ASYMMETRIC SYNTHESES OF (-)-APHANORPHINE AND (-)-EPTAZOCINE

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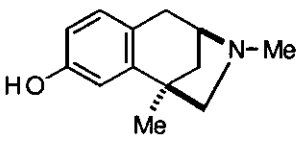
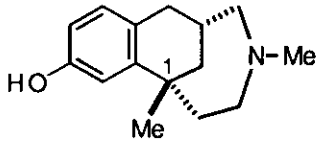
Abstract - Formal asymmetric syntheses of (-)-aphanorphine and (-)-eptazocine were done, utilizing asymmetric nitroolefination reaction of α-methyl-δ-valerolactone and a new aromatization of Diels-Alder adducts of chiral nitroolefins with the Danishefsky's diene.

INTRODUCTION

The compounds having a quaternary asymmetric carbon at benzylic position such as morphine, pentazocine, eptazocine, and aphanorphine exhibit potent pharmacological activities. (-)-Aphanorphine with a benzazepine skeleton is an alkaloid isolated[1] in 1988 from the freshwater blue-green alga, *Aphanizomenon flos-aquae*. The first asymmetric synthesis of (-)-aphanorphine has been reported by Takano *et al.*[2] *via* a kinetic resolution by lipase hydrolysis. Its enantiomer (+)-aphanorphine synthesized by Takano *et al.* has been found to have an anesthetic activity.[3] A synthetic analgesic eptazocine was first synthesized by Shiotani *et al.*[4] in 1973, and its optical active (-)-isomer was prepared through the optical resolution of (-)-tartaric acid salt, but the absolute configuration was not determined.[5] Recently, Shibasaki *et al.* have reported a synthesis of (-)-eptazocine using asymmetric Heck reaction[6a] and determined its absolute configuration at C-1 to be *R* by an X-ray analysis.[6b] The structural analogy and their pharmacological activities of eptazocine and aphanorphine prompted us to synthesize them utilizing the asymmetric nitroolefination[7] developed recently.



(-)-aphanorphine

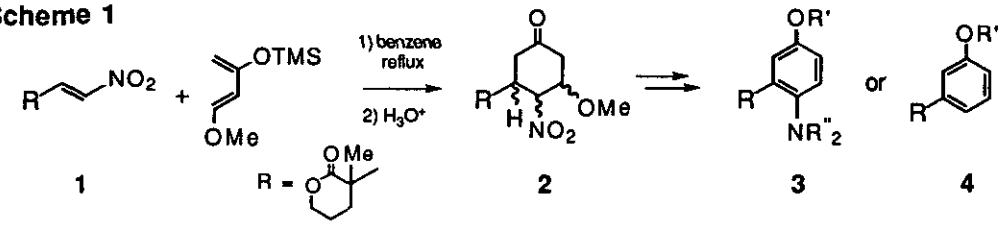


(-)-eptazocine

Resultant optically active nitroolefins[8] have been utilized in the syntheses of natural products through a reductive Nef reaction,[9] a Michael type conjugate addition,[10] or a Diels-Alder reaction[11] as a key reaction to the α,β-unsaturated nitro group. On the synthesis of Calabar bean alkaloid,[11a] we have used the Diels-Alder adduct (**2**) of nitroolefin (**1**) with the Danishefsky's diene. The key step in this aromatization reaction of **2** involved oxidation[12] of cyclohexadiene intermediate with iodine to give 3-alkyl-4-aminophenol

derivatives (**3**). The nitro group remained intact in a similar type of aromatization of the Diels-Alder adduct to give nitrophenol derivatives.[13] We have found another type of aromatization of **2** to give 3-alkylphenol derivatives (**4**), in which the nitro group was eliminated during the aromatization process. Herein we report this aromatization and its application to expeditious formal syntheses of (-)-eptazocine and (-)-aphanorphine.

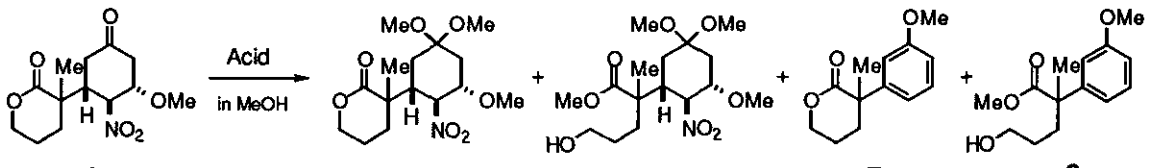
Scheme 1



RESULTS AND DISCUSSION

Firstly, we investigated the aromatization reaction of the Diels-Alder adduct (**2**)[11a] (Table 1). Attempted acetalization of **2** in refluxing methanol with a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) unexpectedly gave an aromatic compound (**8**) along with the desired acetals (**5**) and (**6**) (Run 1). Use of 1.8 equivalents of *p*-TsOH under similar conditions (Run 2) gave the aromatized products (**8**) and *p*-nitroanisole, which would be produced by routes A and B, respectively, shown in Scheme 2.

Table 1. Aromatization of the Diels-Alder Adduct 2

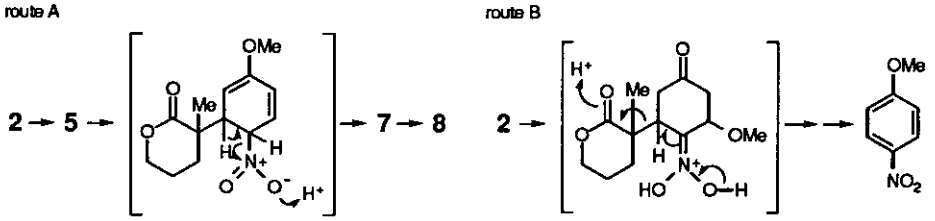


Run	Substrate	*p*-TsOH (equiv.)	Temp. (°C)	Time (h)	Product (Yield, %)
1	**2**	cat. amount	reflux	17	**5** (20), **6** (20), **8** (17)[a]
2	**2**	1.8	reflux	19	**8** (27)[b]
3	**2**	cat. amount	50	2	**5** (98)
4	**5**[c]	1.2	reflux	17	**5** (17), **6** (55), **8** (26)
5	**5**[c]	1.7	reflux	20	**7** (79)
6	**5**[c]	3.2	reflux	52	**7** (30), **8** (45)
7	**6**	1.9	reflux	15	**7** (9), **8** (23)[d]

a) The starting material (**2**) was recovered in 11 % yield.
b) *p*-Nitroanisole was obtained in 38 % yield.
c) Prepared *in situ* from **2** by the treatment with *p*-TsOH (cat.) in MeOH at 50 °C for 2 h.
d) An unseparable mixture of decomposed compounds except for **7** and **8**.

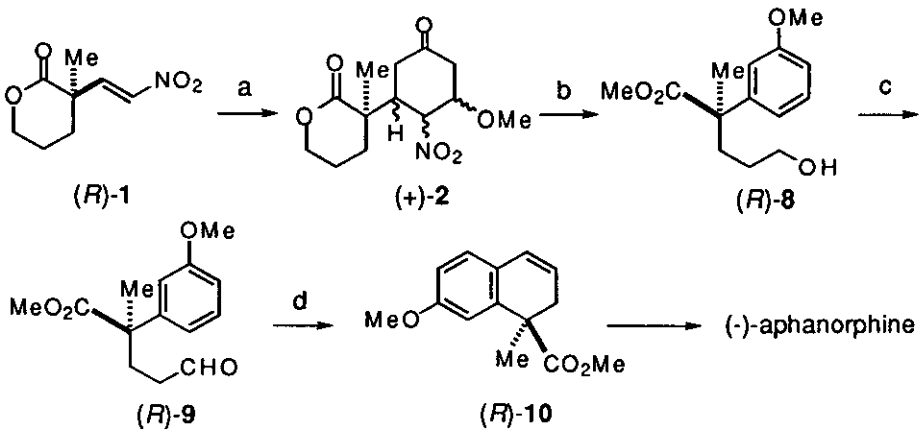
In the presence of catalytic amount of *p*-TsOH, the adduct (**2**) was converted into acetal (**5**) in high yield (Run 3). The acetal (**5**) gave a mixture of the products (Runs 4 and 6) or the sole product (**7**) (Run 5), depending on the amount of the acid and the reaction time. The acetal (**6**) afforded the aromatized alcohols (**7**) and (**8**) in low yield (Run 7). Such aromatized products were not obtained from **2** having phenyl group instead of α-methyllactone. The observed aromatization of **2** probably occurred through **5** *having a lactone ring* by the elimination of two moles of methanol and a mole of nitrous acid. Although the products were varied by minor change of the reaction conditions, the aromatized product (**8**) without nitro group could be obtained in considerable yield, because the lactone (**7**) was converted into **8** with sodium methoxide in 95 % yield.

Scheme 2



We applied this new type of aromatization to an asymmetric synthesis of (-)-aphanorphine (Scheme 3). The nitroolefin lactone [(*R*)-**1**] was prepared by nitroolefination[7] with a chiral nitroenamine derived from D-proline. The Diels-Alder adduct [(+)-**2**] of (*R*)-**1** was converted into the alcohol [(*R*)-**8**] by the method shown in Table 1.

Scheme 3. An Expeditious Formal Synthesis of (-)-Aphanorphine



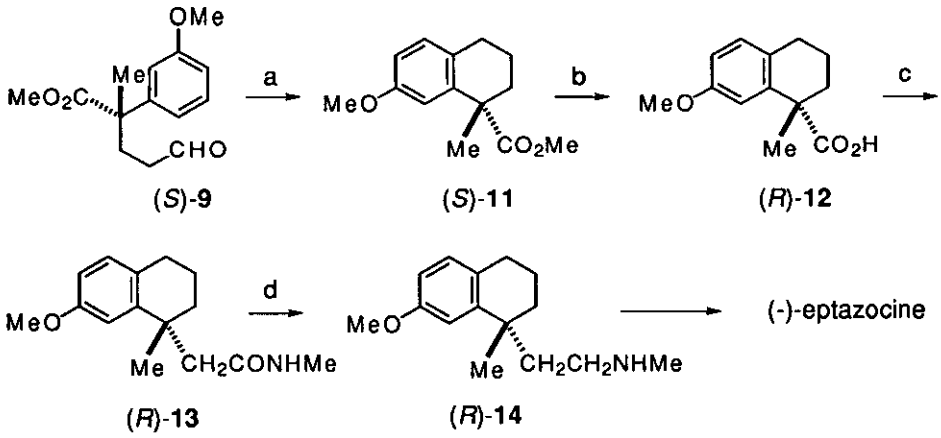
a) 1)Danishefsky's diene (2 eq.), benzene reflux, 48 h 2) 1 % HCl [30 % (2 steps) after recrystallization]; b) *p*-TsOH, MeOH (74 %); c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 (84 %); d) BF_3OEt_2 (1.2 eq.), CH_2Cl_2, -78 ~ -25 °C, 41 %;

The Swern oxidation of the alcohol [(*R*)-**8**] afforded the aldehyde [(*R*)-**9**] in 84 %. In the intramolecular Friedel-Crafts type cyclization, use of boron trifluoride etherate as a Lewis acid converted aldehyde [(*R*)-**9**]

into the dehydrated compound [(*R*)-**10**], whose spectroscopic data and specific rotation (Table 2 in experimental section) were identical with those of Takano's intermediate {$[\alpha]_D^{27}$ -70 (0.97, $CHCl_3$)},[2a] in 41 % yield together with dimeric compound. This transformation constitutes a formal synthesis of (-)-aphanorphine.

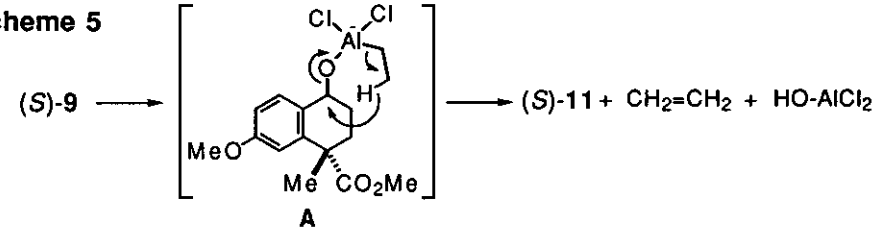
Next we turned our efforts to a formal asymmetric synthesis of (-)-eptazocine, which is a non-opiate analgesic in clinical use (Scheme 4). The Diels-Alder adduct [(-)-**2**] of nitroolefin [(*S*)-**1**], prepared by a nitroolefination using a chiral nitroenamine derived from L-proline, was converted to aldehyde [(*S*)-**9**] by the same route as that for the synthesis of (-)-aphanorphine. Treatment of aldehyde [(*S*)-**9**] with ethylaluminum dichloride gave methyl (*S*)-1-methyl-7-methoxytetrahydronaphtalene-1-carboxylate (**11**) in 68 % yield. It is worthy of note that ethylaluminum dichloride afforded the dihydro derivative (**11**), while boron trifluoride etherate gave a normal cyclization product (**10**). Dihydro derivative (**11**) would be produced by an intramolecular hydride transfer in the initially formed aluminum alkoxide A shown in Scheme 5.

Scheme 4. A Formal Synthesis of (-)-Eptazocine



a) $EtAlCl_2$, CH_2Cl_2, -78 ~ -25 °C, 68 %; b) LiOH, THF-H_2O, 94 %; c) 1) $SOCl_2$ 2) CH_2N_2, 3) Ag_2O , $MeNH_2$, dioxane, 39 % (3 steps); d) $LiAlH_4$, THF, 48 %

Scheme 5



The Arndt-Eistert reaction of the carboxylic acid (**12**) obtained by hydrolysis of (*S*)-**11** gave the corresponding *N*-methylamide [(*R*)-**13**] in 39 %, which was subsequently reduced to *N*-methylamine derivative [(*R*)-**14**] with lithium aluminum hydride in 48 % yield. The specific rotation (Table 2 in experimental section) of (*R*)-**14** was identical with the reported value {$[\alpha]_D^{24}$ +46.3 (1.0, EtOH)}.[5] These transformation constitute a formal synthesis of (-)-eptazocine.

CONCLUSION

We found a new type of aromatization reaction of the Diels-Alder adduct of a nitroalkene and the Danishefsky's diene, in which the nitro group was eliminated under the aromatization conditions. Increasing the amount of *p*-TsOH more than one equivalent in refluxing methanol was found to be best conditions for this aromatization reaction of the acetal (**5**). In the intramolecular Friedel-Crafts type cyclization of the aldehyde (**9**), the reduction or the dehydration could be controlled by the selection of Lewis acid (*i.e.* ethylaluminum dichloride or boron trifluoride etherate) to give **10** or **11**. We demonstrated applications of a new aromatization reaction to expeditious syntheses of (-)-eptazocine and (-)-aphanorphine.

ACKNOWLEDGMENT

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EXPERIMENTAL SECTION

General: Melting points are taken with a micro hot-stage apparatus (Yanagimoto) and are uncorrected. The infrared (ir) spectra are recorded with a Shimadzu IR-410 diffraction grating infrared spectrophotometer and ^{1}H-nmr spectra are obtained with a JEOL JNM-EX-90, JEOL JNM-GX-270, or Varian XL-300 spectrometer with tetramethylsilane as an internal standard. Mass spectra (ms) are determined on a JEOL JMS-01SG, JEOL JMS-SX 102A QQ, Hitachi M-80, or Shimadzu GCMS-QP 1000 mass spectrometer. The hplc analyses were performed with a Shimadzu LC-9A Liquid Chromatograph series using Daicel chiral column (CHIRALCEL OJ). Their data were recorded with a Shimadzu C-R6A Chromatopac. Wakogel C-200 (silica gel) (100-200 mesh, Wako) or Wakogel C-300 (200-300 mesh, Wako) was used for column chromatography, and nacalai tesque silica gel 60 PF_{254} was used for flash column chromatography. Kieselgel 60 F_{254} plate (Merck) was used for thin layer chromatography (tlc) and preparative tlc. Preparative alumina tlc was performed using Aluminiumoxid 60 F_{254} (Type E) (0.25 mm) plate (Merck).

Material: (2*R*)-2-Methyl-2-(3'-methoxy-2'-nitro-5'-oxocyclohexyl)-5-pentanolide [(+)-**2**] and its enantiomer [(-)-**2**] were prepared by the asymmetric nitroolefination reaction followed by the Diels-Alder reaction with Danishefsky's diene.[7, 11a] The racemic lactone (**2**) was prepared by the Diels-Alder reaction of racemic nitroolefin (**1**).[14]

2-Methyl-2-(3'-methoxy-2'-nitro-5',5'-dimethoxycyclohexyl)-5-pentanolide (5), Methyl 5-Hydroxy-2-(3'-methoxy-2'-nitro-5',5'-dimethoxycyclohexyl)-2-methyl-pentanoate (6), and Methyl 5-Hydroxy-2-(3-methoxyphenyl)-2-methylpentanoate (8)

Table 1 typical procedure (Run 4): A mixture of **2** (117 mg, 0.41 mmol) and a catalytic amount of *p*-toluenesulfonic acid monohydrate in methanol (20 ml) was heated at 50 °C for 2 h. After the formation of **5** was detected in tlc [R_f; **2**: 0.43, **5**: 0.60 (ethyl acetate / hexane = 2 / 1)], *p*-toluenesulfonic acid monohydrate (94 mg, 0.49 mmol, 1.2 eq.) was added to the reaction mixture. The resulting mixture was refluxed for 17 h. After the solvent of the reaction mixture was condensed to the half volume, brine was added the mixture was extracted with dichloromethane. The extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Silica gel flash column chromatography (ethyl acetate / hexane = 2 / 1) of the residue gave **5** (23 mg, 17 %), **6** (82 mg, 55 %), and **8** (27 mg, 26 %).

5: pale yellow oil; ^{1}H-nmr ($CDCl_3$, 300MHz) δ: 1.25 (t, *J* = 12.2 Hz, 1H), 1.26 (s, 3H), 1.38 (t, *J* = 13.4 Hz, 1H), 1.68-2.04 (m, 5H), 2.61 (ddd, *J* = 12.6, 5.0 and 2.9 Hz, 1H), 2.79 (dt, *J* = 12.3 and 3.4 Hz, 1H), 3.22 (s, 3H), 3.23 (s, 3H), 3.33

(s, 3H), 3.94 (ddd, J = 11.6, 9.8 and 5.0 Hz, 1H), 4.13-4.22 (m, 1H), 4.34 (dd, J = 11.6 and 9.8 Hz, 1H), 4.39-4.45 (m, 1H); ir ($CHCl_3$): 2950, 1730, 1560, 1465, 1385, 1270, 1160, 1140, 1095, 1045, 1025 cm^{-1}; ms m/z: 331 (M^+, 0.15), 285 (45), 218 (67), 160 (88), 140 (62), 131 (100), 115 (90), 114 (100), 109 (62), 88 (80), 75 (76); HRms calcd for $C_{15}H_{25}NO_7$: 331.1631, found: 331.1647.

6: mp 101-104 °C (ethyl acetate - hexane); ^{1}H-nmr ($CDCl_3$, 300MHz) δ: 1.15-1.34 (m, 4H), 1.21 (s, 3H), 1.45-1.69 (m, 1H), 2.11-2.17 (m, 1H), 2.74 (ddd, J = 13.3, 11.4 and 3.7 Hz, 1H), 3.61 (q, J = 6.1 Hz, 2H), 3.21 (s, 3H), 3.23 (s, 3H), 3.31 (s, 3H), 3.64 (s, 3H), 3.87 (ddd, J = 11.8, 9.8 and 4.7 Hz, 1H), 4.32 (dd, J = 11.4 and 9.8 Hz, 1H); ir ($CHCl_3$): 3500, 3000, 2950, 2840, 1730, 1560, 1465, 1430, 1385, 1340, 1270, 1095, 1045 cm^{-1}; ms m/z: 363 (M^+, trace), 317 (20), 218 (46), 160 (53), 131 (100), 109 (45), 88 (49), 75 (64); HRms calcd for $C_{16}H_{29}NO_8$: 363.1893, found: 363.1924.

8: pale yellow oil; ^{1}H-nmr ($CDCl_3$, 270 MHz) δ: 1.40-1.51 (m, 2H), 1.56 (s, 3H), 1.91-2.13 (m, 2H), 3.61 (t, J = 6.6 Hz, 2H), 3.66 (s, 3H), 3.79 (s, 3H), 6.76-6.89 (m, 3H), 7.24 (t, J = 7.9 Hz, 1H); ir ($CHCl_3$): 3500 (broad), 3019, 2953, 1725, 1256 cm^{-1}; ms m/z: 252 (M^+, 22), 193 (12), 175 (81), 134 (100), 121 (18), 109 (15), 91 (17); HRms calcd for $C_{14}H_{20}O_4$: 252.1370, found: 252.1371.

(2*R*)-2-(3'-Methoxyphenyl)-2-methyl-5-pentanolide (7) and Methyl (2*R*)-5-Hydroxy-2-(3-methoxyphenyl)-2-methylpentanoate (8)

A mixture of (+)-**2** (84 mg, 0.29 mmol) and a catalytic amount of *p*-toluenesulfonic acid monohydrate in methanol (15 ml) was heated at 50 °C for 4 h. After the formation of **5** was detected in tlc [R_f; **2**: 0.43, **5**: 0.60 (ethyl acetate / hexane = 2 / 1)], *p*-toluenesulfonic acid monohydrate (103 mg, 0.54 mmol, 1.7 eq.) was added to the reaction mixture. The resulting mixture was refluxed for 20 h. After the solvent of the reaction mixture was condensed to the half volume, the mixture was extracted with dichloromethane. The extract was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Silica gel column chromatography (ethyl acetate / hexane = 3 / 1) of the residue gave (*R*)-**7** (51 mg, 79 %). (*R*)-**7**: pale yellow oil; ^{1}H-nmr ($CDCl_3$, 300MHz) δ: 1.54 (s, 3H), 1.81-2.00 (m, 3H), 2.45-2.50 (m, 1H), 3.81 (s, 3H), 4.06-4.14 (m, 1H), 4.20-4.30 (m, 1H), 6.80-6.92 (m, 3H), 7.29 (t, J = 7.9 Hz, 1H); ir ($CHCl_3$): 2960, 1730, 1600, 1580, 1485, 1460, 1430, 1290, 1265, 1160, 1110, 1040 cm^{-1}; ms m/z: 220 (M^+, 4.4), 161 (20), 148 (100), 108 (20), 91 (37), 77 (33), 65 (22); Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.62; H, 7.57.

(2*R*)-2-(3'-Methoxyphenyl)-2-methyl-5-pentanolide (**7**) (51 mg) was treated with excess sodium methoxide in methanol (3 ml) at 0 °C for 15 min. The reaction mixture was acidified with 1*N* HCl solution, then extracted with dichloromethane, washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by silica gel column chromatography (ethyl acetate / hexane = 3 / 1) gave (*R*)-**8** (56 mg, 95 %) as a pale yellow oil.

Methyl (*R*)-2-Methyl-2-(3-methoxyphenyl)-5-oxopentanoate (9)

To a mixture of oxalyl chloride (60 µl, 0.69 mmol) in dichloromethane (1.5 ml) was added slowly a dichloromethane (1.0 ml) solution of dimethyl sulfoxide (100 µl, 0.69 mmol) at - 78 °C. After being stirred for 40 min, a dichloromethane (2.0 ml) solution of alcohol [(*R*)-**8**] (110 mg, 0.44 mmol) was added dropwise and stirred for 30 min. Triethylamine (300 µl, 2.2 mmol, 5 eq.) was added at the same temperature, then the resulting mixture was gradually warmed to room temperature within 2 h. The reaction mixture was poured into saturated ammonium chloride solution, extracted with dichloromethane (50 ml x 3). The extract was washed with water, dried ($MgSO_4$), and concentrated *in vacuo*. Silica gel flash column chromatography (AcOEt / hexane = 6 / 1) gave (*R*)-**9** (91.2 mg, 84 %). pale yellow oil; ^{1}H-nmr ($CDCl_3$, 300 MHz) δ: 1.56 (s, 3H), 2.25-2.39 (m, 4H), 3.68 (s, 3H), 3.80 (s, 3H), 6.78-6.87 (m, 3H), 7.26 (t, J = 7.9 Hz, 1H), 9.70 (t, J = 1.2 Hz, 1H); ir ($CHCl_3$): 2950, 2840, 1730, 1600, 1580, 1485, 1460, 1430, 1290, 1045 cm^{-1}; ms m/z: 250 (M^+, 39), 191 (43), 162 (95), 150 (100), 135 (38), 121 (62), 91 (40), 77 (23); HRms calcd for $C_{14}H_{18}O_4$: 250.1205, found: 250.1211.

Methyl (*R*)-1-Methyl-7-methoxy-1,2-dihydronaphthalene-1-carboxylate (10)

To a solution of (*R*)-**9** (9.33 mg, 0.037 mmol) in dichloromethane (20 ml) was added boron trifluoride etherate (5.04 µl, 5.8 mg, 0.041 mmol) at 0 °C and stirred for 30 min. The reaction mixture was treated with 1% HCl solution, then extracted with dichloromethane. The extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Preparative tlc gave (*R*)-**10** (3.6 mg, 42 %) along with the dimer in the range of 20~50% yield. (*R*)-**10**: pale yellow oil; ^{1}H-nmr ($CDCl_3$, 300 MHz) δ: 1.52 (s, 3H), 2.25 (dd of ABd, *J* = 16.9, 4.3, and 1.8 Hz, 1H), 2.95 (dd of ABd, *J* = 16.9, 4.6, and 1.7 Hz, 1H), 3.67 (s, 3H), 3.80 (s, 3H), 5.85 (ddd, *J* = 9.6, 4.6, and 4.3 Hz, 1H), 6.41 (dd, *J* = 9.6 and 1.7 Hz, 1H), 6.73-6.77 (m, 2H), 7.01 (d, *J* = 8.0 Hz, 1H); ir ($CHCl_3$): 2840, 1732, 1609, 1260, 1231 cm^{-1}; ms m/z 232 (M^+, 33), 173 (100), 158 (44), 115 (18); HRms calcd for $C_{14}H_{16}O_3$: 232.1099, found 232.1108. The dimer of **10**: ^{1}H-nmr ($CDCl_3$, 300 MHz) δ: 1.37-1.47 (m, 1H), 1.56 (s, 6H), 1.60-1.70 (m, 1H), 1.85-2.00 (m, 2H), 2.10 (A part of ABd, *J* = 16.3 Hz, 1H), 2.25-2.40 (m, 1H), 2.76 (B part of ABd, *J* = 16.3 Hz, 1H), 3.66 (s, 3H), 3.68 (s, 3H), 3.79 (s, 3H), 3.80 (s, 3H), 6.04 (s, 1H), 6.71-6.80 (m, 4H), 6.93-7.02 (m, 2H); ir ($CHCl_3$): 2960, 1725, 1605, 1495, 1465, 1240, 1170, 1040 cm^{-1}; ms m/z 464 (M^+, 56), 404 (47), 364 (18), 304 (23), 233 (19), 173 (100), 154 (20); HRms calcd for $C_{28}H_{32}O_6$: 464.2199, found 464.2184.

Methyl (*S*)-1-Methyl-7-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxylate (11)

To a solution of aldehyde (*S*)-**9** (90 mg, 0.36 mmol) in dichloromethane (3.0 ml) was added ethylaluminum dichloride (1 M in hexane, 1.2 ml, 3.3 eq.) at - 78 °C, and the reaction mixture was gradually warmed to -25 °C for 3 h. The reaction mixture was poured into water, acidified to pH 2 with 1*N* HCl solution, and extracted with dichloromethane (30 ml x 3). The extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Silica gel flash column chromatography (AcOEt / hexane = 1 / 8) gave (*S*)-**11** (56.7 mg, 68 %). (*S*)-**11**: pale yellow oil; ^{1}H-nmr ($CDCl_3$, 300 MHz) δ: 1.54 (s, 3H), 1.70-1.85 (m, 3H), 2.24-2.30 (m, 1H), 2.71-2.76 (m, 2H), 3.66 (s, 3H), 3.76 (s, 3H), 6.72 (dd, *J* = 6.7 and 2.7 Hz, 1H), 6.74 (br s, 1H), 7.00 (d, *J* = 6.7 Hz, 1H); ir ($CHCl_3$): 2950, 1736, 1610, 1260, 1161, 1061 cm^{-1}; ms m/z 234 (M^+, 19), 175 (100), 134 (12); Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.41; H, 7.91.

(*S*)-1-Methyl-7-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic Acid (12)

A mixture of methyl (*S*)-1-methyl-7-methoxy-1,2-dihydronaphthalene-1-carboxylate [(*S*)-**11**] (2.83g, 12.1 mmol) and LiOH H_2O (4.06 g, 96.8 mmol) in THF (35 ml) and H_2O (35 ml) was refluxed for 59 h. The reaction mixture was washed with ether, after alkalized with adequate 1*N* NaOH solution. The aqueous layer was acidified (pH = 1) with 10 % HCl solution, then extracted with ethyl acetate. The extract was washed with brine, dried ($MgSO_4$), concentrated *in vacuo* to give (*S*)-1-methyl-7-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (**12**) (2.50 g, 94 %). (*S*)-**12**: colorless oil; ^{1}H-nmr ($CDCl_3$, 270 MHz) δ: 1.55 (s, 3H), 1.67-1.91 (m, 3H), 2.27-2.35 (m, 1H), 2.70-2.76 (m, 2H), 3.76 (s, 3H), 6.72 (dd, *J* = 8.3 and 2.6 Hz, 1H), 6.83 (d, *J* = 2.6 Hz, 1H), 7.00 (d, *J* = 8.3 Hz, 1H), 11.74 (br s, 1H); ir ($CHCl_3$): 3300-2500, 1715, 1615, 1507, 1464, 1285, 1240, 1050 cm^{-1}; ms m/z 220 (M^+, 26), 175 (100), 134 (28), 115 (13); Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.56; H, 7.40.

***N*-Methyl-(*S*)-1-Methyl-7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl-acetamide (13)**

A mixture of (*S*)-1-methyl-7-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (*S*)-**12** (85.9 mg, 0.4 mmol) and thionyl chloride (1.2 ml, 16 mmol) was refluxed for 22 h under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure to give crude the acid chloride. To an ether solution (5 ml) of the acid chloride was added a ether solution of diazomethane continuously over 12 h, until the starting acid chloride was consumed on the tlc. The reaction mixture was concentrated *in vacuo* to give crude diazomethyl (*S*)-1-methyl-7-methoxy-1,2,3,4-tetrahydronaphthalenyl ketone. ^{1}H-nmr ($CDCl_3$, 300 MHz) δ: 1.51 (s, 3H), 1.65-1.83 (m, 3H), 2.10-2.16 (m, 1H), 2.72-2.76 (t, *J* = 6.4 Hz, 2H), 3.78 (s, 3H), 4.87 (s, 1H), 6.67 (d, *J* = 2.7 Hz, 1H), 6.76 (dd, *J* = 8.4 and 2.7 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 1H); ir ($CHCl_3$): 2940,

2100, 1610, 1500, 1460, 1370, 1340, 1280, 1150, 1040 cm^{-1}; ms m/z 244 (M^+, 1.3), 216 (31), 175 (100), 173 (37), 159 (31), 128 (32), 115 (46); Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.87; H, 6.55; N, 11.28.

To a mixture of 10 % water solution of Ag_2O (6 ml, 2.6 mmol) and 40 % methylamine solution (1 ml) in dioxane (3 ml) was added a solution of the crude diazoketone in dioxane (3 ml) at room temperature and the resulting mixture was stirred for 5 min. The reaction mixture was extracted with ethyl acetate, after adding of brine. The extract was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by silica gel chromatography ($CHCl_3$: MeOH = 15 : 1) afforded (*S*)-**13** (35.6 mg, 39 %). (*S*)-**13**: pale yellow oil; ^{1}H-nmr ($CDCl_3$, 270 MHz) δ: 2.43 (dd of ABd, *J* = 44.9 and 13.9, 1H), 2.51 (dd of ABd, *J* = 44.9 and 13.9 Hz, 1H), 2.65 (d, *J* = 4.8 Hz, 3H), 2.68-2.71 (m, 2H), 3.78 (s, 3H), 4.90-5.10 (br s, 1H, NH), 6.70 (dd, *J* = 8.4 and 2.6 Hz, 1H), 6.83 (d, *J* = 2.6 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H); ir ($CHCl_3$): 3300, 1653 cm^{-1}; ms m/z 247 (M^+, 22), 174 (100), 159 (64), 115 (16); HRms calcd for $C_{15}H_{21}NO_2$: 247.1571, found 247.1559.

(*R*)-1-(2-*N*-Methylaminoethyl)-1-methyl-7-methoxy-1,2,3,4-tetrahydronaphthalene (14)

A mixture of lithium aluminum hydride (5.6 mg, 0.15 mmol) and *N*-methyl-(*S*)-1-methyl-7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl-acetamide (**13**) (25.6 mg, 0.10 mmol) in ether (3 ml) was refluxed for 30 min. An additional lithium aluminum hydride (2.8 mg, 0.07 mmol) was added and again refluxed for 15 min. The reaction mixture was alkalized with 1 *N* NaOH solution, then extracted with dichloromethane. The extract was washed with brine, dried (K_2CO_3), and evaporated. Purification of the residue by preparative alumina tlc ($CHCl_3$: MeOH = 12 : 1) gave (*R*)-**14** (11.6 mg, 48 %). (*R*)-**14**: pale yellow oil; ^{1}H-nmr ($CDCl_3$, 270 MHz) δ: 1.28 (s, 3H), 1.52-1.99 (m, 6H), 2.36-2.71 (m, 2H), 2.43 (s, 3H), 3.79 (s, 3H), 4.30-4.70 (br s, 1H, NH), 6.67 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.81 (d, *J* = 2.6 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H); ir ($CHCl_3$): 3650-2250, 2932, 1611, 1496, 1283, 1044 cm^{-1}; ms m/z 233 (M^+, 45), 176 (100), 161 (22), 145 (11), 60 (17); HRms calcd for $C_{15}H_{23}NO$: 233.1779, found 233.1779.

Specific rotations and enantiomeric excesses of the synthesized compounds

[(+)-**2**] {$[\alpha]_D^{19}$ +30.9 (c 1.93, $CHCl_3$), 100 %ee} and [(-)-**2**] {$[\alpha]_D^{24}$ -30.1 (c 2.40, $CHCl_3$), 100 %ee} were obtained by recrystallization of the crude Diels-Alder adducts from ethyl acetate - hexane.[11a,15] Their enantiomeric excesses were confirmed by the chiral hplc analyses {DAICEL CHIRALCEL OJ (25 x 0.46); eluent: hexane / isopropanol = 90 / 10; flow rate: 1.0 ml/min.; Temp.: 40 °C; detector: 254 nm; (*R*)-**8**; 13.1 min, (*S*)-**8**; 22.8 min]} of (*R*)-**8** and (*S*)-**8**, derived from (+)-**2** and (-)-**2**, respectively. The recorded specific rotations in Table 2 except for (*R*)-**10** and (*R*)-**14** are independent on the total syntheses, and are based on each purity of the raw materials **2** used.

Table 2. Specific Rotation and Enantiomeric Excess (ee)

Compounds	Specific Rotation	ee (%)
(*R*)-**8**	$[\alpha]_D^{20}$ -26.0° (1.05, $CHCl_3$)	88[a]
(*S*)-**9**	$[\alpha]_D^{23}$ +29.6° (1.59, $CHCl_3$)	93[b]
(*R*)-**10**	$[\alpha]_D^{22}$ -74.4° (0.51, $CHCl_3$)	100[a]
(*S*)-**11**	$[\alpha]_D^{23}$ -13.6° (0.16, $CHCl_3$)	93[b]
(*S*)-**12**	$[\alpha]_D^{24}$ -3.1° (1.46, $CHCl_3$)	100[b]
(*R*)-**14**	$[\alpha]_D^{24}$ +46.3° (0.20, EtOH)	100[b]

a) Determined by a chiral hplc analysis of **8**.
b) Ee of the raw material (**2**) based on the specific rotation of optically pure **2**.

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15. Detail Data of the Diels-Alder adduct (**2**) will be published elsewhere.

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