An asymmetric synthesis of 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (ADTN)

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An asymmetric synthesis of 2-amino-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene, which can be converted to the title compound by a literature procedure, is described. The synthesis, starting from 2-amino-4,5-dimethoxybenzoic acid and the acrylate of *S*-methyl lactate, was accomplished in eight steps in 11% overall yield and >97% optical purity.

Key words: *o*-quinodimethanes, Diels–Alder, asymmetric, cycloaddition, induction, diastereoselective, ADTN.

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On décrit une synthèse asymétrique du 2-amino-6,7-diméthoxy-1,2,3,4-tétrahydronaphtalène qui peut être transformé dans le composé mentionné dans le titre par une procédure décrite dans la littérature. La synthèse, à partir de l'acide 2-amino-4,5-diméthoxybenzoïque et de l'acrylate du lactate de *S*-méthyle, a été réalisée en huit étapes, avec un rendement global de 11% et une pureté optique >97%.

Mots clés : *o*-quinodiméthanes, Diels–Alder, asymétrique, cycloaddition, induction, diastéréosélective, ADTN.

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Introduction

Since the initial discovery that 5,6-dihydroxy-2-(dimethylamino)tetralin possesses dopaminergic activity, many other 2-aminotetralin derivatives have been synthesized and tested for analogous behavior (1; for reviews see 2). These drugs interact with D_2 dopamine receptors and there is interest in them as potential antipsychotic and anti-Parkinsonian drugs. Like many other drugs, the potency of the 2-aminotetralin derivatives as central nervous system active agents is directly related to their absolute stereochemistry (and conformation) (2, 3), which necessitates the preparation of pure enantiomers of the drugs in question. In most instances pure enantiomers have been obtained by resolution of racemic mixtures but the parent compound, (*R*)-(+)-2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (ADTN), has been recently prepared by a chiral pool synthesis starting from (*R*)-*N*-(trifluoroacetyl)aspartic anhydride (4).

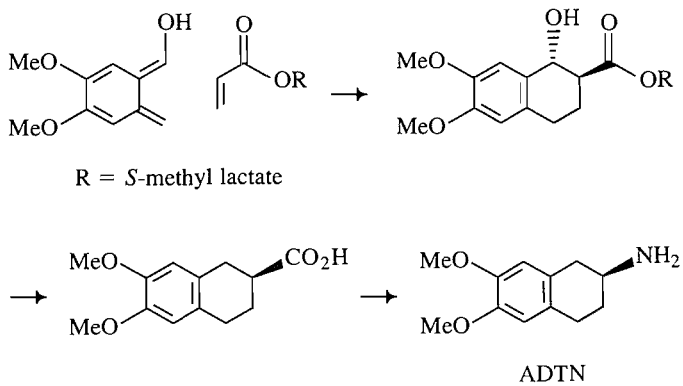
We recently discovered that the acrylate of *S*-methyl lactate adds with high asymmetric induction to α-hydroxy-*o*-quinodimethane (5) and this discovery inspired the proposal of an asymmetric synthesis for ADTN, which is outlined in Scheme 1.

The Diels–Alder cycloaddition would be followed by hydrogenolysis of the hydroxyl group, hydrolysis of the lactyl ester, and, finally, conversion of the carboxylic acid group to the amine by a procedure that has already been published for the racemic acid (6).

If the synthetic route outlined in Scheme 1 could be accomplished it would make possible the asymmetric synthesis of analogs of ADTN via derivatives of the starting *o*-quinodimethane and lactyl acrylate. An asymmetric route of this type would be more versatile than the chiral pool synthesis since the latter is tied to a specific chiral synthon that becomes part of the product molecule.

Results and discussion

Our first task in tackling the proposed synthesis outlined in Scheme 1 was to choose a method of preparing the very reactive and transient *o*-quinodimethane (*o*-QDM). Among the many methods for preparing *o*-QDMs (7), the photolysis of an *o*-methyl benzaldehyde is experimentally the easiest and therefore we prepared 2-methyl-4,5-dimethoxybenzaldehyde **1**, using (in part) published procedures (8–11), as a precursor to the *o*-QDM.



SCHEME 1

Unfortunately, as we previously reported, aldehyde **1** did not form a trappable *o*-QDM on irradiation (11). However, conversion of **1** to the diacetate **3** provided an aldehyde that could be trapped with the acrylate of *S*-methyl lactate to give essentially a single cycloadduct **4** in 85% yield. Although we did not determine the absolute stereochemistry of **4**, we assumed it to be that shown, by analogy to previous work (5).

Disappointingly, the conversion of the cycloadduct **4** to the deoxy derivative *S*-**5**, under a variety of reduction conditions, could not be achieved in high yield without epimerization of the chiral centre at the 2 position, presumably due to dehydration/reduction competing with hydrogenolysis.

In view of the difficulty encountered with the hydrogenolysis of **4**, we turned our attention to alternate methods for the preparation of the dimethoxy *o*-QDM. Following the earlier work of Sammes and co-workers (12), we have previously shown that α-hydroxy-*o*-QDM generated thermally from benzocyclobutenol adds to lactyl acrylate with the same asymmetric selectivity as that generated photochemically from *o*-methylbenzaldehyde (13). Thus we prepared 4,5-dimethoxybenzocyclobutenol **7** from 2-bromo-4,5-dimethoxybenzaldehyde **6** using the method of Durst and co-workers (14) in hopes of using

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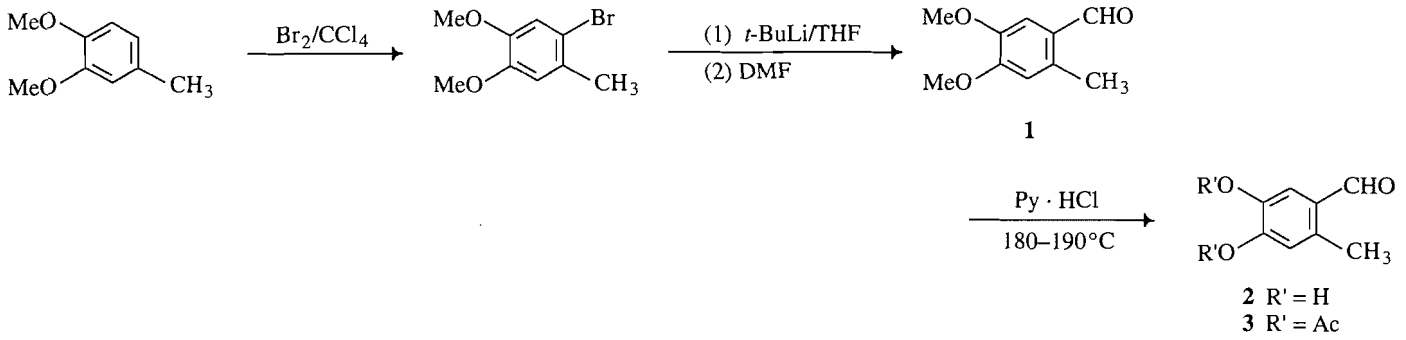
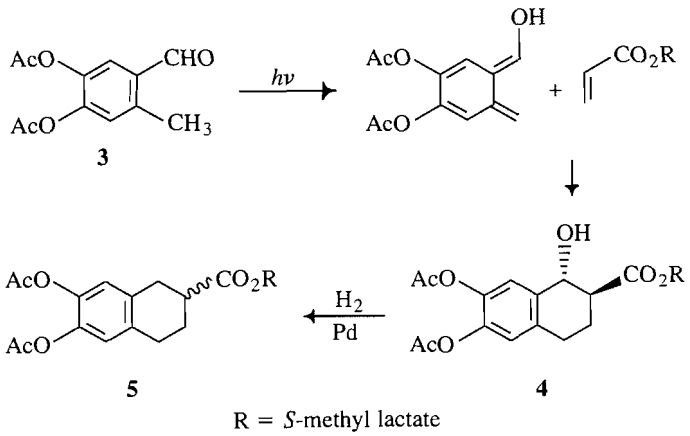


it as an *o*-QDM precursor. The yields of the benzocyclobutenol **7** using Durst's method were rather variable (30–50%) and alternate routes for its synthesis were sought. Although Jung *et al.* had very little success using a benzyne route to prepare 4,5-methylenedioxybenzocyclobutenyl acetate from 4,5-methylenedioxyanthranilic acid (8%) (15), we were able to prepare 4,5-dimethoxybenzocyclobutenyl acetate **8** from 4,5-dimethoxyanthranilic acid in very reasonable yield (45%). The acetate was readily converted to the alcohol **7** with ammonia in methanol (85%).



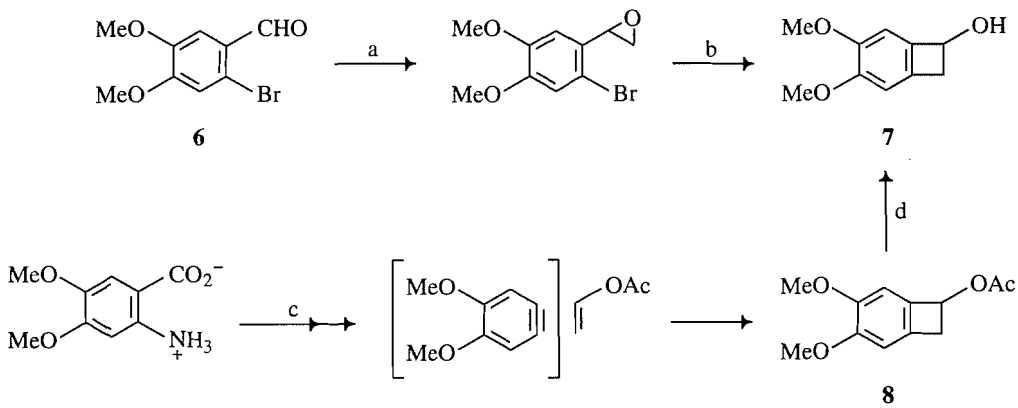
R = *S*-methyl lactate

Heating the benzocyclobutenol **7** in a toluene solution of the acrylate of *S*-methyl lactate gave one major and three minor cycloadducts in the ratio of 9:1 (major:total of minor; from nmr integration). The major cycloadduct **9** could be isolated by chromatography on silica gel in 80% yield. Hydrogenolysis of **9** under rather mild conditions (1 atm H_2 (101.3 kPa), 5% Pd on C, methanol/acetic acid (50:50), room temperature) cleanly gave the deoxy ester **10** in 80% yield. This ester could be hydrolysed to the corresponding acid **11** with potassium carbonate in methanol/water without epimerization of the chiral center. The acid was converted to the hydrochloride salt of the 2-aminotetralin **13** using a method previously developed by Narula and Schuster (16). The amine was recovered from the salt by neutralization with aqueous NaOH and extraction to give material with an $[\alpha]_D^{20}$ −85.7° (lit. (4) $[\alpha]_D$ +86.5 for the *R* isomer).

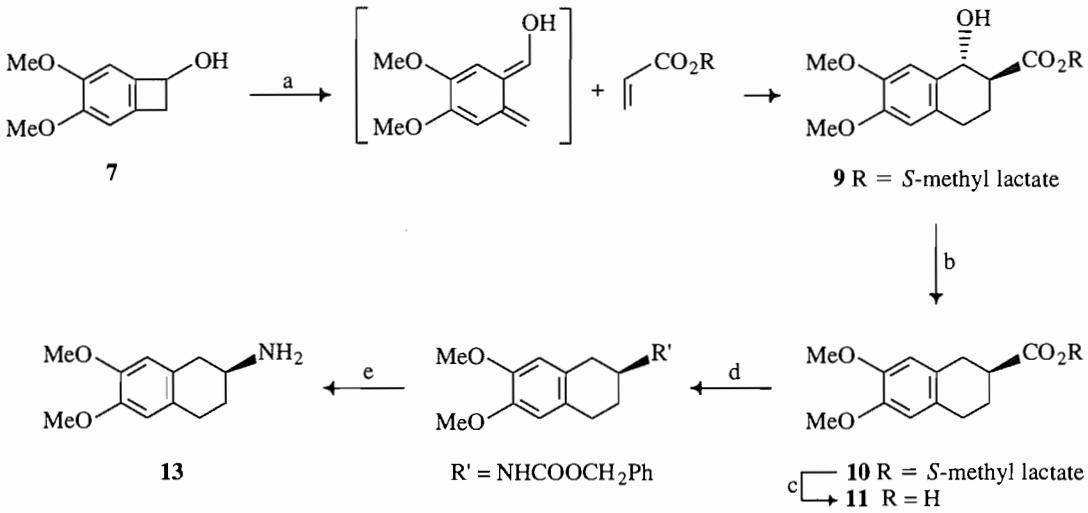
The amine **13** was previously reported to be a yellow oil (4), while we found that it was a crystalline solid with a melting point of 85–86°C. This, as well as small differences between reported nmr data and our nmr data, may be due to small amounts of impurities in the formerly prepared material (4). The configurational purity of **13** was determined by preparation of the amide with (−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (Mosher's acid) and analysis by nmr as has been described previously (4). For comparison purposes the mixture of diastereomeric amides was also prepared from racemic 4,5-dimethoxy-2-aminotetralin. The nmr spectrum of the diastereomeric amides showed well-separated singlets in the aromatic region at 6.24, 6.29, 6.32, and 6.35 ppm when the spectrum was recorded in C_6D_6. The amide from **13** showed major peaks at 6.29 and 6.32 corresponding to the *S*-(−) enantiomer (4). Assuming that the purity of the Mosher's acid was >99%, integration indicated that the optical purity of **13** was >97%. The demethylation of **13** to (*S*)-(−)-ADTN has been described elsewhere (17).

Experimental

The ^{1}H nmr spectra were recorded on a Bruker AM-300 instrument using tetramethylsilane as internal standard. The ir spectra were recorded on a Perkin Elmer 881 spectrometer. Merck Kieselgel 60 or Aldrich 28,859-4 was used for all chromatography. Elemental analyses were performed by Guelph Chemical Laboratories Ltd., Guelph, Ontario, Canada. Exact Mass/mass spectra were obtained on an Analytical VG 7070E-HF instrument. Melting points were measured



(a) $(CH_3)_3S^+I^-$, OH^-; (b) *n*BuLi, $MgBr_2$; (c) *i*-AmONO, heat; (d) NH_3/CH_3OH



(a) 110°C, toluene; (b) H_2/Pd, methanol/acetic acid; (c) K_2CO_3, methanol/water; (d) $(PhO)_2P(O)N_3/Et_3N$, C_6H_6, reflux 2 h; then $C_6H_5CH_2OH$, reflux 24 h; (e) H_2/Pd, 10% HCl/methanol then NaOH

on a hot stage instrument and are uncorrected. Optical rotations were recorded on a Rudolf Research Corporation Autopol III instrument.

2-Bromo-4,5-dimethoxytoluene

A solution of bromine (0.72 g) in CCl_4 (10 mL) was added dropwise to a solution of 3,4-dimethoxytoluene (0.68 g, 4.47 mmol), in CCl_4 (15 mL), with stirring at room temperature until the colour of bromine persisted. The mixture was washed with water, dried ($MgSO_4$), and evaporated to give a red oil (0.919 g, 90%), which was purified by chromatography on silica gel (EtOAc/hexane, 5:95); ^{1}H nmr ($CDCl_3$) δ: 2.32 (s, 3H), 2.82 (s, 3H), 2.83 (s, 3H), 6.72 (s, 1H), 6.99 (s, 1H).

*2-Methyl-4,5-dimethoxybenzaldehyde, **1***

2-Bromo-4,5-dimethoxytoluene (0.221 g, 0.96 mmol) in THF (2 mL) was added to a solution of *tert*-butyllithium (1.53 mL of 1.25 M in pentane, 2 equiv.) in THF (3 mL) at −78°C under nitrogen. After 45 s, *N*,*N*-dimethyl formamide (0.14 g, 2 equiv., anhydrous) in THF (1 mL) was added. The solution was stirred for 5 min at −78°C and then at room temperature for 2 h. The reaction was quenched with aqueous HCl (10%, 10 mL), saturated with sodium chloride, extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated to give an oil (0.144 g). Chromatography of the oil (EtOAc/hexane) gave a colourless solid (100 mg, 58%); mp 71–72°C; ir (CH_2Cl_2): 1733 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 2.63 (s, 3H), 3.92 (s, 3H), 3.95 (s, 3H), 6.69 (s, 1H), 7.35 (s, 1H), 10.22 (s, 1H); ms, *m/e* (rel. %): 181 (11), 180 (100), 179 (45), 165 (19), 151 (15), 109 (17). Exact Mass calcd. for $C_{10}H_{12}O_3$: 180.0783; found: 180.0786.

*2-Methyl-4,5-dihydroxybenzaldehyde, **2***

2-Methyl-4,5-dimethoxybenzaldehyde (0.47 g, 2.61 mmol) was mixed with pyridinium hydrochloride (1.21 g, 4 equiv.) and heated to 180–190°C under nitrogen for 4 h. The mixture was cooled and digested in aqueous 10% HCl (50 mL). Some residual tar was removed by filtration and the filtrate extracted with ethyl acetate. Drying ($MgSO_4$) and evaporation gave a pale green solid (0.336 g, 84%), which could be purified by chromatography on silica (EtOAc/hexane, 60:40); mp 171–173°C; ir (CH_2Cl_2): 3538, 1684 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 2.54 (s, 3H), 6.70 (s, 1H), 7.27 (s, 1H), 10.07 (s, 1H); ms, *m/e* (rel. %): 153 (8), 152 (90), 151 (100), 124 (5), 123 (45). Exact Mass calcd. for $C_8H_8O_3$: 152.0474; found: 152.0472.

*2-Methyl-4,5-diacetoxybenzaldehyde, **3***

2-Methyl-4,5-dihydroxybenzaldehyde (0.206 g, 1.35 mmol), acetic anhydride (0.291 g, 0.27 mL, 2.1 equiv.), and pyridine (0.32 g, 3 equiv.) were dissolved in CH_2Cl_2 (15 mL) and stirred for 1.5 h. The mixture was poured into water (100 mL), stirred for 1 h, then extracted with CH_2Cl_2, washed with 10% aqueous HCl, dried ($MgSO_4$), and evaporated to give a pale yellow solid (0.31 g, 97%), which could be recrystallized from CH_2Cl_2; mp 93–96°C; ir (CH_2Cl_2): 1775, 1705, 1694 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 2.30_4 (s, 3H), 2.30_6 (s, 3H), 2.66 (s, 3H), 7.12 (s, 1H), 7.64 (s, 1H), 10.12 (s, 1H); ms, *m/e* (rel. %): 236 (3), 194 (25), 152 (100), 151 (29), 124 (23). Exact Mass calcd. for $C_{12}H_{12}O_5$: 236.0685; found: 236.0670.

*(1R,2S)-(−)-1-Hydroxy-6,7-diacetoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate of S-methyl lactate, **4***

2-Methyl-4,5-diacetoxybenzaldehyde **3** (0.093 g, 0.394 mmol), the acrylate of *S*-methyl lactate (0.094 g, 1.5 equiv.), and hydroquinone (2 mg) were dissolved in benzene and deoxygenated by flushing with nitrogen. The solution was irradiated (Hanovia 450-W, medium pressure mercury lamp, through 1 mm Pyrex) for 24 h, the solvent evaporated, and the residue chromatographed on silica gel (35–75% EtOAc/hexane) to give a colourless oil (0.132 g, 85%); $[\alpha]_D^{20}$ −24° (*c* 1.43, $CHCl_3$); ir (CH_2Cl_2): 3575, 3492, 1771 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 1.54 (d, 3H, *J* = 7.09), 2.00 (m, 1H), 2.15 (m, 1H), 2.26_5 (s, 3H), 2.26_8 (s, 3H), 2.80 (m, 3H), 3.78 (s, 3H), 4.90 (d, 1H, *J* = 9.54), 5.25 (q, 1H, *J* = 7.09), 6.91 (s, 1H), 7.47 (s, 1H); ms, *m/e* (rel. %): 394 (7), 352 (20), 310 (48), 292 (36), 249 (35), 223 (42). Exact Mass calcd. for $C_{19}H_{22}O_9$: 394.1264; found: 394.1266.

*1-Acetoxy-4,5-dimethoxybenzocyclobutene, **8***

A solution of 4,5-dimethoxyanthranilic acid (1.40 g, 7.08 mmol) in tetrahydrofuran (20 mL) was added to a refluxing solution of vinyl acetate (70 mL) and isoamyl nitrite (1.67 g, 1.9 mL, 2 equiv.) over a period of 30 min. After refluxing for 15 h, the vinyl acetate was evaporated on a rotary evaporator and the resulting brown-red oil distilled in a short path distillation apparatus (0.05 Torr (1 Torr = 133.3 Pa), 130°C) to give 1.24 g of red oil. This oil was chromatographed on silica gel (EtOAc/hexane) to give a pale yellow oil (0.71 g, 45%, solidifies on cooling), which nmr indicated was essentially free of impurities; mp 33–35°C; ir (CH_2Cl_2): 1737 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 2.10 (s, 3H), 3.14 (dd, 1H, *J* = 1.52, 13.9), 3.53 (dd, 1H, *J* = 4.30, 13.9), 3.85 (s, 3H), 3.86 (s, 3H), 5.80 (dd, 1H, *J* = 1.63, 4.30), 6.71 (s, 1H), 6.82 (s, 1H); ms, *m/e* (rel. %): 222 (20), 181 (11), 180 (100), 179 (47), 165 (16), 163 (15), 162 (21). Exact Mass calcd. for $C_{12}H_{14}O_4$: 222.0892; found: 222.0891.

*4,5-Dimethoxybenzocyclobutenol, **7***

Dimethoxybenzocyclobutenyl acetate **8** (0.458 g, 2.06 mmol) was stirred in methanol/NH_4OH (7:3, 10 mL) at room temperature for 6 h. The mixture was acidified with aqueous 10% HCl and extracted with CH_2Cl_2. The resulting crude product (yellow solid) was chromatographed on silica (EtOAc/hexane) to give colourless crystals (0.317 g, 85%); mp 107–109°C; ir (CH_2Cl_2): 3593 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 2.30 (s, 1H), 2.95 (dd, 1H, *J* = 1.4, 13.72), 3.50 (dd, 1H, *J* = 4.20,

13.72), 3.84 (s, 3H), 3.85 (s, 3H), 5.20 (dd, 1H, J = 1.4, 4.2), 6.70 (s, 1H), 6.80 (s, 1H); ms, m/e (rel. %): 181 (12), 180 (100), 179 (58), 165 (24), 151 (53). Exact Mass calcd. for $C_{10}H_{12}O_3$: 180.0787; found: 180.0781.

(1R,2S)-(−)-1-Hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate of S-methyl lactate, ***9***

Dimethoxybenzocyclobutenol **7** (88.0 mg, 0.489 mmol), the acrylate of *S*-methyl lactate (232 mg, 3 equiv., ref. 5), and hydroquinone (2 mg) were dissolved in toluene (7 mL) and refluxed for 6 h. The solvent was evaporated on a rotary evaporator and the resulting oil chromatographed on silica gel (eluant EtOAc/hexane) to give a pale yellow oil (153 mg, 93%), which appeared by nmr to be a mixture of one major and three minor (<9%) isomers. Careful rechromatography on silica gel (25% EtOAc/hexane) gave the major cycloadduct as a colourless oil that would solidify on cooling (132 mg, 80%); mp 76–78°C; $[\alpha]_D^{20}$ −31.6° (*c* 1.33, $CHCl_3$); ir (CH_2Cl_2): 3492, 1739 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.55 (d, 3H, J = 7.12), 2.00 (m, 1H), 2.15 (m, 1H), 2.80 (m, 3H), 3.80 (s, 1H), 3.84 (s, 3H), 3.87 (s, 3H), 4.92 (d, 1H, J = 9.12), 5.25 (q, 1H, J = 7.12), 6.55 (s, 1H), 7.17 (s, 1H); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ: 16.75, 23.73, 27.79, 48.84, 52.85, 55.81, 55.86, 68.68, 70.59, 109.43, 110.55, 127.51, 129.30, 147.56, 148.12, 172.19, 174.54; ms, m/e (rel. %): 339 (10), 338 (52), 321 (10), 320 (34), 233 (42), 206 (63), 205 (51). Exact Mass calcd. for $C_{17}H_{22}O_7$: 338.1367; found: 338.1372.

2S-(−)-6,7-Dimethoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate of S-methyl lactate, ***10***

Cycloadduct **9** (123 mg, 0.362 mmol) and 5% Pd/C (120 mg) were stirred in acetic acid/methanol (50:50, 15 mL) under 1 atm. of H_2 at room temperature for 15 h. The mixture was then filtered, evaporated to near dryness, dissolved in CH_2Cl_2 (50 mL), washed with 5% aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated to a colourless oil that crystallized on standing (95.5 mg, 82%); mp 67–68°C; $[\alpha]_D^{20}$ −37.3° (*c* 0.88, $CHCl_3$); ir (CH_2Cl_2): 1740 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.51 (d, 3H, J = 7.05), 1.85 (m, 1H), 2.20 (m, 1H), 2.70 (m, 3H), 3.00 (m, 2H), 3.75 (s, 3H), 3.85 (s, 6H), 5.14 (q, 1H, J = 7.05), 6.57 (s, 1H), 6.60 (s, 1H); ^{13}C nmr (75.5 MHz, $CDCl_3$) δ: 16.85, 25.61, 27.94, 31.09, 39.72, 52.25, 55.76, 66.28, 68.32, 111.33, 111.52, 126.35, 127.19, 147.02, 147.09, 171.19, 174.72; ms, m/e (rel. %): 322 (96), 192 (7), 191 (58), 190 (100), 189 (21), 175 (24), 176 (11). Exact Mass calcd. for $C_{17}H_{22}O_6$: 322.1416; found: 322.1425.

2S-(−)-6,7-Dimethoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid, ***11***

The ester **10** (113 mg, 0.349 mmol) and potassium carbonate (200 mg) were stirred in methanol/water (20:1, 20 mL) at room temperature for 15 h. Most of the solvent was then evaporated and the residue dissolved in 5% aqueous $NaHCO_3$, washed with CH_2Cl_2, acidified with 10% aqueous HCl, and finally extracted with ethyl acetate. Drying ($MgSO_4$) and evaporation gave a colourless solid that could be recrystallized from CH_2Cl_2/hexane (79.5 mg, 95%); mp 145.5–147°C; $[\alpha]_D^{20}$ −41.8° (*c* 0.67, $CHCl_3$); ir (CH_2Cl_2): 1708 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.85 (m, 1H), 2.25 (m, 1H), 2.75 (m, 3H), 2.95 (m, 2H), 3.84$_1$ (s, 3H), 3.84$_3$ (s, 3H), 6.58 (s, 1H), 6.59 (s, 1H); ms, m/e (rel. %): 237 (13), 236 (100), 191 (9), 190 (22), 175 (21), 164 (26), 159 (15). Exact Mass calcd. for $C_{13}H_{16}O_4$: 236.1049; found: 236.1046.

Benzyloxycarbamate of 2S-(−)-1-amino-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene, ***12***

Dimethoxytetralincarboxylic acid **11** (76.5 mg, 0.324 mmol), diphenylphosphoryl azide (107 mg, 1.2 equiv.), and triethylamine (39.4 mg, 1.2 equiv.) were refluxed in dry benzene for 2 h. Benzyl alcohol (105 mg, 3 equiv.) was added and the mixture refluxed a further 24 h. The solvent was then evaporated and the residual yellow oil chromatographed on silica gel (20% EtOAc/hexane) to give a colourless solid (88.5 mg, 80%); mp 130–131.5°C; $[\alpha]_D^{20}$ −23.3° (*c* 0.56, $CHCl_3$); ir (CH_2Cl_2): 1720 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.80 (m, 1H), 2.05 (m, 1H), 2.60 (dd, 1H, J = 16.0, 7.0), 3.05 (dd, 1H, J = 16.0, 4.80), 2.80 (m, 1H), 3.82 (s, 3H), 3.83 (s, 3H), 4.05 (m, 1H), 4.80 (d, 1H, J = 6.0), 5.10 (s, 2H), 6.52 (s, 1H), 6.57 (s, 1H), 7.35 (m, 5H); ms, m/e (rel. %): 341 (7), 233 (11), 191 (14), 190 (100), 91 (24), 77 (6). Exact Mass calcd. for $C_{20}H_{23}O_4N$: 341.1627; found: 341.1589.

Hydrochloride of 2S-(−)-1-amino-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene

A mixture of carbamate **12** (69.5 mg, 0.204 mmol) and 5% Pd/C (40 mg) in 10% anhydrous HCl in methanol (30 mL) was stirred under H_2 (1 atm) at room temperature for 8 h. The solution was filtered, and evaporated to leave a beige solid (48 mg, 97%) that could be recrystallized from methanol/ether; mp 213–214°C (lit. (4) mp 212–214°C); $[\alpha]_D^{20}$ −65.1° (*c* 0.215, CH_3OH) (lit. (4) $[\alpha]_D$ +73.2); ^1H nmr ($CDCl_3$) δ: 2.05 (m, 1H), 2.40 (m, 1H), 2.85 (m, 2H), 2.06 (dd, 1H, J = 15.4, 10.7), 3.25 (dd, 1H, J = 15.4, 4.38), 3.62 (m, 1H), 3.78 (s, 3H), 3.82 (s, 3H), 6.54 (s, 1H), 6.56 (s, 1H), 8.6 (bs, 3H).

2S-(−)-1-Amino-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene, ***13***

The hydrochloride salt of **13** (see above) (32 mg, 0.131 mmol) was dissolved in dilute aqueous base (0.1 M NaOH, 20 mL) and saturated aqueous NaCl (5 mL) was added. Extraction with CH_2Cl_2, drying ($MgSO_4$), and evaporation gave a colourless oil (16.1 mg, 60%) that solidified on cooling; mp 85–86°C; $[\alpha]_D^{20}$ −85.7° (*c* 0.105, CH_3OH), (lit. (4) $[\alpha]_D$ +86.5); ir (CH_2Cl_2): 3378, 3299 (weak) cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.5–1.74 (m, 3H), 1.98 (m, 1H), 2.50 (dd, 1H, J = 9.23, 15.75), 2.80 (m, 2H), 2.92 (dd, 1H, J = 4.68, 15.75), 3.16 (m, 1H), 3.84 (s, 6H), 6.55 (s, 1H), 6.58 (s, 1H); ms, m/e (rel. %): 208 (6.4), 207 (51), 192 (7.6), 191 (10), 190 (85), 175 (34), 165 (18), 164 (100). Exact Mass calcd. for $C_{12}H_{17}O_2N$: 207.1259; found: 207.1259.

Mosher's acid amide of 2S-(−)-1-amino-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene

The *S*-(−)-amide was prepared from the crude amine **13** using the literature method (4); ^1H nmr (C_6H_6) δ: 1.36 (m, 1H), 1.66 (m, 1H), 2.32 (dd, 1H, J = 15.8, 8.49), 2.43 (m, 2H), 2.81 (dd, 1H, J = 15.8, 5.05), 3.13 (m, 3H), 3.41 (s, 3H), 3.44 (s, 3H), 4.28 (m, 1H), 6.29 (s, 1H), 6.32 (s, 1H), 6.42 (d, 1H, J = 7.72), 7.02–7.2 (m, 3H), 7.74 (d, 2H, J = 7.75). The amide from the racemic amine exhibited the signals above as well as the signals for the other diastereomer. The two sets of signals were well resolved only in the aromatic region where the other diastereomer showed signals at δ 6.24 and 6.35.

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