Asymmetric Synthesis of the Key Intermediates Leading to (−)-Aphanorphine and (−)-Eptazocine

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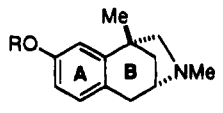
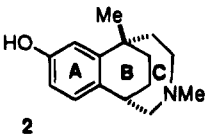
The asymmetric syntheses of two key intermediates, **8** and **15**, in >99% ee are reported. These compounds are prepared by diastereofacial addition of lithiodimethylphenylsilane to chiral naphthyloxazolines followed by methyl iodide trapping. The two stereocenters are formed in greater than 95% ds, and the silyl center is subsequently removed to give the 1,1-disubstituted tetralins **8**, **9**, or **12**. These chiral substances are readily transformed into the titled compounds as described in the literature. The absolute configuration of these intermediates has been confirmed by X-ray analysis and corrects an earlier misassignment.

Introduction

The recent reports on the enantioselective routes to the blue-green algae narcotic (−)-aphanorphine (**1**) or its methyl ether (**1a**) involved a variety of quaternary carbon routes followed by stepwise cyclizations of both B and C rings.[1] Furthermore the elegant asymmetric route to the analgesic (−)-eptazocine (**2**), recently reported by Shibasaki,[2] also required, via a Heck process, the sequential cyclization of the B and C rings. We wish to describe, in this full account, a relatively short route to a single intermediate leading to both systems (**1**, **2**) and formed in >98% ee.



1 R = H
1a R = Me



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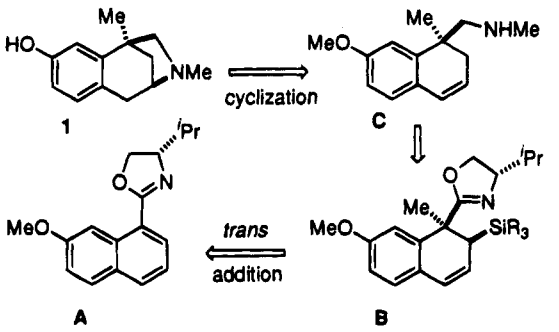
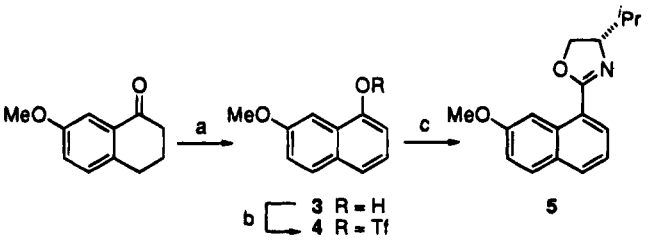
The present route is based on our earlier report[3] of an asymmetric tandem addition to chiral naphthalenes (A) using lithiosilanes as a surrogate "LiH" followed by trapping with various electrophiles to produce an adduct (B) containing two stereocenters (Scheme 1). The remainder of our approach would require transformation of the oxazoline moeity to the requisite amine (C) and then follow the earlier two-step procedure[1] leading to aphanorphine **1**. We have successfully implemented this scheme and found that the chiral nonracemic intermediate B can be readily transformed into another chiral intermediate necessary to reach (−)-eptazocine (**2**). Furthermore we have been able to independently establish the absolute configuration of these substances and in one case observed a discrepency in the previous literature which has now been corrected (vide infra).

Scheme 1



Scheme 2



[a] Reagents: (a) i. Br_2, Et_2O, HCl (catalytic); ii. LiBr, Li_2CO_3, DMF, reflux (91%); (b) Tf_2O, py (93%); (c) i. $Pd(OAc)_2$ (catalytic), $Ph_2P(CH_2)_3PPh_2$ (catalytic), CO, (*S*)-valinol, DMSO; ii. $SOCl_2$; NaOH (74%).

Results and Discussion

The requisite chiral 1,7-disubstituted naphthalene **5** was prepared from commercially available 7-methoxy-1-tetralone by a bromination–dehydrobromination sequence to give naphthol **3** (Scheme 2).[4] This mode of oxidation was found to be preferable to a sulfinylation–dehydrosulfinylation[5] procedure when multigram quantities of the desired naphthol were required. Triflate formation, according to Stang,[6] was found to proceed in high yield to give **4** (93% after chromatography). Formation of the oxazoline **5** was achieved using a procedure

[⊗] Abstract published in *Advance ACS Abstracts,* February 15, 1995.

(1) (a) Gulavita, N.; Hori, A.; Shimizu, Y.; Laszlo, P.; Clardy, J. *Tetrahedron Lett.* **1988**, *29*, 4381. (b) Takano, S.; Inomata, K.; Sato, T.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1591. (c) Takano, S.; Inomata, K.; Sato, T.; Takahashi, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1990**, 290. (d) Dehghani, A.; Bai, X.; Mascarella, S. W.; Bowen, W. D.; Carroll, F. I. *Tetrahedron Lett.* **1994**, *35*, 8969 and earlier references cited. (e) Meyers, A. I.; Dickman, D. A.; Bailey, T. R. *J. Am. Chem. Soc.* **1985**, *107*, 7974. (f) Meyers, A. I.; Bailey, T. R. *J. Org. Chem.* **1986**, *51*, 872.

(2) (a) Takemoto, T.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1993**, *115*, 8477 and references cited therein (b) Kondo, K.; Sodeoka, M.; Mori, M.; Shibasaki, M. *Synthesis* **1993**, 920. (c) Meyers, A. I.; Santiago, B.; Schmidt, W.; *Heterocycles*, in press.

(3) Hulme, A. N.; Meyers, A. I.; *J. Org. Chem.* **1994**, *59*, 952.

(4) Kasturi, T. R.; Arunachalam, T. *Can. J. Chem.* **1968**, *46*, 3625.

(5) Trost, B. M.; Parquette, J. R. *J. Org. Chem.* **1993**, *58*, 1579.

(6) Stang, P. J.; Treptow, W. *Synthesis* **1980**, 283.

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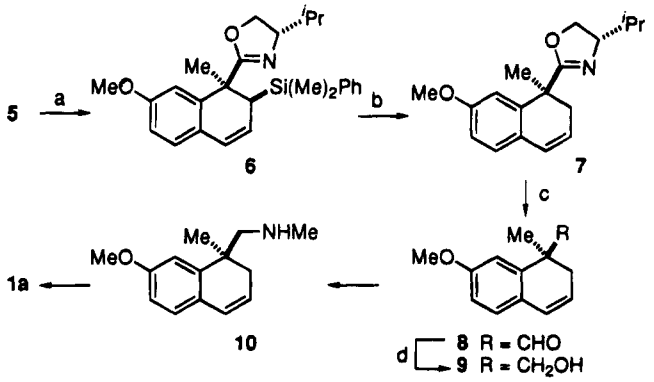
Scheme 3



[a] Reagents: (a) i. $Ph(Me)_2SiLi$, Et_2O:THF (3:1), −78 °C; ii. MeI, −20 °C (79%); (b) i. TBAF, THF (aqueous); ii. $Rh(PPh_3)_3Cl$ (catalytic), toluene, Et_3N, reflux (67%); (c) i. MeOTf, CH_2Cl_2; ii. $NaBH_4$; iii. H^+ (89%); (d) DIBAL-H, Et_2O, −78 °C (84%).

reported earlier from our laboratory.[7] Thus, a DMSO solution of the triflate **4** was treated with CO and valinol, in the presence of the Pd^0 catalyst generated from palladium(II) acetate and 1,3-bis(diphenylphosphino)-propane. The resulting hydroxy amide was immediately converted to the oxazoline **5** by treatment with thionyl chloride followed by basic workup. This allowed an efficient synthesis of the chiral nonracemic naphthyloxazoline **5** in 63% overall yield from the starting tetralone.

With naphthyloxazoline **5** in hand, the asymmetric tandem addition reaction of lithiodimethylphenylsilane ($Ph(Me)_2SiLi$)[8] followed by electrophilic quench with iodomethane was investigated (Scheme 3). Using the previously reported conditions[3] for lithiosilane additions (Et_2O:THF (3:1), −78 °C, 9 h; MeI, −20 °C,14 h) the reaction proceeded with a high degree of diastereoselectivity (dr > 20:1) as assessed by ^1H NMR analysis of the crude mixture. The trans addition product **6** was isolated (81%) as the major diastereomer and could easily be purified in good yield (79% after chromatography). Precedent for the addition reactions of nucleophilic species to naphthyloxazoline systems would suggest that attack of the lithiosilane should occur from the β-face, i.e. away from the bulky directing ^{i}Pr group. The minor diastereomer was also isolated and characterized. Previous studies from our laboratory suggest that this is also a trans addition product, resulting from the opposite facial addition in the initial entry by the lithiosilane.[9] The use of ether in the solvent has been found to be critical to the generation of high diastereofacial selectivity. Its reduced solvent polarity is thought to allow increased complexation of the lithiosilane reagent to the chiral oxazoline, providing some rigidity and order to the transition state.[3]

Protodesilylation of **6** with tetrabutylammonium fluoride gave rise to a mixture of Δ^2:Δ^3 isomers of **7** which were isomerised to the Δ^3 isomer **7** (>98:2), using Wilkinson's catalyst ($Rh(PPH_3)_3Cl$) in refluxing toluene. The yield of **7** was 67% after the two steps. When the reaction was run under similar conditions in refluxing benzene, little or no isomerization was observed. The rate of the reaction was found to increase in the presence of an equivalent of a basic additive such as triethylamine or calcium carbonate (isomerization was complete in 24−30 h and 72−80 h in the absence of an additive).[10] The increase in Δ^3 isomer observed in the protodesilylation of **6** (Δ^2:Δ^3 = 80:20) as opposed to ≥90:10 previously seen in simple naphthalene systems[3] was attributed to the presence of the *p*-methoxy group. Clearly there is a delicate interplay between the steric effects of quenching the intermediate anion at a neopentyl center and the electronic density associated with the neighboring aromatic ring.

Hydrolysis of the oxazoline, using procedures described earlier,[11] gave the unsaturated aldehyde **8** (Scheme 3) in 73% yield. The latter, prepared from another synthetic route, has already been shown to be an intermediate in the synthesis of *O*-methylaphanorphine (**1a**), recently reported by this laboratory.[2c] The aldehyde **8** was earlier transformed into the aminotetralin **10** by reductive amination in 70−72% yield and cyclized to **1a** by one of two routes; either (a) iodine-induced activation of the double bond followed by selective removal of the iodine or (b) aminomercuration with $Hg(TFA)_2$ and subsequent reduction with sodium borohydride.[2c] Treatment of **1a** with boron tribromide[1a] has been shown to produce natural (−)-aphanorphine **1**.

In order to establish that we were correct in assuming that the stereochemical course of the addition to the naphthalene **5** was taking place as expected, the aldehyde **8** was reduced to alcohol **9** (DIBAL-H, −78 °C, 20 min). This alcohol was reported to be a key intermediate in the Takano synthesis of (−)-aphanorphine[1c] and used by Shibasaki to correlate the absolute configuration in his synthesis of (−)-eptazocine.[2a] In our hands this alcohol was found to have a rotation of $[\alpha]_D$ −27.4 (*c* 2.1, $CHCl_3$). However, the sign for the specific rotation was reported to be *R*-(−).[2a] If our mechanistic scheme for addition to naphthyloxazolines, after numerous examples and X-ray verification,[11] was correct, then we should have obtained the *S*-configuration for **7**, **8**, and **9**. On the other hand, we may be observing, for the first time, an alternative mechanistic pathway (tandem *cis* addition) involving lithiosilanes.[9] In order to clarify this discrepancy we were able to obtain good crystalline material from the saturated oxazoline derivative **11** (Scheme 4). With the *S*-stereochemistry at the 4-position of the oxazoline (derived from (*S*)-valinol) on sound footing, it should be a routine task to assess the stereochemistry at the

(7) Meyers, A. I.; Robichaud, A. J.; McKennon, M. J. *Tetrahedron Lett.* **1992**, *33*, 1181.

(8) Fleming, I.; Newton, T. W.; Roessier, F. *J. Chem. Soc., Perkin Trans. I* **1981**, 2527.

(9) Reductive hydrolytic cleavage of the chiral oxazoline from each of the isolated diastereomers results in the formation of both enantiomeric aldehydes. Confirmation of the trans relationship of the addition reaction products in **6** was based on earlier results whereby both diastereomers of **6** were hydrolyzed to the aldehydes, which turned out to be enantiomers. From earlier work (ref 11) on X-ray analysis, the trans relationships were established for these tandem additions. For further evidence in this regard, see also: Meyers, A. I.; Barner, B. A. *J. Am. Chem. Soc.* **1984**, *106*, 1865.

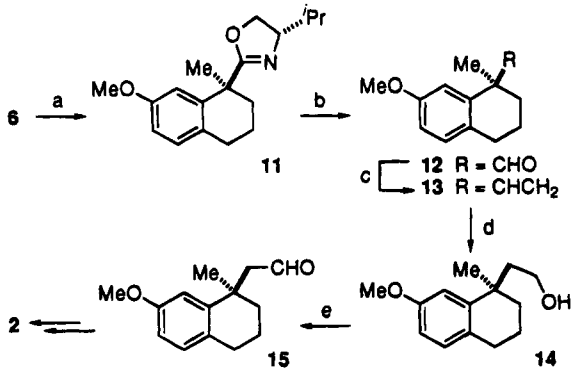
(10) Similar results were observed in the ruthenium-catalyzed hydrogenation of steroids, see: Nishimura, S.; Ichino, T.; Akimoto, A.; Tsuneda, K. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 279.

(11) Meyers, A. I.; Roth, G. P.; Hoyer, D.; Barner, B. A.; Laucher, D. *J. Am. Chem. Soc.* **1988**, *110*, 4611.

(12) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

(13) Professor Shibasaki has recently informed us that the error in the absolute configuration as reported in their paper (ref 2a above) has been independently discovered and verified by an X-ray study in their laboratory. Thus, there is now agreement that the alcohol **9** should be *S*-(−) and not *R*-(−) as reported earlier. A correction to the error in reference 2a above has been submitted to *J. Am. Chem. Soc.* by Professor Shibasaki (private communication).

Scheme 4



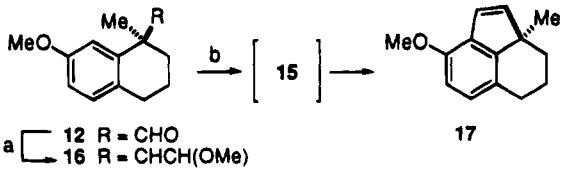
[a] Reagents: (a) i. TBAF, THF (aqueous); ii. Pd/C, H_2, EtOH (86%); (b) i. MeOTf, CH_2Cl_2; ii. $NaBH_4$; iii. H^+ (84%); (c) PPh_3CH_3Br, KHMDS, THF (97%); (d) $Rh(PPh_3)_3Cl$ (catalytic), catecholborane, THF; NaOH, H_2O_2 (89%); (e) Swern (85%).

quaternary benzylic positions of **7**, **8**, and **9**. This was, indeed, accomplished and the X-ray crystal structure confirmed that the stereochemistry in **7** (and therefore **8** and **9**) was *S*-(−) and consistent with all the previous stereochemical results involving the chiral naphthalenes **5** (derived from (*S*)-valinol).[1] The route to (−)-eptazocine was undertaken utilizing the the key silylsubstituted intermediate **6**, previously employed to reach aphanorphine. Nucleophilic desilylation with tetrabutylammonium fluoride (as above) was followed by reduction of the double bond (Pd/C, H_2, EtOH, 17 h) to afford the corresponding tetralin derivative **11** (Scheme 4) in excellent yield (86%). Transformation of the oxazoline to the aldehyde **12** under reductive hydrolytic conditions was also found to proceed in high yield (84%). At this juncture a one-carbon homologation of this aldehyde was required in order to complete the synthesis of **15**, the key intermediate in the Shibasaki synthesis of (−)-eptazocine.[2a] This was achieved via a three-step procedure (Wittig reaction,[14] hydroboration, and Swern oxidation). A number of alternatives to the Wittig reaction were also investigated, including both Tebbe methylenation[15] and reaction of the aldehyde with dimethyltitanocence.[16] However, the Wittig reaction to extend the aldehyde by one carbon was found to give the most consistently high yields of the desired olefin **13** (85−99%).

A rhodium-catalyzed hydroboration by catecholborane[17] was found to be the most efficient means of effecting the transformation to the alcohol **14** (89%), and oxidation to the aldehyde **15** was readily achieved using Swern conditions[18] (85%). Spectroscopic data for aldehyde **15** were found to be in complete agreement with Shibasaki's published data,[2a] including the sign and magnitude of rotation $[\alpha]_D$ +57.5 (*c* 2.6, $CHCl_3$). lit.[2a] $[\alpha]_D$ +56.4 (*c* 1.16, $CHCl_3$).

A more concise approach to the synthesis of aldehyde **15** was also investigated, as shown in Scheme 5. However, after acid hydrolysis of the intermediate enol ether **16**, the only identifiable product to be isolated, albeit in moderate yield (30%), was tricycle **17**. Further investigation of this route was not pursued.

Scheme 5



[a] Reagents: (a) $PPh_3CH_2(OMe)Cl$, KHMDS, THF (75%); (b) *p*-TSA, dioxane:H_2O (1:1) (30%).

In summary, a method for the synthesis of chiral benzylic quaternary centers has been developed in which a silyl group serves as a "surrogate proton" and gives products equivalent to the addition of lithium hydride to a chiral naphthyloxazoline. The synthesis of chiral nonracemic aldehydes **8** and **15**, key intermediates in the syntheses of (−)-aphanorphine and (−)-eptazocine, respectively, has demonstrated the utility of this methodology. These syntheses are attractive due to both their brevity and the high degree of diastereoselectivity that has been achieved in the addition of $Ph(Me)_2SiLi$ to the chiral naphthyloxazoline.

Experimental Section

7-Methoxy-1-naphthol (3). (a) 7-Methoxy-2-bromo-1-tetralone. To a stirred solution of 7-methoxy-1-tetralone (7.0 g, 40 mmol) and HCl (2.0 mL; 1.0 M in ether) in ether (200 mL) at 0 °C was added dropwise a solution of Br_2 (6.4 g, 40 mmol) in $CHCl_3$ (20 mL). [Each drop was added only after the previous drop had completely decolorized.] The reaction mixture was stirred at 0 °C for a further 15 min; then the reaction was quenched with water (150 mL) and the solution was diluted with ether (50 mL). The organic layer was washed with water (150 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give crude 7-methoxy-2-bromo-1-tetralone as a white solid (10.1 g, 99%). A small sample (~30 mg) was recrystallized from hexane/EtOAc for analysis: mp 81 °C; R_f (30% EtOAc in hexane) = 0.47; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 (1H, d, J = 2.8 Hz), 7.17 (1H, d, J = 8.5 Hz), 7.09 (1H, dd, J = 8.5, 2.8 Hz), 4.70 (1H, t, J = 4.2 Hz), 3.81 (3H, s), 3.21 (1H, dddd, J = 16.9, 15.0, 9.4, 5.3 Hz), 2.83 (1H, dt, J = 16.9, 4.4 Hz), 2.55−2.37 (2H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 190.5, 158.5, 135.6, 130.6, 130.0, 122.7, 110.1, 55.4, 50.3, 32.0, 25.2; MS (EI) *m/z* (rel intensity) 256.0 ($[M]^+$, 36), 254.0 ($[M]^+$, 36), 174.1 (50), 148.0 (39), 120.1 (100).

(**b**) To a solution of the α-bromotetralone (10.1 g, 40 mmol) in DMF (200 mL) were added LiBr (8.0 g, 92 mmol) and lithium carbonate (6.0 g, 81 mmol). The reaction mixture was stirred at reflux for 3.5 h and then allowed to cool to rt. The solvent was removed *in vacuo* (short path distillation apparatus, water bath 50 °C) until ~50 mL of DMF remained. This mixture was treated with ice-cold water (200 mL) and extracted with ether (3 × 100 mL). The combined extracts were washed with HCl (150 mL; 1 N aqueous), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash chromatography (20 → 35% EtOAc in hexane) to give naphthol **3** as a creamy-white solid (6.3 g, 91%): mp 102 °C; R_f (30% EtOAc in hexane) = 0.45; IR (thin film, mineral oil) 3500−2700 (br, O−H), 1600, 1586, 1518 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (1H, d, J = 8.9 Hz), 7.47 (1H, d, J = 1.9 Hz), 7.38 (1H, d, J = 8.1 Hz), 7.19−7.14 (2H, m), 6.79 (1H, d, J = 7.4 Hz), 5.37 (1H, br s), 3.94 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 157.2, 150.4, 130.3, 129.3, 125.2, 123.4, 120.5, 119.2, 109.1, 99.9, 55.4; MS (EI) *m/z* (rel intensity) 174.1 ($[M]^+$, 100), 159.0 (24), 145.1 (7), 131.1 (81), 103.0 (25).

7-Methoxy-1-naphthol Triflate (4). To a stirred solution of naphthol **3** (3.00 g, 17.2 mmol) in pyridine (30 mL) at 0 °C was added trifluoromethanesulfonic anhydride (3.19 mL, 19.0 mmol). The reaction mixture was stirred at 0 °C for 5 min and then stirred at 20 °C for 12 h. The reaction mixture was poured into water (40 mL) and extracted with ether (3 × 45

(14) Review: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.
(15) Pine, S. H.; Shen, G. S.; Hoang, H. *Synthesis* **1991**, 165 and references cited therein.
(16) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.
(17) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 6917.
(18) Omura, K.; Swern D. *Tetrahedron* **1978**, *34*, 1651.

mL). The combined extracts were washed with 30 mL each of water, HCl (1 N aqueous) twice, water, and then brine. The combined extracts were dried ($MgSO_4$), filtered through a short bed of silica, and concentrated *in vacuo*. The crude material was purified by flash chromatography (25% EtOAc in hexane) to give triflate **4** as a colorless oil (4.90 g, 93%): R_f (25% EtOAc in hexane) = 0.60; IR (thin film) 1637, 1609, 1510 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (1H, d, J = 8.9 Hz), 7.77 (1H, d, J = 7.8 Hz), 7.42 (1H, d, J = 7.8 Hz), 7.34–7.29 (2H, m), 7.23 (1H, dd, J = 8.9, 2.3 Hz), 3.94 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.1, 144.9, 130.5, 129.7, 128.1, 127.6, 122.7, 120.5, 118.4, 98.6, 55.4; MS (EI) *m/z* (rel intensity) 306.1 ([M]$^+$, 34), 173.1 (100), 145.1 (25), 102.1 (15).

Naphthyloxazoline 5. To a stirred solution of triflate **4** (4.10 g, 13.4 mmol) and 1,3-bis(diphenylphosphino)propane (276 mg, 0.67 mmol) in DMSO (80 mL) was added triethylamine (4.11 mL, 29.5 mmol) followed by (*S*)-valinol (2.99 mL, 26.8 mmol). Palladium(II) acetate (150 mg, 0.67 mmol) was added and the flask immediately flushed with carbon monoxide (double balloon). The flask was immersed in an oil bath (preheated to 70 °C), and the reaction mixture was stirred for 18 h. The reaction mixture was allowed to cool to rt and then diluted with EtOAc (80 mL) and washed with water (80 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organics were washed with HCl (20 mL; 1 N aqueous) and brine (20 mL). The aqueous washings were back-extracted with EtOAc (3 × 20 mL), and then the combined organics were dried ($MgSO_4$), filtered through a short pad of silica gel, and concentrated *in vacuo* to give the crude amide as a cream-colored solid (3.47 g, 90%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (1H, d, J = 8.1 Hz), 7.72 (1H, d, J = 9.0 Hz), 7.66 (1H, d, J = 2.4 Hz), 7.54 (1H, dd, J = 7.1, 1.2 Hz), 7.25 (1H, dd, J = 8.1, 7.1 Hz), 7.15 (1H, dd, J = 9.0, 2.5 Hz), 6.23 (1H, br s, J = 7.9 Hz), 4.07–4.03 (1H, m), 3.90–3.70 (2H, m), 3.87 (3H, s), 2.75 (1H, b s), 2.00–1.93 (1H, m), 1.03 (3H, d, J = 6.8 Hz), 1.01 (3H, d, J = 6.8 Hz).

Thionyl chloride (2.64 mL, 36.2 mmol) was added to a solution of the above amide (3.47 g, 12.1 mmol) in CH_2Cl_2 (40 mL). The reaction mixture was stirred at rt for 25 min and then cooled to 0 °C, and the reaction was quenched with water (30 mL) and then NaOH (30 mL; 4 N aqueous). The reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL), dried ($MgSO_4$), filtered through a short pad of silica gel, and concentrated *in vacuo*. The crude mixture was dissolved in an acetonitrile:water mixture (70 mL:30 mL), and anhydrous K_2CO_3 was added (10 g). The mixture was heated at reflux for 17 h and then allowed to cool to 20 °C. The reaction mixture was diluted with water (20 mL) and the aqueous layer separated and then extracted with CH_2Cl_2 (3 × 30 mL). The combined organics were concentrated *in vacuo*, and the crude mixture was purified by flash chromatography (20% EtOAc in hexane) to give naphthyloxazoline **5** as a colorless oil (2.68 g, 74% from triflate): R_f (20% EtOAc in hexane) = 0.40; $[\alpha]^{20}_D$ −89.8 (*c* 2.6, $CHCl_3$); IR (thin film) 1642 (s), 1591, 1511 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.87 (1H, d, J = 2.6 Hz), 8.07 (1H, dd, J = 7.4, 1.3 Hz), 7.86 (1H, d, J = 8.0 Hz), 7.74 (1H, d, J = 9.0 Hz), 7.33 (1H, dd, J = 8.0, 7.4 Hz), 7.18 (1H, dd, J = 9.0, 2.6 Hz), 4.43 (1H, dd, J = 9.5, 7.9 Hz), 4.27–4.20 (1H, m), 4.10 (1H, t, J = 7.9 Hz), 3.95 (3H, s), 1.95–1.83 (1H, m), 1.12 (3H, d, J = 6.7 Hz), 1.03 (3H, d, J = 6.7 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 163.1, 158.9, 132.7, 131.5, 129.8, 129.4, 129.3, 122.9, 122.3, 118.8, 105.1, 73.7, 69.2, 55.2, 33.3, 18.9, 18.8; MS (EI) *m/z* (rel intensity) 269.3 ([M]$^+$, 30), 226.2 (100), 183.1 (10), 171.1 (27), 140.2 (7). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11. Found: C, 75.91; H, 7.08.

Asymmetric Addition to Naphthyloxazoline: Formation of 6. To a cold (−78 °C) stirred solution of naphthyloxazoline **5** (900 mg, 3.34 mmol) in ether (30 mL) was added a cold (−78 °C) solution of $Ph(Me)_2SiLi$[8] (5.01 mmol in 10 mL THF) *via* cannula. The reaction mixture turned blood red as the silyllithium reagent was added. The reaction mixture was stirred at −78 °C for 10.5 h; then the reaction was quenched with iodomethane (2.08 mL, 33.4 mmol). The reaction mixture was allowed to warm to −20 °C overnight (10.5 h). The reaction was quenched with NH_4Cl solution (50 mL; saturated) and the solution was extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Analysis of the crude ^1H NMR spectra allowed assessment of the diastereomeric ratio as >95:5. The products were separated by flash column chromatography (10 → 20% EtOAc in hexane) to give addition product **6** as a viscous colorless oil (1.112 g, 79%).

Major diastereomer: R_f (20% EtOAc in hexane) = 0.36; $[\alpha]^{20}_D$ +282 (*c* 2.5, $CHCl_3$); IR (solution cell, $CHCl_3$) 1656 (s, C=N), 1606, 1566, 1503, 1248 cm^{-1} (s, Si–Me); ^1H NMR (300 MHz, $CDCl_3$) δ 7.46–7.43 (2H, m), 7.33–7.30 (3H, m), 6.94 (1H, d, J = 8.3 Hz), 6.67 (1H, dd, J = 8.3, 2.5 Hz), 6.46 (1H, d, J = 2.5 Hz), 6.37 (1H, d, J = 9.7 Hz), 5.79 (1H, dd, J = 9.7, 6.4 Hz), 3.72 (3H, s), 3.55 (1H, t, J = 8.5 Hz), 3.24 (1H, ddd, J = 10.0, 8.6, 6.0 Hz), 2.92 (1H, dd, J = 10.0, 8.4 Hz), 2.43 (1H, dd, J = 6.4, 0.7 Hz), 1.76–1.65 (1H, m), 1.61 (3H, s), 0.90 (3H, d, J = 6.8 Hz), 0.85 (3H, d, J = 6.8 Hz), 0.09 (3H, s), 0.05 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.0, 158.5, 140.1, 140.0, 132.6, 128.2, 127.6, 127.0, 126.4, 125.9, 123.4, 112.5, 111.1, 71.5, 68.7, 55.0, 44.1, 36.3, 32.2, 28.8, 18.7, 17.9, −0.6, −5.9; MS (EI) *m/z* (rel intensity) 404.3 ([M]$^+$, 60), 284.1 (7), 246.2 (67), 172.0 (69), 135.1 (100), 107.0 (19). Anal. Calcd for $C_{26}H_{33}NOSi$: C, 74.41; H, 7.93. Found: C, 74.21; H, 8.01.

Minor diastereomer: R_f (20% EtOAc in hexane) = 0.41; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44–7.41 (2H, m), 7.31–7.24 (4H, m), 6.92 (1H, d, J = 8.3 Hz), 6.67 (1H, dd, J = 8.3, 2.6 Hz), 6.35 (1H, d, J = 9.6 Hz), 5.75 (1H, dd, J = 9.6, 6.6 Hz), 3.76 (3H, s), 3.48–3.39 (2H, m), 3.33–3.26 (1H, m), 2.42 (1H, d, J = 6.6 Hz), 1.50 (3H, s), 1.43–1.36 (1H, m), 0.91 (3H, d, J = 6.7 Hz), 0.72 (3H, d, J = 6.7 Hz), 0.05 (3H, s), −0.02 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.0, 158.5, 140.5, 140.0, 133.5, 128.3, 127.4, 127.0, 126.6, 126.3, 123.7, 113.0, 111.2, 72.2, 68.6, 55.1, 43.5, 36.4, 32.7, 28.1, 19.2, 18.3, −1.5, −5.2.

(*S*)-1-Methyl-1-((*S*)-2-oxazolinyl)-7-methoxy1,2-dihydronaphthalene (7). To a stirred solution of addition product **6** (1.11 mg, 2.65 mmol) in THF (25 mL) was added TBAF (2.65 mL, 2.65 mmol; 1.0 M in THF), and the reaction mixture was stirred at rt for 25 min. The reaction was quenched with a $NaHCO_3$ solution (50 mL; saturated), and the solution was diluted with hexane (50 mL). The organic layer was shaken vigorously with HCl (50 mL; 2 N aqueous) to allow oxazoline salt formation, and the aqueous layer was further washed with hexane (2 × 50 mL) to remove the silyl alcohol. The aqueous layer was cooled to 0 °C (ice bath) and then basified using NaOH (60 mL; 2 N aqueous). The aqueous layer was extracted with EtOAc (3 × 50 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give a white solid (725 mg). Analysis of the ^1H NMR spectrum of the crude product allowed the assessment of the ratio of double bond isomers (Δ^2:Δ^3 = 80:20).

Δ^2: R_f (20% EtOAc in hexane) = 0.30; ^1H NMR (300 MHz, $CDCl_3$) δ 7.05 (1H, d, J = 8.4 Hz), 6.88 (1H, d, J = 2.6 Hz), 6.76 (1H, dd, J = 8.4, 2.6 Hz), 6.01 (1H, dt, J = 10.1, 3.5 Hz), 5.72 (1H, dt, J = 10.1, 2.0 Hz), 4.16 (1H, t, J = 8.2 Hz), 3.98–3.85 (2H, m), 3.74 (3H, s), 3.44–3.29 (2H, m), 1.88–1.77 (1H, m), 1.61 (3H, s), 0.97 (3H, d, J = 6.8 Hz), 0.88 (3H, d, J = 6.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.6, 158.0, 138.8, 130.0, 129.5, 125.1, 124.5, 113.4, 111.1, 71.7, 70.1, 55.1, 41.5, 32.3, 28.9, 28.7, 19.0, 17.8.

A stirred solution of the above unsaturated oxazoline mixture (725 mg), triethylamine (0.37 mL, 2.65 mmol), and Wilkinson's catalyst (368 mg, 0.40 mmol) in toluene (25 mL) was heated to reflux (sand bath, 120 °C) for 21.5 h. The reaction mixture was allowed to cool to rt, reduced to ~5 mL *in vacuo*, and then applied directly to the top of a column of silica gel (10 → 15% EtOAc in hexane). The Δ^3 isomer **7** was isolated as a colorless oil (509 mg, 67% from addition product **6**). The ratio of double-bond isomers (Δ^3:Δ^2) was assessed as >98:2 from the ^1H NMR spectrum.

Δ^3: R_f (20% EtOAc in hexane) = 0.25; $[\alpha]^{20}_D$ −5.9 (*c* 2.2, $CHCl_3$); IR (thin film) 1657 (s, C=N), 1607, 1568, 1502 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.97 (1H, d, J = 8.2 Hz), 6.74–6.68 (2H, m), 6.39 (1H, br d, J = 9.7 Hz), 5.72 (1H, ddd, J = 9.2, 5.2, 3.5 Hz), 4.25–4.17 (1H, m), 4.00–3.92 (2H, m), 3.75 (3H, s), 2.95 (1H, dt, J = 17.1, 2.9 Hz), 2.22 (1H, ddd, J = 17.1, 5.2, 1.0 Hz), 1.91–1.80 (1H, m), 1.48 (3H, s), 0.98 (3H, d, J = 6.8 Hz), 0.91 (3H, d, J = 6.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.0, 158.9, 140.0, 127.7, 126.4, 125.9, 123.1, 112.0,

111.6, 71.9, 69.8, 55.1, 41.0, 34.7, 32.4, 25.2, 19.0, 17.8; HRMS (EI) [M$^+$] 285.1727 $C_{18}H_{23}NO_2$ requires 285.1729; MS (EI) *m/z* (rel intensity) 285.2 ([M]$^+$, 10), 270.2 (46), 254.2 (15), 172.1 (100), 158.1 (22), 129.1 (40).

(*S*)-1-Formyl-1-methyl-7-methoxy-1,2-dihydronaphthalene (8). To a solution of the oxazoline **7** (304 mg, 1.07 mmol) in CH_2Cl_2 (10 mL) was added methyl triflate (241 μL, 2.13 mmol). The reaction mixture was stirred at 20 °C for 7.5 h, and then cooled to 0 °C (ice bath), and THF (8 mL) and then MeOH (2 mL) were added, followed immediately by $NaBH_4$ (202.4 mg, 5.35 mmol). The reaction mixture was stirred at 20 °C for 18 h; the reaction was then quenched with NH_4Cl solution (30 mL; saturated) and the solution extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The intermediate oxazolidine was purified by flash chromatography (10% EtOAc in hexane; short column) to remove trace impurities. The oxazolidine was dissolved in THF (10 mL), and HCl (4 mL; 2 M aqueous) was added. The reaction mixture was stirred at 20 °C for 28.5 h; then the reaction was quenched with $NaHCO_3$ solution (30 mL; saturated) and the solution extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4), filtered through a short pad of silica gel, and concentrated *in vacuo* to give aldehyde **8** as a pale yellow oil (193.2 mg, 89%) which required no further purification. R_f (20% EtOAc in hexane) = 0.48; $[\alpha]^{20}_D$ +1.5 (*c* 1.9, $CHCl_3$); IR (thin film) 1725 (s, C=O), 1606, 1568, 1496 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.51 (1H, s), 7.04 (1H, d, *J* = 8.3 Hz), 6.76 (1H, dd, *J* = 8.3, 2.6 Hz), 6.70 (1H, d, *J* = 2.6 Hz), 6.38 (1H, br d, *J* = 9.6 Hz), 5.85−5.79 (1H, m), 3.79 (3H, s), 2.69 (1H, ddd, *J* = 17.2, 4.8, 1.5 Hz), 2.23 (1H, ddd, *J* = 17.2, 3.7, 2.3 Hz), 1.34 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.7, 159.3, 135.9, 128.1, 127.0, 123.0, 112.8, 112.0, 55.3, 49.8, 31.1, 20.0; MS (EI) *m/z* (rel intensity) 202.1 ([M]$^+$, 34), 173.1 (100), 158.1 (91), 141.1 (17), 128.1 (31), 115.1 (51).

(*S*)-1-(Hydroxymethyl)-1-methyl-7-methoxy-1,2-dihydronaphthalene (9). To a stirred solution of aldehyde **8** (56.0 mg, 0.28 mmol) in ether (3.0 mL) at −78 °C was added diisobutylaluminum hydride (0.39 mL, 0.42 mmol; 1.07 M in THF). The reaction mixture was stirred at −78 °C for 25 min; then the reaction was quenched with methanol (2.0 mL) and allowed to warm to 20 °C. The reaction mixture was partitioned between NH_4Cl solution (20 mL; saturated) and EtOAc (3 × 15 mL). The combined extracts were dried ($MgSO_4$), filtered through a short pad of silica gel, and concentrated *in vacuo* to give alcohol **9** as an oil which solidified on standing (47.3 mg, 84%). A sample of this material was purified by radial chromatography (10% EtOAc in hexane) for analysis: mp 47−48 °C; R_f (50% EtOAc in hexane) = 0.44; $[\alpha]^{20}_D$ −27.4 (*c* 2.1, $CHCl_3$); IR (thin film) 1606, 1566, 1489 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (1H, d, *J* = 8.3 Hz), 6.86 (1H, d, *J* = 2.5 Hz), 6.70 (1H, d, *J* = 8.3, 2.5 Hz), 6.36 (1H, br d, *J* = 9.7 Hz), 5.80−5.74 (1H, m), 3.79 (3H, s), 3.53 (2H, AB-q, *J* = 10.8 Hz), 2.69 (1H, br dd, *J* = 17.5, 5.2 Hz), 2.19 (1H, br dt, *J* = 17.5, 2.6 Hz), 1.39 (1H, br s), 1.28 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.0, 141.1, 127.8, 127.0, 126.8, 124.0, 112.2, 110.6, 68.7, 55.2, 39.0, 33.1, 23.0; MS (EI) *m/z* (rel intensity) 204.1 ([M]$^+$, 21), 173.1 (100), 158.2 (88), 128.1 (43), 115.1 (56%). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.43; H, 7.90. Found: C, 76.20; H, 7.89.

(*S*)-1-Methyl-1-[(*S*)-4-isopropyl-2-oxazolinyl]-7-methoxy-1,2,3,4-tetrahydronaphthalene ((*S,S*)-11): (−)-Eptazocine Precursor. To a stirred solution of addition product **6** (1.2 g, 2.8 mmol) in THF (10 mL) was added tetrabutylammonium fluoride (2.8 mL, 2.8 mmol; 1.0 M in THF), and the reaction mixture was stirred at 20 °C for 25 min. The reaction was quenched with NaOH (50 mL; 1 N aqueous), and the solution was extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give a colorless solid. The crude intermediate and palladium on charcoal (100 mg, catalytic) were dissolved in ethanol (25 mL). The reaction flask was flushed three times with hydrogen (double balloon) and then stirred at 20 °C for 16.5 h. The reaction mixture was filtered through a short pad of silica gel (EtOAc) and concentrated *in vacuo*. The reaction mixture was dissolved in hexane (25 mL) and was shaken vigorously with HCl (25 mL; 2 N aqueous) to allow oxazoline salt formation. The aqueous layer was further washed with hexane (2 × 25 mL) to remove the silyl alcohol. The aqueous layer was cooled to 0 °C (ice bath) and then treated with NaOH (30 mL; 2 N aqueous). The aqueous layer was extracted with EtOAc (3 × 25 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (20% EtOAc in hexane) gave oxazoline **11** as a colorless solid (692.6 mg, 86%): mp 86.5−87.5 °C; R_f (20% EtOAc in hexane) = 0.36; $[\alpha]^{20}_D$ −61.1 (*c* 2.0, $CHCl_3$); IR (thin film) 1655 (s, C=N), 1611, 1575, 1504 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (1H, d, *J* = 8.4 Hz), 6.75 (1H, d, *J* = 2.7 Hz), 6.69 (1H, dd, *J* = 8.4, 2.7 Hz), 4.20−4.10 (1H, m), 3.96−3.87 (2H, m), 3.72 (3H, s), 2.80−2.64 (2H, m), 2.28−2.19 (1H, m), 1.97−1.69 (4H, m), 1.57 (3H, s), 0.98 (3H, d, *J* = 6.8 Hz), 0.90 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.5, 157.6, 140.8, 130.2, 128.4, 112.9, 112.2, 71.6, 69.7, 55.1, 40.7, 35.2, 32.3, 29.1, 28.8, 19.6, 19.0, 17.8; MS (EI) *m/z* (rel intensity) 287.2 ([M]$^+$, 100), 244.2 (7), 173.0 (72), 159.1 (48), 114.2 (61%). Anal. Calcd for $C_{18}H_{25}O_2N$: C, 75.22; H, 9.79. Found: C, 75.20; H, 8.85.

(*S*)-1-Formyl-1-methyl-7-methoxy-1,2,3,4-tetrahydronaphthalene (12). To a solution of the oxazoline **11** (681.2 mg, 2.37 mmol) in CH_2Cl_2 (20 mL) was added methyl triflate (0.54 mL, 4.74 mmol). The reaction mixture was stirred at 20 °C for 7.5 h and then cooled to 0 °C (ice bath), and THF (16 mL) and then MeOH (4 mL) were added, followed immediately by sodium borohydride (448 mg, 11.9 mmol). The reaction mixture was stirred at 20 °C for 19 h; then the reaction was quenched with NH_4Cl solution (45 mL; saturated) and the solution extracted with EtOAc (3 × 45 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The oxazolidine was dissolved in THF (20 mL) and HCl (8 mL; 2 M aqueous) was added. The reaction mixture was stirred at 20 °C for 24 h; then the reaction was quenched with $NaHCO_3$ solution (45 mL; saturated) and the solution extracted with EtOAc (3 × 45 mL). The combined organic extracts were dried (Na_2SO_4), filtered through a short pad of silica gel, and concentrated *in vacuo*. Flash chromatography (20% EtOAc in hexane) gave aldehyde **12** as a colorless oil (407.6 mg, 84%): R_f (20% EtOAc in hexane) = 0.48; $[\alpha]^{20}_D$ −18.0 (*c* 2.3, $CHCl_3$); IR (thin film) 1722 (s, C=O), 1611, 1576, 1507 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.49 (1H, s), 7.05 (1H, d, *J* = 8.4 Hz), 6.75 (1H, dd, *J* = 8.4 & 2.7 Hz), 6.57 (1H, d, *J* = 2.7 Hz), 3.75 (3H, s), 2.80−2.64 (2H, m), 2.10−2.02 (1H, m), 1.88−1.77 (2H, m), 1.63−1.55 (1H, m), 1.39 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.6, 157.9, 136.8, 130.6, 129.7, 113.4, 113.1, 55.3, 50.6, 30.9, 29.0, 23.6, 19.2; MS (EI) *m/z* (rel intensity) 204.1 ([M]$^+$, 9), 175.2 (100), 145.1 (12), 128.1 (27), 115.1 (56), 91 (34).

(*S*)-1-Vinyl-1-methyl-7-methoxy-1,2,3,4-tetrahydronaphthalene (13). To a solution of methyltriphenylphosphonium bromide (1.64 g, 4.59 mmol; predried under vacuum) in THF (10 mL) was added potassium bis(trimethylsilyl)amide (5.54 mL, 3.67 mmol; 0.66 M in toluene). The reaction mixture was stirred at 20 °C for 1.5 h and cooled to −78 °C, and then a solution of aldehyde **12** (375 mg, 1.84 mmol) in THF (1 mL, +2 × 1 mL washings) was added via cannula. The reaction mixture was stirred at −78 °C for 1.25 h and then allowed to warm to 20 °C and stirred for a further 3 h. The reaction was quenched with NH_4Cl solution (20 mL; saturated), and the solution was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered through a short pad of silica gel, and concentrated *in vacuo*. Flash chromatography (hexane → 15% EtOAc in hexane) gave alkene **13** as a colorless oil (361.8 mg, 97%): R_f (20% EtOAc in hexane) = 0.64; $[\alpha]^{20}_D$ −21.1 (*c* 3.8, $CHCl_3$); IR (thin film) 1635 , 1610, 1573, 1502 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (1H, d, *J* = 8.4 Hz), 6.75 (1H, d, *J* = 2.7 Hz), 6.69 (1H, dd, *J* = 8.4, 2.7 Hz), 5.95 (1H, dd, *J* = 17.4, 10.6 Hz), 5.03 (1H, dd, *J* = 10.6, 1.4 Hz), 4.87 (1H, dd, *J* = 17.4, 1.4 Hz), 3.76 (3H, s), 2.73−2.69 (2H, m), 1.83−1.60 (4H, m), 1.38 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 157.5, 148.6, 143.5, 129.8, 128.8, 113.6, 111.9, 111.7, 55.2, 41.2, 37.5, 29.4, 28.1, 19.4; MS (EI) *m/z* (rel intensity) 202.1 ([M]$^+$, 100), 187.1 (91), 173.1 (85), 159.0 (74), 144.1 (32), 128.1 (33), 115.1 (41%). Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.96; H, 8.98.

(*S*)-1-(2-Hydroxymethyl)-1-methyl-7-methoxy-1,2,3,4-tetrahydronaphthalene (14). A solution of alkene **13** (328 mg, 1.62 mmol) and Wilkinson's catalyst (30.0 mg, 0.032 mmol) in THF (15 mL) was cooled to −40 °C, and catechol borane (4.86 mL, 4.86 mmol; 1.0 M solution in THF) was added dropwise. The reaction mixture was allowed to warm to 20 °C, stirred for 4 h; and then cooled to 0 °C. Sodium hydroxide (7.5 mL; 3 N aqueous) was carefully added followed by hydrogen peroxide (1.5 mL; 30% aqueous) and the reaction mixture stirred open to the atmosphere for a further 17.5 h. The reaction mixture was partitioned between NaOH (20 mL; 1 N aqueous) and EtOAc (3 × 25 mL). The combined organics were dried ($MgSO_4$), filtered through a short pad of silica gel, and concentrated *in vacuo*. Flash chromatography (25 → 50% EtOAc in hexane) gave alcohol **14** as a colorless oil (317.5 mg, 89%): R_f (50% EtOAc in hexane) = 0.38; $[\alpha]^{20}_D$ +36.2 (*c* 1.8, $CHCl_3$); IR (thin film) 3279 (br, OH), 1613 , 1537 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.95 (1H, d, J = 8.4 Hz), 6.82 (1H, d, J = 2.6 Hz), 6.65 (1H, dd, J = 8.4, 2.6 Hz), 3.76 (3H, s), 3.60−3.49 (2H, m), 2.67−2.64 (2H, m), 2.07−1.72 (4H, m), 1.60−1.54 (1H, m), 1.40 (1H, br s), 1.27 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 157.7, 145.2, 129.9, 128.9, 112.1, 111.1, 59.8, 55.2, 45.8, 36.1, 35.9, 30.8, 29.7, 19.6; MS (EI) *m/z* (rel intensity) 220.2 ($[M]^+$, 20), 175.2 (100), 159.0 (12), 134.1 (15), 115.1 (19).

(*S*)-1-(Formylmethyl)-1-methyl-7-methoxy-1,2,3,4-tetrahydronaphthalene (15). To a cooled (−78 °C) stirred solution of oxalyl chloride (87.9 μL, 1.00 mmol) in CH_2Cl_2 (3 mL) was added DMSO (142 μL, 2.00 mmol), and the reaction mixture was stirred for 1.25 h. A solution of alcohol **14** (111.0 mg, 0.50 mmol) in CH_2Cl_2 (1.0 mL) was added via cannula (2 × 1.0 mL washings), and the reaction mixture was stirred for 2.5 h. The reaction was quenched with triethylamine (418 μL, 3.00 mmol), and the mixture was allowed to warm to 20 °C and stirred for a further 2 h. The mixture was diluted with water (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (20% EtOAc in hexane) gave aldehyde **15** as a colorless oil (93.3 mg, 85%): R_f (50% EtOAc in hexane) = 0.58; $[\alpha]^{20}_D$ +57.5 (*c* 2.6, $CHCl_3$); IR (thin film) 1717 (s, C=O), 1611, 1574, 1503 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.58 (1H, dd, J = 3.4, 2.6 Hz), 6.99 (1H, d, J = 8.4 Hz), 6.80 (1H, d, J = 2.6 Hz), 6.68 (1H, dd, J = 8.4, 2.7 Hz), 3.76 (3H, s), 2.77 (1H, dd, J = 15.2, 2.5 Hz), 2.70 (2H, br t, J = 6.2 Hz), 2.54 (1H, dd, J = 15.2, 3.5 Hz), 1.89−1.68 (4H, m), 1.39 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 203.5, 157.9, 143.6, 130.3, 128.7, 112.1, 111.6, 56.1, 55.2, 36.7, 36.4, 30.5, 29.5, 19.4; MS (EI) *m/z* (rel intensity) 218.2 ($[M]^+$, 29), 174.2 (100), 159.2 (42), 115.1 (44%). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.85; H, 8.37.

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