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Formal syntheses of (−)- and (+)-aphanorphine from (2*S*,4*R*)-4-hydroxyproline

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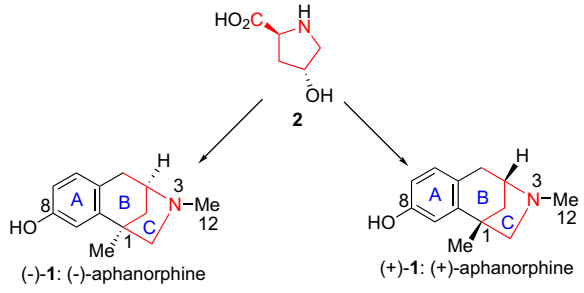
Abstract—We describe the efficient formal syntheses of both natural (−)-aphanorphine and unnatural (+)-aphanorphine from the same commercially available amino acid, (2*S*,4*R*)-4-hydroxyproline. The tricyclic framework was constructed by intramolecular Friedel–Crafts reaction. (1*R*,4*S*)-1-Methyl-8-methoxy-3-(4-toluenesulfonyl)-2,3,4,5-tetrahydro-1,4-methano-3-benzazepine (**8**) was synthesized in six steps from sulfonamide **3**; (−)-aphanorphine methyl ether **24** was obtained in seven steps from lactone **10**. Intramolecular etherification of **18** proceeded with excellent stereoselectivity in the presence of $BF_3 \cdot OEt_2$, which has paved an efficient synthetic route to a series of medicinally attractive heterocycles.

1. Introduction

(−)-Aphanorphine [(−)-**1**, Scheme 1], a novel alkaloid isolated by Shimizu and Clardy from the freshwater blue-green alga *Aphanizomenon flos-aquae* nearly two decades ago,[1] has stimulated tremendous synthetic attention[2] owing to its potential biological activity and unique structure containing tricyclic 3-benzazepine framework that resembles benzomorphane analgesics[3,4] such as pentazocine. Although a number of synthetic strategies have been reported for natural (−)-aphanorphine, unnatural (+)-aphanorphine, and (±)-aphanorphine in the literature,[2] currently there still exists strong demand for developing simpler and more efficient synthetic approaches for these molecules for the purpose of biological studies. Our previous synthesis of (−)-aphanorphine[2r] featured the formation of ring B at the final stage by Friedel–Crafts alkylative cyclization, while in most other strategies ring B was constructed prior to ring C. Moreover, carbohydrates,[5a] terpenes,[5b] and especially amino acids,[5c] have been widely used in the total synthesis of natural products. As shown in Scheme 1, (2*S*,4*R*)-4-hydroxyproline (**2**) was considered as an excellent starting point to secure the advanced tricyclic intermediates for constructing both enantiomers of aphanorphine, which would lead to novel, formal syntheses of (−)-aphanorphine and (+)-aphanorphine based on the 'chiral pool' strategy. Although we were not the first to 'extract' the chiron from **2** in the synthesis of aphanorphine, the previous approach[2m] made use of an initial enolate benzylation of a derivative of **2** and decarboxylation at a later stage, which adversely affected the overall synthetic efficiency in terms of atom economy and stereoselectivity. Moreover, our present research should be of great significance in terms of diversity-oriented synthesis. Some preliminary results along this line have been reported by our laboratory.[2s,y] Herein, we wish to describe the full account of our findings regarding the syntheses of natural (−)-aphanorphine and unnatural (+)-aphanorphine from (2*S*,4*R*)-4-hydroxyproline (**2**).



Scheme 1. Proposed synthesis of (−)- and (+)-aphanorphine.

Keywords: Alkaloid; Aphanorphine; Asymmetric synthesis; Configuration inversion; Intramolecular Friedel–Crafts reaction.
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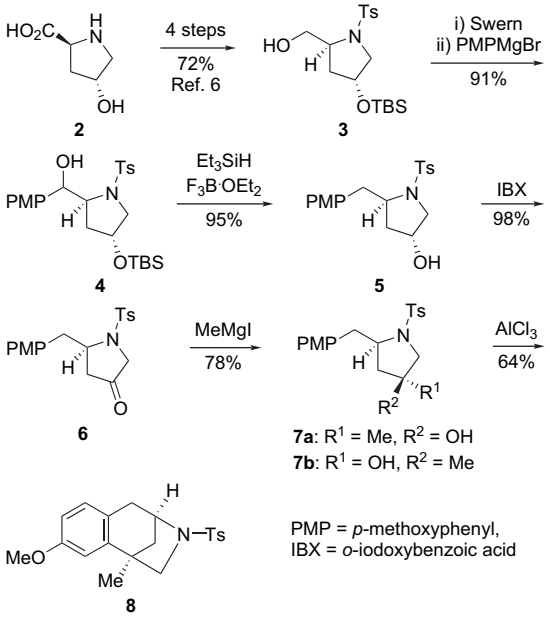
2. Results and discussion

2.1. (A) Formal synthesis of (−)-aphanorphine: synthesis of 8 from 2

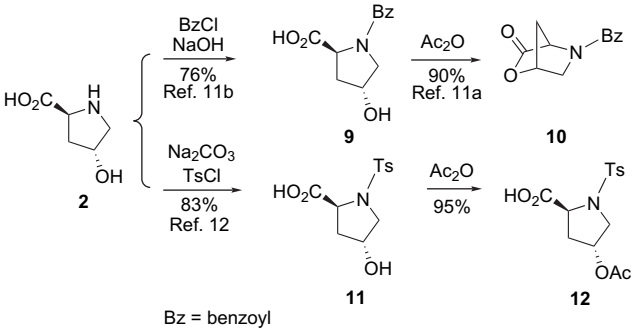
As outlined in Scheme 2, the synthesis of (−)-aphanorphine ((−)-**1**) commenced from alcohol **3**, an intermediate[6] obtainable from **2** in 72% yield by a four-step process. Swern oxidation[7a] of **3** gave a crude aldehyde, which in turn was arylated[8] with 4-methoxyphenylmagnesium bromide to furnish **4** in 91% yield as a single pure compound. Exposure[9] of alcohol **4** to triethylsilane in the presence of $BF_3\cdot OEt_2$ in dichloromethane produced **5** in high yield (95%), as a result of benzylic reductive dehydroxylation with concomitant O-desilylation. Oxidation[7b] with IBX (i.e., *o*-iodoxybenzoic acid) of **5** afforded ketone **6** in 98% yield. Nucleophilic methylation of **6** with methylmagnesium iodide[10] produced the tertiary alcohols **7a/7b** (equally utilizable, 78%). The diastereomeric ratio was measured by ^{1}H NMR integral analysis to be 4:1, presumably favoring **7a** based on steric consideration. By following the previously published protocol from this laboratory,[2r] $AlCl_3$-promoted Friedel–Crafts alkylative cyclization of alcohols **7a/7b** was effected to furnish the desired intermediate **8** as colorless needles (64%). The sample of **8** was in high enantiopurity (99.8% ee), as determined by HPLC analysis [Chiralpak AD column: 250×4.6 mm, UV detector: 254 nm, eluant: hexanes/2-propanol (4:1), flow rate: 0.7 mL/min], indicating that essentially no epimerization ever took place. The $[\alpha]_D^{20}$ of **8** was found to be −14.2 (*c* 0.93, $CHCl_3$) {lit.[2r] $[\alpha]_D^{20}$ −13.4 (*c* 0.969, $CHCl_3$)}. Other spectroscopic data of **8** were also in agreement with those disclosed in the literature.[2r] Thus a new formal synthesis of alkaloid (−)-aphanorphine ((−)-**1**) has been completed, since **8** could further be manipulated to give (−)-**1** in three additional steps (desulfurization, N-methylation, and 8-O-demethylation).



Scheme 2. Synthesis of **8**.

2.2. (B) Formal synthesis of (+)-aphanorphine: synthesis of 24 from 2

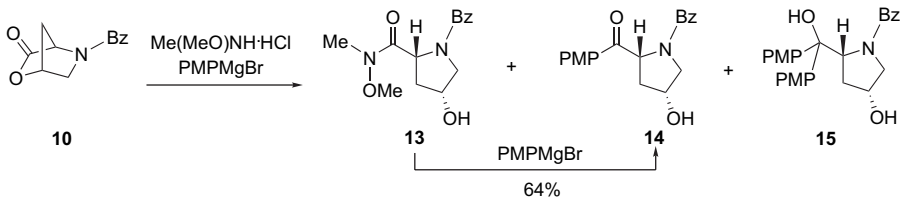
The synthesis of unnatural (+)-aphanorphine from (2*S*,4*R*)-4-hydroxyproline (**2**) featured configuration inversion at C-2 of the amino acid. Chemoselective N-benzoylation (BzCl, NaOH, Et_2O, 0 °C and then room temperature, 24 h, 76%) of **2** produced amide **9** (Scheme 3).[11a] Agitation of **9** in acetic anhydride heated at 90 °C for 5 h effected the requisite lactonization and configuration inversion at C-2 in the same step to provide bicycle **10** in 90% yield, by taking advantage of an efficient protocol developed recently by Rosa and Croce.[11b] Interestingly, treatment of sulfonamide **11**[12] (prepared in 83% yield by selective N-tosylation of **2** with TsCl in the presence of Na_2CO_3) with acetic anhydride at 90 °C for 8 h resulted only in the acylation of the secondary hydroxyl and the acetate **12** was obtained in 95% yield as a colorless solid. The desirable lactonization with configuration inversion at C-2 failed to take place just because the substituent on the nitrogen atom was switched from Bz (in **9**) to Ts (in **11**).



Scheme 3. Cyclization of **9**.

Treating[13] a mixture of lactone **10** and Me(MeO)NH·HCl (120 mol %) in tetrahydrofuran with *p*-methoxyphenylmagnesium bromide (370 mol %) at −10 °C furnished γ-hydroxy-α-amido ketone **14** (27%) along with diamide **13** (55%) and diol **15** (17%) (Scheme 4; Table 1, entry 1). The yield of **14** was increased to 41% when the reaction was run at −78 °C (entry 2). Since additional **14** could be formed from the Weinreb amide **13** in moderate yield (64%) by reacting with excess *p*-methoxyphenylmagnesium bromide (at −35 °C and then room temperature), phenyl ketone **14** could be obtained from lactone **10** in 76% overall yield. For comparison, direct addition of *p*-methoxyphenylmagnesium bromide (130 mol %) to lactone **10** at −78 °C (i.e., without the involvement of Me(MeO)NH·HCl) gave **14** in only 44% yield.

Ketone deoxygenation of **14** was then vigorously pursued (Scheme 5). Initially, a stepwise reduction strategy (i.e., via the benzylic alcohol intermediate) was explored. For instance, reduction of **14** with $NaBH_4$[14] in MeOH at 0 °C for 1 h smoothly formed the diol **18** (88%) essentially as a single diastereomer (dr=70:1). The configuration of the newly generated stereocenter of this diol was assigned based on the Cram rule. To our surprise, exposure of **18** to triethylsilane in the presence of $BF_3\cdot OEt_2$ in dichloromethane (at 0 °C and then room temperature) effected intramolecular etherification rather than benzylic reductive dehydroxylation. In



Scheme 4. Ring opening of **10**.

Table 1. Comparison of the results obtained under different temperatures

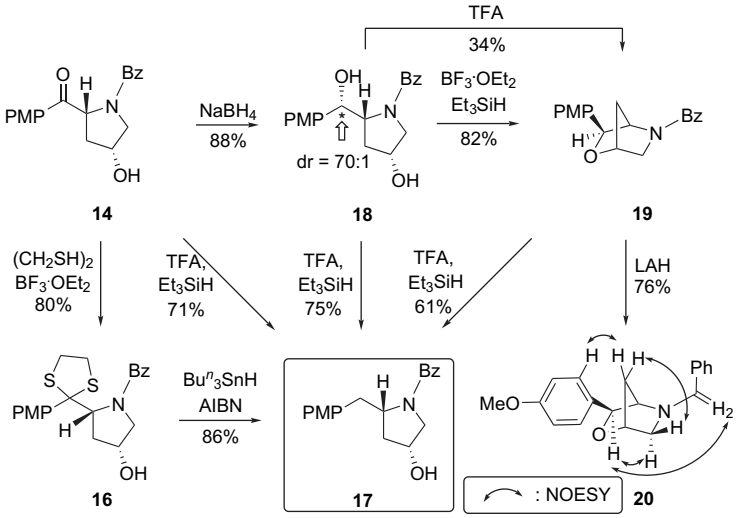
Entry	Me(MeO)NH·HCl (equiv)	PMPMgBr (equiv)	Temperature (°C)	Isolated yield (%)		
				13	**14**	**15**
1	1.2	3.7	−10	55	27	17
2	1.2	3.7	−78	55	41	4

contrast, dehydroxylation of **4** took place smoothly under the same condition, as mentioned above (Scheme 2). The hydroxyl at the C-4 of **18**, situating cis to the α-hydroxy PMB moiety on the pyrrolidine ring, rapidly captured the benzylic cation generated in the system before it was reduced by Et_3SiH. Bicyclic heterocycle **19** was produced (82%) as a pair of rotamers (1.3:1, deduced from the line integrals of ^1H NMR spectrum). Note that the benzylamine derivative **20**, obtained in 76% yield by reducing **19** with $LiAlH_4$ in refluxing THF, proved to be a single pure compound. The PMP substituents of **19** and **20** should occupy the *exo* position according to the NOESY experiments on **20**.

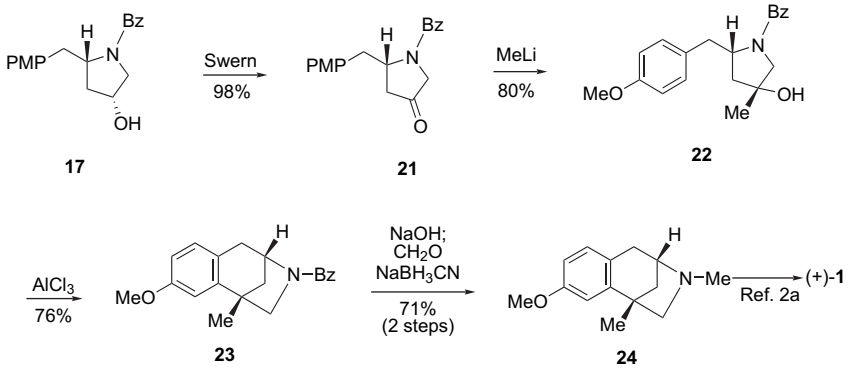
Obviously, $BF_3\cdot OEt_2$ alone was responsible for the intramolecular etherification of **18** and Et_3SiH did not play any role here. Actually, trifluoroacetic acid (TFA) could also bring about the same intramolecular etherification of **18** although ether **19** was obtained in only 34% yield in this case. Next, we were pleased to reveal that exposure of **18** to triethylsilane in the presence of TFA (instead of $BF_3\cdot OEt_2$) afforded **17** in 75% yield. Furthermore, bicycle **19**, inert to the $BF_3\cdot OEt_2/Et_3SiH$ system, could be converted to **17** in 61% yield through reductive ring opening upon treatment with TFA and Et_3SiH. This method even proved to be successful in the case of ketone **14** itself acting as the substrate. Subjecting **14** to Et_3SiH[15] in the presence of TFA produced **17** directly in one step (**17**: 62% and **14**: 13%; the yield of **17** was amounted to be 71% based on the recovered starting material). The remarkable difference between $BF_3\cdot OEt_2/Et_3SiH$ and TFA/Et_3SiH as reducing agent combinations should be noted.

In addition, alcohol **17** could be obtained from ketone **14** via 1,3-dithiolane formation ($HSCH_2CH_2SH$, $BF_3\cdot OEt_2$, CH_2Cl_2, reflux, 80%),[16] followed by desulfurization via a free-radical reaction (*n*-Bu_3SnH, AIBN, MePh, 90 °C; **17**: 73% and **14**: 15%; the yield of **17** was amounted to be 86% based on the recovered starting material).[17]

After alcohol **17** became easily accessible, we focused on completing the formal synthesis of (+)-aphanorphine (Scheme 6). Under the typical Swern condition, secondary alcohol **17** was oxidized to afford pyrrolidinone **21** in excellent yield (98%). Nucleophilic addition of methyllithium[18] to ketone **21** (from the less hindered face) in tetrahydrofuran at −78 °C produced tertiary alcohol **22** in 39% yield (or 80% yield based on the recovered starting material) and in excellent stereoselectivity along with the recovered **21** (52%). The ^1H NMR of **22** showed two sets of peaks for some protons as a result of the presence of two rotamers in a ratio of 5:1. Reduction of **22** with lithium aluminum hydride in refluxing tetrahydrofuran gave the corresponding benzylamine, which displayed only one set of resonance signals in the ^1H NMR spectrum. Aluminum chloride[2r] promoted intramolecular



Scheme 5. Synthesis of **17** and Cyclization of **18**. PMP=*p*-methoxyphenyl, Bz=benzoyl.



Scheme 6. Synthesis of **24**. PMP=*p*-methoxyphenyl, Bz=benzoyl.

Friedel–Crafts reaction of alcohol **22** took place at room temperature to generate the desired alkylative cyclization product **23** as a colorless oil (76%). Thus the tricyclic framework of aphanorphine was rapidly constructed from lactone **10**. Hydrolysis[19] of **23** with 50% aqueous sodium hydroxide solution in refluxing ethanol, followed by N-methylation with formalin and sodium cyanoborohydride in methanol at room temperature, afforded (−)-aphanorphine methyl ether **24** in 71% overall yield for the two steps from **23**. The $[\alpha]_D^{28}$ of **24** was found to be −10.38 (*c* 1.36, $CHCl_3$) {lit.[2a] $[\alpha]_D^{27}$ −7.40 (*c* 0.35, $CHCl_3$), lit.[2v] $[\alpha]_D^{30}$ −9.72 (*c* 0.67, $CHCl_3$), lit.[2i] *ent*-**24** $[\alpha]_D^{21}$ +10.4 (*c* 1.24, $CHCl_3$)}. Other spectroscopic data of **24** were in accord with those reported previously.[2i]

3. Conclusion

In summary, we have accomplished efficient syntheses of (1*R*,4*S*)-1-methyl-8-methoxy-3-(4-toluenesulfonyl)-2,3,4,5-tetrahydro-1,4-methano-3-benzazepine (**8**) in six steps from sulfonamide **3**, and of (−)-aphanorphine methyl ether **24** in seven steps from lactone **10**, both featuring an intramolecular Friedel–Crafts reaction for the construction of ring B. Both **3** and **10** were derived from the same commercially available amino acid, (2*S*,4*R*)-4-hydroxyproline (**2**). The present work constitutes efficient formal syntheses of both natural (−)-aphanorphine and unnatural (+)-aphanorphine. In addition, it is noteworthy that under similar conditions ($BF_3\cdot OEt_2$/Et_3SiH and TFA/Et_3SiH) diol **18** underwent different reactions (intramolecular etherification and reduction, respectively), which would find applications in total synthesis of natural products. Especially, intramolecular etherification of **18** proceeded with excellent stereoselectivity in the presence of $BF_3\cdot OEt_2$, which has paved an efficient synthetic route to a series of medicinally attractive heterocycles.

4. Experimental

4.1. General

Melting points were uncorrected. All solvents and reagents were obtained from commercial sources and used without further purification unless otherwise stated. NMR spectra were recorded in $CDCl_3$, D_2O, CD_3COCD_3, and DMSO-d_6 (^1H at 300 MHz and ^{13}C at 75, 100, and 125 MHz) using TMS as the internal standard. Analytical samples were obtained by chromatography on silica gel. Anhydrous solvents and reagents were obtained as follows: dichloromethane was distilled over calcium hydride under N_2; THF, ether, and toluene were distilled over sodium benzophenone ketyl under N_2.

4.1.1. Compound 4. To a solution of $(COCl)_2$ (2.60 mL, 30.3 mmol) in anhydrous CH_2Cl_2 (60 mL) was added dropwise a solution of DMSO (3.50 mL, 49.3 mmol) in CH_2Cl_2 (20 mL) at −78 °C under Ar. The mixture was stirred for 10 min and then a solution of **3** (7.47 g, 19.4 mmol) in anhydrous CH_2Cl_2 (20 mL) was introduced slowly. After the addition, the mixture was stirred for 0.5 h at −78 °C and Et_3N (15.0 mL, 108 mmol) was added. The dry-ice bath was removed and the mixture was allowed to warm up to room temperature over 10 min. After evaporation of the solvent, the mixture was dissolved in anhydrous THF (50 mL) under Ar. The THF solution was transferred to an addition funnel fitted to a three-necked flask charged with a solution of *p*-methoxyphenylmagnesium bromide in THF (50 mL) [prepared from *p*-methoxyphenyl bromide (12.0 mL, 95.9 mmol)]. The flask was cooled in a dry-ice/acetone bath. The solution of the aldehyde in THF (50 mL) was slowly added while the mixture in the reaction flask was vigorously stirred. After the addition, the reaction mixture was stirred at 0 °C for 3 h, quenched with saturated aqueous NH_4Cl solution, concentrated, and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a residue, which was chromatographed (hexanes/EtOAc, 4:1) to afford adduct **4** (8.67 g, 91%) as a pale yellow syrup: ^1H NMR (300 MHz, CD_3COCD_3) δ 0.00 (s, 3H), 0.05 (s, 3H), 0.82 (s, 9H), 1.25–1.29 (m, 1H), 2.25–2.33 (m, 1H), 2.54 (s, 3H), 3.22 (dd, *J*=10.8, 4.2 Hz, 1H), 3.74 (ddd, *J*=10.8, 4.8, 1.8 Hz, 1H), 3.90 (s, 3H), 3.94–3.99 (m, 1H), 4.60–4.63 (m, 1H), 4.76 (dd, *J*=3.9, 2.1 Hz, 1H), 5.47 (br s, 1H), 7.04 (dd, *J*=8.7, 2.1 Hz, 2H), 7.46 (dd, *J*=8.7, 1.2 Hz, 2H), 7.55 (dd, *J*=7.8, 1.2 Hz, 2H), 7.94 (dd, *J*=7.8, 1.8 Hz, 2H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ −4.9, −4.8, 18.5, 21.4, 26.1, 34.6, 55.4, 58.2, 66.4, 71.1, 74.0, 114.3, 127.5, 128.6, 130.5, 135.0, 135.7, 144.2, 159.6; EIMS: *m*/*z* (%)=354 (100), 137 (41), 91 (35), 200 (27), 355 (26), 155 (21), 476 (1) $[M-CH_3]^+$; Anal. Calcd for $C_{25}H_{37}NO_5SSi$: C 61.07, H 7.58, N 2.85; found C 61.10, H 7.69; N 2.77.

4.1.2. Compound 5. A mixture of **4** (8.04 g, 16.4 mmol) and Et_3SiH (9.0 mL, 56 mmol) in CH_2Cl_2 (80 mL) was cooled to

0 °C by an ice/salt bath. To this cooled solution was added slowly a solution of $BF_3 \cdot OEt_2$ (9.0 mL, 71 mmol) in CH_2Cl_2 (30 mL). The reaction was monitored by TLC. After 3 h, the reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layers were washed with H_2O and brine successively, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (EtOAc) to afford **5** (5.63 g, 95%) as a pale yellow syrup: $[\alpha]_D^{20}$ −78.5 (*c* 0.95, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.68–1.78 (m, 2H), 2.43 (s, 3H), 2.87 (dd, *J*=13.2, 8.4 Hz, 1H), 3.17 (dd, *J*=13.5, 3.3 Hz, 1H), 3.26 (dd, *J*=10.5, 1.5 Hz, 1H), 3.40 (dd, *J*=10.2, 4.2 Hz, 1H), 3.80 (s, 3H), 3.93–3.97 (m, 1H), 4.02–4.08 (m, 1H), 6.83 (dd, *J*=8.7, 1.2 Hz, 2H), 7.16 (dd, *J*=8.7, 1.2 Hz, 2H), 7.33 (d, *J*=8.1 Hz, 2H), 7.78 (d, *J*=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 39.2, 41.0, 55.1, 56.8, 60.0, 69.3, 113.7, 127.7, 128.3, 129.6, 130.7, 134.3, 143.6, 158.2; EIMS: *m*/*z* (%)=240 (100), 91 (38), 155 (36), 121 (19), 68 (7), 361 (1) $[M]^+$; Anal. Calcd for $C_{19}H_{23}NO_4S$: C 63.13, H 6.41, N 3.88; found C 63.25, H, 6.41, N 4.00.

4.1.3. Compound 6. A mixture of **5** (105 mg, 0.290 mmol) and IBX (*o*-iodoxybenzoic acid) (656 mg, 2.34 mmol) in EtOAc (20 mL) was refluxed for 9 h and the solid mass was filtered off. The filtrate was concentrated to give a residue, which was chromatographed (petroleum ether/EtOAc, 3:1) to afford **6** (102 mg, 98%) as a colorless solid: mp 98–99 °C; $[\alpha]_D^{20}$ +61.1 (*c* 0.94, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.25 (d, *J*=7.8 Hz, 2H), 2.44 (s, 3H), 2.87 (AB part of ABX, J_{AB}=13.2, J_{Ax}=8.1, J_{Bx}=3.3 Hz, 2H), 3.55 (AB, J_{AB}=18.6 Hz, 2H), 3.79 (s, 3H), 4.44–4.49 (m, 1H), 6.81 (d, *J*=8.1 Hz, 2H), 7.09 (d, *J*=8.1 Hz, 2H), 7.33 (d, *J*=8.1 Hz, 2H), 7.73 (d, *J*=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 40.9, 41.5, 53.1, 55.1, 58.5, 114.0, 127.1, 127.7, 130.0, 130.7, 134.8, 144.1, 158.6, 209.2; EIMS: *m*/*z* (%)=182 (100), 181 (61), 155 (32), 91 (31), 238 (24), 359 (3) $[M]^+$; Anal. Calcd for $C_{19}H_{21}NO_4S$: C 63.49, H 5.89, N 3.90; found C 63.48, H 5.90, N 3.74.

4.1.4. Compound 7. To a solution of methylmagnesium iodide [prepared from methyl iodide (0.80 mL, 13 mmol)] in anhydrous Et_2O (20 mL) was added dropwise a solution of **6** (655 mg, 1.82 mmol) in anhydrous THF (10 mL). The reaction mixture was refluxed for 24 h and then quenched with saturated aqueous NH_4Cl solution. After removal of organic solvents, the residue was extracted with CH_2Cl_2. The combined extracts were washed with distilled H_2O and brine successively, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (hexanes/EtOAc, 1:1) to afford **7** (532 mg, 78%) as a syrup: ^1H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 2.4H), 1.18 (s, 0.6H), 1.52–1.84 (m, 2H), 1.79 (s, 1H), 2.41 (s, 0.6H), 2.43 (s, 2.4H), 3.07 (d, *J*=10.5 Hz, 1H), 3.18–3.27 (m, 2H), 3.33 (d, *J*=10.2 Hz, 1H), 3.74–3.78 (m, 1H), 3.75 (s, 3H), 6.85 (d, *J*=8.1 Hz, 2H), 7.19 (d, *J*=8.1 Hz, 2H), 7.34 (d, *J*=8.1 Hz, 2H), 7.76 (d, *J*=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (for the major epimer) 21.5, 25.4, 41.1, 43.0, 55.2, 61.5, 61.6, 75.9, 113.9, 127.6, 129.7, 130.0, 130.9, 133.7, 143.7, 158.2; δ (for the minor epimer) 21.5, 24.1, 40.9, 45.4, 55.2, 61.0, 61.6, 75.9, 113.7, 127.7, 129.6, 130.0, 130.6, 133.7, 143.7, 158.2; EIMS: *m*/*z* (%)=254 (100), 91 (46), 155 (27), 121 (23), 255 (16), 375 (0.4) $[M]^+$; Anal. Calcd for $C_{20}H_{25}NO_4S$: C 63.97, H 6.71, N 3.73; found C 64.08, H 6.97, N 3.50.

4.1.5. Compound 8. Compound **7** (532 mg, 1.42 mmol) and pulverized $AlCl_3$ (3.20 g, 24.0 mmol) were mixed in anhydrous CH_2Cl_2 (35 mL). The mixture was stirred at room temperature for 8 h and then quenched with saturated aqueous $NaHCO_3$ solution. The organic phase was washed with distilled H_2O and brine successively, dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (hexanes/EtOAc, 10:1) to afford **8** as a colorless solid. Recrystallization from petroleum ether/EtOAc afforded pure **8** (327 mg, 64%) as colorless needles: mp 161–162 °C. $[\alpha]_D^{20}$ −14.3 (*c* 0.93, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 3H), 1.45–1.49 (m, 1H), 1.80 (d, *J*=11.1 Hz, 1H), 2.43 (s, 3H), 2.94 (d, *J*=16.8 Hz, 1H), 3.02 (dd, *J*=9.0, 2.4 Hz, 1H), 3.13 (d, *J*=16.2 Hz, 1H), 3.41 (dd, *J*=9.0, 1.2 Hz, 1H), 3.79 (s, 3H), 4.37–4.41 (m, 1H), 6.71–6.80 (m, 2H), 6.99 (d, *J*=8.4 Hz, 1H), 7.27 (d, *J*=8.4 Hz, 2H), 7.71 (d, *J*=8.4 Hz, 2H); EIMS: *m*/*z* (%)=173 (100), 174 (56), 357 (30) $[M]^+$, 91 (25), 159 (25).

4.1.6. Compound 9. To a solution of (2*S*,4*R*)-4-hydroxyproline (**2**, 10 g, 0.076 mol) in cold aqueous NaOH solution (1.0 M, 200 mL, 0.20 mol) was added freshly distilled BzCl (12 mL, 0.10 mol) in Et_2O (200 mL). The mixture was stirred for 24 h and the ether layer was then separated off. The aqueous layer was washed with Et_2O, cooled in an ice-bath, and acidified with hydrochloric acid. The solid was collected by filtration, washed with several portions of Et_2O to remove residual benzoic acid, and dried to provide **9** (13.55 g, 76%) as a colorless solid: mp 192–194 °C; $[\alpha]_D^{26}$ −135.8 (*c* 1.38, EtOH); ^1H NMR (300 MHz, D_2O) δ 2.10–2.21 (m, 1H), 2.41 (dd, *J*=13.8, 7.8 Hz, 1H), 3.43 (d, *J*=12.3 Hz, 1H), 3.80 (dd, *J*=12.0, 3.0 Hz, 1H), 4.40–4.46 (m, 1H), 4.66 (dd, *J*=9.6, 8.4 Hz, 1H), 7.38–7.53 (m, 5H).

4.1.7. Compound 10. A mixture of **9** (3.00 g, 12.8 mmol) and acetic anhydride (22 mL) was heated at 90 °C under nitrogen for 5 h, cooled to room temperature, concentrated, and taken up in dichloromethane. The organic phase was washed with cold water, dried (Na_2SO_4), and concentrated. The residue was chromatographed (petroleum ether/EtOAc, 2:5) to yield **10** (2.5 g, 90%) as a colorless solid: mp 128–130 °C; $[\alpha]_D^{25}$ −93.0 (*c* 1.14, EtOH); ^1H NMR (300 MHz, $CDCl_3$) δ 2.11 (dd, *J*=10.8, 1.2 Hz, 1H), 2.29 (d, *J*=10.5 Hz, 1H), 3.60–3.80 (m, 1H), 3.80 (d, *J*=10.2 Hz, 1H), 4.60 (br s, 1H), 5.24 (br s, 1H), 7.40–7.55 (m, 3H), 7.63 (d, *J*=7.2 Hz, 2H).

4.1.8. Compound 11. To a solution of (2*S*,4*R*)-4-hydroxyproline (**2**, 5.0 g, 38 mmol) in water (40 mL) were added Na_2CO_3 (8.5 g, 80 mmol) at 0 °C. Then *p*-toluenesulfonyl chloride (8.73 g, 45.8 mmol) was added in several portions over a period of 20 min. The slurry was then warmed to room temperature and allowed to stir for 48 h. The reaction mixture was acidified with concentrated HCl solution to pH 2 and the crude product was isolated via filtration. The filter cake was washed with 0.01 M HCl solution and dried in vacuum oven at 60 °C for 12 h to yield **11** (9.01 g, 83%) as a colorless solid: mp 149–151 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 1.90–2.00 (m, 2H), 2.39 (s, 3H), 3.08 (d,

J=10.8 Hz, 1H), 3.45 (dd, J=9.9, 3.3 Hz, 1H), 4.04 (t, J=8.1 Hz, 1H), 4.15–4.30 (m, 1H), 4.84 (s, 1H), 7.40 (d, J=7.5 Hz, 2H), 7.69 (d, J=7.8 Hz, 2H), 12.71 (s, 1H).

4.1.9. Compound 12. A mixture of **11** (350 mg, 1.23 mmol) and acetic anhydride (2 mL) was heated at 90 °C under nitrogen for 8 h, cooled to room temperature, concentrated, and the residual acetic anhydride was neutralized with saturated aqueous $NaHCO_3$ solution. The mixture was acidified with HCl solution to pH 2 and extracted with CH_2Cl_2/IPA (3:1). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (EtOAc/MeOH, 4:1) to yield **12** (382 mg, 95%) as a colorless solid: mp 55–57 °C; $[\alpha]_D^{25}$ −76.4 (c 1.38, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.50 (s, 3H), 2.06–2.16 (m, 1H), 2.24 (dd, J=14.4, 7.5 Hz, 1H), 2.40 (s, 3H), 3.36 (d, J=12.9 Hz, 1H), 3.64 (dd, J=12.9, 3.9 Hz, 1H), 4.06 (dd, J=9.6, 7.2 Hz, 1H), 5.02 (s, 1H), 7.46 (d, J=7.8 Hz, 2H), 7.71 (d, J=7.8 Hz, 2H), 12.94 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 19.7, 20.5, 35.7, 53.5, 59.5, 72.2, 127.1, 129.3, 133.6, 143.2, 169.1, 172.5; ESI-MS: m/z (%)=328 (100) $[M+H]^+$, 345 (15) $[M+NH_4]^+$, 350 (28) $[M+Na]^+$. HRMS (MALDI): calcd for $C_{14}H_{18}NO_6S$ $[M+H]^+$ 328.0855; found 328.0849.

4.1.10. Compounds 13, 14 and 15 (from 10). A solution of 4-methoxyphenylmagnesium bromide (0.278 M, 19.0 mL, 5.28 mmol), prepared from 4-bromoanisole and Mg in THF, was added to a mixture of **10** (300 mg, 1.38 mmol) and Me(MeO)NH·HCl (162 mg, 1.66 mmol) in THF (18 mL) under nitrogen at −78 °C. The mixture was stirred at −78 °C for 10 h, quenched with saturated aqueous NH_4Cl solution, and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (petroleum ether/EtOAc, 1:1, 1:2 then 0:1) to afford sequentially **15** (26 mg, 4%), **14** (187 mg, 41%), and **13** (212 mg, 55%) as colorless solids. Compound **15**: mp 146–148 °C; $[\alpha]_D^{23}$ −71.8 (c 0.97, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84–1.93 (m, 1H), 2.30–2.41 (m, 1H), 3.10–3.30 (m, 2H), 3.55–3.67 (m, 1H), 3.71 (s, 3H), 3.83 (s, 3H), 4.15–4.30 (m, 1H), 5.15–5.25 (m, 1H), 5.44–5.55 (m, 1H), 6.76 (d, J=6.6 Hz, 2H), 6.92 (d, J=9.0 Hz, 2H), 7.22–7.50 (m, 9H). ESI-MS: m/z (%)=416 (100) $[M-OH]^+$, 456 (39) $[M+Na]^+$; Anal. Calcd for $C_{26}H_{27}NO_5$: C 72.04, H 6.28, N 3.23; found C 71.84, H 6.26, N 3.11. Compound **13**: mp 126–128 °C; $[\alpha]_D^{24}$ −150.3 (c 1.23, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.02 (d, J=10.8 Hz, 1H), 2.34–2.44 (m, 1H), 3.30 (s, 3H), 3.71 (s, 2H), 3.94 (s, 3H), 4.32 (d, J=10.5 Hz, 1H), 5.18 (s, 1H), 5.24 (d, J=10.2 Hz, 1H), 7.36–7.45 (m, 3H), 7.51–7.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.2, 36.7, 55.0, 59.0, 61.2, 71.3, 127.0, 128.2, 130.1, 135.8, 169.9, 173.6; ESI-MS: m/z (%)=218 (100) $[M-N(MeO)Me]^+$, 279 (20) $[M+H]^+$, 301 (93) $[M+Na]^+$; HRMS (MALDI): calcd for $C_{14}H_{18}N_2O_4Na$ $[M+Na]^+$ 301.1164; found 301.1159. Compound **14**: mp 152–154 °C; $[\alpha]_D^{28}$ −162.9 (c 0.87, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.0 (d, J=13.8 Hz, 1H), 2.38–2.48 (m, 1H), 3.76 (s, 2H), 3.87 (s, 3H), 4.30–4.40 (m, 1H), 4.46 (d, J=10.5 Hz, 1H), 5.70 (d, J=9.6 Hz, 1H), 6.97 (d, J=8.4 Hz, 2H), 7.38–7.45 (m, 3H), 7.53 (d, J=6.3 Hz, 2H), 8.12 (d, J=7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.8, 55.5, 57.9, 59.4, 70.8, 113.9, 127.3, 128.0, 128.2, 130.3, 131.1, 135.4, 164.0, 169.3, 198.0; ESI-MS: m/z (%)=326 (100) $[M+H]^+$, 348 (64) $[M+Na]^+$, 673 (34) $[2M+Na]^+$; Anal. Calcd for $C_{19}H_{19}NO_4$: C 70.14, H 5.89, N 4.31; found C 70.00, H 5.89, N 4.14.

4.1.11. Compound 14 (from 13). A solution of 4-methoxyphenylmagnesium bromide (0.275 M, (7.5+12) mL, 5.36 mmol), prepared from 4-bromoanisole and Mg in THF, was added to a solution of **13** (212 mg, 0.762 mmol) in THF (7 mL) at −35 °C. The mixture was warmed gradually to room temperature, stirred at that temperature for 4 h, quenched with saturated aqueous NH_4Cl solution, concentrated, and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to give a residue, which was chromatographed (petroleum ether/EtOAc, 1:2) to afford **14** (159 mg, 64%) as a colorless solid.

4.1.12. Compound 16. A mixture of **14** (4.20 g, 12.9 mmol), 1,2-ethanedithiol (4.4 mL, 52 mmol), and $BF_3\cdot OEt_2$ (0.66 mL, 5.2 mmol) in dry CH_2Cl_2 (110 mL) was refluxed for 4 days. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (petroleum ether/EtOAc, 3:2) to yield **16** (4.17 g, 80%) as a colorless solid: mp 168–170 °C; $[\alpha]_D^{25}$ +68.0 (c 0.92, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.75–1.85 (m, 1H), 2.36–2.50 (m, 1H), 2.61 (d, J=6.6 Hz, 1H), 3.02–3.10 (m, 3H), 3.26–3.34 (m, 2H), 3.55–3.65 (m, 1H), 3.79 (s, 3H), 3.95–4.08 (m, 1H), 5.30 (t, J=7.5 Hz, 1H), 6.84 (d, J=8.4 Hz, 2H), 7.33–7.45 (m, 3H), 7.49 (d, J=6.6 Hz, 2H), 7.78 (d, J=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.2, 38.3, 38.5, 55.2, 57.7, 62.5, 69.2, 80.1, 112.8, 128.1, 128.2, 130.0, 130.8, 134.5, 135.5, 158.8, 171.7; ESI-MS m/z (%)=402 (100) $[M+H]^+$, 424 (16) $[M+Na]^+$. HRMS (MALDI): calcd for $C_{21}H_{23}NO_3S_2Na$ $[M+Na]^+$ 424.1017; found 424.1012.

4.1.13. Compound 17 from 16. To a stirred solution of **16** (4.03 g, 10.0 mmol) in dry toluene (100 mL) maintained at 90 °C under argon was added a solution of tributyltin hydride (11.0 mL, 40.9 mmol) and AIBN (660 mg, 4.02 mmol) in toluene (25 mL). The reaction mixture was stirred for 2.5 h, cooled to room temperature, quenched with saturated aqueous $NaHCO_3$ solution, and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (petroleum ether/EtOAc, 3:2 then 1:2) to provide recovered **16** (617 mg, 15%) and **17** (2.26 g, 73%; or 86% brsm). Compound **17**, a colorless solid: mp 70–72 °C; $[\alpha]_D^{26}$ +95.7 (c 0.91, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70–2.20 (m, 2H), 2.55–3.05 (m, 1.5H), 3.08–3.24 (m, 1.5H), 3.50–3.60 (m, 1H), 3.78 (s, 3H), 4.00–4.30 (m, 1H), 4.40–4.60 (m, 1H), 6.55–6.70 (m, 1H), 6.87 (d, J=8.1 Hz, 1.5H), 7.20 (d, J=7.8 Hz, 1.5H), 7.35–7.50 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.0, 37.8, 55.1, 57.0, 57.6, 69.2, 113.6, 126.2, 127.1, 128.1, 130.1, 130.6, 136.4, 158.0, 170.0; ESI-MS m/z (%)=312 (100) $[M+H]^+$, 333 (73) $[M+Na-H]$, 366 (15) $[M+MeOH+Na]^+$, 645 (21) $[2M+Na]^+$; HRMS (EI): calcd for $C_{19}H_{21}NO_3$ 311.1521; found 311.1518.

4.1.14. Compound 17 from 14. To a stirred solution of **14** (150 mg, 0.461 mmol) in trifluoroacetic acid (3 mL) at 0 °C was added Et_3SiH (0.60 mL, 3.8 mmol). The mixture was stirred at room temperature for 36 h. After removal of most of the solvent, the residue was quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (petroleum ether/EtOAc, 1.5:1 then 1:2) to give sequentially **17** (89 mg, 62% or 71% brsm) as a colorless solid, **14** (19 mg, 13%).

4.1.15. Compound 17 from 18. To a stirred solution of **18** (150 mg, 0.458 mmol) in trifluoroacetic acid (3 mL) at 0 °C was added Et_3SiH (0.60 mL, 3.8 mmol). The mixture was stirred at room temperature for 3 h. Standard work-up and chromatography by the procedure described for the conversion of **14** to **17** gave **17** (107 mg, 75%).

4.1.16. Compound 17 from 19. To a stirred solution of **19** (41 mg, 0.13 mmol) in trifluoroacetic acid (1 mL) at 0 °C was added Et_3SiH (0.17 mL, 1.1 mmol). The mixture was stirred at room temperature for 18.5 h. Standard work-up and chromatography by the procedure described for the conversion of **14** to **17** gave **17** (25 mg, 61%).

4.1.17. Compound 18. To a solution of **14** (240 mg, 0.738 mmol) in MeOH (5 mL) at 0 °C was added $NaBH_4$ (110 mg, 2.91 mmol). The reaction mixture was stirred at this temperature for 1 h, and then acetone was added to quench the excess $NaBH_4$. The mixture was concentrated, diluted with saturated aqueous NH_4Cl solution, and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (petroleum ether/EtOAc, 1:2) to give **18** (212 mg, 88%) as a colorless solid: mp 70–72 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51–1.59 (m, 1H), 1.81–1.90 (m, 1H), 3.23–3.36 (m, 2H), 3.56 (dd, J=11.4, 6.0 Hz, 1H), 3.77 (s, 3H), 4.08 (dd, J=11.1, 5.4 Hz, 1H), 4.62 (dd, J=13.8, 7.5 Hz, 1H), 4.89 (d, J=7.5 Hz, 1H), 5.67 (s, 1H), 6.85 (d, J=8.4 Hz, 2H), 7.30 (d, J=8.4 Hz, 2H), 7.36–7.46 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.2, 55.1, 57.9, 63.3, 68.7, 77.7, 113.6, 126.9, 128.2, 130.3, 133.7, 135.7, 159.0, 173.0, 229.5; ESI-MS m/z (%)=310 (93) $[M-OH]^+$, 350 (100) $[M+Na]^+$, 382 (29) $[M+MeOH+Na]^+$, 677 (80) $[2M+Na]^+$; HRMS (EI): calcd for $C_{19}H_{19}NO_3$ $[M-H_2O]$ 309.1365; found 309.1373. A small amount of the epimer of **18** (as the minor product) was also isolated. *epi*-**18**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.97–2.10 (m, 2H), 3.50–3.58 (m, 2H), 3.82 (s, 3H), 4.20–4.27 (m, 1H), 4.60–4.67 (m, 1H), 5.52–5.58 (m, 1H), 6.91 (d, J=8.1 Hz, 2H), 7.33–7.52 (m, 7H); ESI-MS m/z (%)=310 (100) $[M-OH]^+$, 328 (41) $[M+H]^+$.

4.1.18. Compound 19. *(a) From **18** in the presence of $BF_3\cdot OEt_2$ and Et_3SiH:* a mixture of **18** (113 mg, 0.345 mmol) and Et_3SiH (0.44 mL, 2.76 mmol) in CH_2Cl_2 (18 mL) was cooled in an ice/salt bath to 0 °C. To this cooled solution was added slowly $BF_3\cdot OEt_2$ (0.32 mL, 2.5 mmol). When the reaction reached completion as judged by TLC, the mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (petroleum ether/EtOAc, 1:1) to give **19** (88 mg, 82%) as a colorless oil, rotamers (1.3:1): $[\alpha]_D^{26}$ −157.9 (c 1.37, $CHCl_3$). Major rotamer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61 (d, J=10.2 Hz, 1H), 1.82 (d, J=10.2 Hz, 1H), 3.66 (s, 2H), 3.72 (s, 3H), 4.22 (s, 1H), 4.84 (s, 1H), 5.12 (s, 1H), 6.81 (d, J=8.7 Hz, 2H), 7.02 (d, J=8.4 Hz, 2H), 7.40–7.53 (m, 3H), 7.53–7.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.1, 55.1 (probably corresponding to two types of carbon), 65.2, 76.1, 84.6, 113.7, 126.0, 126.9, 128.5, 130.2, 131.5, 136.2, 158.9, 169.0. Minor rotamer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.67 (d, J=10.5 Hz, 1H), 1.93 (d, J=9.9 Hz, 1H), 3.47 (s, 2H), 3.76 (s, 3H), 4.71 (s, 1H), 4.87 (s, 1H), 5.16 (s, 1H), 6.88 (d, J=8.4 Hz, 2H), 7.29 (d, J=8.7 Hz, 2H), 7.40–7.53 (m, 3H), 7.53–7.62 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.5, 53.5, 57.3, 61.6, 76.3, 84.0, 113.6, 126.4, 127.2, 128.2, 130.3, 132.1, 135.7, 158.8, 170.1; ESI-MS m/z (%)=310 (100) $[M+H]^+$, 332 (17) $[M+Na]^+$, 350 (12) $[M+NH_4+Na]^+$, 364 (43) $[M+MeOH+Na]^+$, 641 (35) $[2M+Na]^+$; Anal. Calcd for $C_{19}H_{19}NO_3$: C 73.77, H 6.19, N 4.53; found C 73.63, H 6.30, N 4.47.

*(b) From **18** in the presence of TFA:* a stirred solution of **18** (100 mg, 0.305 mmol) in trifluoroacetic acid (3 mL) was stirred at room temperature for 6.5 h. Standard work-up and chromatography by the procedure described above gave **19** (32 mg, 34%).

4.1.19. Compound 20. To a suspension of $LiAlH_4$ (29 mg, 0.763 mmol) in THF (4 mL) at room temperature was added a solution of **19** (59 mg, 0.19 mmol) in THF (6 mL). The mixture was refluxed for 30 min and then cooled to room temperature. A small quantity of Na_2SO_4 solid and several drops of H_2O were added to the reaction mixture. The solid mass was filtered off and the filtrate was concentrated to give a residue, which was chromatographed (petroleum ether/EtOAc, 2:1) to give **20** (43 mg, 76%) as a pale yellow oil: $[\alpha]_D^{26}$ −104.9 (c 0.87, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.66 (dd, J=10.2, 2.1 Hz, 1H), 1.75 (d, J=9.9 Hz, 1H), 2.69 (d, J=9.9 Hz, 1H), 2.98 (dd, J=9.6, 1.2 Hz, 1H), 3.35 (s, 1H), 3.79 (s, 3H), 3.94 (dd, J=20.7, 12.3 Hz, 2H), 4.60 (s, 1H), 5.24 (s, 1H), 6.86 (d, J=8.7 Hz, 2H), 7.15 (d, J=8.7 Hz, 2H), 7.25–7.50 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.6, 55.1, 57.3, 59.8, 66.9, 77.5, 78.9, 113.4, 126.2, 127.0, 128.3, 128.5, 133.8, 139.3, 158.3; ESI-MS m/z (%)=296 (100) $[M+H]^+$; HRMS (MALDI): calcd for $C_{19}H_{22}NO_2$ $[M+H]^+$ 296.1651; found 296.1645.

4.1.20. Compound 21. To a solution of $(COCl)_2$ (78 μL, 0.91 mmol) in CH_2Cl_2 (5 mL) was added dropwise a solution of DMSO (0.13 mL, 1.8 mmol) in CH_2Cl_2 (3 mL) at −78 °C. The mixture was stirred at −78 °C for 10 min and a solution of **17** (70 mg, 0.22 mmol) in CH_2Cl_2 (3 mL) was added. The mixture was stirred at −78 °C for 30 min and Et_3N (0.38 mL, 2.7 mmol) was added. The reaction mixture was allowed to warm to room temperature. Standard work-up and evaporation gave a residue, which was chromatographed (petroleum ether/EtOAc, 2:1) to afford **21** (68 mg, 98%) as a pale yellow solid: mp 98–100 °C; $[\alpha]_D^{27}$ +8.2 (c 1.14, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40–3.10

(m, 4H), 3.40–3.80 (m, 2H), 3.78 (s, 3H), 4.10–5.35 (m, 1H), 6.71–7.22 (m, 4H), 7.37–7.52 (m, 5H); ESI-MS *m/z* (%)=310 (85) $[M+H]^+$, 332 (56) $[M+Na]^+$, 364 (100) $[M+MeOH+Na]^+$; Anal. Calcd for $C_{19}H_{19}NO_3$: C 73.77, H 6.19, N 4.53; found C 73.93, H 6.24, N 4.32.

4.1.21. Compound 22. A solution of MeLi (1.0 M, 1.20 mL, 1.20 mmol) was added dropwise to a solution of **21** (277 mg, 0.895 mmol) in anhydrous THF (15 mL) at −78 °C. After 2 h, the mixture was quenched with saturated aqueous NH_4Cl solution, concentrated, and extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (petroleum ether/EtOAc, 5:2 then 3:2) to afford recovered **21** (143 mg, 52%) and **22** (113 mg, 39%; or 80% brsm). Compound **22**, a colorless solid: mp 121–123 °C; $[\alpha]_D^{27}$ +107.9 (*c* 0.85, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 2.5H), 1.44 (s, 0.5H), 1.91 (d, *J*=7.2 Hz, 2H), 2.26 (s, 1H), 2.96–3.10 (m, 1H), 3.13–3.35 (m, 2.5H), 3.70–3.82 (m, 0.5H), 3.79 (s, 3H), 4.00–4.15 (m, 0.17H), 4.40–4.50 (m, 0.83H), 6.56–6.77 (m, 0.66H), 6.85 (d, *J*=7.2 Hz, 1.67H), 7.18 (d, *J*=7.8 Hz, 1.67H), 7.38–7.45 (m, 3H), 7.45–7.55 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.2, 37.7, 42.8, 55.1, 58.1, 62.2, 75.1, 113.7, 126.3, 127.2, 128.2, 130.1, 130.7, 136.5, 158.1, 170.2; ESI-MS *m/z* (%)=326 (100) $[M+H]^+$, 348 (39) $[M+Na]^+$, 380 (8) $[M+MeOH+Na]^+$; Anal. Calcd for $C_{20}H_{23}NO_3$: C 73.82, H 7.12, N 4.30; found C 73.95, H 7.11, N 4.17.

4.1.22. Compound 23. $AlCl_3$ (4.14 g, 31.0 mmol) was added to a solution of **22** (0.718 g, 2.21 mmol) in dry CH_2Cl_2 (45 mL). The mixture was stirred at room temperature for 27 h and poured into saturated aqueous $NaHCO_3$ solution. The solid mass was filtered off and the two layers of the filtrate were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed successively with water and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (petroleum ether/EtOAc, 3:1) to give **23** (513 mg, 76%) as a colorless oil: $[\alpha]_D^{28}$ +76.2 (*c* 1.53, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 2H), 1.59 (s, 1H), 1.90–2.10 (m, 2H), 2.81 (s, 0.67H), 2.98 (dd, *J*=17.1, 2.4 Hz, 0.67H), 3.30–3.54 (m, 2.66H), 3.76 (s, 2H), 3.80 (s, 1H), 4.32–4.37 (m, 0.33H), 4.85–4.91 (m, 0.67H), 6.70–6.80 (m, 1.65H), 6.86 (d, *J*=2.4 Hz, 0.35H), 6.97 (d, *J*=8.4 Hz, 0.35H), 7.07 (d, *J*=8.4 Hz, 0.65H), 7.30–7.37 (m, 3.25H), 7.41–7.48 (m, 1.75H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 20.8, 34.8, 37.3, 40.0, 41.0, 41.9, 42.2, 54.7, 54.9, 55.0, 56.4, 61.5, 64.1, 109.4, 109.5, 111.4, 111.5, 124.0, 125.3, 126.1, 126.5, 127.8, 128.1, 129.1, 129.2, 129.9, 130.2, 136.7, 137.2, 144.7, 145.6, 157.5, 157.9, 168.7, 169.8; ESI-MS *m/z* (%)=308 (100) $[M+H]^+$, 330 (6) $[M+Na]^+$, 362 (19) $[M+MeOH+Na]^+$; HRMS (EI): calcd for $C_{20}H_{21}NO_2$ 307.1572; found 307.1570.

4.1.23. Compound 24. To a solution of **23** (459 mg, 1.49 mmol) in ethanol (7 mL) was added 50% aqueous NaOH solution (7 mL). The mixture was refluxed for 24 h, cooled to room temperature, concentrated, neutralized with saturated aqueous NH_4Cl solution, and extracted with CH_2Cl_2/IPA (3:1). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (CH_2Cl_2/MeOH/Et_3N, 100:10:1) to give the hydrolysis product.

A mixture of the above hydrolysis product, formalin (containing 37% CH_2O, 1.4 mL, 18 mmol), and $NaCNBH_3$ (95%, 990 mg, 15.0 mmol) in MeOH (18 mL) was stirred overnight at room temperature. After evaporation of the volatiles, the residue was partitioned between 5% HCl and ether, and the two layers were separated. The aqueous layer was washed one more time with ether and the organic layer was discarded. The aqueous layer was made basic with concentrated NH_4OH solution and extracted with CH_2Cl_2/IPA (3:1). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed (CH_2Cl_2/MeOH/Et_3N, 100:2:1) to give (−)-aphanorphine methyl ether **24** (230 mg, 71% for two steps from **23**) as a colorless oil: $[\alpha]_D^{28}$ −10.38 (*c* 1.36, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 3H, CH_3), 1.83 (d, *J*=11.1 Hz, 1H, $0.5CH_2$), 2.01 (dd, *J*=11.1, 6.0 Hz, 1H, $0.5CH_2$), 2.46 (s, 3H, NCH_3), 2.74 (d, *J*=6.0 Hz, 1H, $0.5CH_2$), 2.81 (s, 1H, $0.5CH_2$), 2.84 (s, 1H, $0.5CH_2$), 3.02 (d, *J*=16.8 Hz, 1H, $0.5CH_2$), 3.37–3.40 (m, 1H, NCH), 3.75 (s, 3H, OCH_3), 6.67 (dd, *J*=8.4, 2.1 Hz, 1H, CH), 6.77 (s, 1H, CH), 7.00 (d, *J*=8.4 Hz, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 35.3, 41.3, 41.4, 42.9, 54.9, 61.1, 71.0, 109.1, 110.8, 125.6, 129.9, 147.6, 157.5; EIMS *m/z* (%)=218 (18) $[M+H]^+$, 217 (48) $[M]^+$, 202 (100), 159 (64), 144 (28), 115 (38); HRMS (EI): calcd for $C_{14}H_{19}NO$ 217.1467; found 217.1460.

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