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Enantioselective synthesis of (*R*)-(−)-praziquantel (PZQ)

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Abstract—Praziquantel **8** (2-cyclohexylcarbonyl-1,2,3,6,7,11b-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinoline-4-one), a powerful anti-worm drug, has been synthesized in its enantiopure form via asymmetric transfer hydrogenation according to the Noyori protocol. Initially, the reduction of prochiral imine **4** afforded product **5** in 62% ee, but a single crystallization amplified the enantiomeric purity to 98% ee. The final (*R*)-(−)-praziquantel **8** was prepared in three subsequent steps in 56% chemical yield.

1. Introduction

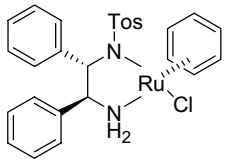
Praziquantel (PZQ, l,2-cyclohexylcarbonyl-1,2,3,6,7,11b-hexahydro-4*H*-pyrazino[2,1-*a*]isoqunoline-4-one) **8**, is a drug of tremendous importance in treating schistosomiasis and soil-transmitted helminthiasis.[1,2] The recently estimated global number of cases of infection with *Schistosoma* spp. approaches 200 million, with 650 million being at risk of infection. Praziquantel **8** is still the sole existing drug for these diseases.[3] Although its precise mode of action still remains unknown, the mechanism that involves tegumental damage and paralytic muscular contraction of parasites is known to relay solely on the (*R*)-(−)-enantiomer of PZQ, the other one being its harmless distomer. However, due to both economic reasons and uncertain long-term side effects associated with the administration of large doses of racemic PZQ, it seems advisable to develop an enantioselective route to this important isoquinoline derivative. Numerous synthetic approaches to racemic praziquantel, including a recent report utilizing a solid support,[4] have been published to date.[5–11] The problem of stereoselective construction of this rather simple molecule has attracted much less attention and only one contribution to this field by Zhang et al.[12] can be found in the literature. The Pictet–Spengler reaction of the intermediate containing the Andersen reagent was claimed to effectively control the transfer of stereochemistry.[12]

2. Results and discussion

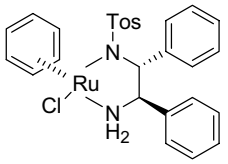
Having been encouraged by the rather positive results in the enantioselective formation of isoquinoline[13] and β-carboline[14] derivatives with the use of an asymmetric transfer hydrogenation protocol,[15,16] we decided to apply this catalytic methodology to a praziquantel synthesis with the hope to make it attractive from an industrial point of view.

Imine **4**, a suitable prochiral substrate, was prepared in 75% overall yield from *N*-phthaloylglycine chloride **1** and phenylethylamine **2** via the Bischler–Napieralski cyclization[17] on intermediate amide **3** (Scheme 1).

Subsequent asymmetric transfer hydrogenation on imine **4** was performed under classical Noyori conditions.[18] Initially, a combination of *N*-tosyl-(1*R*,2*R*)-diphenylethylenediamine[19] and $[RuCl_2(\eta^6\text{-benzene})]_2$ formed a catalyst (*R*,*R*)-**9**, which was then used in S/C = 160 ratio in the presence of a formic acid:triethylamine mixture (Fig. 1).



(*S*,*S*)-**9**



(*R*,*R*)-**9**

Figure 1. Chiral ruthenium catalysts.

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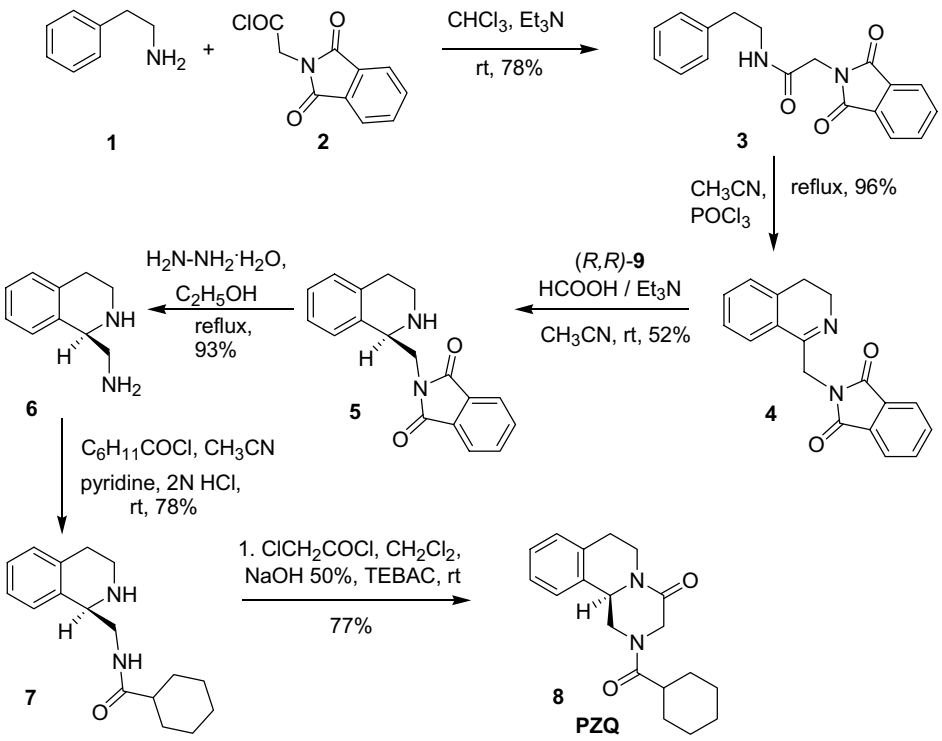

Scheme 1.

Product **5**, which was formed in 52% isolated yield, showed the specific rotation $[\alpha]_D^{23} = +52.0$, which upon comparison with the literature[12] value $[\alpha]_D^{23} = -60.7$ for apparent enantiopure **5**, appeared to be of 86.0% enantiomeric excess. On the basis of a sign of the specific rotation, the absolute stereochemistry assignment reported by Zhang et al.[12] appears to be incorrect. Moreover, when amine **5** was transformed into its amide derivative **10** with (*S*)-Mosher acid, both the spectroscopic (^{1}H NMR) and chromatographic methods revealed the presence of diastereomers in an 81:19 ratio. The formation of diastereomeric amides derived from amine **5** indicated that the previously reported data[12] did not correspond to an enantiopure substance. Indeed, we found that amine **5** obtained in our experiment could be quite effectively recrystallized to afford a substance of $[\alpha]_D^{23} = +84.0$, a value, which remained unchanged upon repeated crystallization. The complete enantiomeric purity of this sample was further confirmed by ^{1}H NMR and chromatographic data of its (*S*)-Mosher acid derivative.

In a parallel experiment, when *N*-tosyl-(1*S*,2*S*)-diphenylethylenediamine was used to prepare the catalyst (*S*,*S*)-**9**, and the resultant amine (*S*)-**5** was subjected to the formation of the amide derivative with (*R*)-Mosher acid, the absolute stereochemical outcome was additionally confirmed by X-ray analysis of compound **10** (Fig. 2).

In the search for improved chiral induction during the hydrogenation step, we examined several other ligands known to be highly effective,[20] including those already utilized by us.[13] The attempted application of those ligands was unsuccessful and only *N*-tosyl-(1*R*,2*R*)-cyclohexanediamine gave product **5** in a non-racemic form with 4% ee. Therefore, it seems that the classical Noyori's catalyst remains the most effective in the reduction of imine **4**. Although amine **5** was initially formed with only a moderate enrichment (62% ee), it can be effectively transformed into the enantiopure form upon one recrystallization from chloroform/diethyl ether mixture.

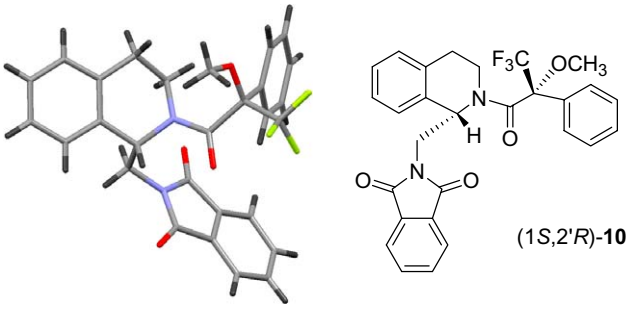

Figure 2. Structural analysis of compound (1*S*,2′*R*)-**10**.

Subsequent treatment of amine **5** with hydrazine in refluxing ethanol afforded diamine **6** in 93% yield,[21] which was then subjected to a reaction with cyclohexanecarbonyl chloride in dichloromethane in the presence of potassium carbonate. Under these conditions,[12] cyclohexanoyl derivative **7** was obtained in 24% yield only but the undesired *N*,*N*-dicyclohexanoyl amide was formed in 49% yield. Much better results were obtained using a selective procedure described by Cizin et al.,[22] upon which only monoamide **7** was isolated in 78% yield. Finally, monocyclohexanoyl derivative **7** was converted to enantiopure praziquantel **8** with chloroacetyl chloride in 77% yield, under Schotten–Bauman conditions in a mixture of dichloro-

methane and 50% (aq) NaOH in the presence of TEBA chloride.[23]

3. Conclusions

In conclusion, an effective method for the enantioselective preparation of praziquantel is described, starting with easily available phenylethyl amine, phthalyl anhydride and glycine. The asymmetric transfer hydrogenation proved to be a key step for chirality induction.

4. Experimental

The 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. The spectra were measured in $CDCl_3$ and are given as δ values (in ppm) relative to TMS. Mass spectra were collected on Quatro LC Micromass and LCT Micromass TOF HiRes apparatus. Optical rotations were measured on a Perkin–Elmer 247 MC polarimeter. TLC analyses were performed on silica gel plates (Merck Kiesegel GF_{254}) and visualized using UV light or iodine vapour. Column chromatography was carried out at atmospheric pressure using Silica Gel 60 (230–400 mesh, Merck) using mixtures of chloroform/methanol as eluents. Melting points were determined on a Boetius hot-plate microscope and were uncorrected. All solvents used in the reactions were anhydrous. The single crystal X-ray measurement was carried out on a KUMA KM4 CCD κ-axis diffractometer. After initial corrections and data reduction, intensities of reflections were used to solve and consecutively refine the structure.

4.1. *N*-Phthalimidoacetyl-β-phenylethylamnine 3

To a stirred solution of β-phenylethylamine **1** (11.2 g, 90.3 mmol) and triethylamine (26.0 mL, 0.18 mol) in $CHCl_3$ (300 mL), a solution of phthalylglycyl chloride (20.7 g, 92.6 mmol) dissolved in $CHCl_3$ (100 mL) was added over 20 min. The mixture was stirred at room temperature for 2 h and then was treated with aqueous Na_2CO_3 solution and extracted with chloroform (2×50 mL). The organic phase was washed with brine (2×50 mL), dried over $MgSO_4$ and the solvent was evaporated in vacuo. The residue was purified by crystallization from MeOH to give 22.0 g of product **3** (77%) as colourless solid, mp = 186–188 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.81 (t, $J = 6.5$ Hz) 2H-β to NH; 3.52 (apparent q, $J = 6.5$ Hz) 2H-α to NH; 4.28 (s) 2H; 5.87 (broad s) N–H; 7.15–7.18 (m) 3H–Ar; 7.22–7.26 (m) 2H–Ar; 7.72–7.76 (m) 2H–Pht.; 7.85–7.89 (m) 2H–Pht. ^{13}C NMR (125 MHz, $CDCl_3$): δ 35.4; 40.84; 40.9; 123.6; 126.5; 128.64; 128.79; 131.9; 134.3; 138.5; 166.0; 167.7. LRMS (ESI) $m/z = 331.0$ $[M+Na]^+$.

4.2. 3,4-Dihydro-1-phthalimidomethylisoquinoline 4

This procedure was adapted from the lit.[17] To a stirred suspension of *N*-phthalimidoacetyl-β-phenylethylamnine **3** (10.0 g, 32.4 mmol) in CH_3CN (100 mL), a volume of 8.9 mL (97.3 mmol) of $POCl_3$ was added in one portion. The mixture was refluxed for 1 h (light yellow colour developed), cooled to room temperature and concentrated under reduced pressure. Toluene (100 mL) and 36% HCl (50 mL) were added to the residue and the mixture was heated at reflux for 0.5 h and then cooled to room temperature. The water phase was then alkalized with (aq) NH_3, extracted with $CHCl_3$ and dried over $MgSO_4$. Column chromatography on silica gel using chloroform as eluent allowed the separation of imine **4** (1.50 g, 16% yield, 96% yield based on the consumed amide). Crystallization from $CHCl_3$/hexane/Et_2O (5:30:0.5) gave the analytical sample of **4** as colourless crystals mp = 201–203 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.68 (t, $J = 3.5$) 2H-4; 3.61 (tt, $J_1 = 1$ Hz, $J_2 = 3.5$ Hz) 2H-3; 4.93 (t, $J = 1$ Hz) 2H-1′; 7.27 (dd, $J_1 = 0.5$ Hz, $J_2 = 7.5$ Hz) 1H-5; 7.33 (td, $J_1 = 1.5$ Hz, $J_2 = 7.5$ Hz) 1H-6; 7.38 (td, $J_1 = 1.5$ Hz, $J_2 = 7.5$ Hz) 1H-7; 7.52 (dd, $J_1 = 1.0$ Hz, $J_2 = 7.5$ Hz) 1H-8. ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.9; 41.2; 46.8; 123.4; 123.8; 126.9; 127.5; 127.7; 130.9; 132.4; 133.8; 137.8; 158.7; 168.3. LRMS (ESI) $m/z = 313.0$ $[M+Na]^+$.

4.3. (1*R*)-(+)-1-Phthalimidomethyl-1,2,3,4-tetrahydroisoquinoline 5

Catalyst (*R*,*R*)-**9** was pre-formed from $[RuCl_2(C_6H_6)]_2$ (6 mg, 24 μmol) and (1*R*,2*R*)-1,2-diphenyl-*N*-(*p*-toluoylsulfonyl)ethylenediamine (7.3 mg, 20 μmol) in 4 mL of CH_3CN. To a solution of imine **4** (870 mg, 3.00 mmol) in CH_3CN (5 mL), a 5:2 formic acid/triethylamine mixture (2.5 mL) was introduced, followed by the addition of the pre-formed catalyst. The mixture was then stirred at room temperature for 5 h and after evaporation of the solvents, the residue was made basic with aqueous K_2CO_3 solution and extracted with chloroform. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified with column chromatography on silica gel using chloroform/methanol 0–0.8% MeOH as a solvent system to afford 454 mg (52% yield) of compound (+)-(*R*)-**5** as colourless needles $[\alpha]_D^{23} = +52.0$ (*c* 1, $CHCl_3$); recrystallization from chloroform/diethyl ether (1:4) mixture gave 210 mg of pure enantiomer mp = 174–176 °C, $[\alpha]_D^{23} = +84.0$ (*c* 1, $CHCl_3$), $[\alpha]_D^{23} = +81.6$ (*c* 1, acetone), lit.[12] $[\alpha]_D^{23} = -60.7$ (*c* 0.5, acetone), ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.73 (s) N–H; 2.78 (m) 2H-4; 2.97 (m) 1H-3; 3.27 (m) 1H-3; 3.89 (dd, $J_1 = 14$ Hz, $J_2 = 3.5$ Hz) 1H-1′; 4.08 (dd, $J_1 = 14$ Hz, $J_2 = 3.5$ Hz) 1H-1′; 4.36 (dd, $J_1 = 11$ Hz, $J_2 = 3.5$ Hz) 1H-1; 7.12–7.33 (m) 4H-5,6,7,8; 7.72 (m) 2H-5′,6′; 7.87 (m) 2H-4′,7′. ^{13}C NMR (125 MHz, $CDCl_3$): δ 29.5; 38.8; 42.5; 54.2; 123.4; 126.0; 126.7; 126.9; 129.6; 132.15; 133.9; 135.6; 135.9, 168.9. HRMS (ESI) calcd for $C_{18}H_{17}N_2O_2$ ($[M+H]^+$): 293.1290. Found: 293.1297. Enantiomer (−)-(*S*)-**5** was obtained as colourless needles using (*S*,*S*)-**9** form of the catalyst; $[\alpha]_D^{23} = -52.8$; recrystallization from chloroform/diethyl ether (1:4) mixture gave pure enantiomer; mp = 175–176 °C, $[\alpha]_D^{23} = -83.4$ (*c* 1, $CHCl_3$).

4.4. (1*R*)-(−)-1-Aminomethyl-1,2,3,4-tetrahydroisoquinoline 6

This procedure was adapted from the work of Humber.[21] To a solution of (1*R*)-(+)-**5** (290 mg, 0.98 mmol) in 8 mL

of ethanol was added 0.1 mL (2.73 mmol) of anhydrous hydrazine in ethanol (0.5 mL). The mixture was refluxed for 40 min, cooled to room temperature, concentrated under reduced pressure and then heated again for 40 min with 5 mL of 36% hydrochloric acid. The precipitate was filtered off and the filtrate made alkaline with solid sodium hydroxide and extracted with $CHCl_3$ (4×10 mL) to afford a colourless oil (150 mg, 93.5%); $[\alpha]_D^{23} = -78.7$ (*c* 1, $CHCl_3$), lit.[12] $[\alpha]_D^{23} = -55.6$ (*c* 0.5, acetone). The ^{1}H NMR spectrum was similar to that described by Beaumont et al.[24] and Jones et al.[25] ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.22 (s) 3H–N–H_2, N–H; 2.72–2.85 (m) 2H-4; 3.00–3.04 (m) 3H-3, 1′; 3.17–3.21 (m) 1H-1′; 3.98 (t, $J = 5.5$) 1H-1; 7.09–7.18 (m) 4H–Ar. ^{1}H NMR (500 MHz, $CDCl_3 + D_2O$): δ 2.72–2.81 (m) 2H-4; 2.98–3.03 (m) 3H-3, 1′; 3.16–3.19 (m) 1H-1′; 3.95 (t, $J = 5.5$) 1H-1; 7.10–7.15 (m) 4H–Ar. ^{13}C NMR (125 MHz, $CDCl_3$): δ 29.8; 40.3; 46.3; 57.5; 126.0; 126.09; 126.2; 129.4; 135.9; 136.7. HRMS (ESI) calcd for $C_{10}H_{15}N_2$ ($[M+H]^+$): 163.1235. Found: 163.1219.

4.5. (1*R*)-(−)-1-(*N*-Cyclohexylcarbonylamido methyl)-1,2,3,4-tetrahydroisoquinoline 7

This compound was obtained by the procedure described by Cizin et al.[22] To a stirred solution of diamine (1*R*)-**6** (150 mg, 0.91 mmol) in 1.5 mL of CH_3CN, pyridine (0.1 mL, 0.1 mmol) and 2 N hydrochloric acid (0.45 mL, 0.91 mmol), a solution of cyclohexanecarbonyl chloride (0.13 mL, 0.1 mmol) dissolved in 0.5 mL $CHCl_3$ was slowly introduced during 1 h. The mixture was stirred at room temperature for 2 h and then concentrated under reduced pressure. Diethyl ether (5 mL) ether was added to the residue and the mixture was extracted with 1 N HCl (2×2 mL). The water phase was made alkaline with 30% NaOH solution, extracted with $CHCl_3$ (4×10 mL) and the organic phase was dried over $MgSO_4$. The crude product was purified with column chromatography on silica gel using chloroform/methanol 0.1–0.4% MeOH as a solvent system to afford 190 mg (78%) of compound (−)-(*R*)-**7** as a pale yellow crystals (crystallization from Et_2O/hexane), mp = 111–112.5 °C, $[\alpha]_D^{23} = -17.6$ (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.16–1.29 (m) 4H–Cy; 1.35–1.47 (m) 2H–Cy; 1.64–1.84 (m) 4H–Cy; 2.73–2.83 (m) 2H-4; 3.01–3.06 (m) 1H-3; 3.13–3.18 (m) 1H-3; 3.32–3.37 (m) 1H-1′; 3.76–3.81 (m) 1H-1′; 4.09 (dd, $J_1 = 3.5$ Hz, $J_2 = 9.0$ Hz) 1H-1; 6.29 (s) 1H–N–H; 7.08–7.20 (m) 4H–Ar. ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.72; 25.73; 25.75; 29.5; 29.61; 29.64; 39.82; 43.27; 45.48; 55.03; 126.2; 126.5; 126.6; 129.3; 135.3; 135.7; 176.5. HRMS (ESI) calcd for $C_{17}H_{25}N_2O$ ($[M+H]^+$): 273.1967. Found: 273.1980.

4.6. (1*R*)-(−)-2-Cyclohexylcarbonyl-1,2,3,6,7,11b-hexahydro-4*H*-pyrazino[2,1-*a*]isoqunoline-4-one, praziquantel (PZQ) 8

This compound was obtained according to the procedure described by Sergovskaya and Chernyak.[23] To a stirred solution of amine (1*R*)-**7** (110 mg, 0.39 mmol) in 1.0 mL CH_2Cl_2, a solution of 50% NaOH (0.12 mL, 2.33 mmol) was added, followed by the addition of a solution of chloroacetyl chloride (0.034 mL, 0.43 mmol) in 0.15 mL of CH_2Cl_2. After 0.5 h, TEBAC (9 mg, 0.04 mmol) was added and the mixture was heated and stirred for 2 h at reflux. After that time, a portion of 3 mL of water was added and the mixture extracted with CH_2Cl_2 (2×3 mL). The organic phase was washed with water (2×2 mL), 5% HCl (2 mL), again with water (2 mL) and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified with column chromatography on silica gel using chloroform/methanol 0–0.3% MeOH as a solvent system to afford 93 mg (77%) of (1*R*)-(−)-**8**, mp = 113–115 °C, lit.[26] Mp = 107–108 °C; $[\alpha]_D^{23} = -135.0$ (*c* 1, $CHCl_3$), $[\alpha]_D^{23} = -126.9$ (*c* 1, EtOH 99.8%), lit.[26] $[\alpha]_D^{23} = -146.9$, lit.[27] $[\alpha]_D^{23} = -132.4$ (*c* 1, EtOH); the NMR spectra were in full accordance with the published data for the racemate.[9,28]

4.7. (1*S*)-1-Phthalimidomethyl-2-[(2′*R*)-3′,3′,3′-trifluoro-2′-methoxy-2′-phenylpropanoyl]-1,2,3,4-tetrahydroisoquinoline 10

The Mosher acid chloride was prepared without isolation: (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (42 mg, 0.18 mmol) and $SOCl_2$ (0.02 mL, 0.27 mmol) in toluene (2.5 mL) was heated at reflux for 3 h. To a stirred solution of amine (1*S*)-**5** (40 mg, 0.14 mmol) and triethylamine (0.04 mL, 0.27 mmol) in $CHCl_3$ (7 mL), a pre-formed Mosher acid chloride (0.043 g, 0.17 mmol) in $CHCl_3$ (3 mL) was added dropwise and after 0.5 h, the reaction mixture was treated with saturated $NaHCO_3$ solution and extracted with $CHCl_3$. The organic phase was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product purified via column chromatography on silica gel using with $CHCl_3$/CH_3OH (98:2) as eluent to give (1*S*,2″*R*)-**10** (60 mg, 86%) as a colourless crystals, mp = 187–189 °C, $[\alpha]_D^{23} = +35.0$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.69 (m) 1H; 3.02 (m) 1H; 3.18 (m) 1H; 3.56 (d, $J = 2.0$ Hz) 3H–OCH_3; 3.78 (m) 2H; 4.17 (m) 1H; 6.13 (dd, $J_1 = 4.5$ Hz, $J_2 = 10.0$ Hz) 1H-1; 7.12 (m) 1H–Ar; 7.20–7.24 (m) 2H–Ar; 7.29 (m) 2H–Ar; 7.34–7.38 (m) 2H–Ar; 7.39–7.44 (m) 2H–Ar; 7.78 (m) 2H-5′,6′; 7.96 (m) 2H-4′,7′. ^{13}C NMR (125 MHz, $CDCl_3$): δ 27.7; 39.0; 41.1; 52.1; 56.1; 84.8 (q, $^2J_{CF} = 25.5$ Hz); 123.4; 124.9 (q, $^1J_{CF} = 131$ Hz); 126.0; 126.4; 126.5; 127.5; 127.9; 128.3; 128.9; 129.4; 132.2; 133.3; 133.55; 133.59; 134.1; 134.3; 165.9; 167.9.

The parallelepiped colourless crystal of **10** of dimension $0.3 \times 0.35 \times 0.4$ mm was placed on Kuma KM4 κ-axis diffractometer. Mo Kα radiation ($\lambda = 0.71073$ Å) and the $\omega - 2\theta$ scan mode were used to collect the data. After locating and centring 32 strong reflections with $13 < 2\theta < 21.5°$ the orthorhombic unit cell of dimensions $a = 9.5670(19)$, $b = 10.920(2)$, $c = 23.452(5)$ Å and $\alpha = \beta = \gamma = 90°$ and $V = 2450.1(8)$ Å^3 was established. The observed systematic absences led us to ascertain the $P2_12_12_1$ space group. The unit cell contains $Z = 4$ molecules of **10** of general formula $C_{28}H_{23}F_3N_2O_4$. Crystal density is of $D_x = 1.379$ Mg/m^3 (g/cm^3), whereas $F(000) = 1056$, μ(Mo Kα) = 0.108 mm^{-1}. Two thousand six hundred and fourteen reflections were collected up to $2\theta = 44.41°$. Of these, 2453 of them were independent ($R_{int} = 0.0375$ for symmetry related reflections). Direct methods from SHELXS93 were used to solve the structure whereas SHELXL93 software was employed for structure refinement.

All carbon, nitrogen, oxygen and fluorine atoms were located from the E maps and subsequent difference density maps, whereas hydrogen atoms were located geometrically using standard geometrical criteria. In the final cycles of structure refinement all non-hydrogen atoms were refined anisotropically whereas remaining atoms were treated as fixed contributors, placed geometrically with their isotropic displacement parameters being related to the displacement parameters of the corresponding carbon atoms. Final R and wR were of 0.0285 and 0.0757, respectively, for 1757 observed reflections with $I > 2\sigma(I)$. The data were deposited with Cambridge Crystallographic Data Centre under the number CCDC 604432.

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