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Synthesis, resolution and absolute configuration of a tolperisone metabolite

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Abstract—1-(4′-Hydroxymethyl-phenyl)-2-methyl-3-(piperidine-1-yl)-propane-1-one **M2**, a metabolite of tolperisone, was synthesised in a solvent-free Mannich reaction. The optical resolution was carried out by diastereoisomeric salt formation and separation, for which three resolving agents ((2*R*,3*R*)-*O*,*O*′-dibenzoyl tartaric acid, (2*R*,3*R*)-*O*,*O*′-di-*p*-toluoyl tartaric acid and (*R*)-2-hydroxy-4-(2-methoxyphenyl)-5,5-dimethyl-1,3,2-dioxaphosphorinane-2-oxide (anicyphos)) were found. The absolute configuration of **M2** was determined by the single-crystal X-ray diffraction method. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

According to a previous investigation of the metabolism of tolperisone,[1] the main metabolic pathway involves oxidation of the aromatic methyl group to a hydroxymethyl and then to a carboxylic acid group. *d*-Tolperisone is a classic muscle relaxant agent, while the *l*-enantiomer has bronchodilatory and peripheral vasodilatory activity.[2] As the metabolites may also carry different biological activities, we decided to synthesise the major metabolites and their enantiomers. Herein, our work[3] on the tolperisone metabolic pathway is continued: synthesis and resolution of 1-(4′-hydroxymethyl-phenyl)-2-methyl-3-(piperidine-1-yl)-propane-1-one (**M2**, Fig. 1) is presented.

2. Results and discussion

2.1. Synthesis of M2

To form the desired molecule, 4′-methyl-propiophenone **1** was first brominated with *N*-bromosuccinimide.[4] The attempted direct hydrolysis of the resulting 4′-bromomethyl-propiophenone **2** to 4′-hydroxymethyl-propiophenone **3** was unsuccessful both in aqueous and methanolic NaOH solution, due to extensive dimer or methyl ether formation. 4-Hydroxymethyl-propiophenone **3** was then obtained by converting the bromide to an acetyl group followed by hydrolysis. Mannich reaction without solvent yielded **M2** (Fig. 1).

2.2. Resolution of M2

Searching the literature we found some amino ketones structurally analogous to **M2** that had been resolved using dibenzoyl tartaric acid.[5–7] Following several unsuccessful attempts to resolve **M2** we finally found that two tartaric acid derivatives, (2*R*,3*R*)-*O*,*O*′-dibenzoyl-tartaric acid (DBTA) and (2*R*,3*R*)-*O*,*O*′-di-*p*-toluoyl-tartaric acid (DPTTA), were suitable for enantioseparation. With DBTA the diastereoisomeric salt containing the (*S*)-enantiomer precipitated with low e.e. (Table 1, entry 1). Resolution experiments using DPTTA, however, gave unexpected results: the first experiments yielded the (*S*)-enantiomer with reasonable optical purity (Table 1, entry 2), but, after this, the crystallised diastereoisomeric salt always contained the (*R*)-isomer and the e.e. was considerably lower than in the initial resolution experiments. As precipitation of the (*R*)-isomer became consistent and reproducible, we optimised the reaction conditions and obtained the highest e.e. values of around 80% (Table 1, entry 3)

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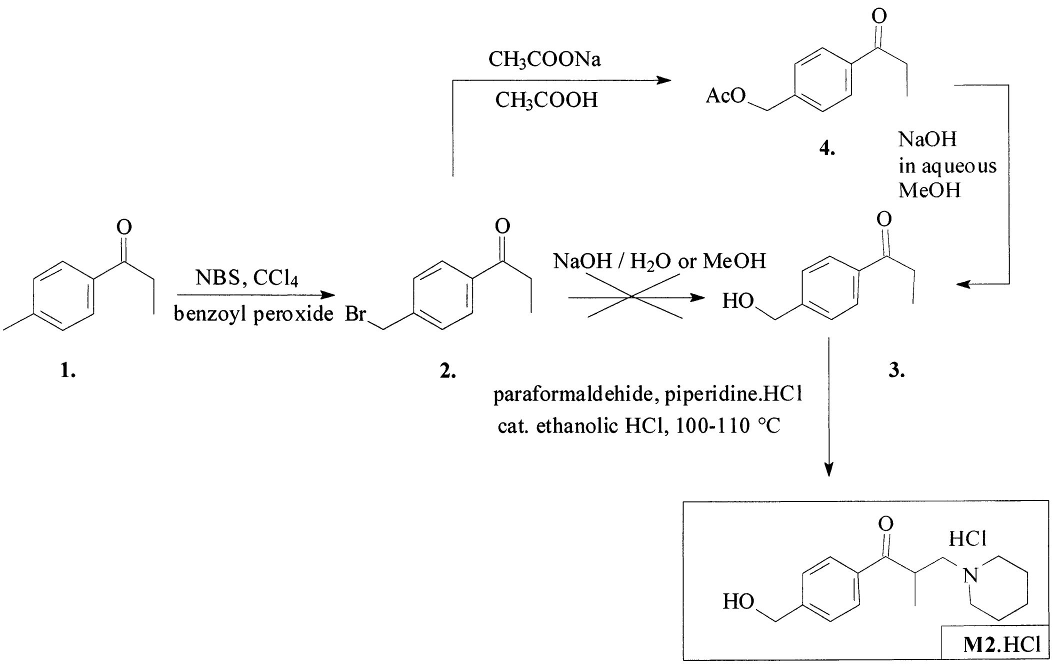

Figure 1. Synthesis of **M2**.

when the reaction was completed in acetone/ethyl acetate mixture by 0.5 molar equivalents of resolving agent and using about half an equivalent of achiral additive (acetic acid). Table 1 contains the detailed results for the resolution (see Fig. 2).

The enantiomeric purity of the resulting mixture is not critical as it can be quite effectively enriched by recrystallisation. The pure enantiomer is physically different from the mixture as while the racemic mixture is powdery, the pure enantiomer is a needle-like crystalline material.

2.3. Determination of the absolute configuration

The diastereroisomeric salts formed with DBTA or DPPTA were unsuitable for X-ray analysis so it was necessary to search for another resolving agent. After

Table 1. Optical resolution of **M2**: conditions and results

Entry	Resolving agent	Solvent	Diastereoisomeric salt			Mother liquor		
			Config. of **M2**	OP (%)	Yield (%)[a]	Config. of **M2**	OP (%)	Yield (%)[a]
1	DBTA	Acetone	*S*	11	86	*R*	6	104
2	DPTTA	Acetone	*S*	38	40	*R*	17	138
3	DPTTA/AcOH	Acetone/EtOAc	*R*	79	92	*S*	80	85
4	Anicyphos	Acetone	*R*	86	70	*S*	51	110

[a] Yields refer to 50% of the racemate.

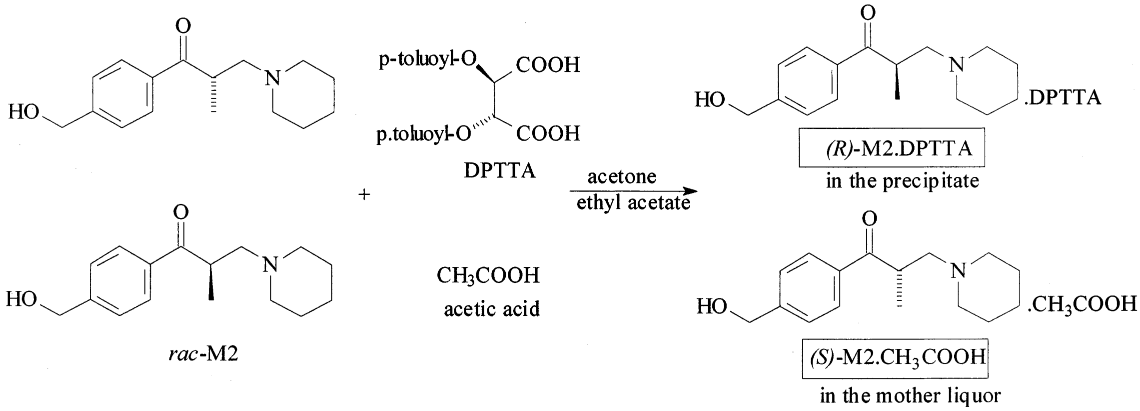

Figure 2. Resolution of **M2** with di-*p*-toluoyl tartaric acid.

Table 2. Crystal data, data collection and refinement parameters

Empirical formula	$C_{28}H_{40}NO_7P{\cdot}0.81(C_3H_6O)$
Formula weight	580.69
Temperature (K)	293(2)
Radiation and wavelength (Å)	Mo-Kα, $\lambda=0.710730$
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	
a (Å)	10.410(2)
b (Å)	8.576(1)
c (Å)	18.533(1)
β (°)	95.93(1)
Volume (Å^3)	1645.7(4)
Z	2
D_{calcd} (mg/m^3)	1.172
Absorption coefficient, μ (mm^{-1})	0.129
F(000)	624
Crystal colour	Colourless
Crystal description	Prism
Crystal size (mm)	$0.55\times0.30\times0.25$
Absorption correction	Psi-scan
Max. and min. transmission	0.9894 and 0.9659
θ-Range for data collection (°)	$2.62\leq\theta\leq29.96$
Index ranges	$-14\leq h\leq14$; $-12\leq k\leq12$; $-26\leq l\leq26$
Reflections collected	11003
Completeness to 2θ	0.985
Number of standard reflections	3
Decay (%)	8
Independent reflections	9408 [$R_{\text{int}}=0.0156$]
Reflections $I>2\sigma(I)$	5091
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	9408/11/388
Goodness-of-fit on F^2	0.888
Absolute structure parameter	0.01(7)
Final R indices [$I>2\sigma(I)$]	$R_1=0.0467$, $wR_2=0.1004$
R indices (all data)	$R_1=0.1035$, $wR_2=0.1108$
Max. and mean shift/esd	0.001; 0.000
Largest diff. peak and hole (e Å^{-3})	0.275 and -0.158

screening several acids we found that (*R*)-(+)-2-hydroxy-4-(2-methoxyphenyl)-5,5-dimethyl-1,3,2-dioxaphosphorinane-2-oxide (anicyphos) forms a crystalline diastereoisomeric salt with **M2**. The yield and optical purity values are good (Table 1, entry 4). Although this resolving agent (Fig. 3) was not the immediate first choice for large scale resolution due to the price of the anicyphos, the diastereoisomeric salt proved to be excellent for single-crystal X-ray diffraction analysis.

X-Ray diffraction analysis showed the (−)-enantiomer to have (*R*) absolute configuration (Fig. 4, Table 2 contains the crystallographic data).

3. Experimental

3.1. Materials and methods

The ^{1}H NMR spectra were recorded at 250 MHz on a Bruker WM250 spectrometer. Chemical shift values are expressed in ppm values on the δ scale. IR spectra of thin film and KBr samples were taken on a Perkin–Elmer 1600 Series FT-IR spectrophotometer. Optical rotations were determined on a Perkin–Elmer 241 polarimeter. Thin-layer chromatography was carried out using POLYGRAM® SIL G/UV$_{254}$ sheets. Spots were visualised by UV light or by treatment with 5% ethanolic phosphomolybdic acid solution and heating of the dried plates. DPTTA and DBTA were purchased from Aldrich. All solvents used were freshly distilled.

The enantiomeric purity of the samples having the highest optical rotatory power was justified by the ^{1}H NMR method as described. Those samples contained no detectable signals for the other enantiomer so they were assumed to be homochiral. Throughout the paper the optical purity was determined by relating the o.r.p. to the o.r.p. of the above mentioned enantiopure sample ($[\alpha]_D^{20}=28.1$, $c=1$, methanol).

3.2. Preparation of 4′-bromomethyl-propiophenone 2

To 4′-methyl-propiophenone **1** (80 g, 0.54 mol) in CCl_4 (600 mL) *N*-bromosuccinimide (96 g, 0.54 mol) and benzoyl-peroxide (1 g) were added and the mixture was heated slowly to its boiling point during vigorous stirring. N.B. In case of contaminated *N*-

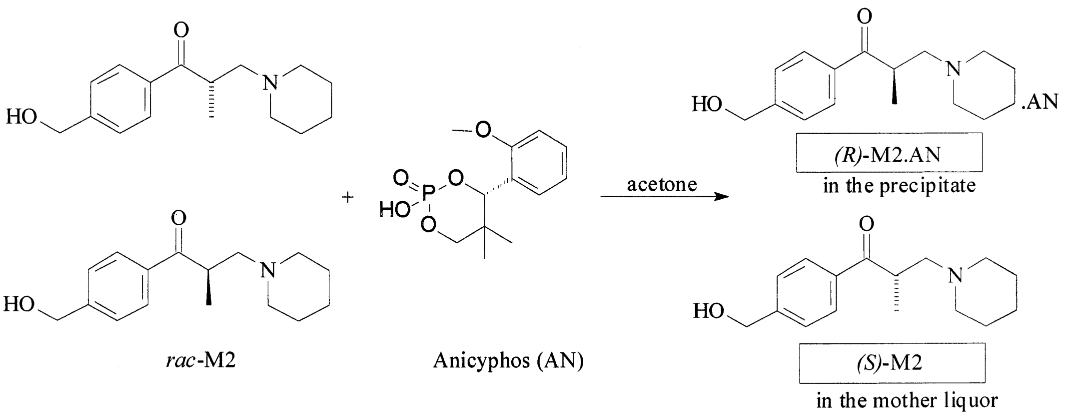

Figure 3. Resolution of **M2** by anicyphos.

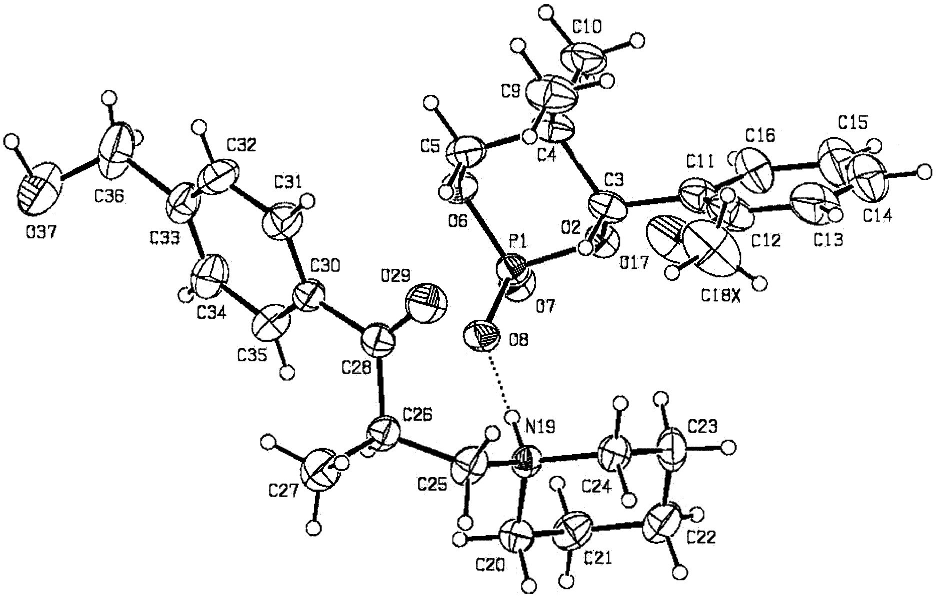

Figure 4. Structure of the diastereoisomeric salt.

bromosuccinimide the reaction mixture will foam heavily. After the reaction mixture lost its colour (1.5–6 h of boiling), it was cooled to 5°C, the precipitated succinimide was removed by filtration and washed with CCl_4. Evaporation of the filtrate gave a thick oil residue from which precipitation began at low temperature. The crystals were filtered and washed with hexane. The crude product was used directly in further conversions. The colour of the product can vary between colourless and purple depending on the starting materials, but it does not influence the further reactions.

Yield: 64.8 g (52.9%), mp 57–58°C. ^{1}H NMR ($CDCl_3$) 1.20 (t, 3H, H_3, 7.23 Hz), 2.97 (q, 2H, H_2, 7.19 Hz), 4.47 (s, 2H, Ar-CH_2-Br), 7.45 (m, 2H, Ar-H), 7.91 (m, 2H, Ar-H). FT-IR (KBr, cm^{-1}): 3440, 2971, 1683, 1222. Calcd for $C_{10}H_{11}BrO$: C, 52.89; H, 4.88; Br, 35.18. Found: C, 52.64; H, 4.86; Br, 35.29%.

3.3. Preparation of 4′-acetoxymethyl-propiophenone 3

A mixture of 4′-bromomethyl-propiophenone **2**, (18 g, 0.08 mol), anhydrous NaOAc (13 g, 0.158 mol) and glacial acetic acid (36 mL) was stirred under reflux for 2 h. After cooling, water (300 mL) was added, and the mixture was extracted by diethyl ether. The organic phase was washed with NaOH solution, dried over Mg_2SO_4 and evaporated. The product was isolated as a yellow oil (13.8 g, 84.4%) that needs no further purification. Bp 126°C (0.8 mmHg). ^{1}H NMR ($CDCl_3$) 1.20 (t, 3H, H_3, 7.27 Hz), 2.11 (s, 3H, acetic CH_3), 2.98 (q, 2H, H_2, 7.26 Hz), 5.14 (s, 2H, Ar-CH_2-O), 7.42 (d, 2H, Ar-H, 8.15 Hz), 7.93 (d, 2H, Ar-H, 8.24 Hz). FT-IR (film, cm^{-1}): 2978, 1740, 1646, 1224, 1044. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H 6.84. Found: C, 69.59; H, 6.86%.

3.4. Preparation of 4′-hydroxymethyl-propiophenone 4

To 4′-acetoxymethyl-propiophenone **3** (13.8 g, 6.7 mmol) in methanol (14 mL) a solution of NaOH (5.4 g, 13.5 mmol) in water (6 mL) was added. The solution was stirred under reflux for 15 min, and the solvent was evaporated. To the residue, water (50 mL) was added, the mixture was extracted with diethyl ether, and the organic extract dried over Na_2SO_4 and evaporated. The crystalline residue was triturated with hexane and dried completely to afford white crystals of **4** (10.0 g, 91%), mp 52–53°C. ^{1}H NMR ($CDCl_3$) 1.21 (t, 3H, H_3, 7.27 Hz), 1.98 (s, 1H, OH), 2.99 (q, 2H, H_2, 7.27 Hz), 4.76 (s, 2H, Ar-CH_2-O), 7.43 (d, 2H, Ar-H, 7.68 Hz), 7.95 (d, 2H, Ar-H, 8.21 Hz). FT-IR (KBr, cm^{-1}): 3456, 2863, 1674, 1608, 1228, 1059, 793. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.48; H, 7.39%.

3.5. Preparation of racemic M2

To a mixture of 4′-hydroxymethyl-propiophenone **4** (15 g, 0.09 mol), piperidine hydrochloride (12 g, 0.099 mol), paraformaldehyde (6 g, 0.2 mol) and ethanolic HCl (2 mL) was added and the reaction mixture was stirred at 100–110°C for 2 h. At this temperature the reaction mixture melted. After cooling the reaction mixture to room temperature, water (100 mL) was added, the mixture was extracted with dichloromethane (3×15 mL), then it was treated with NaOH (6 g) in water (40 mL) to alkaline pH. The yellow oil was extracted with dichloromethane (3×40 mL) and the organic phase was dried and evaporated. The product was triturated with hexane and filtered. The crude product was recrystallised from a mixture of ethyl acetate and hexane to afford **M2** as a white solid (10.3 g, 39.4 mmol, 43.2%), mp 103–104°C. ^{1}H NMR ($CDCl_3$) 1.19 (d, 3H, H_{2Me}, 6.96 Hz), 1.39 (m, 2H), 1.51 (m, 4H), 2.42 (m, 6H), 2.89 (m, 1H), 3.76 (m, 1H, H_{kir}), 4.78 (s, 2H, $H_{4'Me}$), 7.46 (d, 2H, H_{Ar}, 8.09 Hz), 7.97 (d, 2H, H_{Ar}, 8.06 Hz). FT-IR (KBr, cm^{-1}): 3427, 3112, 2941, 2804, 1672, 1231, 1062. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.88; H, 8.87; N, 5.38%.

3.6. General procedure for resolution of M2

Racemic **M2** (14.49 g, 55.4 mmol), DPTTA (9.64 g, 24.9 mmol) and acetic acid (1.74 mL, 30.5 mmol) were dissolved in a mixture of EtOAc (22 mL) and acetone (11 mL). The mixture was stirred for 2 h and the resultant precipitate was collected by filtration and washed with ethyl acetate. The diastereomeric salt was suspended in water (32 mL), cc. HCl (3 mL) was added, and the mixture was extracted with ethyl acetate (66 mL). The aqueous phase was treated with NaOH to alkaline pH. After filtration the precipitate was washed with water and hexane, and a yellowish crystalline material was obtained (6.68 g, 25.6 mmol). $[\alpha]_D = -22.2$ [$c = 1$, methanol].

The crystallisation mother liquor was acidified with cc. HCl and extracted with ethyl acetate (30 mL). After treating the aqueous phase with base until; alkaline the solid was filtered, washed with water and hexane and dried to afford of yellowish crystals, (6.14 g, 23.3 mmol). $[\alpha]_D = +22.6$ [$c = 1$, methanol].

3.7. Enantiomeric enrichment

(a) Enantiomeric mixture of **M2** (6.14 g, $[\alpha]_D = +22.6$ [$c = 1$, methanol]) was recrystallised three times from a small amount of methanol to yield white crystals (3.63 g, 59%), $[\alpha]_D = +28.1$ [$c = 1$, methanol], mp 121–124°C.

(b) Enantiomeric mixture of **M2** (6.68 g, $[\alpha]_D = -22.2$ [$c = 1$, methanol]) was recrystallised three times from a small amount of methanol to yield of white crystals (3.61 g, 54%), $[\alpha]_D = -28.0$ [$c = 1$, methanol], mp 122–125°C.

3.8. Determination of the enantiomeric excess

The e.e. of the above samples was determined with the aid of (*R*)-(−)-1-(9-anthryl)-2,2,2-trifluoroethanol. At the ^{1}H NMR spectrum of *rac*-**M2** and the chiral solvating agent (molar ratio: 1:1.96) the H_{2Me} signal was split into two doublets: 1.07 ppm, 1.12 ppm, $\Delta = 27.8$ Hz. In the spectra of the two enantiomeric mixtures ($[\alpha]_D = +28.1$ and -28.0 [$c = 1$, methanol], respectively) with the chiral solvating agent only one enantiomeric peak was detectable, so we can assume them enantiomerically pure (e.e.>97%).

3.9. Resolution of M2 by anicyphos

Racemic **M2** (10 g, 38 mmol) and anicyphos (5.21 g, 19.1 mmol) was dissolved in acetone (100 mL) and the solution was allowed to crystallise. The crystals were filtered and washed with acetone then dried to afford product (8.08 g). The diastereoisomeric salt was dissolved in water, acidified, and the precipitate was collected by filtration (3.76 g, 13.8 mmol, 72%). The filtrate was treated with base to render it alkaline and the precipitated base was collected by filtration (3.50 g, 13.4 mmol, 70%), $[\alpha]_D = -24.3$ [$c = 1$, methanol], enantiomeric purity = 86% mp 121–124°C.

The mother liquor of the resolution was evaporated. After addition of water it was acidified with cc. HCl and the precipitated anicyphos was filtered and washed with water. The mother liquor was treated with base until alkaline and the precipitated base collected by filtration and washed with water then dried to afford a white solid (5.48 g, 21.0 mmol, 110%), $[\alpha]_D = +14.5$ [$c = 1$, methanol], enantiomeric purity = 51.6%, mp 122–123°C.

3.10. X-Ray crystallography[8–13]

Crystals were obtained as follows: the diastereoisomeric salt of (*R*)-(−)-**M2** (0.3 g, 1.14 mmol, $[\alpha]_D = -28.0$ ($c = 1$, methanol)) and anicyphos (0.31 g, 1.15 mmol) were dissolved in hot acetone–ethanol (4.5–0.5 mL). The solution was cooled to room temperature, inoculated and left to crystallise overnight.

Crystal data: $C_{28}H_{40}NO_7P{\cdot}0.81(C_3H_6O)$, Fwt: 580.69, colourless, prism, size: 0.55×0.30×0.25 mm, monoclinic, space group $P2_1$, $a = 10.410(2)$, $b = 8.576(1)$, $c = 18.533(1)$ Å, $\alpha = 90.00$, $\beta = 95.93(1)$, $\gamma = 90.00°$, $V = 1645.7(4)$ Å^3, $T = 293(2)$ K, $Z = 2$, $F(000) = 624$, $Dx = 1.172$ Mg/m^3, $m = 0.129$ mm^{-1}.

Cell parameters were determined by least-squares of the setting angles of 25 ($16.07 \le \theta \le 17.17°$) reflections.

Intensity data were collected on an Enraf–Nonius CAD4 diffractometer (graphite monochromator; Mo-Kα radiation, $\lambda = 0.710730$ Å) at 293(2) K in the range $2.62 \le \theta \le 29.96°$ using $\omega/2\theta$ scans. Backgrounds were measured half the total time of peak scans. The intensities of three standard reflections were monitored regularly (every 60 min). The intensities of the standard reflections indicated a crystal decay of 8% (the data were corrected for decay).

A total of 11003 reflections were collected of which 9408 were unique [$R_{int} = 0.0156$, $R(\sigma) = 0.0691$]; intensities of 5091 reflections were greater than $2\sigma(I)$. Completeness to $\theta = 0.985$.

A psi-scan absorption correction was applied to the data (the minimum and maximum transmission factors were 0.9659 and 0.9894).

The structure was solved by direct methods (and subsequent difference syntheses).

Anisotropic full-matrix least-squares refinement on F^2 for all non-hydrogen atoms yielded $R_1 = 0.0467$ and $wR_2 = 0.1004$ for 5091 [$I > 2\sigma(I)$] and $R_1 = 0.1035$ and $wR_2 = 0.1108$ for all (9408) intensity data (number of parameters = 388, goodness-of-fit = 0.888, absolute structure parameter $x = 0.01(7)$, the maximum and mean shift/esd is 0.001 and 0.000).

The maximum and minimum residual electron density in the final difference map was 0.275 and −0.158 e Å^{-3}.

The weighting scheme applied was $w = 1/[\sigma^2(F_o^2) + (0.0603P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$.

Hydrogen atomic positions were calculated from assumed geometries (except H19 and H37 that were located in difference maps). Hydrogen atoms were included in structure factor calculations but they were not refined. The isotropic displacement parameters of the hydrogen atoms were approximated from the U_{eq} value of the atom they were bonded to.

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