Total synthesis of (-)-praziquantel: an anthelmintic drug

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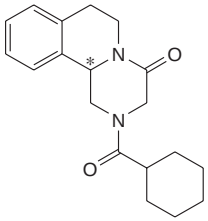
The optically pure (–)-praziquantel was synthesised using phenylethylamine as starting material in 12% overall yield. The key step was achived by a chiral auxiliary mediated Pictet–Spengler reaction.

Keywords: (-)-praziquantel, total synthesis, Pictet–Spengler reaction

Praziquantel (PZQ), 2-cyclohexylcarbonyl-1,2,3,6,7,11b-hexahydro-4*H*-pyrazino[2,1- *a*] isoquinoline-4-one, is an anthelmintic drug with a broad activity against trematodes and schistosomes. PZQ is included in the WHO Model List of Essential Drugs because it is the drug of first choice in the treatment of schistosomiasis. According to the WHO, an estimated of 200 million people are infected with schistosomiasis.[1]



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(–)-Praziquantel has the advantage of high efficacy and low toxicity compared with *rac*-praziquantel because the therapeutic effect of praziquantel resides in its (–)-isomer.[2] Since a short review on the synthesis of praziquantel was reported in 1978,[3] several approaches for the synthesis of praziquantel have appeared.[4] The total systhesis of optically pure (–)-praziquantel has not been reported to date. In order to obtain optically pure (–)-praziquantel, enantiopure tetrahydro-isoquinoline **5** based on a chiral auxiliary mediated Pictet–Spengler reaction was synthesised (Scheme 1).[5]

Enantiopure *N*-*p*-tolylsulfinylphenylethylamines **2** was prepared by treatment of the corresponding phenylethylamine with *n*-butyllithium. Reaction of the anion with the commercially available Andersen reagent (1*S*,2*R*,5*S*)-menthyl-(*R*)-*p*-toluene-sulfinate afforded **2** in 83% yield and excellent enantiopurity.

The *N*-acetalphthalimide **3** was obtained by treatment of phthalimide and bromoacetal in the presence of KOH as base and toluene as solvent at 80 °C. Reaction of **2** with **3** in the presence of BF_3-OEt_2 resulted in the desired ring-closed product **4** in high yield and good diastereoselectivity based on a chiral auxiliary mediated Pictet-Spengler reaction.[6] Removal of the chiral auxiliary proceeded without racemization upon treatment with HCl in ethanol at 0 °C. The diastereomerically pure tetrahydro-isoquinoline **5** was obtained in good yield and excellent enantiopurity.

Treatment of **5** with hydrazine monohydrate in ethanol at reflux afforded **6** in 88% yield. Reaction of **6** with cyclohexanecarbonyl chloride in dichloromethane in the presence of potassium carbonate afforded **7** in 95% yield. Finally, treatment of **7** with chloroacetyl chloride in the presence of potassium carbonate as base and DMF as solvent and warming from room temperature to 80 °C furnished firstly intermediate **8**. Intermediate **8** was easily transformed into (–)-praziquantel under the same conditions in 82% overall yield and excellent enantiopurity (Scheme 2).

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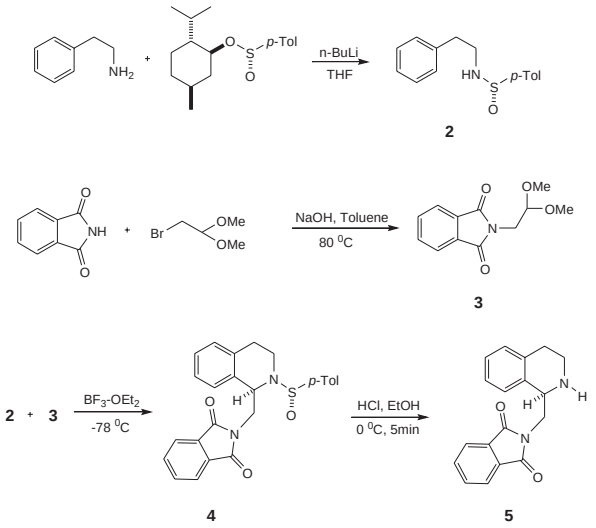
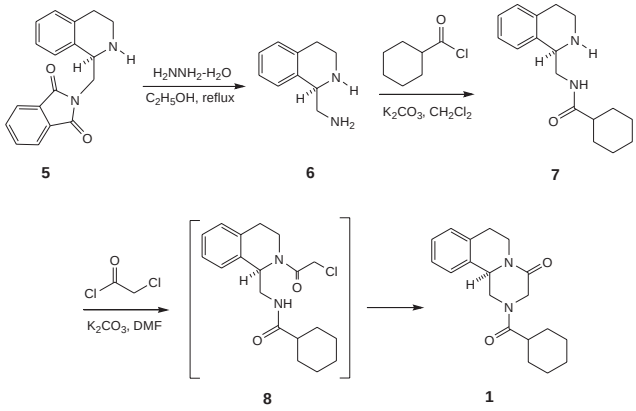


Scheme 1



Scheme 2

In summary, we have reported an efficient synthetic route of (-)-praziquantel in which the commercially available phenylethylamine, phthalimide and bromoacetal were used as starting materials. Enantiopure tetrahydro-isoquinoline **5** as key intermadiate was obtained by a chiral auxiliary mediated Pictet-Spengler reaction.

Experimental

N-p-Tolylsulfinyl phenylelhylamine (**2**): To a solution of phenylethylamine (10 mmol) in THF (100 ml) at -78 °C was added a solution of *n*-BuLi (11 mmol) in hexane. The reaction mixture was allowed to warm to room temperature and added to a solution of (1*S*,2*R*,5*S*)-menthyl- (*R*)-*p*-toluenesulfinate (10 mmol) in THF. The reaction was quenched after 1 h by the addition of an aqueous solution of Na_2HPO_4 (50 ml, 1 M). Extractive workup and recrystallisation yielded **2** (83%), $[\alpha]_D$ = –63.1 (C = 0.5, acetone), ^{1}H NMR (300 MHz, $CDCl_3$): 6.92–7.36 (m, 9H), 5.20 (s, 1H),

2.78–3.09 (m, 4H), 2.25 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): 137.7, 134.2, 132.5, 128.1, 127.2, 126.8, 125.7, 122.5, 43.2, 33.0, 20.6; MS (*m/z*): 259.4(calculated:259.4).

N-Dimethoxyacetal of phthalimide (**3**): To a solution of phthalimide (10 mmol) in toluene (100 ml) was added NaOH (12 mmol) and bromoacetal (12 mmol). The reaction mixture was heated to 80 °C for 10 h and then cooled to room temperature. The solvent was removed *in vacuo*. To residue was added water (50 ml) and CH_2Cl_2 (50 ml) and stirred for 10 min. The mixture was separated and the aqueous layer was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$ and the solvent was removed *in vacuo*. Recrystallisation yielded **3** (87%), ^{1}H NMR (300 MHz, $CDCl_3$): 7.92–8.16 (m, 2H), 7.56–7.71(m, 2H), 4.78 (t, *J* = 5.4 Hz, 1H), 3.85 (d, *J* = 7.0 Hz, 2H), 3.32 (s, 6H); ^{13}C NMR (300 MHz, $CDCl_3$): 163.6, 133.2, 131.8, 126.6, 95.9, 48.4, 45.0; MS (*m/z*): 235.2 (calculated:235.2).

Preparation of the tetrahydroisoquinoline (**4**): A solution of **2** (3 mmol) and **3** (4.5 mmol) in dry methylene chloride (50 ml) was cooled to –78 °C. BF_3-OEt_2 (6 mmol) was added and the reaction mixture was stirred at –78 °C for 3 h. The reaction was quenched with triethylamine, and the solvents were removed *in vacuo*. Separation of the diastereomers using flash chromatography with gradient elution yielded **4** (63%), $[\alpha]_D$ = –105.2 (C = 0.5, acetone), ^{1}H NMR (300 MHz, $CDCl_3$): 6.95–8.09 (m, 12H), 4.92 (dd, *J* = 12.9 Hz, 4.2 Hz, 1H), 4.25 (d, *J* = 13.6 Hz, 1H), 3.93 (d, *J* = 13.6 Hz, 1H), 2.77–3.15 (m, 4H), 2.25 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): 164.5, 137.8, 136.3, 135.2, 134.8, 132.5, 132.2, 129.1, 128.6, 126.9, 126.5, 125.0, 122.2, 118,7, 47.3, 45.6, 42.7, 28.3, 19.2; MS (*m/z*): 431.6 (calculated:431.5).

Hydrolysis of the tolylsulfinate (**5**): Concentrated hydrochloric and (0.5 ml) was added to a solution of **4** (1.2 mmol) in ethanol (10 ml) at 0 °C. After stirring for 5 min at 0 °C a saturated solution of K_2CO_3 (10 ml) was added. Extractive workup and flash chromatography yielded **5** (82%), $[\alpha]_D$ = –60.7° (C = 0.5, acetone), ^{1}H NMR (300 MHz, $CDCl_3$): 7.25–8.07 (m, 8H), 4.76 (dd, *J* = 10.5 Hz, 2.5 Hz, 1H), 4.38 (d, *J* = 15.0 Hz, 1H), 4.05 (d, *J* = 15.0 Hz, 1H), 2.78–3.05 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$): 163.8, 138.6, 136.2, 133.7, 132.9, 132.0, 130.5, 129.6, 126.7, 123.4, 51.5, 49.2, 48.3, 31.4; MS (*m/z*): 292.4 (calculated:292.3).

Hydrolysis of the phthalimide (**6**): Hydrazine monohydrate (1 mmol) was added to a solution of **5** (0.8 mmol) in ethanol (6 ml), and the mixture was stirred at reflux for 4 h. The reaction mixture was cooled to room temperature. The solvents were removed *in vacuo*. Recrystallisation yielded **6** (88%), $[\alpha]_D$ = –55.6 (C = 0.5, acetone), ^{1}H NMR (300 MHz, $CDCl_3$): 7.10–7.27 (m, 4H), 4.53 (dd, *J* = 10.5 Hz, 3.3 Hz, 1H), 3.32 (d, *J* = 8.6 Hz, 1H), 3.01 (d, *J* = 7.8 Hz, 1H), 2.68–2.96 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$): 136.7, 134.2, 129.5, 128.0, 125.5, 123.8, 56.2, 52.1, 48.2, 30.3; MS (*m/z*): 162.2 (calculated:162.2).

1-[N-Cyclotexylcarbonylamido methyl]-tetrahydroisoquinolone (**7**): Potassium carbonate (1 mmol) and cyclohexanecarbonyl chloride (0.6 mmol) were added to a solution of **6** (0.5 mmol) in dry methylene chloride (6 ml). The mixture was stirred at room temperature for 10 h. The reaction was quenched with a saturated solution of NH_4Cl (10 ml). The mixture was separated and the aqueous layer was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$ and the solvent was removed *in vacuo*. Flash chromatography yielded **7** (95%), ^{1}H NMR (300 MHz, $CDCl_3$): 7.11–7.27 (m, 4H), 6.20 (s, 1H), 4.82 (dd, *J* = 10.5 Hz, 4.2 Hz, 1H), 3.82 (d, *J* = 12.9 Hz, 1H), 3.45 (d, *J* = 15.0 Hz, 1H), 2.71–3.93 (m, 4H), 2.35 (m, 1H), 1.32–1.78 (m, 10H); ^{13}C NMR (300 MHz, $CDCl_3$): 175.2, 138.8, 137.6, 129.3, 127.0, 126.4, 124.5, 52.3, 50.6, 47.7, 37.6, 30.8, 26.9, 26.3, 24.1; MS (*m/z*): 272.4 (calculated:272.4).

(–)-Praziquantel (**1**): Potassium carbonate (2 mmol) and chloroacetyl chloride (0.36 mmol) were added to a solution of **7** (0.3 mmol) in dry DMF (3 ml). The mixture was stirred at room temperature for 12 h, and then heated to 90 °C for 10 h. The reaction was quenched with a saturated solution of NH_4Cl (5 ml) and CH_2Cl_2 (5 ml) was added. Extractive workup and flash chromatography yielded **1** (57%), m.p. 135–137 °C, $[\alpha]_D$ = –58.6 (C = 0.5, CH_2Cl_2), IR (KBr, cm^{-1}): 2935, 2852, 1648, 1465; ^{1}H NMR (300 MHz, $CDCl_3$): 7.18–7.29 (m, 4H), 5.05 (dd, *J* = 12.8 Hz, 2.5 Hz, 1H), 4.67–4.80 (m, 2H), 4.48 (d, *J* = 17.2 Hz, 1H), 4.06 (d, *J* = 17.2 Hz 1H), 2.80–2.95 (m, 4H), 2.46 (m, 1H), 1.28–1.80 (m, 10H); ^{13}C NMR (300 MHz, $CDCl_3$): 174.7, 164.6, 135.1, 132.7, 129.5, 127.7, 127.1, 125.6, 55.3, 48.1, 45.5, 41.0, 39.1, 29.4, 29.2, 28.0, 25.8; MS (*m/z*): 312.2 (calculated: 312.2).

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6 Diastereomeric ratio determined by ^{1}H-NMR is 93:7, $[\alpha]_D$= –51.6 (C = 0.5, CH_2Cl_2) and yield is 88%.