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Key indicators

Single-crystal X-ray study  
T = 293 K  
Mean  $\sigma(C-C)$  = 0.004 Å  
R factor = 0.042  
wR factor = 0.139  
Data-to-parameter ratio = 7.8

For details of how these key indicators were automatically derived from the article, see <http://journals.iucr.org/e>.

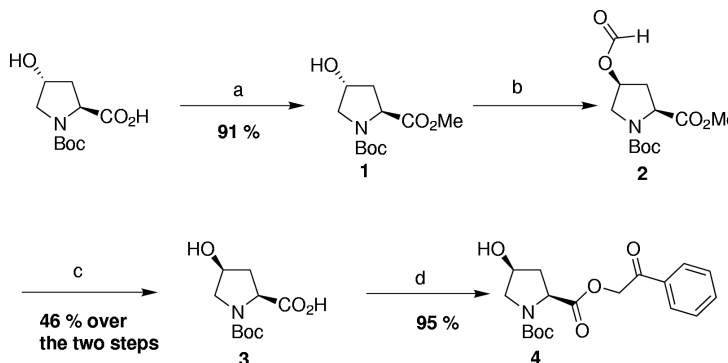
Phenacyl (2*S*,4*S*)-1-*tert*-butoxycarbonyl-4-hydroxyprolinate

The title compound, C<sub>18</sub>H<sub>23</sub>NO<sub>6</sub>, is a 4-hydroxyproline derivative of the type found in many compounds with biological activity. The crystal structure involves an intermolecular O—H...O hydrogen bond, linking molecules into a chain along a screw axis.

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Comment

Proline and its 4-substituted derivatives are important amino acids in many naturally occurring bioactive peptides, such as gramicidin (Tamaki *et al.*, 1985), and have been extensively used in the pharmaceutical industry as angiotensin-converting enzyme (ACE) inhibitors, including Captopril (Ondetti *et al.*, 1977) and Enalapril (Patchett *et al.*, 1980). Moreover, the hydroxyproline scaffold offers three points of attachment (the amine, the hydroxyl and the carboxyl groups), making it a good candidate for library production (Vergnon *et al.*, 2004). We present here the structure of the title compound, (4).

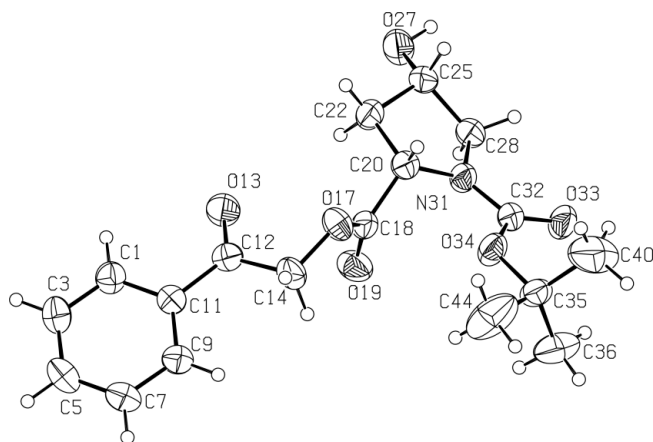


In the crystal structure of (4), an intermolecular hydrogen bond is observed between hydroxyl group O27 and carbonyl atom O33 [O27—H27 = 0.92 (5) Å, H27...O33<sup>i</sup> = 1.82 (5) Å, O27...O33<sup>i</sup> = 2.733 (3) Å and O27—H27...O33<sup>i</sup> = 169 (5)°; symmetry code: (i)  $x + \frac{1}{2}, -y + \frac{1}{2}, -z + 1$ ].

Experimental

In the reaction scheme, the steps are as follows: (a) Cs<sub>2</sub>CO<sub>3</sub>, MeOH, H<sub>2</sub>O then CH<sub>3</sub>I, dimethylformamide (DMF), 24 h, room temperature; (b) PPh<sub>3</sub>, diisopropylazodicarboxylate (DIAD), HCO<sub>2</sub>H, tetrahydrofuran (THF), 16 h, room temperature; (c) NaOH, H<sub>2</sub>O, THF, 3 h, 273 K then room temperature; (d) Cs<sub>2</sub>CO<sub>3</sub>, MeOH, H<sub>2</sub>O then phenacyl bromide (PacBr), DMF, 30 min, room temperature.

Commercially available reagents and solvents were used as received. Anhydrous solvents were distilled; THF was purified by distillation over sodium and benzophenone. Flash column chromatography was performed on silica gel (40–60 μm)



**Figure 1**  
A view of the title compound, (4), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

purchased from Merck.  $^1\text{H}$  NMR spectra were recorded at 250 MHz on a Bruker instrument and chemical shifts are reported as  $\delta$  (p.p.m., internal reference trimethylsilane). Low-resolution mass spectra were acquired using a Jeol DX-100 instrument with positive mode fast atom bombardment (FAB), with 4-nitrobenzyl alcohol as matrix. Optical rotations were measured on a Perkin–Elmer 241 polarimeter in a 10 cm cell.

(2*S*,4*R*)-*N*-*tert*-butoxycarbonyl-4-hydroxyproline (5.92 g, 25.6 mmol, 1 equivalent) was dissolved in water (7 ml) and methanol (52 ml), and a 20% aqueous solution of  $\text{Cs}_2\text{CO}_3$  was added until the pH was 7. The solvents were then evaporated under reduced pressure and the remaining residue was dissolved in anhydrous DMF (65 ml) under argon. To this solution was added methyl iodide (2.55 ml, 41.0 mol, 1.6 equivalents) and the resulting mixture was stirred for 24 h at room temperature. The reaction was quenched by addition of brine (65 ml) and then extracted with EtOAc (3  $\times$  65 ml). The combined organic layers were successively washed with water (5  $\times$  65 ml), a saturated aqueous solution of  $\text{NaHCO}_3$  (130 ml) and brine (130 ml). They were dried over anhydrous  $\text{MgSO}_4$  and concentrated under reduced pressure. Compound (1) was obtained as a yellow oil (5.70 g, 91%) and was used directly for the next step.

To a solution of (1) (5.64 g, 23.0 mmol, 1 equivalent), triphenylphosphine (12.1 g, 45.9 mmol, 2 equivalents) and formic acid (1.75 ml, 45.9 mmol, 2 equivalents) in anhydrous THF (60 ml) under argon was added dropwise a 40% solution of diisopropylazodicarboxylate (8.91 ml, 45.9 mmol, 2 equivalents) in THF. The resulting mixture was stirred for 16 h at room temperature and then quenched with a saturated aqueous solution of  $\text{NaHCO}_3$  (250 ml). After extraction with EtOAc (3  $\times$  100 ml), the combined organic layers were dried over anhydrous  $\text{MgSO}_4$  and concentrated under reduced pressure. The crude product was purified by flash column chromatography (cyclohexane–EtOAc, 7:3) and compound

(2) [ $R_f$  = 0.26 (cyclohexane–EtOAc, 7:3)] was obtained, together with diisopropyl-1,2-hydrazine dicarboxylate and triphenylphosphine.

This mixture (about 15 g) was used directly for the saponification step. It was dissolved in THF (60 ml) and a solution of 1 *N* NaOH (75.8 ml, 75.8 mmol) was added dropwise at 273 K. The mixture was stirred for 3 h at room temperature and then neutralized with 1 *N* HCl (20 ml). The solution was then concentrated under reduced pressure and the resulting residue was dissolved in water (40 ml). It was washed with EtOAc (2  $\times$  100 ml), acidified to pH 2 with 1 *N* HCl, and finally extracted with EtOAc (6  $\times$  130 ml). The combined organic layers were dried over anhydrous  $\text{MgSO}_4$  and evaporated to dryness. The crude product was recrystallized (EtOAc–cyclohexane) to obtain compound (3) (2.46 g, 46%) as a white powder.

To a solution of (3) (1.54 g, 6.64 mmol, 1 equivalent) in MeOH (27 ml) was added a solution of  $\text{Cs}_2\text{CO}_3$  (1.09 g, 3.32 mmol, 0.5 equivalents) in water (17 ml) at 273 K. The solvents were evaporated under reduced pressure and the remaining residue dissolved in anhydrous DMF (33 ml) under argon. Phenacyl bromide (1.32 g, 6.64 mmol, 1 equivalent) was added dropwise at 273 K and the resulting mixture was stirred at room temperature for 30 min. It was filtered and the filtrate was evaporated. The resulting oil was dissolved in EtOAc (100 ml) and successively washed with water (5  $\times$  35 ml) and a saturated aqueous solution of  $\text{NaHCO}_3$  (2  $\times$  30 ml), dried over anhydrous  $\text{MgSO}_4$ , and evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (cyclohexane–EtOAc 1:1 to 3:7) and the title compound, (4) (2.21 g, 95%), was obtained as a white solid. It was dissolved in ethyl acetate and colourless crystals (cube-shaped) were obtained with *n*-hexane as precipitant.

Spectroscopic analysis (atom numbers as in Fig. 1, with H atoms following sequentially in the same scheme):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ,  $\delta$ , p.p.m.): 7.92 (2H, *d*,  $J$  = 8.0 Hz, H9), 7.62 (1H, *t*,  $J$  = 8.4 Hz, H5), 7.50 (2H, *t*,  $J$  = 6.5 Hz, H7), 5.57 and 5.32 (1H, AB system,  $J_{AB}$  = 16.5 Hz, H14), 5.42 (1H, *s*, H14), 4.53 (1H, *m*, H25), 4.44 (1H, *m*, H20), 3.40 to 3.80 (2H, *m*, H28), 2.48 (2H, *m*, H22), 1.47 and 1.45 (9H, 2  $\times$  *s*, H36, H44, H40);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ,  $\delta$ , p.p.m.): 192.03 and 191.90 (C12), 173.42 (C18), 154.31 and 153.47 (C32), 134.00 (C11), 133.55 (C5), 128.71 (C9), 127.61 (C3), 80.22 (C35), 70.98 and 69.98 (C25), 66.25 and 65.98 (C14), 57.76 and 57.54 (C20), 55.82 and 55.34 (C28), 38.99 and 38.14 (C22), 28.14 (C36, C44, C40); FAB $^+$ , NBA: 350 ( $M+1\text{H}$ ) $^+$ ;  $R_f$  = 0.19 (cyclohexane–EtOAc, 1:1),  $[\alpha]_D^{25}$  (*c* 1.02,  $\text{CHCl}_3$ ) =  $-47.1$ ; m.p. 431 K.

#### Crystal data

$\text{C}_{18}\text{H}_{23}\text{NO}_6$   
 $M_r$  = 349.37  
Orthorhombic,  $P2_12_12_1$   
 $a$  = 9.653 (2) Å  
 $b$  = 9.780 (2) Å  
 $c$  = 19.179 (4) Å  
 $V$  = 1810.6 (6) Å $^3$   
 $Z$  = 4  
 $D_x$  = 1.282 Mg m $^{-3}$

Mo  $K\alpha$  radiation  
Cell parameters from 7664 reflections  
 $\theta$  = 3.8–26.6°  
 $\mu$  = 0.10 mm $^{-1}$   
 $T$  = 293 (2) K  
Cube, colourless  
0.3  $\times$  0.3  $\times$  0.3 mm

Data collection

Nonius KappaCDD area-detector diffractometer	1811 reflections with $I > 2\sigma(I)$
$\varphi$ scans	$R_{\text{int}} = 0.038$
Absorption correction: none	$\theta_{\text{max}} = 26.6^\circ$
13 679 measured reflections	$h = -12 \rightarrow 12$
2006 independent reflections	$k = -12 \rightarrow 12$
	$l = -22 \rightarrow 22$

Refinement

Refinement on $F^2$	$w = 1/[\sigma^2(F_o^2) + (0.1P)^2 + 0.053P]$
$R[F^2 > 2\sigma(F^2)] = 0.042$	where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.139$	$(\Delta/\sigma)_{\text{max}} < 0.001$
$S = 0.90$	$\Delta\rho_{\text{max}} = 0.13 \text{ e } \text{\AA}^{-3}$
2006 reflections	$\Delta\rho_{\text{min}} = -0.13 \text{ e } \text{\AA}^{-3}$
257 parameters	Extinction correction: <i>SHELXL97</i>
H atoms treated by a mixture of independent and constrained refinement	(Sheldrick, 1997)
	Extinction coefficient: 0.22 (6)

The hydroxy H atom was located in a difference map and refined freely. Other H atoms were positioned geometrically and refined as riding, with C—H = 0.93–0.98 Å and freely refined  $U_{\text{iso}}$  values, except that  $U_{\text{iso}}(\text{H})$  was fixed at 0.15 Å<sup>2</sup> for the *tert*-butyl group. In the absence of significant anomalous scattering effects, Friedel pairs were merged. The absolute configuration is assumed from the synthesis.

Data collection: *COLLECT* (Nonius, 1998); cell refinement: *DENZO* and *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO* and *SCALEPACK*; program(s) used to solve

structure: *SIR97* (Altomare *et al.*, 1999); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEPII* (Johnson, 1976); software used to prepare material for publication: *PLATON* (Spek, 2003).

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