Synthesis of (15*RS*)-11-Deoxy-11-Oxacarbacyclin Methyl Ester

John Mann * and Alison Thomas
Chemistry Department, University of Reading, Whiteknights, Reading, Berkshire RG6 2AD

(1*R*,2*S*,5*S*)-2-Diphenyl-t-butylsiloxymethyl-3-oxabicyclo[3.3.0]octan-7-one (**3**), prepared from D-ribonolactone, has been converted in six steps into the biologically active prostacyclin analogue (15*RS*)-11-deoxy-11-oxacarbacyclin methyl ester (**2**; X = O).

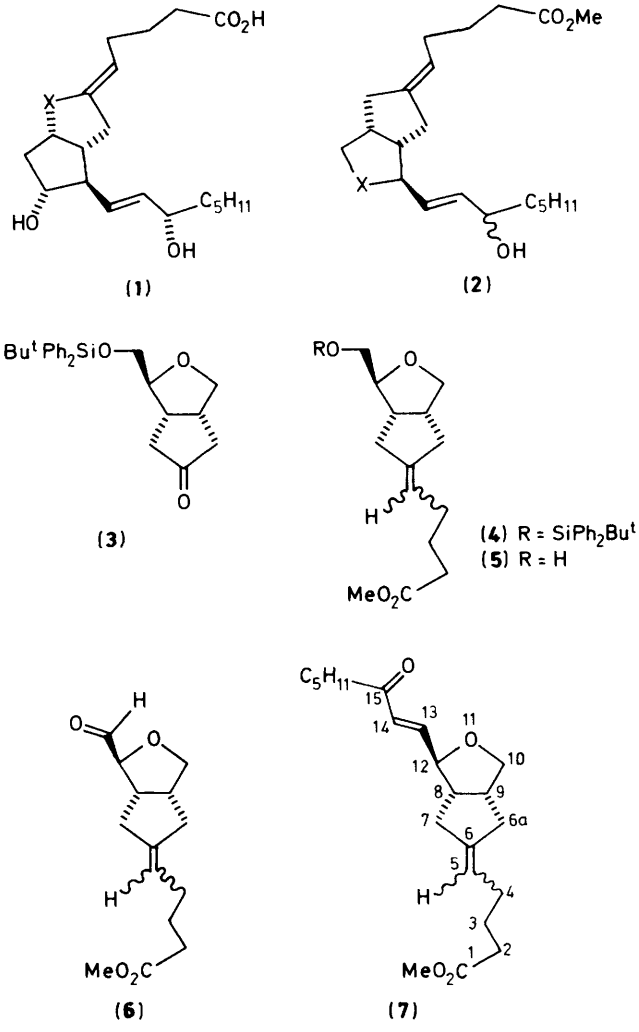
In the 10 years since prostacyclin (PGI_2) (**1**; X = O) was discovered by Moncada, Vane, and co-workers,[1] numerous syntheses of this prostanoid [2] and of structural analogues [3] have been reported. It is the most potent endogenous inhibitor of platelet aggregation known, though its short biological half-life (*ca.* 5 min) precludes widespread clinical use. One of the first analogues to combine improved stability with good biological potency was carbacyclin (**1**; X = CH_2), and a recent report by Gandolfi *et al.*[4] claimed that 11-deoxy-11-thiacarbacyclin (**2**; X = S) also possessed interesting biological properties. This prompted us to attempt a synthesis of the corresponding 11-oxa analogue (**2**; X = O) for biological evaluation. An obvious chiral starting material for this synthesis is the oxabicycle (**3**), prepared by us previously,[5] and we give details here of the conversion of this compound into analogue (**2**; X = O).†

The prostacyclin side-chain was applied to (**3**) by means of a Wittig reaction with (4-carboxybutyl)triphenylphosphonium bromide and potassium t-butoxide to yield (**4**) (R = $SiPh_2Bu^t$) after esterification with diazomethane (78% yield following chromatography). No attempt was made, at this stage, to separate the two isomers. The diphenyl-t-butylsilyl group was then removed using fluoride and the alcohol (**5**) (mixture of *E*- and *Z*-isomers) was obtained in near quantitative yield.

Oxidation to the aldehyde (**6**) was at first attempted using Collins oxidation [6] (CrO_3 in pyridine), and this produced a yellow oil containing some of the desired product, but in poor yield. Success was attained using Swern oxidation [7] (oxalyl chloride in Me_2SO), and crude aldehyde (including some hydrate) was obtained in 80% yield. This was used without purification in a Horner-Emmons olefination [8] with the anion of dimethyl (2-oxoheptyl)phosphonate, and the two 15-oxo compounds *E*- and *Z*-(**7**) were isolated after extensive flash chromatography. The major, most polar, isomer was shown to be the *E*-isomer by 2D Cosy-45 n.m.r. analysis in conjugation with n.O.e. experiments. Full details are given in the Experimental section, but key features included enhancement of the signals due to 3-H, 4-H, and most importantly 7α-H upon saturation of the olefinic signal at 5.2 p.p.m. The *E*:*Z* ratio was *ca.* 5:1 indicating that the original Wittig reaction had provided primarily the desired stereochemistry.

Finally, reduction of compound *E*-(**7**) with sodium borohydride in methanol at 0 °C yielded the 11-oxacarbacyclin analogue (**2**; X = O) as a mixture of C-15 epimers (78% yield).

Preliminary biological evaluation was carried out by Dr. G. M. Smith (Robert Gordon's Institute of Technology, Aberdeen), and the mixture of epimers (**2**; X = O) inhibited by 50% the aggregation of rabbit platelets, induced by ADP, at a concentration of *ca.* 100 μM. This means that the racemate (**2**; X = O) is about 1 000 times less potent than carbacyclin (**1**; X = CH_2). However, since the synthetic route is short and potentially flexible, it would in principle allow access to other (more potent) analogues.



Experimental

All general methods are given in the preceding paper.

(1S,2S,5R)-2-*Diphenyl-t-butylsiloxymethyl*-7-(4-*methoxycarbonylbutylidene*)-3-*oxabicyclo*[3.3.0]*octane*,‡ (**4**).—Dry THF

† Whilst this work was in progress Kojima *et al.*[9] reported a synthesis of (**2**) using 4-oxocyclopentane-1,2-dicarboxylic acid as starting material. The synthesis proceeded in 18 steps and was achiral.

‡ Unless otherwise specified, a mixture of *E*- and *Z*-isomers was present. Resolution of the isomers was achieved at the penultimate stage of the synthesis.

Table 1. 400 MHz ^{1}H N.m.r. data for compound *E*-(7)

δ (p.p.m.)	Multiplicity	Integration (number of H)	Assignment	Coupling constant (Hz)
0.82	t	3	20-H	$J_{19,20}$ 7
1.18	complex	4	18-, 19-H	
1.55	quintet	2	17-H	*J* 7.5
1.6	quintet	2	3-H	*J* 7.5
1.95	m	1	4-H	
2.00	m	1	4-H	
2.05	m	1	6a-H	
2.1	m	1	7α-H	
2.24	t	2	2-H	$J_{2,3}$ 7.5
2.3	m	1	6a-H	
2.4	m	1	8-H	
2.48	t	2	16-H	$J_{16,17}$ 7.5
2.5	m	1	7β-H	
2.73—2.8	complex	1	9-H	$J_{10,9}$ 7.5 $J_{10,9}$ 5.8
3.38	dd	1	10-H	J_{gem} 8.8
3.60	s	3	CO_2Me	
3.91	ddd	1	12-H	$J_{12,13}$ 5.5 $J_{12,14}$ 1.6 $J_{8,12}$ 6.5
4.12	dd	1	10-H	J_{gem} 8.8
5.18—5.24	m	1	5-H	
6.23	dd	1	14-H	J_{trans} 16 $J_{12,14}$ 1.6
6.72	dd	1	13-H	J_{trans} 16

Table 2. 400 MHz ^{1}H N.m.r. data for compound *Z*-(7)

δ (p.p.m.)	Multiplicity	Integration (number of H)	Assignment	Coupling constant (Hz)
0.82	t	3	20-H	$J_{19,20}$ 7.5
1.18	complex	4	18-, 19-H	
1.5	quintet	2	17-H	*J* 7.5
1.6	quintet	2	3-H	*J* 7.5
1.95	m	1	4-H	
2.0	m	1	4-H	
2.05	m	1	6a-H	
2.1	m	1	7-H	
2.24	t	2	2-H	$J_{2,3}$ 7.5
2.3	m	1	6a-H	
2.4	m	1	8-H	
2.48	t	2	16-H	$J_{16,17}$ 7.5
2.5	m	1	7-H	
2.66—2.75	m	1	9-H	$J_{10,9}$ 7.5 $J_{10,9}$ 5.8
3.38	dd	1	10-H	J_{gem} 8.8
3.60	s	3	CO_2Me	
3.91	ddd	1	12-H	$J_{12,14}$ 1.5 $J_{12,13}$ 5.3 $J_{8,12}$ 6.5
4.10	dd	1	10-H	J_{gem} 8.8
5.16—5.24	m	1	5-H	
6.22	dd	1	14-H	J_{trans} 16 $J_{12,14}$ 1.5
6.73	dd	1	13-H	J_{trans} 16

(120 ml) was added to a stirred mixture of (4-carboxybutyl)-triphenylphosphonium bromide (6.33 g, 0.014 mol) plus potassium t-butoxide (3.205 g, 0.029 mol) under N_2 at room temperature. The bright orange suspension so formed was stirred for 30 min and the ketone (**3**) (1.407 g, 5.37 mmol) in dry THF (20 ml) was then added. The reaction mixture was stirred at room temperature overnight. Saturated aqueous ammonium chloride was then added until the orange colour disappeared (*ca.* 120 ml), followed by 5% aqueous HCl (*ca.* 2 ml) until the mixture was just acid to litmus. The product was extracted into ether (50 ml), which was dried ($MgSO_4$) and concentrated under reduced pressure to a pale yellow oil which was not further purified. The crude mixture of isomeric alkenes displayed the following characteristics: R_F 0.27 and 0.30 [light petroleum–EtOAc, (3:1; 8 ml) + 3 drops glacial acetic acid]; δ (60 MHz; $CDCl_3$) 1.08 (9 H, s, Bu^t), 1.4—2.6 (12 H, complex), 3.2—4.2 (5 H, complex), 5.2 (1 H, br s, C=CH), 7.2—7.8 (10 H, complex, 2 × Ph), and 9.5 (1 H, br s, CO_2H).

The crude acid mixture was taken up in ether and a solution of diazomethane in ether was added until N_2 evolution ceased and t.l.c. [light petroleum–EtOAc (3:1)] showed the reaction to be complete. The reaction mixture was concentrated under reduced pressure to a yellow oil which was purified by flash chromatography [light petroleum–EtOAc (9:1)]. Two columns were needed to obtain the *E*/*Z* mixture (1.38 g, 78%) as a colourless oil free from contaminating material. No attempt was made to separate the *E*/*Z* isomers at this stage and the mixture displayed the following characteristics: R_F 0.29 and 0.32 [light petroleum–EtOAc (9:1)]; $\nu_{max.}$(neat) 2 980, 2 970, 2 900, 1 765, 1 755, 1 610, 1 450, 1 380, 1 130, 930, 840, 760, and 720 cm^{-1}; δ (220 MHz; $CDCl_3$) 1.06 (9 H, s, Bu^t), 1.66 (2 H, q, *J* 7 Hz, 3-H), 1.95—2.22 (4 H, m, 4-H_2, 6a-, 7-H), 2.30 (2 H, t, *J* 7 Hz, 2-H), 2.40—2.56 (3 H, m, 6a, 7-, 8-H), 2.66—2.80 (1 H, m, 9-H), 3.41 (1 H, dd, J_{gem} 9, $J_{9,10}$ 6 Hz, 10-H), 3.65 (3 H, s, CO_2Me), 3.54—3.80 (3 H, m, 12-H, 13-H_2), 4.06 (1 H, m, 10-H), 5.24 (1 H, m, C=CH), 7.67—7.79 and 7.30—7.46 (6 H + 4 H, 2 × m, 2 × Ph) (prostacyclin numbering has been used for the n.m.r. data throughout this Experimental section) [Found: M^+ − Bu, 435.1998. Calc. for $C_{26}H_{31}O_4Si$: (*M* − Bu) 435.1992].

(1S,2S,5R)-2-*Hydroxymethyl*-7-(4-*methoxycarbonylbutylidene*)-3-*oxabicyclo*[3.3.0]*octane* (**5**).—A solution of tetrabutylammonium fluoride in THF (1M; 5.6 ml, 5.6 mmol) was added to a solution of the silyl ether (**4**) (1.38 g, 2.8 mmol) in dry THF (10 ml) at 0 °C. The pale yellow solution was allowed to warm to room temperature and was then stirred for 4 h. Water (25 ml) was added to the golden orange reaction mixture and the product extracted into ether (4 × 30 ml). The combined organic extracts were washed with saturated aqueous sodium chloride (10 ml), dried ($MgSO_4$) and concentrated under reduced pressure to a yellow oil. The product was purified by flash chromatography (ether) to give the products (*E*/*Z* mixture) as a colourless oil (0.69 g, 97%), R_F 0.32 and 0.24 (ether); $\nu_{max.}$(neat) 3 480br, 2 980, 2 880, 1 760, 1 355, 1 190, and 1 060 cm^{-1}; δ (220 MHz; $CDCl_3$) 1.66 (2 H, q, *J* 7 Hz, 3-H), 1.95—2.22 (4 H, complex, 4H_2, 6a-, 7-H), 2.30 (2 H, t, *J* 7 Hz, 2-H), 2.30—2.40 (1 H, br, OH), 2.40—2.56 (3 H, complex, 6a-, 7-, 8-H), 3.40 (1 H, dd, J_{gem} 8, $J_{9,10}$ 6 Hz, 10-H), 3.50—3.60 and 3.64—3.78 (3 H, complex, 12-H, 13-H_2), 3.64 (3 H, s, CO_2Me), 4.10 (1 H, m, 10-H), 5.24 (1 H, m, C=CH) (Found: M^+, 254.1525. Calc. for $C_{14}O_4H_{22}$: *M*, 254.1518).

(1S,2S,5R)-2-*Formyl*-7-(*methoxycarbonylbutylidene*)-3-*oxabicyclo*[3.3.0]*octane* (**6**).—(*a*) *Attempted Collins oxidation.* Chromium trioxide (0.794 g, 7.94 mmol) was added to a stirred solution of pyridine (1.3 ml, 1.25 g, 0.16 mol) in dichloromethane (10 ml). The reaction mixture was stirred vigorously at room temperature and a deep red colouration was obtained. The alcohol (**5**) (0.025 g, 0.99 mmol) in dichloromethane (2 ml) was then added with vigorous stirring and the reaction mixture immediately turned black. After 1 h, the dichloromethane was decanted off and the residual oil further washed with dichloromethane. The combined organic extracts were washed with HCl (8 ml; 2M) and then concentrated under reduced pressure to a yellow oil. T.l.c. (ether) indicated the presence of a number of

components and purification by flash chromatography [light petroleum–ether (1:9)] was attempted. A yellow oil was obtained (74 mg, 30%) which ran as a streak on t.l.c., and which contained elements of the aldehyde (**6**) plus its hydrate as shown by ^{1}H n.m.r. and i.r.

(*b*) *Swern oxidation.* Dry Me_2SO (0.21 ml, 0.24 g, 3 mmol) was added to oxalyl chloride (0.12 ml, 0.18 g, 1.38 mmol) in dichloromethane (3 ml, dry) at −60 °C. The white suspension formed was stirred for 15 min and the alcohol (**5**) (0.319 g, 1.26 mmol) in dry dichloromethane (2 ml) was added and stirring was continued for a further 20 min. Triethylamine (0.9 ml, 0.64 g, 6.28 mmol) was then added and the reaction mixture warmed to room temperature. A yellow, gelatinous precipitate was formed which dissolved on addition of water (4 ml). Stirring was continued for *ca.* 10 min and then the organic layer was separated; the aqueous layer being re-extracted with dichloromethane (10 ml). The combined organic extracts were washed successively with 5% aqueous HCl, water, dilute aqueous sodium carbonate, and water, then dried ($MgSO_4$) and concentrated under reduced pressure to a pale yellow oil (0.25 g, 80% crude yield), $\nu_{max.}$(neat) 3 440br and 1 740br cm^{-1}; δ(60 MHz; $CDCl_3$) 3.6 (3 H, s, CO_2Me), 5.1—5.3 (1 H, br signal, C=CH), 9.7 (1 H, d, CHO).

11,15-*Dideoxy*-15-*oxo*-11-*oxacarbacyclin Methyl Ester* (**7**).—Sodium hydride (0.123 g suspension in oil; assume 50% recovery from oil = 62 mg, 2.57 mmol,) was washed with light petroleum (redistilled 30—40 °C × 3) to remove the oil, dried (water pump) and placed under nitrogen. Dry THF (15 ml) was added followed by dimethyl 2-oxoheptylphosphonate (0.5 ml, 0.57 g, 2.57 mmol) and the reaction mixture stirred at room temperature for 30 min. A white, gelatinous precipitate formed to which the crude aldehyde (**6**) (0.324 g, 1.29 mmol) in THF (3 ml, dry) was added and the reaction mixture was stirred at room temperature overnight. Water (10 ml) was added to the yellow solution which formed and the product was extracted 3 times with ether. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to a pale yellow oil. T.l.c. [ether–light petroleum (1:3); 2 elutions] then indicated two major u.v. active components contaminated with a number of minor components. Purification was achieved by extensive flash chromatography using various solvent systems to remove all the contaminating material. The product was eventually obtained as a mixture of the *E* and *Z* isomers (115 mg, 26%). The two isomers were separated to some degree by careful flash chromatography [light petroleum–ether (3:1)]. The mixed fractions were combined with mixed fractions from another experiment and flash chromatographed again as above. The more polar isomer proved to be the major isomer (*ca.* 5:1) and was shown to be the required *E*-isomer, R_F 0.30 [light petroleum–ether, (3:1) 2 elutions]; δ (400 MHz; $CDCl_3$)—see Table 1 (Found: M^+, 348.2302. Calc. for $C_{21}O_4H_{32}$: *M*, 348.2292).

The minor (*Z*) isomer showed R_F 0.41 [light petroleum–ether (3:1) 2 elutions]; δ (400 MHz; $CDCl_3$)—see Table 2 (Found: M^+, 348.2301. Calc. for $C_{21}O_4H_{32}$: *M*, 348.2292).

The mixture displayed the following characteristics: $\nu_{max.}$(neat) 1 740, 1 700, 1 670, 1 630, 1 430, 1 315, 1 250, and 1 170 cm^{-1}.

(15RS)-11-*Deoxy*-11-*oxacarbacyclin Methyl Ester* (**2**; X = O).—The ketone (**7**; *E*-isomer) (46 mg, 0.132 mmol) was dissolved in methanol (6 ml; AR) and the solution cooled to 0 °C before the addition of sodium borohydride (*ca.* 20 mg, excess). The reaction mixture was stirred for 3.5 h at 0 °C, water (4 ml) was then added and the mixture acidified with dilute HCl (2M). The product was extracted 3 times into ether and the ethereal extracts were dried ($MgSO_4$) and concentrated under reduced pressure to an oil which was purified by flash chromatography [light petroleum–ether (2:3)]. This was followed by a second column [light petroleum–ether (1:1)] to achieve some separation of the 15-OH epimers. The total yield was 36 mg (78%), comprising a more polar epimer (15 mg), a less polar epimer (8 mg), plus a mixture of the two epimers (13 mg). The mixture of epimers displayed the following characteristics: R_F 0.25 [light petroleum–ether (2:3)]; $\nu_{max.}$(neat) 3 410br, 1 730, 1 440, 1 170, and 1 050 cm^{-1}; δ (200 MHz; $CDCl_3$) 4.00—4.05 (1 H, br signal, OH) and 5.72 (2 H, m, 13-, 14-H).

The remainder of the spectrum was as for compound (**7**)—see Tables (Found: M^+, 350.2454. Calc. for $C_{21}H_{34}O_4$: *M*, 350.2448).

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