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A concise enantioselective synthesis of 1-[(*S*)-3-(dimethylamino)-3,4 dihydro-6,7-dimethoxyquinolin-1(2*H*)-yl]propan-1-one, (*S*)-903

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ABSTRACT

A concise enantioselective synthesis of (*S*)-903, an inotropic agent, is described in nine linear steps and 95% ee based on asymmetric dihydroxylation of cinnamate ester and Co-catalyzed multifunctional reduction of several functional groups leading to the construction of core tetrahydroquinolin-3-ol, as the key steps.

1. Introduction

Substituted tetrahydroquinoline derivatives bearing various simple and complex substituents are of medicinal and industrial importance due to their pronounced activity in many physiological processes.[1,2] These core structures are present in numerous other pharmacological agents such as Sumanirole maleate (PNU9566 E) **1**, an anti-depressant agent for the treatment of Parkinson's disease,[3] Anachelin H **2**, a secondary metabolite recently isolated from the cyanobacterium *Anabaena cylindrica*, which serves as a ligand for iron (siderophores) mediating iron uptake,[4] and Vesnarinone **3**, a positive inotropic agent.[5] 1-[(*S*)-3-(Dimethylamino)-6,7-dimethoxytetrahydroquinoline propanone **4** has been identified as potentially interesting positive inotropic agent[6] (Fig. 1). Also, tetrahydroquinoline-based inhibitors have also been found to be the most potent among several structural classes of protein farnesyl transferase inhibitors.[7] Among the diverse strategies that have been devised for the synthesis of tetrahydroquinolines,[1b,8] the partial reduction of the heteroaromatic ring system has emerged as one of the most useful routes.[9] In contrast, only few methods currently exist in the literature for the asymmetric synthesis of 3-substituted tetrahydroquinolines. Prominent strategies include the oxidative aza-annulation of chiral amino acids;[10] the Rh-catalyzed reduction of α-amino cinnamates[11] and asymmetric dihydroxylation;[12] and the epoxidation[10] of olefins followed by cyclization with aromatic amino group. Notably, the reported synthesis of (*S*)-903 has been achieved by making use of chiral starting materials involving lengthy reaction sequences.[5]

In continuation with our studies on simultaneous reduction of multifunctional moieties,[13] we have recently reported a process involving a Co-catalyzed one-step reduction of nitro cyclic sulfite **5** to give the corresponding 3-hydroxytetrahydroquinoline **6**, which proceeds via the multifunctional reduction of several functional groups in a single step (Scheme 1).[14] We proposed that the simultaneous reduction of both nitro and cyclic sulfite groups takes place to give the unstable species **A**, which underwent cyclization to afford hydroxylactam **B**. Finally, the reduction of lactam carbonyl in **B** assisted by α-hydroxyl group resulted in the formation of tetrahydroquinoline **6.**

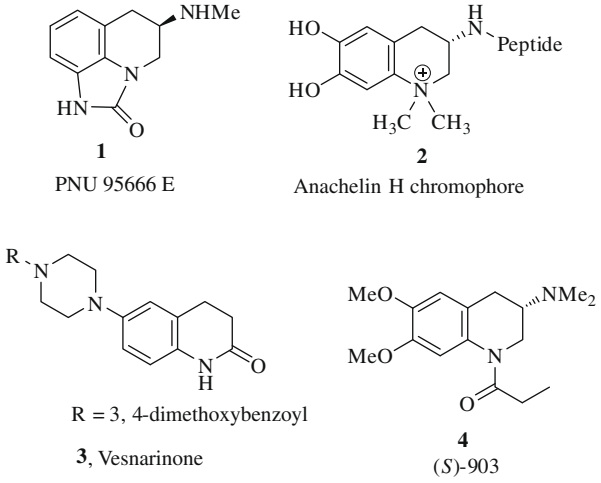

Figure 1. Structures of tetrahydroquinoline derivatives.

Herein, we report the application of this simple procedure for the asymmetric synthesis of 1-[(*S*)-3-(dimethylamino)-6,7-dimethoxytetrahydroquinoline-propanone, (*S*)-903 **4**.

2. Results and discussion

The asymmetric synthesis of (*S*)-903 **4** was carried out starting from commercially available 3,4-dimethoxybenzaldehyde, which

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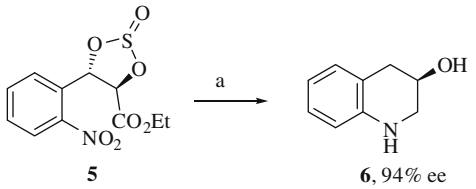


5 6, 94% ee

Scheme 1. Reagents and conditions: (a) $CoCl_2{\cdot}6H_2O$ (1 mol %), $NaBH_4$ (4 equiv), EtOH, 0–25 °C, 12 h.

on Wittig olefination produced (*E*)-ethyl 3-(3,4-dimethoxyphenyl)acrylate **7** in 95% yield. The Os-catalyzed asymmetric dihydroxylation[15] of (*E*)-ethyl 3-(3,4-dimethoxyphenyl)acrylate **7** was carried out using $(DHQ)_2$-PHAL as the chiral ligand to provide the chiral diol **8** in 95% yield. Initially, the regioselective nitration of the aromatic nucleus with concentrated HNO_3 was achieved, although in lower yields, when the reaction was carried out in acetic acid as solvent. However, the nitration with concentrated HNO_3 in CH_2Cl_2 as solvent proceeded smoothly to give nitro diol **9** as a single regioisomer in 70% yield. Nitro diol **9** was then treated with thionyl chloride to produce nitro cyclic sulfite **10** in quantitative yield.[16] When **10** was subjected to Co-catalyzed multifunctional reduction with $NaBH_4$, tetrahydroquinolin-3-ol **11** was obtained in 78% yield (Scheme 2). During this reduction process, we observed that the simultaneous reduction of the nitro, the reductive opening of cyclic sulfite, the reduction of ester moiety, and the cyclization, all had occurred in a single step to produce tetrahydroquinolin-3-ol **11** in high yields.[14] Mechanistically, we propose that simultaneous reduction of both nitro and cyclic sulfite groups in **10** takes place to give the unstable species **A**, which undergoes cyclization to afford hydroxylactam **B**. Finally, the reduction of lactum carbonyl in **B** assisted by α-hydroxyl group resulted in the formation of tetrahydroquinoline **11** (Scheme 3). The amine functionality in **11** was then protected as its amide **12** [$(EtCO)_2O$), Et_3N, CH_2Cl_2]. The enantiomeric purity of **12** was determined to be 95% ee by HPLC analysis. The free hydroxyl group in **12** was then activated as its mesylate **13** followed by its S_N2 displacement with NaN_3 gave the azidoamide **14** in 91% yield over two steps with complete inversion {$[\alpha]_D^{25} = +38.2$ (*c* 2, $CHCl_3$)}. The reduction of azide **14** [10% Pd/C, H_2 (1 atm), MeOH)] followed by dimethylation of the resulting amine (HCHO, HCO_2H, reflux) gave **4** in 73% yield and 95% ee {$[\alpha]_D^{25} = -3.2$ (*c* 1, EtOH), lit.[6] $[\alpha]_D^{25} = -3.3$ (*c* 1, EtOH)}.

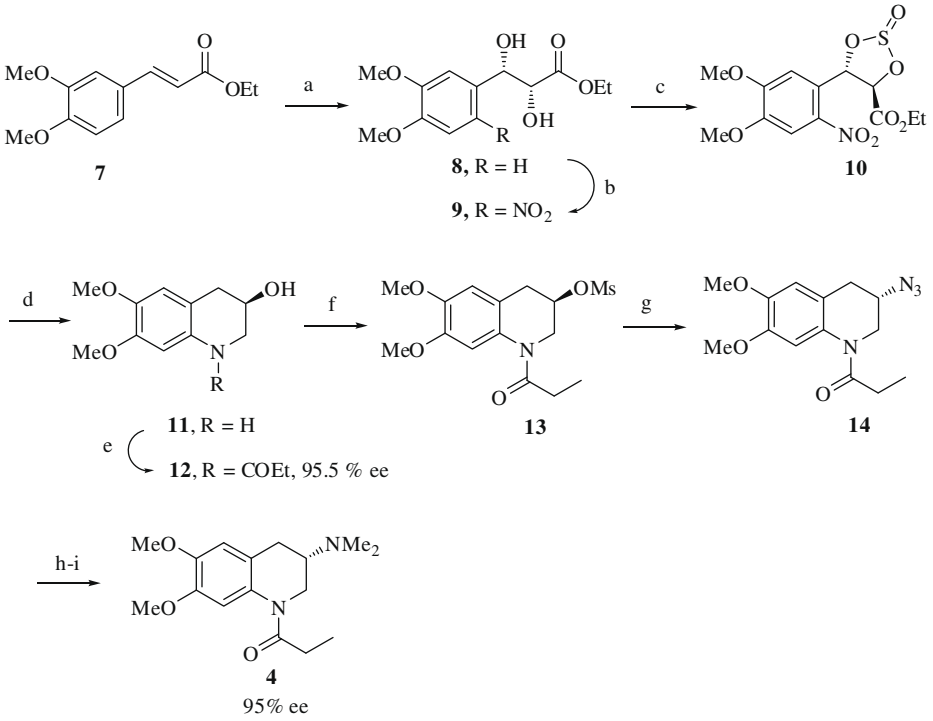
3. Conclusion

In conclusion, we have achieved the concise synthesis of (*S*)-903 **4** in nine linear steps with an overall yield of 24% and 95% ee by employing the asymmetric dihydroxylation of cinnamate ester coupled with a novel Co-catalyzed multifunctional reduction of several functional groups that led to the construction of tetrahydroquinoline core as the key steps.

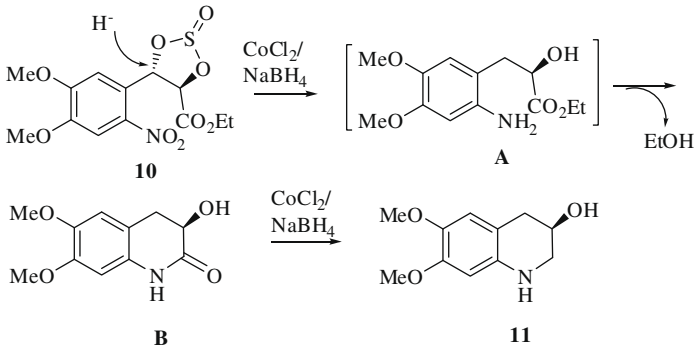
4. Experimental

4.1. General experimental

All melting points were measured on a Büchi 535 melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on Bruker AV200 MHz digital NMR spectrometer in $CDCl_3$ or CD_3OD. The solvents were purified and dried by the standard procedures prior to use; petroleum ether of the boiling range 60–80 °C was used for column chromatography. Optical rotations were measured using sodium D line on a JASCO-P-1020-polarimeter. Infrared spectra were recorded on Perkin–Elmer FT-IR spectrometer. Elemental analyses were carried out with a Carlo Erba CHNS-O analyzer. Enantiomeric excess of the products was determined by Mosher's ester analysis, Chiral HPLC [Column: Cromasil 5-Cellu-



Scheme 2. Reagents and conditions: (a) K_2OsO_4 (0.1 mol %), $(DHQ)_2$-PHAL (0.5 mol %), $K_3Fe(CN)_6$ (3 equiv), K_2CO_3 (3 equiv), $MeSO_2NH_2$ (1 equiv), *tert*-BuOH/H_2O (1:1), 25 °C, 24 h, 95%; (b) concd HNO_3, CH_2Cl_2, 0–25 °C, 30 min 70%; (c) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, 30 min; (d) $CoCl_2{\cdot}6H_2O$ (1 mol %), $NaBH_4$ (4 equiv), EtOH, 0–25 °C, 12 h, 78% over two steps; (e) $(EtCO)_2O$, Et_3N, CH_2Cl_2, 0 °C, 6 h, 82%; (f) MsCl, Et_3N, CH_2Cl_2, 0 °C, 10 min; (g) NaN_3, DMF, 80 °C, 12 h, 91% over two steps; (h) H_2 (1 atm), 10% Pd/C, MeOH, 25 °C, 12 h; (i) HCHO, HCO_2H, 80 °C, 3 h, 73% over two steps.



Scheme 3. Mechanistic pathway for the Co-catalyzed reduction of nitro cyclic sulfite.

Coat, Length 250 mm, i.d. 4.6 mm, wavelength: 220 nm], or comparing the specific rotation of the known compounds. All evaporations were performed under reduced pressure. For column chromatography, silica gel (230–400 mesh) was employed.

4.2. (*E*)-Ethyl 3-(3,4-dimethoxyphenyl)acrylate 7

To a stirred solution of 3,4-dimethoxybenzaldehyde (4.72 g, 20 mmol) in benzene (50 mL), $Ph_3P{=}CHCO_2Et$ (8.70 g, 25 mmol) was added. It was then refluxed for 4 h under a N_2 atmosphere. After completion of reaction, benzene was distilled out to give the crude product. Chromatographic purification of the crude product [silica gel (230–400 mesh) and petroleum ether/ethyl acetate (90:10) as eluent] afforded cinnamate **7** (4.5 g). Yield: 95%, gum; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34 (t, J = 7.1 Hz, 3H), 3.91 (s, 6H) 4.25 (q, J = 7.1 Hz, 2H), 6.29 (d, J = 15.9 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 7.04–7.14 (m, 2H), 7.61 (d, J = 15.9 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 14.1, 55.4, 55.5, 59.9, 109.3, 110.7, 115.6, 122.2, 127.1, 144.1, 148.9, 150.8, 166.6. Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.01; H, 6.77.

4.3. (2*R*,3*S*)-Ethyl 2,3-dihydroxy-3-(3,4-dimethoxyphenyl)propanoate 8

A 500-mL RB flask was charged with $K_3Fe(CN)_6$ (14.8 g mmol), K_2CO_3 (6.21 g, 45 mmol), $MeSO_2NH_2$ (1.42 g, 15 mmol), *tert*-BuOH (75 mL), and H_2O (75 mL). The reaction mixture was stirred for 10 min after which $(DHQ)_2$-PHAL (1 mol %) and K_2OsO_4 (0.2 mol %) were added and stirred for an additional 30 min. To the reaction mixture, ester **7** was added and allowed to stir for 24 h at 25 °C. After the completion of the reaction, sodium bisulfite (5 g) was slowly added at 0 °C. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layer was washed with brine (200 mL), dried over sodium sulfate, and concentrated under reduced pressure to yield the crude product. Flash column chromatographic purification [silica gel (230–400 mesh) and petroleum ether/EtOAc (60:40) as an eluent] afforded **8** in pure form. Yield: 95%; Gum, $[\alpha]_D^{25} = +3.5$ (c 1.5, $CHCl_3$); IR ($CHCl_3$): 848, 939, 1047, 1240, 1373, 1446, 1517, 1737, 2983, 3500 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.28 (t, J = 7.1 Hz, 3H), 3.88 (s, 3H), 3.90 (s, 3H), 4.27 (q, J = 7.1 Hz, 2H), 4.35 (d, J = 3.1 Hz, 1H), 4.95 (d, J = 3.1 Hz, 1H), 6.84–6.98 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.8, 55.6, 55.7, 61.7, 74.2, 74.8, 109.4, 110.6, 118.4, 132.4, 148.4, 148.6, 172.6. Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.47; H, 6.63.

4.4. (2*R*,3*S*)-Ethyl 2,3-dihydroxy-3-(4,5-dimethoxy-2-nitrophenyl)propanoate 9

To a stirred solution of diol **8** (2.70 g, 10 mmol) in CH_2Cl_2 (40 mL), concd HNO_3 (2 mL, d = 1.4) was added dropwise at 0 °C. The mixture was stirred for 30 min and progress of the reaction was monitored by TLC. After completion, 50 mL of water was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhyd Na_2SO_4, and concentrated under reduced pressure to give the crude product that was purified by column chromatography [silica gel (230–400 mesh) and petroleum ether/EtOAc (60:40) as an eluent] to give 2.2 g of **9** in pure form. Yield: 70%; yellow solid, mp: 131 °C; $[\alpha]_D^{25} = +105.2$ (c 1, $CHCl_3$); IR ($CHCl_3$): 787, 848, 937, 1049, 1240, 1371, 1747, 2985, 3460, 3640 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34 (t, J = 7.1 Hz, 3H), 3.95 (s, 3H), 4.01 (s, 3H), 4.33 (q, J = 7.1 Hz, 2H), 4.51(d, J = 2.2 Hz, 1H), 5.85 (d, J = 2.2 Hz, 1H), 7.33 (s, 1H), 7.65 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.3, 55.1, 55.3, 60.1, 69.0, 72.7, 106.1, 111.0, 132.3, 138.3, 146.6, 152.1, 171.6. Anal. Calcd for $C_{13}H_{17}NO_8$: C, 49.52; H, 5.43; N, 4.44. Found: C, 49.65; H, 5.23; N, 4.55.

4.5. Nitro cyclic sulfite 10

To a stirred solution of nitro diol **9** (1.90 g, 6.0 mmol) and triethylamine (3.00 mL, 18 mmol) in CH_2Cl_2 (20 mL), was added freshly distilled thionyl chloride (0.5 mL, 7 mmol) dropwise under a nitrogen atmosphere at 0 °C and allowed to stir at 0 °C for 30–45 min (monitored by TLC). The reaction mixture was quenched by the addition of cold water (20 mL) and a saturated solution of $NaHCO_3$ (20 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were washed with brine, dried over anhyd Na_2SO_4, and concentrated under reduced pressure to give crude nitro cyclic sulfite **10**. Nitro cyclic sulfite was found to be very labile and air sensitive, which was then subjected to Co-catalyzed reduction without purification. Yield: 92%; Gum; IR ($CHCl_3$): 648, 771, 914, 1066, 1278, 1340, 1525, 1585, 1748, 2976, 3028 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.35 (t, J = 7.2 Hz, 3H), 3.09 (s, 6H), 4.30–3.41 (q, J = 7.2 Hz, 2H), 6.12 (d, J = 5.9 Hz, 1H), 6.50 (d, J = 5.9 Hz, 1H), 7.28 (s, 1H), 7.68 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.54, 56.09, 56.27, 62.58, 83.58, 105.95, 109.60, 125.96, 139.36, 148.69, 153.77, 166.10.

4.6. (*R*)-1,2,3,4-Tetrahydro-6,7-methoxyquinolin-3-ol 11

To a stirred solution of nitro cyclic sulfite **10** (6 mmol) and $CoCl_2{\cdot}6H_2O$ (14 mg, 1 mol %) in 95% ethanol (30 mL), $NaBH_4$ (0.91 g, 24 mmol) was added at 0 °C and allowed to stir at 25 °C for 12 h. After completion of reaction, it was poured into ice cold water to form a black precipitate. To the aqueous layer, 100 mL of ethyl acetate was added, and the combined mixture was passed through Celite. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine (2 × 50 mL), dried over anhyd Na_2SO_4, and concentrated under reduced pressure to give the

crude product. Chromatographic purification of the crude product [flash silica gel (230–400 mesh) and petroleum ether/ethyl acetate/Et_3N (60:38:2)] gave 1.02 g of pure (*R*)-1,2,3,4-tetrahydro-6,7-methoxyquinolin-3-ol **11**. Yield: 78%; gum; $[\alpha]_D^{25} = +25.4$ (*c* 1.26, $CHCl_3$); IR ($CHCl_3$): 769, 1215, 1423, 1647, 3456 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.63–2.73 (dd, *J* = 3.9, 16.5 Hz, 1H), 2.85 (br s, 2H), 2.92–3.02 (dd, *J* = 4.3, 16.5 Hz, 1H), 3.20–3.22 (m, 2H), 3.78 (s, 3H), 3.79 (s, 3H), 4.13–4.22 (m, 1H), 6.12 (s, 1H), 6.50 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 34.2, 47.6, 55.5, 56.3, 63.3, 99.3, 110.1, 113.9, 137.2, 141.6, 148.0; MS: 209, 194, 176, 166, 148, 133, 120, 103, 91, 77, 65, 44. Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.09; H, 7.17; N, 6.61.

4.7. 1-[(*R*)-3, 4-Dihydro-3-hydroxy-6,7-dimethoxyquinolin-1(2*H*)-yl]propan-1-one 12

To a stirred solution of tetrahydroquinolin-3-ol **11** (4 mmol) and Et_3N (1.4 mL, 10 mmol) in 20 mL of CH_2Cl_2, propionic anhydride (6.5 mL, 5 mmol) was added at 25 °C, and was stirred for 3 h. The progress of the reaction was monitored by TLC and after completion of reaction, saturated aq $NaHCO_3$ (30 mL) was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine (2 × 25 mL), dried over anhyd Na_2SO_4, and concentrated under reduced pressure to give the crude product. Chromatographic purification [silica gel (230–400 mesh) and petroleum ether/ethyl acetate (60:40)] of the crude product gave amido alcohol **12** in pure form. Yield: 82%; Gum; Chiral Column: Cromasil 5-CelluCoat column, length 250 mm, i.d. 4.6 mm, wavelength: 220 nm, flow rate 0.8 mL per min. Mobile phase: 10% isopropyl alcohol in hexane. Retention time: 27.608 (97.7%) and 30.850 (2.2%). Ee = 95.5%; $[\alpha]_D^{25} = +8.7$ (*c* 1.15, $CHCl_3$); IR ($CHCl_3$): 846, 937, 1240, 1388, 1514, 1660, 1751, 2983, 3529 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.18 (t, *J* = 7.3 Hz, 3H), 2.56 (q, *J* = 7.3 Hz, 2H), 2.67–2.78 (dd, *J* = 4.6, 16.5 Hz, 1H), 2.98–3.09 (dd, *J* = 5.4, 16.5 Hz, 1H), 3.86 (s, 6H), 3.74–3.95 (m, 2H), 4.32 (m, 1H), 6.63 (br s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 8.6, 27.4, 35.0, 49.7, 55.6, 65.0, 108.0, 111.1, 122.4, 130.7, 146.3, 174.3; MS: 265, 209, 194, 176, 166, 148, 133, 120, 104, 91, 77, 57, 44. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.43; H, 7.19; N, 5.22.

4.8. (*R*)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-propionylquinolin-3-yl methane-sulfonate 13

To a stirred solution of amide **12** (4 mmol) and triethyl amine (1.4 mL, 10 mmol) in 20 mL of CH_2Cl_2, methane sulfonyl chloride (5 mmol, 0.5 mL) was added at 0 °C. It was then stirred for 15 min. After completion of the reaction (monitored by TLC), a saturated aq solution of $NaHCO_3$ (30 mL) was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine (2 × 25 mL), dried over anhyd Na_2SO_4, and concentrated under reduced pressure to give crude mesylate. An attempt to purify mesylate was unsuccessful as they undergo elimination readily. Since the mesylate was difficult to purify, it was converted to the corresponding azide without purification. However, the formation of mesylate **13** was confirmed by its TLC, ^1H and ^{13}C NMR spectra. ^1H NMR (200 MHz, $CDCl_3$): δ 1.18 (t, *J* = 7.3 Hz, 3H), 2.52 (q, *J* = 7.3 Hz, 2H), 3.04 (s, 3H), 2.95–3.22 (m, 2H), 3.72–3.82 (m, 1H) 3.86 (s, 6H), 3.81–3.92 (m, 1H), 4.06–4.33 (m, 1H), 5.22 (m, 1H), 6.63 (br s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 9.6, 27.4, 33.0, 38.3, 46.4, 55.8, 74.3, 108.2, 11.0, 128.5, 130.9, 147.1, 173.6.

4.9. 1-[(*R*)-3-Azido-3,4-dihydro-6,7-dimethoxyquinolin-1(2*H*)-yl]propan-1-one 14

To a stirred solution of mesylate **13** in dry DMF (10 mL), was added NaN_3 (1.30 g, 20 mmol). It was then stirred for 16 h at 80 °C. After completion of the reaction (monitored by TLC), it was poured into 50 mL of ice cold water and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (2 × 25 mL), dried over anhyd Na_2SO_4, and concentrated under reduced pressure to give the crude product. Chromatographic purification of the crude product [silica gel (230–400 mesh) and petroleum ether/ethyl acetate (70:30)] gave azide **14** in pure form. Yield: 91%; Gum; $[\alpha]_D^{25} = +38.2$ (*c* 2, $CHCl_3$); IR ($CHCl_3$): 757, 1043, 1217, 1514, 1650, 1735, 2110, 3018 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.22 (t, *J* = 7.3 Hz, 3H), 2.57 (q, *J* = 7.3 Hz, 2H), 2.78–2.88 (dd, *J* = 5.5, 16.0 Hz, 1H), 3.04–3.15 (dd, *J* = 5.4, 16.6 Hz, 1H), 3.72–3.82 (m, 1H) 3.89 (s, 3H), 3.90 (s, 3H), 3.99–4.13 (m, 2H), 6.68 (br s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 9.5, 27.4, 31.7, 46.5, 55.7, 55.8, 56.1, 108.1, 110.9, 119.8, 130.8, 146.8,146.9, 173.3. Anal. Calcd for $C_{14}H_{18}N_4O_3$: C, 57.92; H, 6.25; N, 19.30. Found: C, 57.88; H, 6.20; N, 19.33.

4.10. 1-[(*R*)-3-(Dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1(2*H*)-yl]-propan-1-one 4

To a solution of azide **14** (2 mmol) in methanol (10 mL), was added 10% Pd/C (40 mg). It was stirred under H_2 (1 atmosphere, balloon pressure) for 12 h. After completion of reaction (monitored by TLC), it was passed through column packed with Celite and concentrated under reduced pressure to afford the crude amine. To the crude amine, 40% aq solution HCHO (1 mL) and HCO_2H (2 mL) were added, and the resulting mixture was refluxed for 3 h. After completion of the reaction, a saturated aq $NaHCO_3$ solution (10 mL) was added, and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with brine (2 × 20 mL), dried over anhyd Na_2SO_4, and concentrated under reduced pressure. Chromatographic purification of the crude product [silica gel (230–400 mesh) and petroleum ether/ethyl acetate/triethyl amine (60:38:2) as eluent] gave pure (*S*)-903 **4**. Yield: 73%; mp 136 °C [lit.[5] 135–137 °C]; $[\alpha]_D^{25} = -3.2$ (*c* 1, EtOH) {lit. $[\alpha]_D^{25} = -3.3$ (*c* 1, EtOH)};[5] IR ($CHCl_3$): 760, 1049, 1211, 1511, 1647, 1743, 3018, 3450 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.12 (t, *J* = 7.3 Hz, 3H), 2.35 (s, 6H), 2.46 (q, *J* = 7.3 Hz, 2H), 2.80–2.91 (m, 2H), 3.23–3.54 (m, 2H), 3.82 (s, 3H), 3.83 (s, 3H), 6.64 (br s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 9.8, 27.5, 29.5, 41.3, 41.4, 55.9, 55.9, 61.4, 61.8, 108.2, 111.1, 128.6, 131.8, 146.9, 173.0. Anal. Calcd for $C_{15}H_{21}N_2O_3$: C, 64.96; H, 7.63; N, 10.10. Found C, 64.82; H, 7.60; N, 10.27.

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