An Effective Route to (–)-Aphanorphine Using D-Tyrosine as a Chiral Building Block

Min Li,*[a] Peijie Zhou,[a] Hans F. Roth[b]

[a] Department of Neurosciences, Georgetown University Medical Center, 4000 Reservoir Road NW, Washington DC 20057, USA
Fax +1(202)6870617; E-mail: ml258@georgetown.edu

[b] Orgchem Technologies, Inc, 2201 W. Campbell Dr, Chicago, IL 60612, USA

Received 1 August 2006

Abstract: A stereoselective approach toward a naturally occurring alkaloid, (–)-aphanorphine, has been achieved via a series of reactions from Boc-D-tyrosine.

Keywords: aphanorphine, rhodium 1,3-dicarbonyl carbenoid, C–H insertion, intra-annular chirality transfer, thioketal

Aphanorphine (**1**) is a tricyclic alkaloid featuring a 3-benzazepine skeleton, which bears a striking similarity to the synthetic analgesic pentazocine (**2**) (Figure 1).[1] The first isolation of **1** was reported by Clardy and co-workers[2] in 1988 from the freshwater blue-green alga *Aphanizomenon flosaquae* along with other neurotoxins, such as saxitoxin and neosaxitoxin.

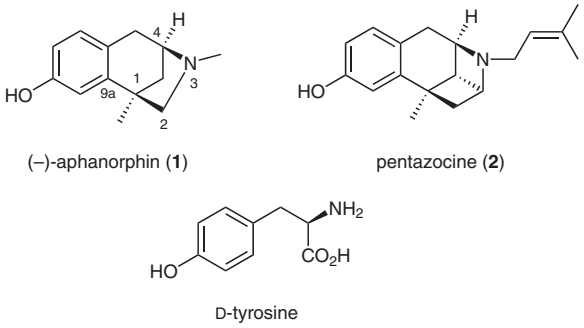
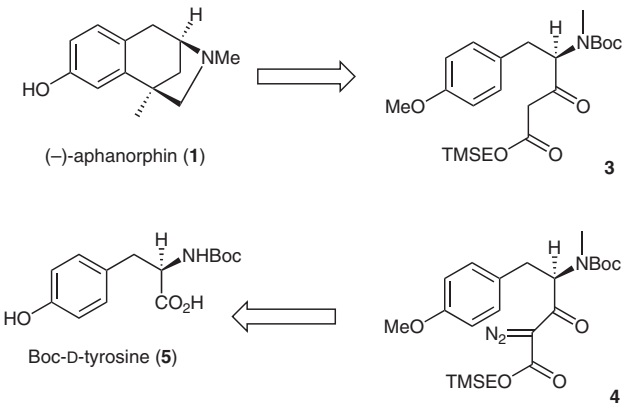


Figure 1 (–)-Aphanorphin (**1**), pentazocine (**2**) and D-tyrosine

Due to its significant bioactivity and highly rigid structure, the narcotic aphanorphine (**1**) has received significant attention and diverse synthetic strategies toward **1** have been developed by different research teams.[3] A formal synthesis of **1** was realized by Fadel and Arzel in 1997,[4] using an enzyme-catalyzed asymmetrization as a key step. Later, Ishibashi and co-workers[5] reported a Bu_3SnH-mediated aryl radical cyclization to establish the scaffold of (–)-aphanorphine (**1**) with high selectivity. In 2001 and 2003, Funk[6] and Zhai[7] published their synthetic endeavors, respectively. In constructing the A/B fused ring system, both groups employed a Lewis acid catalyzed intramolecular electrophilic ring cyclization. Most recently, Honda[8] and Gallagher[3] reported their entries to (–)-aphanorphine (**1**). Honda's group employed a samarium diiodide promoted reductive carbon–nitrogen bond cleavage to provide a benzazepinone as a key intermediate. Gallagher and co-workers[3] successfully applied a lactam methodology by using cyclic sulfamidates as lactam precursors.[9] As part of our long-term drug discovery program employing chiral pool substrates, we have recently launched an asymmetric synthesis of (–)-aphanorphine (**1**) and its analogues. Herein, we wish to report an alternative synthesis of **1**, which complements Honda's strategy, by using commercially available Boc-D-tyrosine as the starting material.

As outlined in the retrosynthetic analysis, our approach toward (–)-aphanorphine (**1**) relied on a substrate-controlled asymmetric alkylation of ester **3** to establish the benzylic quaternary carbon center. The 3-benzapine skeleton of **3** could be constructed via a rhodium 1,3-dicarbonyl carbenoid-mediated C–H insertion to generate the C(1)–C(9a) bond. This called for a 1,3-dicarbonyl precursor **4**, which in turn could be prepared from commercially available Boc-D-tyrosine **5** (Scheme 1).

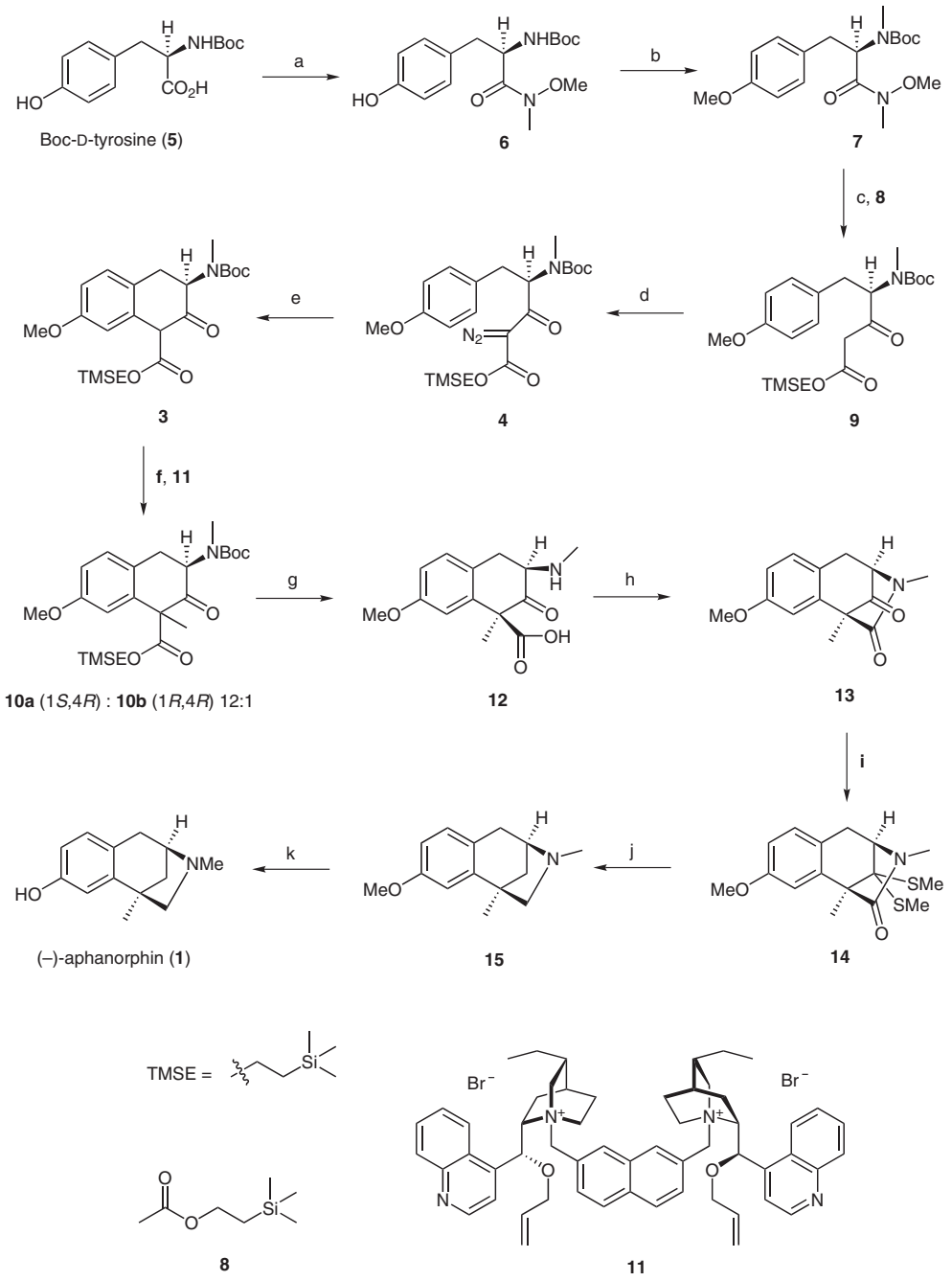


Scheme 1 Retrosynthetic analysis of aphanorphine (**1**)

The implementation of this strategy is delineated in Scheme 2. Boc-D-tyrosine **5** was coupled with *N*,*O*-dimethylhydroxylamine hydrochloride to give the corresponding Weinreb amide **6** in 87% yield without any noticeable racemization (^{1}H NMR).[10] Further methylation of the amine as well as the side chain was performed according to the procedures reported by Gesson.[11] However, obvious isomerization (9:1) was observed as evidenced from ^{1}H NMR spectrum and hence slightly modified reac-

SYNTHESIS 2007, No. 1, pp 0055–0060
Advanced online publication: 12.12.2006
DOI: 10.1055/s-2006-958931; Art ID: M04806SS

tion conditions (– 20 °C, 16 h) were applied to circumvent the strong base-induced racemization. Consequently, intermediate **7** was obtained in a moderate 75% yield with a negligible racemization ratio of 98:2 as indicated by chiral-phase HPLC.[12] On treatment with an excess amount of **8**, which was prepared according to the protocols reported by Shioiri and co-workers,[13] compound **7** was cleanly converted into the desired 1,3-dicarbonyl intermediate **9**. The transformation of **9** to a 2-diazo-1,3-dicarbonate proceeded uneventfully in mild conditions,[14] giving the desired compound **4** as a sole product. However, use of excess *p*-toluenesulfonyl azide made the purification of **4** extremely difficult and that would inevitably contaminate the desired product. Therefore, somewhat less than the stoichiometric amount of *p*-toluenesulfonyl azide was employed in performing this reaction.[14]



Scheme 2 *Reagents and conditions*: (a) DCC, DMAP, *N*,*O*-dimethylhydroxylamine hydrochloride, CH_2Cl_2, r.t., 87%; (b) NaH, MeI, DMF, –20 °C, 75%; (c) LDA, **8**, THF, –78 °C to 25 °C, 97%; (d) DIPEA, TsN_3, CH_2Cl_2, r.t., 88%; (e) $Rh_2(OAc)_4$, CF_3CONH_2, CH_2Cl_2, r.t., 78%; (f) aq 50% KOH, MeI, **11**, toluene, –40 °C, 90%; (g) CF_3CO_2H, CH_2Cl_2, r.t.; (h) BEP, DIPEA, –20 °C to r.t., 93% in two steps; (i) MeSH, Me_3SiCl, $CHCl_3$, r.t., 86%; (j) $LiAlH_4$, THF, r.t. to reflux, 83%; (k) BBr_3, CH_2Cl_2, –20 °C to 0 °C, 88%.

With **4** in hand, we then investigated the construction of the A/B fused rings. Considering the high activity of the rhodium 1,3-dicarbonyl carbenoid,[15] we explored the means to direct the reaction towards the formation of desired C–H insertion product **3**. Exposure of **4** to rhodium diacetate furnished **3** in 54% yield along with a minor product identified as an azulene derivative (24%).[16] As an optimization, we explored the carbenoid-induced cyclization by employing rhodium trifluoroacetamide as the catalyst, which has been successfully used by Moody and coworkers[17] in their synthetic endeavors towards diazonamide A. Similarly to Moody's result, the more active rhodium trifluoroacetamide facilitated the cyclization of **4** by enhancing the yield and shortening the reaction time as well. The desired **3** was obtained in 78% yield, which could suffice the amount requirement for further modification.

The next task was the stereoselective introduction of a methyl group onto the C1 of ring B via the alkylation of 1,3-dicarbonate **3**. As outlined in our retrosynthetic strategy, we hypothesized that the chiral amine function at C4 would serve to direct the asymmetric alkylation. The methylation of **3** proceeded to deliver the methylated diastereomers in a total 93% yield by employing NaH and MeI at fairly low temperature (–40 °C). Further flash chromatographic purification gave the desired (1*S*,4*R*)-**10a** and the unwanted (1*R*,4*R*)-**10b** in a ratio of 73:27, which was unsatisfactory. Further optimization involved lowering the reaction temperature as well as the utilization of chiral ligand such as (–)-sparteine.[18] However, no significant improvement was observed for the enantioselectivity of establishing the quaternary carbon center. To overcome this problem, we employed a phase-transfer alkylation in the presence of a catalytic amount of cinchona-derived ammonium salt **11**, which has been developed and successfully used for synthesis of both natural and non-natural products.[19] This method greatly enhanced the stereoselectivity of the methylation by affording the desired compound **10a** and its diastereomer **10b** in a ratio of 12:1 (based on isolated yield).

Intermediate **10a** was further subjected to trifluoroacetic acid to effect the concurrent removal of both the Boc and TMSE groups,[20] giving **12** as a key precursor for ensuing B/C ring conjugation. The establishment of the (–)-aphanorphine skeleton was accomplished in 95% yield by employing 2-bromo-1-ethylpyridinium tetrafluoroborate (BEP) as a coupling reagent, which has been widely used in peptide bond formation.[21] The desired intramolecular coupling compound **13** was obtained as a sole product while the unwanted intermolecular amide bond formation was not observed.

At the final stage of the total synthesis, we designed a concomitant reduction of the amide and ketone, which called for a thioketal precursor. However, even though the conventional reagents 1,3-propanedithiol and 1,2-ethanedithiol were used for the thioketal construction,[22] possibly due to the steric hindrance of substrate **13**, the yield was unsatisfactory (27–41%) and most of starting material was recovered. Further optimization led to the utilization of the least bulky methanethiol,[23] which successfully converted the ketone **13** to the corresponding thioketal **14** in 86% yield. Employing a known protocol,[3,24] ensuing reduction and deprotection proceeded completely in a consistent manner to deliver the target (–)-aphanorphine (**1**), whose spectral data were identical to those previously reported.[2]

In summary, an alternative total synthesis of (–)-aphanorphine (**1**) was accomplished using D-tyrosine as a chiral building block. This synthesis featured a rhodium carbenoid-mediated C–H insertion and an asymmetric phase-transfer methylation as key steps. It merits comment that by switching from D-tyrosine to L-tyrosine, the enantiomer of (–)-aphanorphine (**1**) could also be obtained in an optically pure form.

Chemicals were purchased from Aldrich or Acros Chemical Corporation and used without further purification. Solvents were distilled before use: CH_2Cl_2 was distilled from CaH_2 and THF was distilled from sodium wire. All reactions were performed under inert atmosphere (argon or N_2) unless otherwise noted. NMR spectra were recorded with a Varian Unity INOVA 300 at 300 MHz (^{1}H), 75 MHz (^{13}C) at 25 °C. ^{1}H chemical shifts (δ) were reported in ppm with Me_4Si (δ = 0.00) or $CDCl_3$ (δ = 7.26) as internal standards. ^{13}C chemical shifts were reported with $CDCl_3$ (δ = 77.00) or Me_4Si (δ = 0.00) as internal standards. Optical rotations were recorded at r.t. TLC was performed on Merck silica gel 60 F_{254} glass plates. Flash column chromatography was performed using Merck silica gel (35–75 mesh).

***tert*-Butyl (*R*)-3-(4-Hydroxyphenyl)-1-[methoxy(methyl)amino]-1-oxopropan-2-ylcarbamate (6)**

To a solution of commercially available Boc-D-tyrosine (4.8 g, 17.0 mmol) in CH_2Cl_2 (12 mL), was added *N*,*O*-dimethylhydroxylamine hydrochloride (2.0 g, 20.5 mmol) and DCC (4.2 g, 20.5 mmol). The solution was cooled to 0 °C, and DMAP (150 mg) and Et_3N (8.5 mL) were added. The mixture was allowed to warm up to r.t. and stirred for 4 h. The resulting light brown solution was poured into ice-water (30 mL) and extracted with EtOAc (3 × 30 mL). The organic layers were combined and washed successively with H_2O (3 × 20 mL) and brine (3 × 20 mL). After drying (Na_2SO_4), the solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (R_f 0.25, MeOH–CH_2Cl_2, 1:100) to afford compound **6** as an off-white solid; yield: 4.8 g (87%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 (s, 9 H), 2.05 (s, 3 H), 3.33 (s, 3 H), 3.45 (m, 2 H), 4.93 (t, *J* = 9.3 Hz, 1 H), 6.68 (d, *J* = 8.5 Hz, 2 H), 6.92 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.96, 29.01, 33.53, 55.37, 56.22, 70.64, 125.38, 127.29, 129.99, 137.78, 158.96, 173.95.

HRMS: *m*/*z* calcd for $C_{16}H_{24}N_2O_5$: 324.1685; found: 324.1688.

***tert*-Butyl (*R*)-1-[Methoxy(methyl)amino]-3-(4-methoxyphenyl)-1-oxopropan-2-yl(methyl)carbamate (7)**

To a solution of compound **6** (4.5 g, 14.0 mmol) in DMF (40 mL) at –20 °C (dry ice-MeCN cold bath), was added NaH (1.2 g, 60% in mineral oil, 30 mmol) in small portions. After the H_2 evolution had ceased, MeI (5.7 g, 40 mmol) was added dropwise. The mixture was allowed to stir at the same temperature for 3 h before crushed ice (5 g) was added. The mixture was extracted with EtOAc (3 × 30 mL) and the organic layers were combined and washed successively with H_2O (3 × 20 mL) and brine (3 × 20 mL). After drying

(Na_2SO_4), the solvent was removed on a rotary evaporator, and the crude product was purified by flash column chromatography (R_f 0.35, hexanes–EtOAc–Et_3N, 10:4:1) to afford the title compound **7** as a colorless solid; yield: 3.7 g (75%); $[\alpha]_D^{25}$ –7.2 (*c* = 0.55, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 (s, 9 H), 2.13 (s, 3 H), 2.30 (s, 3 H), 3.35 (s, 3 H), 3.39 (s, 3 H), 3.46 (m, 2 H), 4.89 (t, *J* = 9.0 Hz, 1 H), 6.66 (d, *J* = 8.5 Hz, 2 H), 6.92 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.96, 29.10, 33.63, 37.32, 55.37, 56.22, 58.65, 71.10, 125.39, 128.64, 129.99, 134.06, 158.58, 173.88.

HRMS: *m*/*z* calcd for $C_{18}H_{28}N_2O_5$: 352.1998; found: 352.1996.

2-(Trimethylsilyl)ethyl (4*R*)-4-[*tert*-Butoxycarbonyl(methyl)amino]-5-(4-methoxyphenyl)-3-oxopentanoate (9)

To a solution of 2-trimethylsilylethyl acetate (**8**; 2.4 g, 15 mmol) in THF (30 mL) at –78 °C, was added LDA (1.0 M in THF, 15.0 mL, 15 mmol) dropwise. The resulting pale yellow solution was stirred at the same temperature for 30 min and a solution of compound **7** (3.52 g, 10 mmol) in THF (20 mL) was added dropwise via syringe. The mixture was allowed to warm up slowly to r.t. and stirred for 6 h. Using an ice bath, the mixture was cooled to 0 °C and quenched by adding sat. aq NH_4Cl (15 mL). Most of the solvent was removed under reduced pressure and the residue was extracted with EtOAc (3 × 50 mL). The organic layers were then combined and washed with brine (3 × 30 mL) and dried (Na_2SO_4). After concentration under reduced pressure, the crude product obtained was purified by flash column chromatography (R_f 0.38, hexanes–EtOAc–Et_3N, 6:2:1) to afford the title compound **9** as a colorless solid; yield: 4.38 g (97%); $[\alpha]_D^{25}$ –3.3 (*c* = 0.30, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.04 (s, 9 H), 1.03 (t, *J* = 6.9 Hz, 2 H), 1.48 (s, 9 H), 2.26 (s, 3 H), 3.35 (s, 3 H), 3.41–3.46 (m, 4 H), 4.10 (t, *J* = 6.9 Hz, 2 H), 4.93 (t, *J* = 9.2 Hz, 1 H), 6.67 (d, *J* = 8.8 Hz, 2 H), 6.90 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.66, 12.03, 28.99, 29.72, 32.78, 37.35, 55.02, 56.53, 58.88, 70.27, 75.36, 126.67, 128.96, 128.98, 133.09, 159.25, 171.24, 175.43.

HRMS: *m*/*z* calcd for $C_{23}H_{37}NO_6Si$: 451.2389; found: 451.2393.

2-(Trimethylsilyl)ethyl (4*R*)-4-[*tert*-Butoxycarbonyl(methyl)amino]-2-diazo-5-(4-methoxyphenyl)-3-oxopentanoate (4)

To a solution of compound **9** (3.6 g, 8.0 mmol) in anhyd CH_2Cl_2 (20 mL), was added successively TsN_3 (1.5 g, 7.6 mmol) and DIPEA (15 mL). The mixture was allowed to stir at r.t. for 2 h and filtered through a short silica gel column. The column was washed with CH_2Cl_2 (2 × 20 mL) and the filtrates were combined, and concentrated under reduced pressure to give a pale brown crude product. The residue was further purified by flash column chromatography (R_f 0.33, hexanes–EtOAc–Et_3N, 6:2:1) to afford compound **4** as a pale brown syrup; yield: 3.3 g (88%). Unconsumed compound **9** (293 mg) was recovered.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.03 (s, 9 H), 1.05 (t, *J* = 6.7 Hz, 2 H), 1.46 (s, 9 H), 2.26 (s, 3 H), 3.33 (s, 3 H), 3.43–3.45 (m, 2 H), 4.13 (t, *J* = 6.8 Hz, 2 H), 4.99 (t, *J* = 9.5 Hz, 1 H), 6.68 (d, *J* = 8.8 Hz, 2 H), 6.93 (d, *J* = 8.8 Hz, 2 H).

2-(Trimethylsilyl)ethyl (3*R*)-3-[*tert*-Butoxycarbonyl(methyl)amino]-7-methoxy-2-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylate (3)

To a solution of compound **4** (956 mg, 2.0 mmol) in anhyd CH_2Cl_2 (10 mL) at r.t., was added successively trifluoroacetamide (0.1 mL) and $Rh_2(OAc)_4$ (40 mg, 0.18 mmol). The mixture was allowed to stir at r.t. until all the starting material **4** had been consumed (approximately 3 h). The mixture was filtered through a short silica gel column and the column was washed with CH_2Cl_2 (2 × 10 mL). The filtrates were combined and concentrated under reduced pressure to afford a pale brown residue as the crude product. After flash column chromatographic purification (R_f 0.35, CH_2Cl_2–EtOAc–Et_3N, 10:2:1), the desired compound **3** was obtained as an off-white syrup which solidified slowly at r.t.; yield: 700 mg (78%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.03 (s, 9 H), 1.05 (t, *J* = 6.8 Hz, 2 H), 1.46 (s, 9 H), 2.26, 2.27 (s, 3H), 3.33 (s, 3 H), 3.43–3.46 (m, 2 H), 4.15 (t, *J* = 6.6 Hz, 2 H), 4.99 (t, *J* = 9.0 Hz, 1 H), 5.35 (s, 1 H), 6.67 (dd, *J* = 8.0, 3.2 Hz, 1 H), 6.72 (d, *J* = 2.9 Hz, 1 H), 7.03 (d, *J* = 8.0 Hz, 1 H).

2-(Trimethylsilyl)ethyl (1*S*,3*R*)-3-[*tert*-Butoxycarbonyl(methyl)amino]-7-methoxy-2-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylate (10a) and 2-(Trimethylsilyl)ethyl (1*R*,3*R*)-3-[*tert*-Butoxycarbonyl(methyl)amino]-7-methoxy-2-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylate (10b)

To a solution of compound **3** (613 mg, 1.36 mmol) in toluene (10 mL), was added chiral ligand **11** (83 mg, 0.16 mmol) and MeI (400 mg, 2.72 mmol). The suspension was cooled to –40 °C (dry ice-CCl_4 cold bath). With vigorous stirring, aq KOH (2.0 mL, 17.2 mmol) was added dropwise and the resulting pale yellow solution was allowed to stir at the same temperature till all the starting material had been consumed (5 h). The suspension was allowed to warm up to r.t. and diluted with EtOAc (30 mL), washed successively with sat. aq NH_4Cl (3 × 15 mL) and brine (3 × 15 mL) and dried (Na_2SO_4). After concentration and flash chromatographic purification (R_f 0.36 for **10a**, R_f 0.33 for **10b**, CH_2Cl_2–EtOAc–Et_3N, 10:2:1), the desired product **10a** was obtained as a colorless solid, along with its diastereomer **10b**.

Compound 10a

Yield: 523 mg (83%); $[\alpha]_D^{25}$ +8.2 (*c* = 0.15, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.05 (s, 9 H), 1.06 (t, *J* = 7.2 Hz, 2 H), 1.45 (s, 3 H), 1.50 (s, 9 H), 2.36 (s, 3 H), 3.26–3.28 (m, 2 H), 3.43 (s, 3 H), 4.08 (t, *J* = 7.3 Hz, 2 H), 4.83 (t, *J* = 7.8 Hz, 1 H), 6.66 (dd, *J* = 8.2, 3.2 Hz, 1 H), 6.70 (d, *J* = 2.9 Hz, 1 H), 7.02 (d, *J* = 8.2 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 8.73, 12.00, 22.65, 23.24, 41.05, 42.83, 43.15, 57.06, 57.58, 62.17, 71.00, 109.62, 109.96, 128.38, 135.65, 146.88, 152.23, 159.63, 168.65, 171.34.

HRMS: *m*/*z* calcd for $C_{24}H_{37}NO_6Si$: 463.2390; found: 463.2389.

Compound 10b

Yield: 43 mg (7%); $[\alpha]_D^{25}$ +16.7 (*c* = 0.12, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.05 (s, 9 H), 1.05 (t, *J* = 6.7 Hz, 2 H), 1.46 (s, 3 H), 1.48 (s, 9 H), 2.28 (s, 3 H), 3.36 (s, 3 H), 3.35–3.38 (m, 2 H), 4.15 (t, *J* = 6.9 Hz, 2 H), 4.58 (t, *J* = 9.0 Hz, 1 H), 6.68 (dd, *J* = 8.0, 3.0 Hz, 1 H), 6.76 (d, *J* = 3.0 Hz, 1 H), 6.99 (d, *J* = 8.2 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 8.76, 12.05, 23.18, 25.03, 42.04, 42.11, 47.33, 58.28, 63.52, 72.80, 109.00, 111.99, 126.12, 134.32, 147.88, 151.99, 159.96, 166.83, 170.52.

Compound 13

To a solution of **10** (269 mg, 0.58 mmol) in anhyd CH_2Cl_2 (5.0 mL), was added CF_3CO_2H (0.6 mL) and the mixture was allowed to stir at r.t. overnight. The solvent was removed under reduced pressure to give a light brown syrup. The residue was dissolved in toluene (20 mL) and subjected to azeotropic distillation to give crude **12** (148.8 mg). Under argon, crude **12** (148.8 mg) was dissolved in anhyd CH_2Cl_2 (5.0 mL) and BEP[18] (159 mg, 0.58 mmol) was added. The mixture was cooled to –20 °C and DIPEA (1.2 mL) was added dropwise. The resulting yellow solution was allowed to warm up to r.t. slowly and stirred for 3 h. After concentration under reduced pressure and flash chromatographic purification (R_f 0.35, $CHCl_3$–

MeOH, 40:1), compound **13** was obtained as an off-white amorphous solid; yield: 132 mg (93% for two steps); $[\alpha]_D^{25}$+15.5 (*c* = 0.25, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 (s, 3 H), 2.56 (s, 3 H), 2.72 (d, *J* = 9.6 Hz, 1 H), 2.79 (s, 1 H), 3.66 (m, 1 H), 3.80 (s, 3 H), 6.69 (dd, *J* = 8.0, 2.8 Hz, 1 H), 6.70 (d, *J* = 2.8 Hz, 1 H), 7.09 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 42.23, 42.69, 43.15, 55.38, 61.35, 70.89, 109.12, 111.26, 125.50, 130.27, 147.83, 156.92, 166.83, 168.56.

Compound 14

To a solution of compound **13** (120 mg, 0.49 mmol) in anhyd $CHCl_3$ (5 mL), was added MeSH (150 mg, 3.1 mmol). The solution was cooled to 0 °C and TMSCl (336 mg, 3.1 mmol) was added dropwise. The mixture was allowed to warm up slowly to r.t. and stirred overnight. Et_3N (2.0 mL) was then added and the solvent was removed on a rotary evaporator to afford a pale brown syrup. The residue was purified by flash column chromatography (R_f 0.28, $CHCl_3$–MeOH, 40:1) to give compound **14** as a colorless syrup; yield: 136 mg (86%); $[\alpha]_D^{25}$ +3.9 (*c* = 0.20, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.43 (s, 3 H), 2.28 (2 s, 6 H), 2.50 (s, 3 H), 2.73 (br s, 1 H), 2.76 (br s, 1 H), 3.39 (m, 1 H), 3.83 (s, 3 H), 6.71 (dd, *J* = 7.8, 2.8 Hz, 1 H), 6.72 (d, *J* = 2.8 Hz, 1 H), 7.07 (d, *J* = 8.2 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.04, 42.33, 43.96, 46.87, 46.88, 60.00, 62.03, 72.82, 100.02, 115.35, 124.60, 126.56, 130.03, 135.70, 137.25, 159.39.

HRMS: *m/z* calcd for $C_{16}H_{21}NO_2S_2$: 323.1013; found: 323.1009.

Compound 15

To a solution of compound **14** (120 mg, 0.37 mmol) in THF (5 mL) at r.t., was added a suspension of $LiAlH_4$ (72 mg, 1.90 mmol) in THF (1 mL). The mixture was allowed to reflux until the starting material had been consumed (8 h). The mixture was allowed to cool to r.t. and powdered $Na_2SO_4{\cdot}10H_2O$ (300 mg) was added in small portions. After H_2 evolution had ceased, the solid was filtered through a pad of Celite and washed with THF (3 × 10 mL). The filtrates were combined and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (R_f 0.36, $CHCl_3$–MeOH–Et_3N, 50:1:1) to give compound **15** as a colorless syrup; yield: 64 mg (83%); $[\alpha]_D^{25}$ +10.2 (*c* = 0.25, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 (s, 3 H), 1.85 (d, *J* = 10.2 Hz, 1 H), 2.00 (dd, *J* = 9.6, 6.0 Hz, 1 H), 2.46 (s, 3 H), 2.71 (d, *J* = 9.2 Hz, 1 H), 2.77 (br s, 1 H), 2.78–2.90 (m, 2 H), 3.38 (m, 1 H), 3.79 (s, 3 H), 6.68 (dd, *J* = 8.2, 2.7 Hz, 1 H), 6.78 (d, *J* = 2.7 Hz, 1 H), 7.02 (d, *J* = 8.2 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.32, 34.90, 41.23, 41.62, 43.18, 55.35, 61.31, 70.82, 109.15, 111.23, 125.52, 130.23, 147.80, 157.93.

Aphanorphine (1)

To a solution of compound **15** (50 mg, 0.23 mmol) in CH_2Cl_2 (2 mL) at –20 °C (dry ice-MeCN cold bath), was added BBr_3 (1.0 M CH_2Cl_2 solution, 0.55 mL, 0.55 mmol). After stirring for 2 h at –20 °C, the mixture was allowed to warm up slowly to 0 °C and stirred for another 2 h at the same temperature. MeOH (2.0 mL) was added dropwise and the resulting light brown solution was stirred at 0 °C for 30 min before Et_3N (5.0 mL) was added. After stirring for another 30 min, the solvent was removed under reduced pressure. The crude product was purified by flash chromatography to afford **1**; yield: 41 mg (88%); $[\alpha]_D^{25}$ –20.2 (*c* = 0.15, MeOH).

^{1}H NMR (300 MHz, CD_3OD): δ = 1.43 (s, 3 H), 1.86 (d, *J* = 10.8 Hz, 1 H), 2.02 (dd, *J* = 11.0, 5.8 Hz, 1 H), 2.48 (s, 3 H), 2.73 (d, *J* = 9.2 Hz, 1 H), 2.83 (d, *J* = 16.6 Hz, 1 H), 2.87 (d, *J* = 9.2 Hz, 1 H), 3.03 (d, *J* = 16.6 Hz, 1 H), 3.43 (q, *J* = 2.8 Hz, 1 H), 6.52 (d, *J* = 2.3 Hz, 1 H), 6.65 (d, *J* = 2.3 Hz, 1 H), 6.91 (dd, *J* = 8.2, 2.2 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.61, 36.53, 42.10, 42.74, 44.22, 63.55, 72.61, 110.92, 114.58, 125.26, 131.23, 148.57, 156.55.

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