further purification. An analytical sample was obtained by flash chromatography on silica gel (EtOAc–hexanes, 1 : 1).

Mp: 169–170 °C; IR (neat): 3434, 2932, 1720, 1509, 1274, 1247, 1202, 1150, 1103, 1027, 961 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.29 (d, 2H, J = 8.7), 6.83 (d, 2H, J = 8.7), 6.46 (d, 1H, J = 15.7), 6.09–5.98 (m, 1H), 3.80 (s, 3H), 2.75–2.70 (dd, 1H, J = 7.2, 14.0), 2.58–2.51 (dd, 1H, J = 7.8, 14.0), 1.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.7, 159.1, 134.2, 129.8, 127.5, 120.7, 114.0, 74.8, 55.3, 43.6, 25.3; MS (APCI, pos.): m/z 236 (M^+); HRMS (CI, TOF): m/z 236.1046 (236.1049 calc. for $C_{13}H_{16}O_4$ (M^+)); $[\alpha]_D^{25}$ −9.5 (*c* 0.5, $CHCl_3$).

(*R*)-*E*-2-Hydroxy-5-(4-methoxyphenyl)-*N*,2-dimethylpent-4-enamide (11)

To a stirred solution of the acid **10** (0.12 g, 0.51 mmol) in THF at 0 °C, was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) hydrochloride (145 mg, 0.76 mmol), ethyl cyanoglyoxylate-2-oxime (0.10 g, 0.76 mmol) and a solution of methylamine (2.0 M in THF, 0.50 mL, 1.01 mmol). The mixture was stirred at 0 °C for 24 h and then at ambient temperature for 8 h. Aqueous hydrochloric acid (10 mL, 1.0 M) was added and the mixture was stirred for 5 min. The THF was removed under reduced pressure and the aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (10 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (EtOAc–hexanes, 7 : 3) to provide 55 mg (44%) of the amide **11** as a yellow gum.

IR: 3350, 2928, 1648, 1510, 1245, 1172, 1029 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.28–7.27 (d, 2H), 6.87–6.80 (br, 1H), 6.84–6.81 (d, 2H, J = 8.8), 6.45–6.42 (d, 1H, J = 15.8), 6.04–5.98 (ddd, J = 6.8, 8.4, 15.4, 1H), 3.79 (s, 3H), 2.84–2.80 (ddd, 1H, J = 1.3, 6.9, 8.5), 2.81 (d, 3H, J = 4.9), 2.46–2.42 (ddd, 1H, J = 1.0, 8.5,

9.5), 1.45 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.2, 159.2, 134.4, 129.7, 127.4, 121.6, 114.0, 75.5, 55.3, 43.7, 26.1, 26.0; MS (APCI pos): *m*/*z* 250.1 (M + H); HRMS (CI, TOF): *m*/*z* 250.1445 (250.1443 calculated for $C_{14}H_{20}NO_3$ (M + H)).

(*R*)-*E*-2-Hydroxy-*N*-methoxy-5-(4-methoxyphenyl)-2-methylpent-4-enamide (13)

To solution of the acid **10** (400 mg, 2.54 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added 4-methylmorpholine (0.29 mL, 2.66 mmol), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (536 mg, 2.80 mmol), methoxyamine hydrochloride (634 mg, 7.6 mmol) and solid Na_2CO_3 (694 mg, 7.6 mmol). The resulting clear, brown solution was warmed to ambient temperature and stirred for 24 h. Aqueous HCl (0.5M, 5 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution, dried (Na_2SO_4) and concentrated to provide 480 mg (72%) of the amide **13** as a brown gum. This was pure by ^{1}H NMR and was used without further purification. An analytical sample was obtained by flash chromatography on silica gel (EtOAc–hexanes, 7 : 3).

IR (neat): 3431, 2925, 1704, 1607, 1511, 1363, 1246, 1169 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.14 (bs, 1H), 7.29 (d, 2H, *J* = 8.7), 6.85 (d, 2H, *J* = 8.7), 6.48 (d, 1H, *J* = 15.8), 6.07–5.97 (m, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 2.90–2.85 (dd, 1H, *J* = 7.2, 13.8), 2.44–2.40 (dd, 1H, *J* = 8.4, 13.8), 2.25 (bs, 1H), 1.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.8, 159.2, 134.5, 129.0, 127.4, 121.1, 114.0, 75.5, 64.3, 55.3, 43.7, 26.0; MS (APCI pos.): *m*/*z* 266 (M + 1); HRMS (EI pos, TOF): *m*/*z* 265.1315 (265.1314 calc. for $C_{14}H_{19}NO_4$ (M^+)); $[\alpha]_D^{25}$ = +10.9 (c 1, $CHCl_3$).

(3*R*)-3-Hydroxy-5-(hydroxy(4-methoxyphenyl)methyl)-1-methoxy-3-methylpyrrolidin-2-one (14)

To a stirred solution of the amide **13** (130 mg, 0.48 mmol) in CH_2Cl_2 (5 mL) at −10 °C (ice-salt bath) was added bis(trifluoroacetoxy)iodobenzene (252 mg, 0.58 mmol). The solution was stirred at −10 °C for 90 min and aqueous NaOH (2.5M, 1.0 mL) was added. The mixture was stirred vigorously for 5 min at ambient temperature and the resulting biphasic mixture was separated. Aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to provide a brown solid which was purified by flash chromatography on silica gel (EtOAc–hexanes, 4 : 1) to provide 88 mg (68%) of the pyrrolidone **14** as a 5 : 1 mixture of diastereomers.

IR (neat): 3367, 1691, 1511, 1244, 1174, 1024 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): Major diastereomer: δ 7.28–7.27 (d, 2H, *J* = 6.5 Hz), 6.92–6.89 (d, 2H, *J* = 8.7 Hz), 5.14 (br d, 1H, *J* = 2.3), 4.05–4.03 (m, 1H), 3.91 (s, 3H), 3.81 (s, 3H), 2.21–2.20 (d, 1H, *J* = 2.9), 2.12–2.08 (dd, 1H, *J* = 6.0, 13.7), 1.84–1.79 (dd, 1H, *J* = 8.1, 13.7), 1.44 (s, 3H). Visible peaks for the minor diastereomer: δ 7.96–7.94 (d, 2H, *J* = 9.0), 7.00–6.98 (d, 2H, *J* = 9.0), 4.20–4.16 (m, 1H), 3.90 (s, 3H), 3.81 (s, 3H), 2.19–2.17 (d, 1H, *J* = 12.3), 2.04–2.00 (dd, 1H, *J* = 5.4, 13.4), 1.94–1.90 (dd, 1H, *J* = 8.0, 14.0); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 159.3, 131.2, 127.0, 113.9, 71.6, 69.2, 62.1, 59.6, 55.3, 30.8, 24.9; visible peaks for minor diastereomer: δ 130.8, 128.1, 61.7, 34.3; MS (APCI, pos.): *m*/*z* 282 (M + 1); HRMS: *m*/*z* 282.1342 (282.1341 calculated for $C_{14}H_{20}NO_5$ (M + H).

(3*R*,5*R*)-5-(4-Methoxybenzyl)-3-hydroxy-1-methoxy-3-methylpyrrolidin-2-one (15)

To a mixture of the pyrrolidinone **14** (180 mg, 0.64 mmol) and triethylsilane (1.02 mL, 6.4 mmol) at 0 °C was added trifluoroacetic acid (0.24 mL, 3.2 mmol) and the mixture was stirred vigorously at ambient temperature for 7 h (the biphasic reaction mixture turned homogeneous after 7 h). Aqueous NaOH (1.0 M, 2.0 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to provide 280 mg of a white solid which was purified by flash chromatography on silica gel (8 : 2 EtOAc–hexanes) to obtain 130 mg (94%) of **15** as a white solid.

Mp: 95–97 °C; IR (neat): 3391, 1707, 1510, 1249, 1181, 1023 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13–7.08 (d, 2H, *J* = 8.4), 6.85 (d, 2H, *J* = 8.4), 4.11–4.09 (m, 1H), 3.87 (s, 3H), 3.79 (s, 3H), 3.07–3.03 (dd, 1H, *J* = 3.7, 13.7), 2.75–2.70 (dd, 1H, *J* = 8.0, 13.7), 2.5 (bs, 1H), 2.16–2.12 (dd, 1H, *J* = 7.7, 13.7), 1.75–1.71 (dd, 1H, *J* = 5.9, 13.7), 1.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 158.6, 130.6, 127.7, 114.1, 71.4, 62.0, 55.3, 54.9, 37.5, 36.7, 25.2; MS (APCI, pos.): *m*/*z* 266.1 (M + 1); HRMS *m*/*z* 265.1312 (265.1314 calculated for $C_{14}H_{19}NO_4$ (M^+); $[\alpha]_D^{25}$ −4.9 (*c* 1, $CHCl_3$).

(3*R*,5*R*)-5-(4-Methoxybenzyl)-3-hydroxy-3-methylpyrrolidin-2-one (16)

To a solution of pyrrolidone **15** (60 mg, 0.22 mmol) in CH_3CN:H_2O (15 : 1, 6.0 mL) was added $Mo(CO)_6$ (119 mg, 0.45 mmol) and the mixture was heated to reflux under nitrogen for 24 h. The reaction mixture turned yellow after 2 h and gradually turned green and then black. After 24 h the mixture was cooled to room temperature and concentrated. The black residue (180 mg) was purified by flash chromatography on silica gel (hexanes–EtOAc, 3 : 7 followed by EtOAc–MeOH, 9.5 : 0.5) to provide 37 mg (71%) of the pyrrolidone **16** as a white solid.

Mp: 87–89 °C; IR (neat): 3301, 2932, 1692, 1604, 1110, 612 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD): δ 7.13–7.11 (d, 2H, *J* = 8.6), 6.87–6.85 (d, 2H, *J* = 8.7), 3.96–3.89 (m, 1H), 3.76 (s, 3H), 2.85–2.79 (dd, 1H, *J* = 5.7, 13.5), 2.68–2.61 (dd, 1H, *J* = 7.4, 13.6), 2.18–2.08 (dd, 1H, *J* = 6.6, 13.3), 1.82–1.75 (dd, 1H, *J* = 6.5, 13.7), 1.24 (s, 3H); ^{13}C NMR (75 MHz, $MeOD_4$): δ180.3, 160.1, 131.5, 130.5, 115., 75.3, 55.7, 53.5, 42.9, 42.0, 24.8; MS (APCI pos.): *m*/*z* 235.3 (M^+); HRMS (EI pos, TOF): *m*/*z* 235.1203 (235.1208 calc. for $C_{13}H_{17}NO_3$ (M^+)); $[\alpha]_D^{25}$ −5.5 (*c* 1.0, acetone).

(3*R*,5*R*)-5-(4-Methoxybenzyl)-3-methylpyrrolidin-3-ol (17)

To a suspension of lithium aluminum hydride (129 mg, 3.4 mmol) in THF (1 mL) at 0 °C was added a solution of the pyrrolidinone **16** (100 mg, 0.42 mmol) in THF (3 mL) dropwise. The mixture was warmed to room temperature and then heated to reflux for 12h. The mixture was cooled to 0 °C and water (0.1 mL), aqueous NaOH (2.5 M, 1.3 mL) and water (0.3 mL) were added sequentially with a 15 min stirring period between each addition and 20 min stirring after the last addition. The resulting mixture was filtered with suction and

the white precipitate was washed with THF (2 × 10 mL). The combined filtrates were dried (Na_2SO_4) and concentrated. The residue was dissolved in EtOAc (3 mL) and the solution was extracted with aqueous HCl (1 M, pH 5, 2 × 3 mL). The combined extracts were cooled (<5 °C) and basified to pH 9 with NaOH pellets. The basic solution was extracted with EtOAc (3 × 10 mL) and the combined extracts were dried (Na_2SO_4) and concentrated to provide 74 mg (79%) of the pyrrolidine **17** as a yellow gum. This was pure by ^{1}H NMR and was directly used further. An analytical sample was obtained by flash chromatography on silica gel (CH_2Cl_2–MeOH, 9 : 1 containing 1% aq. ammonia).

IR (neat): 3301, 2924, 1511, 1243, 1034 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13 (d, 2H, J = 8.6, Ar*H*), 6.85 (d, 2H, J = 8.6), 3.80 (s, 3H), 3.69–3.64 (m, 1H), 2.97–2.90 (AB system, 2H, J = 11.2), 2.75–2.67 (ABX system, 2H, J = 7.0, 13.6), 1.94–1.91 (dd, 1H, J = 6.3, 13.2), 1.51–1.46 (dd, 1H, J = 9.3, 13.2), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.1, 131.5, 129.9, 113.9, 79.0, 59.7, 59.4, 55.3, 47.3, 41.5, 26.4; MS (APCI pos.): m/z 222.1 (M + 1); HRMS (CI+): m/z 222.1489 (222.1494 calc. for $C_{13}H_{20}NO_2$(M + H)); $[\alpha]_D^{25}$ −70.0 (c 0.5, $CHCl_3$).

(−)-(3*R*,5*R*)-5-(4-Methoxybenzyl)-3-methyl-1-tosylpyrrolidin-3-ol (18)

To stirred solution of *p*-toluenesufonyl chloride (19.4 mg, 0.10 mmol) in THF (0.5 mL) was added freshly distilled triethyl amine (19.0 μL, 0.14 mmol) at 0 °C, followed by a solution of the amine **17** (15 mg, 0.07 mmol) in THF (1.0 mL). The mixture was stirred for 8 h at ambient temperature and saturated, aqueous $NaHCO_3$ (2 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (hexanes–EtOAc, 1 : 1) to provide 19 mg (75%) of **18** as an off-white foam.

IR: 3508, 2929, 1511, 1331, 1245, 1151, 1088, 1033 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (d, 2H, J = 8.1), 7.34 (d, 2H, J = 8.1), 7.15 (d, 2H, J = 8.6), 6.83 (d, 2H, J = 8.6), 4.02–3.94 (m, 1H), 3.78 (s, 3H), 3.40–3.37 (dd, 1H, J = 2.3, 12.4), 3.32–3.29 (dd, 1H, J = 3.5, 13.5), 3.17 (d, 1H, J = 12.4), 2.89–2.81 (dd, 1H, J = 8.8, 13.5), 2.42 (s, 3H), 1.80–1.75 (ddd, 1H, J = 2.3, 6.9, 13.4), 1.63–1.57 (dd, 1H, J = 9.7, 13.3), 1.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.3, 143.6, 135.0, 130.6, 129.72, 129.65, 127.8, 113.8, 76.0, 61.6, 61.1, 55.2, 45.6, 41.0, 24.2, 21.6; MS (APCI pos.): m/z 376.1 (M + 1); HRMS (CI pos. TOF): m/z 376.1589 (376.1583 calc. for $C_{20}H_{26}NO_4S$ (M + H)); $[\alpha]_D^{25}$ −76.8 (c 0.5, $CHCl_3$).

(−)-(1*R*,4*S*)-8-Methoxy-1-methyl-3-tosyl-2,3,4,5-tetrahydro-1*H*-1,4-methanobenzo[*d*]azaepin (19)

This was prepared from **18** (12 mg, 0.03 mmol) and $AlCl_3$ (44 mg, 0.34 mmol) in CH_2Cl_2 (1 mL) at 0 °C according to the literature procedure.[4f] Purification of the crude product by flash chromatography on silica gel (hexanes–EtOAc 4.9 : 1) provided 8 mg (72%) of **19** as a pale yellow solid.

Mp: 136–138 °C (lit.[2b] mp: 136–138 °C); IR: 2924, 1336, 1291, 1236, 1154, 1093, 1043, 809 cm^{-1}; MS: (APCI pos.): m/z 358.1 (M + 1); HRMS (EI+): m/z 357.1394 (357.1399 calc. for $C_{20}H_{23}NO_3S$ (M^+); $[\alpha]_D^{25}$ −18.9 (c 0.9, $CHCl_3$; lit.[2b] $[\alpha]_D^{25}$ −16.9 (c 0.89, $CHCl_3$); HPLC: Chiralpak AD-H, hexanes/2-propanol 72/25, 254 nm, t_1 = 7.4 min (minor), t_2 = 8.9 min (major), Ee: 91%. (lit.[3a] t_1 = 8.04 min (major), t_2 = 9.80 min (minor) for (+)-**19**). Other spectroscopic data (^{1}H NMR, ^{13}C NMR) is in agreement with reported data.[4f]

(−)-(1*R*,4*S*)-8-Methoxy-1-methyl-4,5-dihydro-1*H*-1,4-methanobenzo[d]azepine-3(2H)-carbaldehyde (20)

To a solution of **17** (30 mg, 0.13 mmol) in CH_2Cl_2 (2.5 mL) was added acetic formic anhydride (14 μL, 0.15 mmol). The mixture was stirred at room temperature for 4 h and then concentrated under reduced pressure to provide 29 mg (97%) the *N*-formyl derivative as a yellow gum. This was dissolved in CH_2Cl_2 (0.5 mL) and the solution was added dropwise to a cold (0 °C), stirred suspension of $AlCl_3$ (162 mg, 1.21 mmol) in CH_2Cl_2 (0.5 mL). The mixture was then stirred at ambient temperature for 24 h, cooled to 0 °C and saturated aqueous $NaHCO_3$ (2 mL) was added. The biphasic solution was transferred to a separatory funnel and extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were dried (Na_2SO_4) and concentrated to provide a pale yellow gum. Purification by flash chromatography on silica gel (9.5 : 0.5 CH_2Cl_2–MeOH) provided 23 mg (88%) of **20** as a colourless gum.

IR: 2955, 1657, 1612, 1417, 1233, 1036 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): major rotamer : δ 8.34 (s, 1H), 7.00–6.98 (d, 1H, J = 8.3), 6.82 (d, 1H, J = 2.6), 6.75–6.71 (dd, 2H, J = 2.6, 8.3), 4.42–4.41 (m, 1H), 3.78 (s, 3H), 3.54–3.52 (d, 1H, J = 11.2), 3.25–3.22 (d, 2H, J = 12.1), 2.94–2.91 (d, 2H, J = 16.6), 2.03–2.00 (dd, 1H, J = 1.4, 5.5), 1.98–1.95 (dd, 1H, J = 1.3, 5.0), 1.55 (s, 3H), minor rotamer: δ 8.1(s, 1H), 7.03–7.01 (d, 1H, J = 8.4), 6.84 (d, 1H, J = 2.6), 4.65–4.64 (m, 1H), 3.79 (s, 3H), 3.49–3.47 (d, 1H, J = 9.2), 3.41–3.39 (d, 1H, J = 9.2), 3.14–3.11 (dd, 1H, J = 2.8, 16.5), 1.55 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): major rotamer: δ 160.3, 157.9, 145.4, 130.2, 123.8, 111.6, 109.7, 58.8, 55.1, 52.5, 41.4, 38.9, 34.9, 20.7, minor rotamer: 160.4, 157.8, 144.6, 130.4, 125.2, 111.5, 109.8, 63.7, 60.6, 54.7, 40.4, 20.5; MS: (APCI pos.): m/z 232.1 (M + 1); HRMS (EI+): m/z 231.1264 (231.1259 calc. for $C_{14}H_{17}NO_2$ (M^+); $[\alpha]_D^{25}$ −23.2 (c 1, $CHCl_3$).

(+)-8-*O*-Methylaphanorphine (2)

A solution of the formamide **20** (10 mg, 0.04 mmol) in ether (0.5 mL) was added to a stirred suspension of lithium aluminium hydride (5 mg, 0.12 mmol) in diethylether (0.5 mL) at 0 °C and the resulting mixture was stirred at ambient temperature for 7 h. The mixture was then cooled to 0 °C and treated sequentially with water (3 μL), aqueous NaOH (2.5 M, 50 μL), and water (9 μL) with 5 min of stirring after each addition. The resulting mixture was filtered with suction and the solid residue was washed several times with ether. The combined filtrates were dried (Na_2SO_4) and concentrated to provide 7 mg (74%) of (+)-8-*O*-methylaphanorphine (**2**) as a yellow liquid.

IR: 2923, 1611, 1577, 1290, 1040, 804 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.02–7.01 (d, 1H, J = 8.3, Ar*H*), 6.78–6.77 (d, 1H, J = 2.6, Ar*H*), 6.68–6.66 (dd, 1H, J = 2.6, 8.3, Ar*H*), 3.77 (s, 3H, OCH_3), 3.40–3.39 (m, 1H, NC*H*), 3.04–3.00 (d, 1H, J = 16.7, CH_2), 2.86–2.84 (dd, 1H, J = 3.1, 7.9, ArCH_2), 2.83 (d, 1H, J = 9.0, ArCH_2), 2.75–2.73 (d, 1H, J = 9.0, NCH_2), 2.47 (s, 3H, OCH_3), 2.03–2.00 (dd, 1H, J = 5.2, 10.8, CH_2), 1.86–1.84 (d, 1H, J = 10.9, CH_2) 1.48 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.4

(Ar*C*-OCH_3), 147.9 (Ar*C*-CCH_3), 130.0 (Ar*C*), 125.9 (ArC_{ipso}), 110.7 (Ar*C*), 109.2 (Ar*C*), 71.2 (*C*H-NCH_3), 61.1 (CH_2-NCH_3), 55.0 (OCH_3), 43.0 (CH_2), 41.3 (NCH_3), 35.5 (CCH_3), 29.5 (CH_2), 21.3 (CH_3); MS (APCI pos): *m*/*z* 218.1 (M + 1); HRMS (CI pos. TOF): *m*/*z* 217.1467 (217.1467 calc. for $C_{14}H_{19}NO$ (M^+); $[\alpha]_D^{25}$ = +11.3 (c 0.4, ($CHCl_3$), lit.[2g] $[\alpha]_D^{23}$: +9.39 (c 0.30, $CHCl_3$). Other spectroscopic data (^{1}H NMR, ^{13}C NMR) is in agreement with reported data.[4f]

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