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Enantioselective synthesis of (1*R*)-1-(hydroxymethyl)-2-acetyl-1,2,3,4-tetrahydro-β-carboline from L-(+)-tartaric acid

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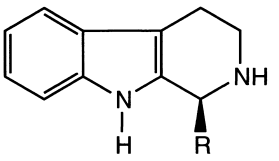
Abstract

(1*R*)-1-(Hydroxymethyl)-2-acetyl-1,2,3,4-tetrahydro-β-carboline was synthesized in several steps from tryptamine and L-(+)-tartaric acid in good enantiomeric purity (98% ee). The absolute stereochemistry was assigned.

1. Introduction

The tetrahydro-β-carbolines are present in many organisms where they play a remarkable role. Their biological activity has been the subject of extensive scientific research. It has been confirmed that β-carbolines are psychoactive compounds found in the mammalian body.[1,2] Moreover, hallucinogenic activity of β-carbolines is the major reason for a lot of attention being paid to their potential usage as psychotherapeutic drugs.[3] Due to these facts, several strategies for the synthesis of tetrahydro-β-carboline ring systems such as tetrahydroharmane **1**,[4] and the analogue **2**[5] have been developed.



1 R = CH_3
2 R = Benzyl

During the formation of the tetrahydro-β-carboline ring system via the Pictet–Spengler reactions, L-tryptophan,[6] L-tryptophan methyl ester[7] or its *N*-substituted derivatives such as *Abrine* methyl ester[8] and *N*-benzyltryptophan methyl ester[9] are most frequently utilized as sources of chirality. However, there are also examples of the asymmetric Pictet–Spengler reaction using chiral

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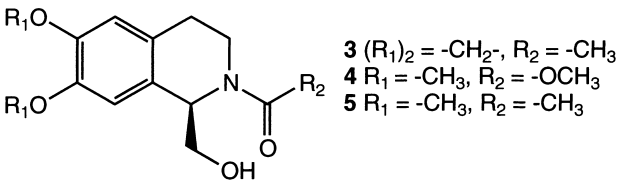
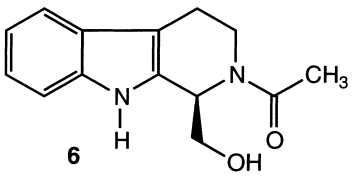
aldehyde substrates[10] and similar reactions using azalactones[11] as arylacetaldehyde equivalents. The chiral Lewis acid-promoted cyclization of nitrones has also been utilized.[12,13] An important entry to indole alkaloids is achieved by the Bischler–Napieralski reaction which is of significance in this area of chemistry. The Bischler–Napieralski reaction is very often used in tetrahydroisoquinoline construction when the induction of chirality can be realized by the stereoselective reduction of 1-substitued 3,4-dihydroisoquinolinium salt possessing a chiral auxiliary,[14] nucleophilic additions to *N*-substituted isoquinolinum salt,[15,16] catalytic asymmetric hydrogenation with chiral iridium(I) complexes,[17,18] or with the thiazazincolidine complex.[19]

2. Results and discussion

In our previous studies on the enantioselective synthesis of isoquinoline alkaloids we have found that compounds **3**–**5** may serve as a crucial chiral substrate in several approaches.[20,21] Consequently, we regarded compound **6** as capable of playing an analogous role in indole alkaloid chemistry.

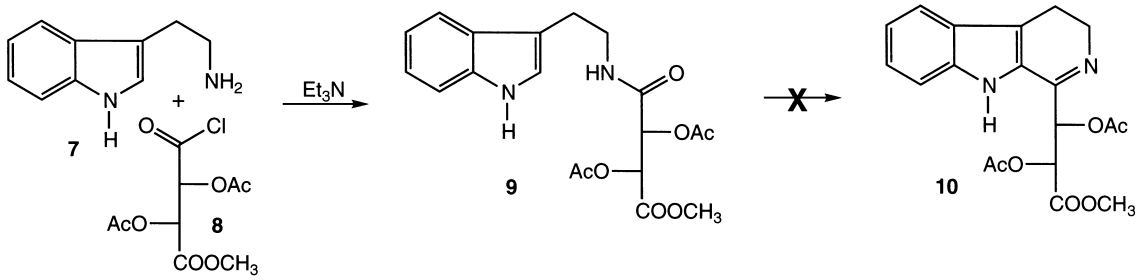


3 $(R_1)_2$ = -CH_2-, R_2 = -CH_3
4 R_1 = -CH_3, R_2 = -OCH_3
5 R_1 = -CH_3, R_2 = -CH_3



6

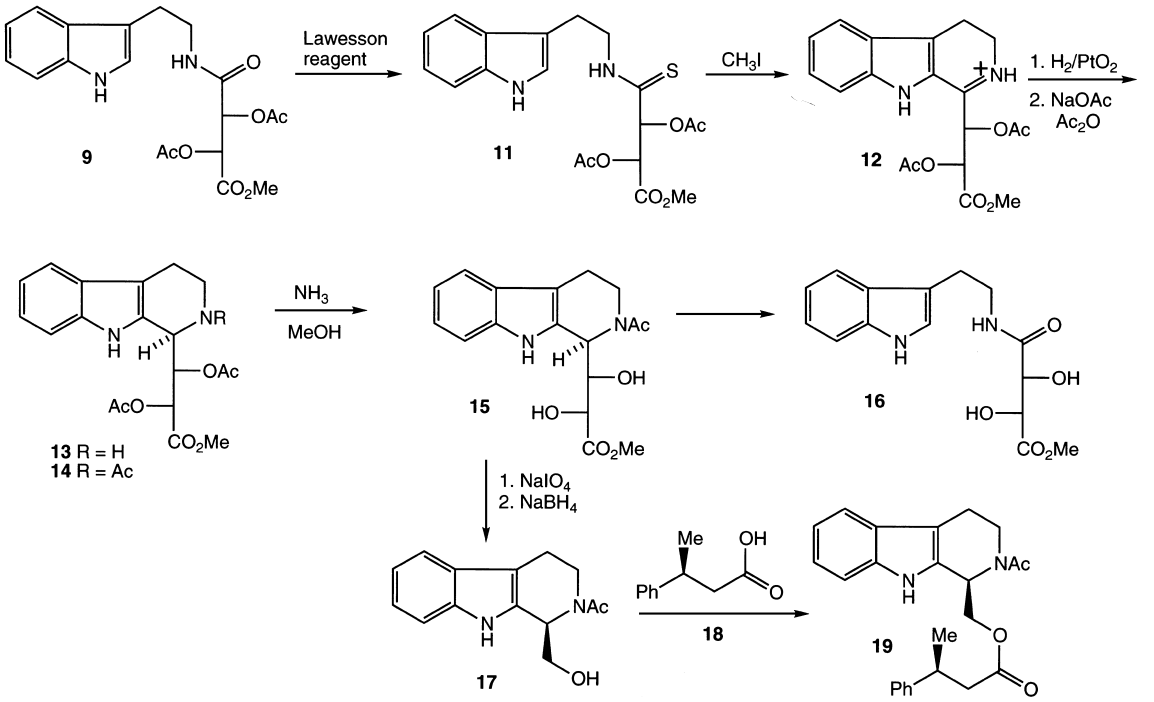
Being encouraged by positive results in the use of L-(+)-tartaric acid[21] as a chiral inductor, we decided to apply the same approach in the indole series. Natural tartaric acid was converted to its derivative methyl 2,3-di(acetoxy)-4-chloro-4-oxobutanoate **8** by the known procedure.[22,23] The condensation of tryptamine **7** with compound **8** in the presence of triethylamine in dry tetrahydrofuran gave compound **9** in 97% yield (Scheme 1).



Scheme 1.

Simple amides derived from biogenic amines usually cyclize to form the corresponding isoquinoline or β-carboline systems only under rather drastic conditions, and this process sometimes tends to be accompanied by an extensive decomposition. Indeed, all our attempts to cyclize amide **9** failed, despite the use of virtually all known Bischler–Napieralski conditions. We therefore decided to apply a rather rarely used method introduced by Ishida[24] which consists of a conversion of the amide into a thioamide followed by methyl iodide-assisted cyclization. Thus, amide **9** was treated with Lawesson reagent[25] to give thioamide **11** in excellent yield. Subsequent

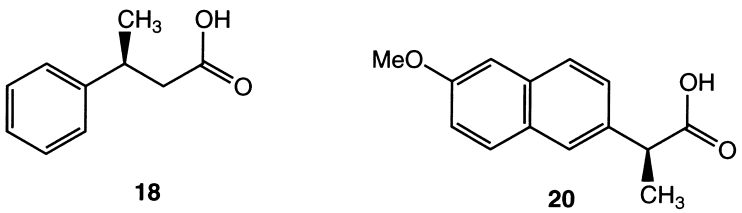
treatment with methyl iodide in aprotic solvent brought about the formation of the salt **12** in good yield (Scheme 2).



Scheme 2.

The catalytic hydrogenation of compound **12** gave intermediate amine **13**. We had already observed that aminoesters related to compound **13** were very unstable and sensitive to air oxidation. Therefore, compound **13** was acetylated without isolation, finally giving compound **14** in 70% yield. Treatment of **14** with ammonia in methanol at 0°C gave compound **15** but prolonged contact with the base promoted an undesirable ring-opening reaction that gave amide **16** as a predominant product (Scheme 2). Immediate treatment of **15** with sodium periodate followed by in situ borohydride reduction allowed us to overcome the problem (Scheme 2). Eventually, final alcohol **17** was isolated in 42% yield (from salt **12**).

The enantiomeric purity of compound **17** was found to be above 98% ee on the basis of a ^{19}F NMR experiment of its Mosher acid ester, prepared from (*R*)-(+)-MPTA.[26] In order to establish the absolute configuration at the C-2 carbon centre, we first utilized (*S*)-(+)-naproxen **20** as a source of known stereochemistry. Surprisingly, a BOP-mediated esterification of **17** with (*S*)-(+)-naproxen **20** caused complete racemization of the acidic component.[27]



Consequently, we chose another chiral, non-racemic acid less prone to racemization. Indeed, when (*S*)-3-phenylbutyric acid **18** of known absolute configuration[28] was used in the same conditions as in the case of naproxen, an ester **19** was formed as a sole product, from which a crystal, suitable for the X-ray analysis, was obtained. The absolute stereochemistry at C-2 carbon atom within a β-carboline moiety was then established as (*R*) (Fig. 1). This result provides clear indication of a stereochemical outcome of the hydrogenation step of salt **12**. It is interesting to note, however, that the opposite chirality is formed during an analogous procedure in the isoquinoline series[29,30] also starting from natural tartaric acid.

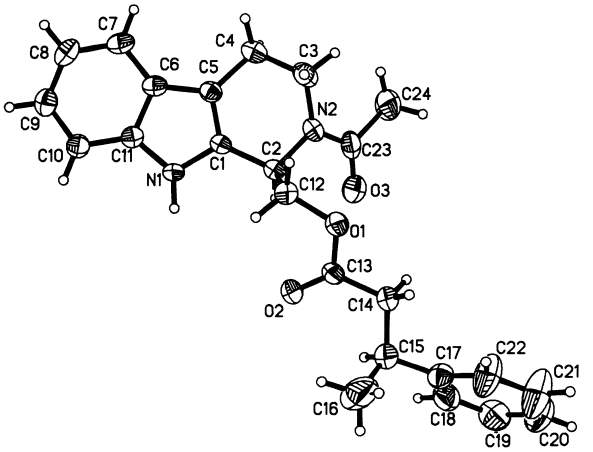


Figure 1. ORTEP diagram for compound **19**

In conclusion, L-(+)-tartaric acid has proved to be an effective chiral precursor in the asymmetric synthesis of β-carboline derivatives.

3. Experimental

NMR spectra were recorded on a Varian Unity Plus spectrometer operating at 500 MHz for ^{1}H NMR and at 125 MHz for ^{13}C NMR and 471 MHz for ^{19}F NMR. Tetramethylsilane (TMS) or solvents were used as internal standards. Chemical shifts are reported in ppm. Mass spectra were collected on an AMD 604 apparatus; high resolution mass spectra were acquired using LSIMS (positive ion mode). Optical rotation was measured on a Perkin–Elmer 247 MC polarimeter. TLC analyses were performed on Merck 60 silica gel glass plates and visualized using iodine vapour. Column chromatography was carried out at atmospheric pressure using silica gel 60 (230–400 or under 400 mesh, Merck). X-Ray intensity data for **19** were measured at $T = 293$ K on a Kuma KM4 diffractometer with MoKα radiation ($\lambda = 0.71073$ Å). Structure was solved by direct methods, aided by the XS program,[32] and refined with full-matrix least-squares method using the XL program from SHELXTL.[33]

3.1. Preparation of compound *9*

A suspension of 9.84 g (50 mmol) of tryptamine hydrochloride **7** and 19 mL (150 mmol) of triethylamine in 200 mL of dry 1,4-dioxan was stirred magnetically under argon. To the above

reaction mixture a solution containing 20 g (75 mmol) of compound **8**[22,23] in 100 mL of dry 1,4-dioxane was introduced dropwise. The reaction was stirred at room temperature for 15 hours. The solvent was then evaporated in vacuo and the residue was dissolved in 200 mL of chloroform. The organic phase was washed with $NaCl_{aq}$, HCl (1%, aqueous), $NaHCO_{3aq}$, and dried ($MgSO_4$). Evaporation of the solvent gave a foam, which was crystallized from ether to yield 18.9 g (48.5 mmol, 97%) of compound **9**.

Analytical data for compound **9**: mp 125–126°C; $[\alpha]_D^{23} = -23.0$ (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ: 8.20 (1H, s, NH), 7.60–7.05 (5H, m), 6.30 (1H, t, J = 6 Hz, amide NH), 5.70 (1H, d, J = 2.5 Hz), 5.60 (1H, d, J = 2.5 Hz), 3.70 (3H, s), 3.65 (2H, m, J = 6.5 Hz, J = 6 Hz), 3.00 (2H, t, J = 6.5 Hz), 2.05 (3H, s), 1.90 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 169.5, 168.7, 167.4, 165.4, 136.4, 127.3, 122.4, 122.2, 119.8, 118.5, 112.5, 111.4, 71.8, 71.4, 52.8, 39.9, 25.1, 20.3, 20.3.

3.2. Preparation of compound **11**

A mixture of 18.0 g (46.1 mmol) of compound **9** and 11.19 g (27.66 mmol) of Lawesson's reagent in 250 mL of 1,2-DME was stirred at reflux under argon. When all of the substrate was consumed (12 h, TLC monitoring) the solvent was removed under reduced pressure. The residue was dissolved in AcOEt and then washed with $NaHCO_{3aq}$ and dried. Removal of the solvent gave a crude product (16.7 g) from which 14.8 g (36.41 mmol, 79%) of yellow crystals were obtained by quenching with diethyl ether.

Analytical data for compound **11**: mp 88–90°C; $[\alpha]_D^{23} = +23.2$ (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ: 8.20 (1H, s, N_aH), 7.60–7.05 (5H, m), 6.30 (1H, t, J = 6 Hz, N_bH), 5.70 (1H, d, J = 2.5 Hz), 5.60 (1H, d, J = 2.5 Hz), 3.70 (3H, s, -OCH_3), 3.65 (2H, m, J = 6.5 Hz, J = 6 Hz), 3.00 (2H, t, J = 6.5 Hz), 2.05 (3H, s, -$OCOCH_3$), 1.90 (3H, s, -$OCOCH_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 169.5, 168.7, 167.4, 165.4, 136.4, 127.2, 122.3, 122.2, 119.7, 118.5, 112.5, 111.4, 71.8, 71.4, 52.8, 39.9, 25.1, 20.3, 20.2; LSIMS (+) NBA 8 kV *m*/*z* (%): 143 (100), 144 (62), 407 $(M+H)^+$ (34), 423 (26), 813 $(2M+H)^+$ (1.1).

3.3. Preparation of compound **12**

A solution containing 14.0 g (34.44 mmol) of compound **11** and 4.3 mL (68.88 mmol) of methyl iodide and one drop of DMF in 300 mL of acetone was refluxed under argon for 8 h. After this period, the reaction mixture was cooled to room temperature and filtered to give 11.3 g (22.60 mmol, 66%) of yellow crystals.

Analytical data for compound **12**: mp 203–205°C; $[\alpha]_D^{23} = +39.0$ (*c* 1.1, EtOH); ^1H NMR ($CDCl_3$, 200 MHz) δ: 7.85 (1H, s), 7.7–7.5 (4H, m), 5.75 (1H, d, J = 2.5 Hz), 7.65 (1H, d, J = 2.5 Hz), 3.85 (3H, s), 3.75–3.65 (2H, m), 3.40–3.3 (2H, m), 2.15 (3H, s), 2.10 (3H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 169.4, 168.7, 166.8, 165.2, 136.6, 128.3, 122.7, 123.2, 118.2, 117.9, 113.1, 111.8, 72.3, 71.9, 53.1, 40.6, 23.5, 21.3, 20.2.

3.4. Preparation of compound **14**

To a solution containing 3.6 g (7 mmol) of compound **12** in 100 mL of acetic acid and 1 mL of concentrated hydrochloric acid 300 mg of PtO_2 was added. The reaction mixture was stirred under hydrogen for 24 h. Hydrogen was then replaced by argon and then 3 g (36.6 mmol) of sodium acetate and 3.0 mL (30 mmol) of acetic anhydride were added. The catalyst was filtered

off and the solvents were evaporated in vacuo. The crude product was dissolved in 100 mL of $CHCl_3$ and the organic phase was washed with $NaHCO_{3aq}$, brine and dried. Column chromatography (silica gel, 99.4:0.6 chloroform:methanol) afforded 2.1 g (5.1 mmol, 70%) of compound **14**.

Analytical data for compound **14**: mp 161–164°C; $[\alpha]_D^{23} = -71.5$ (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ: 8.1 (NH, s), 7.5–7.1 (4H, m), 6.05 (1H, d, J = 8,5 Hz), 5.56 (1H, dd, J = 8.5 Hz, J = 2 Hz), 5.21 (1H, d, J = 2 Hz), 3.72 (3H, s), 2.94–2.79 (4H, m), 2.29 (3H, s), 2.21 (3H, s), 2.00 (3H, s) [2.19 (3H, s), 2.06 (3H, s), stable conformers in the ratio 2.75:1]; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 170.3, 169.0, 168.0, 162.3, 136.2, 129.5, 126.3, 122.5, 119.7, 118.4, 111.4, 110.7, 72.3, 70.5, 52.7, 47.6, 41.9, 22.3, 21.8, 21.5, 20.5; LSIMS (+) NBA 8 kV *m*/*z* (%): 171 (62), 199 (43), 213 (41), 225 (100), 356 (17), 416 (5.1), 417 $(M+H)^+$ (3.5).

3.5. Preparation of compound *17*

To a solution containing 2 g (4.8 mmol) of compound **14** in 50 mL of methanol 0.5 mL of ammonia solution (25%) was added. When the substrate was consumed (6 h, TLC monitoring) the solvent was removed under reduced pressure. Column chromatography (silica gel, 95:5 chloroform:methanol) afforded compound **15** which was very unstable at temperatures above 20°C. Because of possible decomposition a sample of 0.33 g (1 mmol) of compound **15** was dissolved in 50 mL of water and cooled to 0°C. To the above solution 0.86 g (4 mmol) of sodium periodate in 5 mL of water was added. After 1 h 0.5 mL of ethylene glycol and 100 mg (2.64 mmol) of $NaBH_4$ were introduced subsequently. The residue was then taken up into 20 mL of $CHCl_3$ and dried. Column chromatography (silica gel, 90:10 chloroform:methanol) afforded 146 mg (0.62 mmol, 62%) of compound **17**.

Analytical data for compound **17**: mp 189–191°C; $[\alpha]_D^{23} = +17.3$ (*c* 0.2, EtOH); ^1H NMR ($CDCl_3$, 500 MHz) δ: 8.91 (1H, s, disappeared with D_2O), 8.62 (1H, disappeared with D_2O), 7.48 (1H, d, J = 7.5 Hz), 7.35 (1H, d, J = 8 Hz), 7.18 (1H, dt, J = 8 Hz, J = 7.5 Hz, J = 1 Hz), 7.10 (1H, ddd, J = 8 Hz, J = 7.5 Hz, J = 1 Hz), 5.76 (1H, t, J = 6.5 Hz), 4.06–3.88 (3H, m), 3.51–3.45 (1H, m), 2.85 (2H, m), 2.25 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 171.1, 136.2, 131.7, 126.3, 121.9, 119.4, 117.9, 111.2, 108.2, 64.1, 51.6, 42.5, 22.1, 21.9; LSIMS (+) NBA 8 kV *m*/*z* (%): 171 (33), 226 (45), 245 $(M+H)^+$ (31). LSIMS HR: calculated for $C_{24}H_{32}N_2O_7SNa$ $(M+Na)^+$: 267.11096; found: 267.11016.

Analytical data for compound **16**: ^1H NMR ($CDCl_3$, 500 MHz) δ: 8.12 (1H, s, disappeared with D_2O), 7.60 (1H, d, J = 7.5 Hz), 7.36 (1H, d, J = 7.5 Hz), 7.20 (1H, ddd, J = 8 Hz, J = 7.5 Hz, J = 1.3 Hz), 7.12 (1H, dt, J = 7.5 Hz, J = 1.3 Hz), 7.05 (1H, d, J = 2.5 Hz), 6.76 (1H, disappeared with D_2O), 4.70 (1H, d, J = 2 Hz), 4.36 (1H, d, J = 2 Hz), 3.80 (3H, s), 3.68–3.59 (4H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 173.2, 170.7, 136.4, 127.2, 122.3, 122.2, 119.5, 118.6, 112.6, 111.3, 77.2, 72.5, 53.1, 39.6, 25.1

3.6. Preparation of compound *19*

To a solution containing 300 mg (1.2 mmol) of alcohol **17** and 197 mg (1.2 mmol) of (*S*)-3-phenylbutyric acid **18** and 0.5 mL (3.6 mmol) of triethylamine in 30 mL of dry tetrahydrofuran a sample of 575 mg (1.3 mmol) of BOP[31] reagent was added. The reaction mixture was stirred under argon. When all of the substrate was consumed (24 h, TLC monitoring) the solvent was removed under reduced pressure. The residue was dissolved in 20 mL of methylene chloride. The

organic solution was washed with brine and dried. Column chromatography (silica gel, 99.8:0.2 chloroform:methanol) afforded 407 mg (1 mmol, 83%) of compound **19**.

Analytical data for compound **19**: mp 155–156°C, $[\alpha]_D^{23} = +220.0$ (c 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ: 8.59 (1H, s, disappeared with D_2O), 7.48–7.11 (9H, m), 5.93 (1H, t, J = 6.0 Hz), 4.44–4.21 (2H, m), 3.52–3.46 (1H, m), 3.28–3.15 (1H, m), 2.91–2.48 (5H, m) [2.21 (3H, s), 2.06 (3H, s), stable conformers in the ratio 3.1:1] [1.31 (3H, d, J = 7.0 Hz), 1.20 (3H, s, J = 7.0 Hz), stable conformers in the ratio 3.1:1]; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 172.2, 169.5, 145.5, 136.3, 130.1, 128.7, 128.5, 126.7, 126.6, 126.4, 126.3, 122.1, 119.5, 118.0, 111.2, 109.1, 64.6, 48.2, 42.6, 42.1, 36.2, 22.0, 21.8, 21.7.

Crystal data for compound **19**: $C_{24}H_{26}N_2O_3$, $M = 456.52$, monoclinic space group $P2_1$; $a = 8.5720(17)$, $b = 6.0390(12)$, $c = 20.496(4)$ Å, $\beta = 92.63(3)°$, $V = 1059.9(4)$ Å^3, $Z = 2$, and $D_x = 1.224$ Mg/m^3. Clear colourless columnar 0.6×0.4×0.2 mm crystal, $\mu(MoK\alpha) = 0.081$ mm^{-1}, 3041 reflections measured, 2950 independent ($R_{int} = 0.0336$), 1892 observed [$I > 2\sigma(I)$]. Least squares on F^2 (all reflections), $R = 0.0455$, $wR = 0.1585$ (all).

Acknowledgements

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