Total Synthesis and *X*-Ray Crystal Structure of 13,14-Didehydro-11-deoxy-11-methyl-15-oxoprostaglandin E_1

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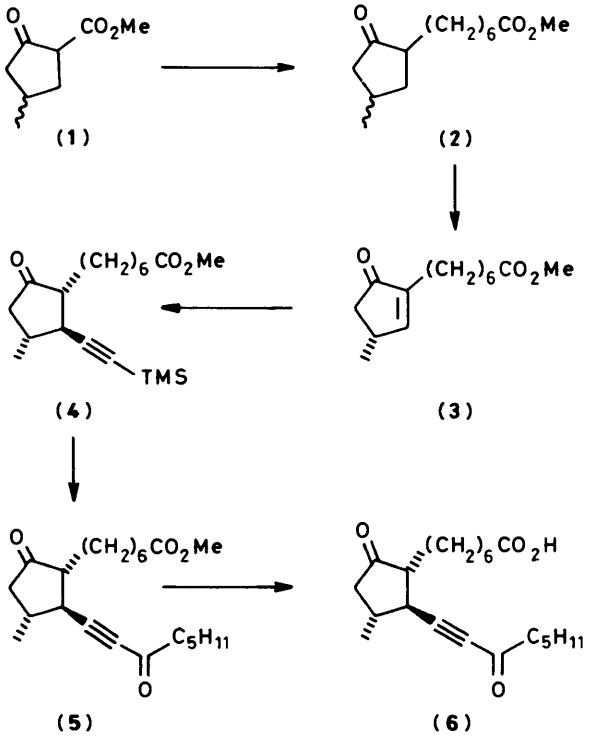
A new 11-methylated prostaglandin analogue bearing the unusual 13,14-didehydro-15-oxo bottom side-chain has been prepared by total synthesis. Its complete structure has been established unambiguously by a single crystal *X*-ray analysis.

During our earlier work on the synthesis[1] and biological properties[2] of 11-deoxy-7-oxaprostaglandin analogues, we found that incorporation of the 13,14-didehydro-15-oxo (ynone) group into the bottom side-chain resulted in unexpectedly potent and selective activity in cytoprotection screens.[3] To extend those observations to systems more closely resembling the natural prostaglandins, we wanted to synthesize and test analogues with the normal top side-chains and with substitution at C-11. Based on the analogy with 11-methyl-16,16-dimethyl PGE_2, which has been shown to be a potent and stable cytoprotective compound,[4] the corresponding 11-methyl versions of our ynone prostanoids made attractive targets. The total synthesis of 13,14-didehydro-11-deoxy-11-methyl-15-oxoprostaglandin E_1 (**6**) was therefore undertaken, and we now report the successful completion of that work, including a complete structural determination of the product by single-crystal *X*-ray analysis.

Results and Discussion

The total synthesis of the target analogue (**5**) is illustrated in the Scheme below. Our starting material was the known[5] oxo ester (**1**), synthesized by Dieckmann cyclization of dimethyl 3-methyladipate. Although this cyclization produces both possible regioisomers, the desired 4-methyl isomer (**1**) is favoured over the 3-methyl compound in a ratio of *ca.* 2.5:1, consistent with the literature reports.[5] Alkylation of (**1**) with ethyl 7-bromoheptanoate[6] followed by decarboxylation gave oxo ester (**2**) in 48% overall yield after fractional distillation. Analysis of the ^{13}C and ^1H n.m.r. spectra of (**2**) revealed that it was a mixture of *cis* and *trans* isomers contaminated only slightly by the 3-methyl regioisomer, most of which was apparently removed during the distillation. Following an analogous literature procedure,[7] the oxo ester (**2**) was converted into the enone (**3**) by (i) enol acetate formation using acetic anhydride and toluene-*p*-sulphonic acid, (ii) bromination of the enol acetate to give the bromo ketone, and (iii) dehydrohalogenation of the crude bromo ketone with lithium bromide in refluxing dimethylformamide. Since the enone (**3**) has only one chiral centre, both the *cis* and *trans* isomers of (**2**) yield the same product (a racemate), and flash chromatography of the crude enone thus gave the pure product (**3**).



Scheme.

After several attempts at attaching an acetylenic bottom side-chain onto the enone (**3**), we eventually settled on a two-step procedure involving the nickel catalyzed conjugate addition reaction described by Schwartz *et al.*[8] Thus, the elements of (trimethylsilyl)acetylene were added to (**3**) yielding (**4**). The adduct (**4**) has the all-*trans* ring stereochemistry, as demonstrated by the *X*-ray structure described below. Also present in the reaction mixture was a diastereoisomer (*ca.* 10—25% of the total weight), which could not be purified enough to allow structural assignment. Attachment of the rest of the bottom side-chain was effected by treating (**4**) with aluminium trichloride and hexanoyl chloride[9] to give the final product, purified by flash chromatography on silica gel. The ^{13}C n.m.r. spectrum of this material showed that it was a single isomer whose connectivity was clearly consistent with structure (**5**); however, the relative stereochemistry at the three chiral centres of (**5**) could not be unambiguously established. Since it is well known that stereochemistry can have pronounced effects on the biological activity of prostaglandins, we decided to convert the methyl ester (**5**) into its free acid form in the hope that it would crystallize, allowing an *X*-ray structural determination.

Because of the sensitivity of the ynone group to base, hydrolysis of (**5**) was accomplished indirectly. Non-stereoselective reduction (sodium borohydride in methanol) of the two oxo groups of (**5**) gave the corresponding diol as a mixture of stereoisomers. Hydrolysis with sodium hydroxide yielded the free acid, again as a mixture of isomers, which was reoxidized with Jones reagent to the diketone (**6**). Compound (**6**) did solidify, and could be recrystallized from ethyl acetate–hexane at 0 °C to afford single crystals suitable for *X*-ray crystallography. The *X*-ray analysis, illustrated below, demonstrates conclusively that the relative stereochemistry of our

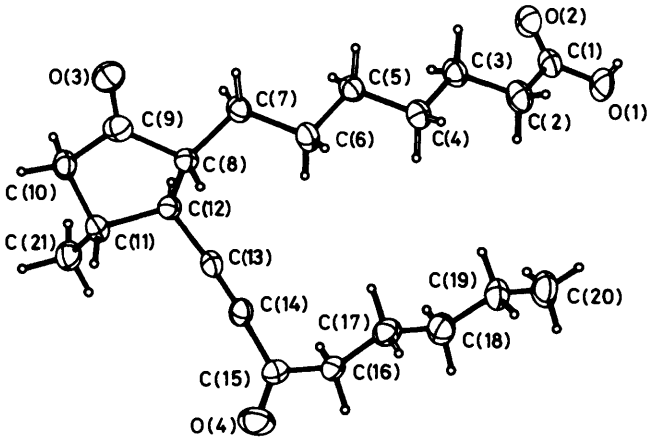


Figure. Perspective drawing of compound (**6**), 13,14-didehydro-11-deoxy-11-methyl-15-oxoprostaglandin E_1, illustrating 50% probability ellipsoids. H-Atoms are drawn artificially smaller

product is all-*trans*, conforming to that of the natural prostaglandins. The compound exhibits the classical hairpin conformation, whereas the related analogue 13,14-didehydro-11-deoxy-15-oxoprostaglandin E_1 has an unusual L-shaped conformation in the solid state.[10] The five-membered ring has a twist-envelope conformation. The molecules exist as hydrogen-bonded dimers involving the carboxy groups of adjacent molecules. The oxo groups do not participate in hydrogen bonds.

The gastric cytoprotective activity of compound (**5**) and related analogues will be reported separately.

Experimental

2-Methoxycarbonyl-4-methylcyclopentanone (**1**).—Toluene (100 ml) and sodium spheres (14.57 g, 0.634 mol) were combined in a flame-dried, argon-purged 1-l flask. Methanol (90 ml, 2.22 mol) was added dropwise through an addition funnel with stirring. A vigorous exothermic reaction ensued and the mixture soon reached reflux temperature, at which it was kept for 2 h. After dilution with toluene (400 ml), a solution of dimethyl 3-methyladipate (59.75 g, 0.317 mol) in toluene (50 ml) was added *via* an addition funnel to the mixture at 70 °C. A distillation head was attached and methanol was slowly removed as the toluene–methanol azeotrope. After 0.5 h the reaction solution became a solid mass. Heating was continued until the distillate head temperature reached 110 °C (2 h). The mixture was cooled to room temperature and 1M HCl (667 ml, 0.667 mol) was slowly worked into the solid mass to produce two clear layers. The toluene layer was separated and the aqueous layer was extracted with ether (2 × 250 ml). The organic portions were combined and washed with saturated aqueous $NaHCO_3$ (250 ml), and the aqueous layer was back-extracted with ether (250 ml). The combined organic layers were dried ($MgSO_4$), filtered, concentrated under reduced pressure and distilled at 76 °C (2 Torr) to yield (**1**) (43.21 g, 87% yield) as a colourless liquid [lit.,[5] b.p. 117—119 °C (16 Torr)]. G.c. analysis (27 m × 0.25 μm DB-1 capillary column) indicated a 2.5:1 mixture of regioisomers. Highfield ^1H and ^{13}C n.m.r. revealed the presence of at least three isomeric products; δ (270 MHz; $CDCl_3$) 3.75 (s), 3.72 (s), 3.72 (s), 3.3 (m), 2.8 (d, *J* 10.5 Hz), 2.5 (m), 2.0 (m), 1.5 (m), 1.19 (2 sets of overlapping doublets, *J* = 6.6 Hz), and 1.12 (d, *J* 6.6 Hz); δ_C (67.8 MHz; $CDCl_3$) 211.1, 210.9, 210.6, 169.1, 168.9, 62.2, 55.6, 52.9, 51.6, 51.5, 45.6, 37.9, 35.8, 35.0, 34.6, 34.3, 28.9, 28.6, 19.6, 19.1, and 18.5; $\nu_{max.}$(neat) 2 972, 2 885, 1 760, 1 730, 1 461, 1 439, 1 340, 1 263, 1 210, 1 150, and 1 124 cm^{-1}.

Oxo Ester (**2**).—2-Methoxycarbonyl-4-methylcyclopentanone (**1**) (30.90 g, 0.20 mol), ethyl 7-bromoheptanoate (46.93 g, 0.20 mol), K_2CO_3 (54.67 g, 0.40 mol), and dry acetone (400 ml) were combined in a dried, 1-l flask equipped with a mechanical stirrer, condenser, and drying tube. The mixture was refluxed for 18 h, cooled to room temperature, and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure, diluted with water (242 ml) and concentrated H_2SO_4 (122 ml), and then refluxed for 18 h. The mixture was cooled to room temperature and extracted with ether (3 × 200 ml). The combined ether extracts were washed with water and saturated brine (200 ml each), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The dark residue was dissolved in methanol (700 ml) and concentrated H_2SO_4 (0.6 ml), refluxed for 2 h, and then kept for 18 h at room temperature. The solution was concentrated under reduced pressure to remove most of the methanol and then diluted with ether (300 ml) and washed with water and saturated $NaHCO_3$ (100 ml each). The ether layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure and the product was fractionally distilled to yield (**2**) (20.15 g, 42% yield) as a clear, light yellow liquid, b.p. 112—125 °C (0.05 Torr). G.c. analysis (3% OV-101) revealed a single component of >95% purity; δ_C (20 MHz; $CDCl_3$) 220.8, 174.2, 51.4, 50.9, 47.0, 46.8, 46.5, 38.6, 36.9, 34.0, 30.5, 29.7, 29.6, 29.2, 29.0, 28.3, 27.7, 27.4, 24.9, 20.8, and 20.3; δ_H (60 MHz; $CDCl_3$) 3.7 (s, 3 H), 2.3 (br m, 7 H), and 1.4 (br m, 16 H); $\nu_{max.}$(neat) 2 960, 2 940, 2 862, 1 741, 1 460, 1 440, 1 201, and 1 162 cm^{-1}.

Enone Ester (**3**).—The oxo ester (**2**) (33.04 g, 0.137 mol), acetic anhydride (61.8 ml, 0.654 mol), and toluene-*p*-sulphonic acid hydrate (0.28 g, 1.5 mmol) were charged to a flask (250 ml) equipped with a short fractionating column topped with a distillation head. The mixture was heated at 180 °C to allow slow distillation of the acetic acid as it formed (head temperature 120—130 °C). The conversion was monitored by g.c. (200 °C isothermal; 3% OV-101) and t.l.c. (silica; hexane–EtOAc, 4:1) analyses. After 12 h the conversion was >95% complete. The bath was cooled to room temperature and added to 0.5M $NaHCO_3$ (1.2 l) with stirring. After 15 min the mixture was extracted with hexane (3 × 250 ml), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield the enol acetate (35.40 g, 92% yield) as a brown liquid which assayed at >95% purity by g.c., the sole contaminant being residual oxo ester; δ_C (20 MHz; $CDCl_3$) 173.7, 168.3, 142.5, 125.2, 51.0, 39.2, 39.0, 33.7, 28.5, 26.5, 25.8, 24.5, 21.7, and 20.3; δ_H (270 MHz; $CDCl_3$) 3.65 (s, 3 H), 2.64 (br m, 1 H), 2.41 (br m, 2 H), 2.29 (t, *J* 7 Hz, 2 H), 2.12 (s, 3 H), 1.96 (br m, 3 H), 1.61 (m, 3 H), 1.3 (br m, 7 H), 1.07 (d, 3 H, *J* 6.6 Hz); $\nu_{max.}$(neat) 2 960, 2 938, 2 860, 1 740, 1 700w, 1 440, 1 372, 1 216, and 1 182 cm^{-1}.

A mixture of $CaCO_3$ (12.24 g, 0.122 mol) in water (117 ml) was mechanically stirred at 0 °C while solutions of the enol acetate (33.51 g, 0.119 mol) in $CHCl_3$ (15 ml) and bromine (6.39 ml, 0.125 mol) in $CHCl_3$ (17.5 ml) were added simultaneously over 15 min. The mixture was stirred for an additional 20 min at 0 °C and then quenched with 10% $NaHSO_4$ and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with 10% $NaHSO_4$, dried ($MgSO_4$), filtered, and concentrated under reduced pressure at 30 °C. A mixture of LiBr (21.66 g, 0.249 mol), Li_2CO_3 (20.68 g, 0.28 mol), and dry DMF (156 ml) was concentrated under reduced pressure three times with benzene (to remove any water present), and set up to reflux. The above bromo ketone was cautiously added to this refluxing mixture. After 30 min the mixture was cooled to room temperature and poured into a separatory funnel containing an excess of 1M HCl. Ether extraction, drying ($MgSO_4$), filtration, and concentration under reduced pressure afforded the crude enone which was bulb-to-bulb distilled (150—200 °C at 0.065 Torr) and then

chromatographed in several small batches (silica; Hexane–EtOAc, 4:1; R_F = 0.20) to yield pure compound (**3**) (10 g, 33%) as a clear yellow liquid; δ_H (270 MHz; $CDCl_3$) 7.09 (s, 1 H), 3.58 (s, 3 H), 2.80 (br m, 1 H), 2.55 (dd, *J* 6.3 Hz, 18.8 Hz, 1 H), 2.22 (t, *J* 7.3 Hz, 2 H), 2.06 (t, *J* 7.3 Hz, 2 H), 1.87 (dd, *J* 2.0 Hz, 18.8 Hz, 1 H), 1.54 (br m, 2 H), 1.40 (br m, 2 H), 1.24 (br m, 4 H), and 1.08 (d, *J* 7.3 Hz, 3 H); δ_C (67.8 MHz; $CDCl_3$) 209.6, 174.0, 162.5, 145.1, 51.3, 43.2, 33.9, 33.2, 28.8, 28.7, 27.4, 24.7, 24.3, and 20.2; *m/z* (NH_3 c.i.) 256 (MNH_4^+, base peak) and 239 (MH^+); $\nu_{max.}$(neat) 2 930, 2 860, 1 738, 1 703, 1 630, 1 435, 1 200, 1 170, and 897 cm^{-1} (Found: M^+, 238.1571. Calc. for $C_{14}H_{21}O_3$: *M*, 238.1569); h.p.l.c. analysis showed (**3**) to be 96% pure.

(*Trimethylsilyl*)*acetylene Derivative* (**4**).—A solution of (trimethylsilyl)acetylene (0.62 g, 6.3 mmol) in toluene (25 ml) and Et_2O (25 ml) in a flame-dried 100-ml flask under argon was cooled at 0 °C whilst butyl-lithium in hexane (1.55M; 4.3 ml, 6.6 mmol) was added. The reaction was stirred for 15 min at 0 °C after which dimethylaluminium chloride in hexane (1.0M; 6.6 ml, 6.6 mmol) was added. After the addition was complete the reaction mixture was stirred for 45 min at 0 °C and then for 30 min at ambient temperature. The contents of the flask were then transferred by syringe and needle to a reaction flask (250 ml) containing the catalyst, composed of [Ni(acac)$_2$] (0.17 g, 0.6 mmol) and di-isobutylaluminium hydride in toluene (1M; 0.6 ml, 0.6 mmol) dissolved in Et_2O (25 ml) at 0 °C. A solution of the enone ester (**3**) (0.71 g, 3.0 mmol) in Et_2O (5 ml) was added dropwise over 10 min. The reaction was stirred for 1.5 h at 0 °C and a further 1.5 h at ambient temperature. The reaction was quenched by adding saturated aqueous KH_2PO_4 (100 ml) to the flask. Just sufficient 10% HCl was added to dissolve any solids, and the organic layer was separated from the aqueous layer. The aqueous layer was extracted with ether, and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and saturated brine, dried ($MgSO_4$), filtered, and evaporated. The residue was flash chromatographed using hexane–EtOAc (4:1). A total of 812 mg of product (mixture of isomers, 81% yield) and 45 mg of starting material was collected from the column; δ_C (67.8 MHz; $CDCl_3$) 217.2, 174.1, 107.1, 86.8, 56.1, 51.3, 45.7, 42.6, 36.5, 34.0, 29.2, 28.9, 28.7, 26.4, 24.8, 18.3, and 0.0; δ_H (60 MHz; $CDCl_3$) 0.15 (s, 9 H), 1.33 (m, 14 H), 2.20 (m, 6 H), and 3.55 (s, 3 H).

13,14-*Didehydro*-11-*deoxy*-11-*methyl*-15-*oxo* PGE_1 *Methyl Ester* (**5**).—A suspension of $AlCl_3$ (0.16 g, 1.2 mmol) in CH_2Cl_2 (8 ml) was stirred at 0 °C under argon while a solution of hexanoyl chloride (0.16 g, 1.2 mmol) in CH_2Cl_2 (2 ml) was added. The mixture was stirred for 30 min at 0 °C after which compound (**4**) (0.20 g, 0.6 mmol) in CH_2Cl_2 (2 ml) was added dropwise and the reaction was stirred for 3 h at 0 °C. The resulting mixture was diluted with Et_2O (50 ml) and washed sequentially with 1M HCl, 1M $NaHCO_3$, and saturated aqueous NaCl. The organic layer was then dried ($MgSO_4$), filtered, and evaporated and the residue (217 mg) chromatographed over silica gel with hexane–EtOAc (4:1) to give the desired product (**5**) (95 mg, 44%); $\nu_{max.}$(neat) 2 950, 2 925, 2 200, 1 730, 1 665, 1 440, 1 235, 1 165, 1 010, 840, and 720 cm^{-1}; δ_C (67.8 MHz; $CDCl_3$) 215.6, 188.0, 174.1, 92.9, 82.2, 55.7, 51.3, 45.6, 45.5, 41.3, 36.2, 33.9, 31.0, 29.2, 28.8, 28.6, 26.4, 24.8, 23.8, 22.3, 18.4, and 13.8; δ_H (270 MHz; $CDCl_3$) 3.62 (s, 3 H), 2.51 (t, *J* 7.6 Hz, 2 H), 2.26 (t, *J* 7.6 Hz, 2 H), 1.77 (dd, *J* 11.5 Hz, 18.5 Hz, 1 H), 1.22 (d, *J* 6.3 Hz, 3 H), and 0.87 (s, 1 H) (Found: M^+, 362.2460. Calc. for $C_{22}H_{31}O_4$: *M*, 362.2457).

Conversion of the Ester (**5**) *into the Free Acid* (**6**).—A flame-dried flask was purged with argon, charged with $NaBH_4$ (7.9 mg, 0.21 mmol) and methanol (2 ml), and cooled to −10 °C. A solution of the ester (**5**) (68.2 mg, 0.188 mmol) in methanol (2 ml) was then added. A second portion (7.9 mg) of $NaBH_4$ was added 0.5 h later. T.l.c. analysis then indicated that the reaction was complete. The reaction mixture was added to 1M HCl (25 ml) and extracted with CH_2Cl_2; the combined organic portions

Table 1. Summary of crystal data and details of data collection

Crystal data	
Formula	$C_{21}H_{32}O_4$
Formula wt.	348.5
a/Å	5.602(1)*
b/Å	8.668(?)
c/Å	21.685(3)
α/°	89.41(1)
β/°	89.76(2)
γ/°	76.64(10)
V/Å^3	1 024.5
Space group	$P\bar{1}$ (No. 2)
Z	2
d_c/g cm^{-1}	1.13
F(000)	380
T °C	−80
Data collection	
Crystal size (mm)	0.43 × 0.17 × 0.11
λ(Mo-*K*)/Å	0.710 73
μ/cm^{-1}	0.71
Data sphere (°)	$3 < 2\theta < 45$
Scan mode	ω − 2θ
Scan rate (°/min)	variable, 4—29.3
Miller index range	*h* 0 to 5, *k* −9 to 9, *l* −23 to 23
Reflections measured	3 006
Unique reflections measured	2 674
Unique reflections used $\lvert F_o\rvert > 4\sigma(\lvert F_o\rvert)$	1 818
Check reflections	$\bar{2}00$,020,004
Intensity variation	≤2.2% relative
Absorption correction	(corrected) None

* By least-squares refinement on diffractometer angles for 22 automatically centred, general reflections.

Table 2. Atom co-ordinates (× 10^4) and temperature factors (Å^2 × 10^3) for compound (**6**)

Atom	*x*	*y*	*z*
O(1)	18 204(4)	2 068(2)	5 019(1)
O(2)	17 729(3)	−195(2)	5 443(1)
O(3)	2 670(3)	670(2)	8 346(1)
O(4)	7 938(4)	8 083(2)	8 913(1)
C(1)	17 039(5)	1 233(4)	5 375(1)
C(2)	14 820(5)	2 213(3)	5 688(1)
C(3)	13 518(5)	1 273(3)	6 113(1)
C(4)	11 496(5)	2 309(3)	6 496(1)
C(5)	10 124(5)	1 369(3)	6 904(1)
C(6)	8 386(5)	2 376(3)	7 360(1)
C(7)	7 042(5)	1 411(3)	7 764(1)
C(8)	5 640(4)	2 298(3)	8 303(1)
C(9)	3 963(4)	1 379(3)	8 620(1)
C(10)	4 196(5)	1 462(3)	9 306(1)
C(11)	5 520(5)	2 790(3)	9 419(1)
C(12)	7 190(4)	2 688(3)	8 844(1)
C(13)	8 094(4)	4 143(3)	8 763(1)
C(14)	8 682(5)	5 387(3)	8 726(1)
C(15)	9 302(5)	6 931(3)	8 686(1)
C(16)	11 634(5)	7 014(3)	8 360(1)
C(17)	11 486(5)	6 778(3)	7 665(1)
C(18)	13 854(5)	6 856(3)	7 335(1)
C(19)	13 756(6)	6 669(4)	6 644(1)
C(20)	16 196(6)	6 627(4)	6 321(2)
C(21)	6 899(6)	2 671(4)	10 022(1)

Table 3. Bond lengths (Å) and bond angles (°) for compound (**6**)

O(1)–C(1)	1.323(4)	O(2)–C(1)	1.216(4)
O(3)–C(9)	1.213(3)	O(4)–C(15)	1.216(3)
C(1)–C(2)	1.499(4)	C(2)–C(3)	1.516(4)
C(3)–C(4)	1.522(4)	C(4)–C(5)	1.518(4)
C(5)–C(6)	1.518(3)	C(6)–C(7)	1.518(4)
C(7)–C(8)	1.518(3)	C(8)–C(9)	1.524(4)
C(8)–C(12)	1.549(4)	C(9)–C(10)	1.497(4)
C(10)–C(11)	1.529(4)	C(11)–C(12)	1.546(3)
C(11)–C(21)	1.513(4)	C(12)–C(13)	1.472(4)
C(13)–C(14)	1.200(4)	C(14)–C(15)	1.461(4)
C(15)–C(16)	1.499(4)	C(16)–C(17)	1.527(4)
C(17)–C(18)	1.520(4)	C(18)–C(19)	1.511(4)
C(19)–C(20)	1.527(5)		
O(1)–C(1)–O(2)	122.7(2)	O(1)–C(1)–C(2)	113.7(2)
O(2)–C(1)–C(2)	123.6(3)	C(1)–C(2)–C(3)	114.0(2)
C(2)–C(3)–C(4)	113.4(2)	C(3)–C(4)–C(5)	113.5(2)
C(4)–C(5)–C(6)	113.9(2)	C(5)–C(6)–C(7)	113.0(2)
C(6)–C(7)–C(8)	115.2(2)	C(7)–C(8)–C(9)	112.8(2)
C(7)–C(8)–C(12)	116.7(2)	C(9)–C(8)–C(12)	102.7(2)
O(3)–C(9)–C(9)	123.8(2)	O(3)–C(9)–C(10)	126.0(2)
C(8)–C(9)–C(10)	110.2(2)	C(9)–C(10)–C(11)	105.6(2)
C(10)–C(11)–C(12)	102.3(2)	C(10)–C(11)–C(21)	115.2(2)
C(12)–C(11)–C(21)	113.6(2)	C(8)–C(12)–C(11)	105.3(2)
C(8)–C(12)–C(13)	115.2(2)	C(11)–C(12)–C(13)	111.2(2)
C(12)–C(13)–C(14)	174.9(3)	C(13)–C(14)–C(15)	117.8(3)
O(4)–C(15)–C(14)	119.6(3)	O(4)–C(15)–C(16)	122.8(3)
C(14)–C(15)–C(16)	117.5(2)	C(15)–C(16)–C(17)	112.4(2)
C(16)–C(17)–C(18)	112.4(2)	C(17)–C(18)–C(19)	114.0(3)
C(18)–C(19)–C(20)	113.6(3)		

were filtered and concentrated under reduced pressure. The crude product was dissolved in methanol (10 ml) and 1M NaOH (3.12 ml) was added to the solution. After 4 days at room temperature, t.l.c. analysis indicated complete consumption of the ester. The reaction was concentrated under reduced pressure and extracted from 1M HCl (25 ml) with CH_2Cl_2 (3 × 25 ml). The combined organic layers were concentrated under reduced pressure and the residue was taken up in acetone (5 ml), and cooled to 0 °C. Jones reagent was then added dropwise until the orange colour persisted. The mixture was stirred for 10 min, after which the excess of reagent was destroyed by the addition of isopropyl alcohol; the reaction mixture was then filtered and concentrated to give the crude acid. Purification by m.p.l.c. (40:10:0.25 hexane–THF–HOAc) afforded pure compound (**6**) (42.1 mg, 64% yield) which solidified at −10 °C overnight, and was recrystallized from EtOAc–hexane (0 °C with seeding) to give white crystals, m.p. 30.5—31.0 °C, suitable for *X*-ray crystallography.

X-Ray Structure Determination of Compound (**6**).—All *X*-ray measurements were made on a Syntex $P2_1$ diffractometer equipped with a Mo-target *X*-ray tube, an incident-beam graphite monochromator, and a Syntex LT-1 low-temperature attachment. The experimental details for the intensity data collection are given in Table 1. All structural calculations were performed in a Data General Eclipse S-250 computer using the SHELXTL [11] crystallographic software. Scattering factors for all atoms were taken from ref. 12. The structure was solved by direct methods and was refined by blocked-cascade least-squares procedures to $R = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.043$, $R_w = \{\Sigma(w||F_o| - |F_c||^2)/\Sigma w|F_o|^2\}^{\frac{1}{2}} = 0.045$, $W = (\sigma^2(|F_o|) + 0.0005|F_o|^2)^{-1}$ and $S = 1.23$. Hydrogen atom locations were obtained from a difference electron density map. A final difference Fourier map contained peaks below ± 0.25 e Å^{-3}. The final atomic co-ordinations are given in Table 2. Bond lengths and bond angles are given in Table 3. Listings of thermal parameters and hydrogen atom parameters are available on request from the Cambridge Crystallographic Data Centre.*

* See Instructions for Authors (1987), *J. Chem. Soc., Perkin Trans. 1*, 1987, Issue 1.

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