(±)-4-Oxo-9-deoxy-9-azaprostaglandin I_2 derivatives. Very stable prostacyclin analogs[1]

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The synthesis of 4-oxo-9-deoxy-9-azaprostaglandin I_2 (**23***a*) and two ω-chain analogues thereof (**23***c* and **23***e*) is described. The most salient features of the synthetic process used were (*a*) introduction of the nitrogen functionality at C-9 by [3,3] sigmatropic rearrangement of the trichloroacetamidate **5***b* to the trichloroacetamide **6**, (*b*) transformation of **6** into the bicyclic lactam **7** with sodium borohydride, (*c*) stereospecific introduction of the 11α-hydroxyl group via the bromohydrin **8***a*, and (*d*) attachment of the α chain by extrusion of sulfur from the thioimidates **20** by the Eschenmoser sulfide contraction process.

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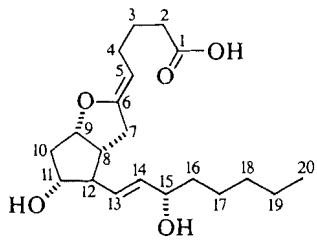
On décrit la synthèse de l'oxo-4 déoxy-9 aza-9 prostaglandine I_2 (**23***a*) et de deux de ses analogues avec une chaîne ω (**23***c* et **23***e*). Les caractéristiques principales du processus de synthèse utilisé sont (*a*) l'introduction d'une fonction azotée en C-9 par une transposition sigmatropique [3,3] du trichloroacétamidate **5***b* en trichloroacétamide **6**, (*b*) l'utilisation du borohydrure de sodium pour transformer le composé **6** en la lactame bicyclique **7**, (*c*) l'introduction stéréospécifique du groupement hydroxyle en 11α par le biais de la bromohydrine **8***a* et (*d*) l'attache de la chaîne α par une extrusion de soufre à partir des thioimidates **20** en faisant appel au processus d'Eschenmoser pour la contraction des sulfures.

[Traduit par la revue]

Prostacyclin (PGI_2, **1**) is the most powerful endogenous inhibitor of platelet aggregation discovered to date (1, 2). The endocyclic enol ether moiety present in this molecule renders it exceedingly sensitive to acidic conditions and even at physiological pH its half-life is only ca. 3 min. It is thus ineffective orally and when it is administered by intravenous infusion its physiological effects disappear rapidly after termination of the infusion. Considerable effort has been devoted to the synthesis of prostacyclin analogues with reduced acid sensitivity and improved metabolic stability. The acid sensitivity problem has been solved by stratagems such as replacement of the enol ether oxygen by other atoms (e.g., sulfur, nitrogen, or carbon), resonance stabilization in the vinylogous sense (for example, with an oxo group at C-4 (3) or a nitrile moiety at C-5 (4)), inductive stabilization by suitably placed electron attracting substituents (e.g. fluorine at C-7 (5) or C-10 (6)), etc. (for reviews on this subject, see refs. 7–9). Metabolic stability has been conferred upon prostacyclin derivatives by the incorporation of a wide variety of structural modifications into the upper (α) and lower (ω) side chains (7–9). It occurred to us that the prostacyclin analogue **2** was a particularly attractive synthetic target because of the minimal acid sensitivity, good chemical stability, and marked preference for the hydrogen bonded *Z* isomeric form associated with the vinylogous amide functionality (10, 11).

It was our intention of effect the introduction of the vinylogous amide moiety of **2** by the Eschenmoser sulfide contraction reaction (10) and thus the lactam **3** was an obvious starting material. One such compound (**3**, R^1 = Ac, R^2 = OTHP) had already been synthesized by Bartmann *et al.* (12) in seven steps from the Corey lactone **4** (13). In our hands,



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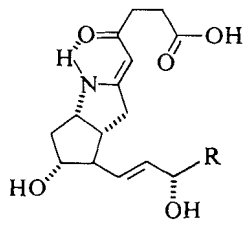

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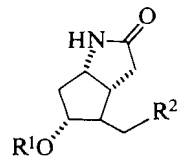

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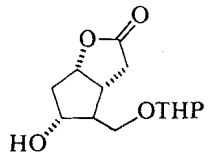

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this reaction sequence was not easily reproducible and therefore another synthetic route to lactams of this class was devised. Thus, the readily available unsaturated ester **5***a* (ref. 14, Scheme 1) was converted into the trichloroacetamidate **5***b*, which underwent [3,3] sigmatropic rearrangement (15) to the allylic trichloroacetamide **6** (54% yield from **5***a*) in boiling xylene (133°C in Mexico City!). This compound was transformed directly into the unsaturated bicyclic lactam **7** (80%) on reductive deacylation with ethanolic sodium borohydride at 60°C (16). The structure on this compound is fully supported by the 300-MHz nmr spectrum (Table 1). *N*-Bromosuccinimide in wet dimethylsulfoxide (17) effected the conversion of **7** into a single bromohydrin **8***a* in 72% yield. The stereo- and regiochemistry shown in **8***a* was originally assigned by analogy to that observed for the products obtained from the very closely related bicyclic unsaturated systems **10**, **11**, and **12** with *N*-bromoacetamide in aqueous acetone (18), iodine acetate in

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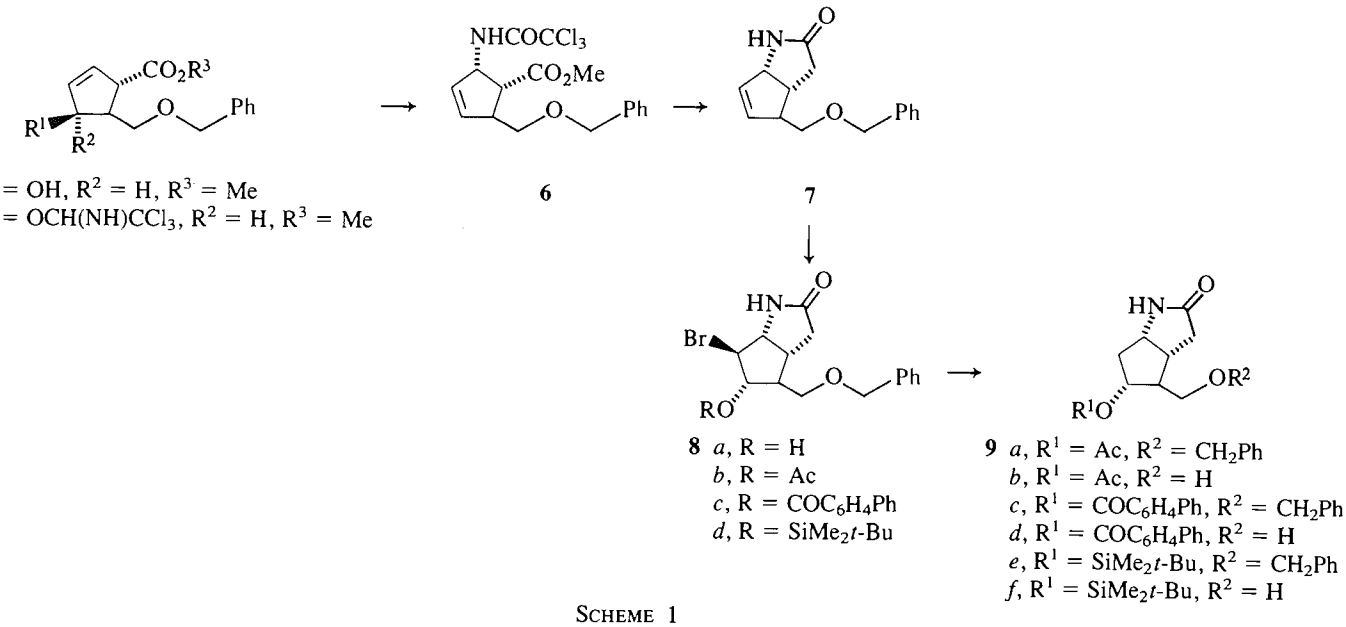


5 *a*, R^1 = OH, R^2 = H, R^3 = Me
b, R^1 = $OCH(NH)CCl_3$, R^2 = H, R^3 = Me

6

7

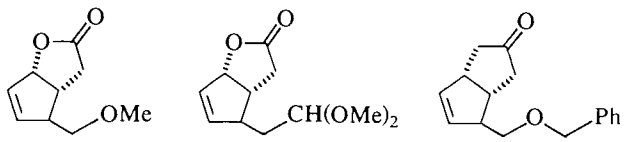
8 *a*, R = H
b, R = Ac
c, R = COC_6H_4Ph
d, R = $SiMe_2t$-Bu

9 *a*, R^1 = Ac, R^2 = CH_2Ph
b, R^1 = Ac, R^2 = H
c, R^1 = COC_6H_4Ph, R^2 = CH_2Ph
d, R^1 = COC_6H_4Ph, R^2 = H
e, R^1 = $SiMe_2t$-Bu, R^2 = CH_2Ph
f, R^1 = $SiMe_2t$-Bu, R^2 = H

SCHEME 1

dry acetic acid (19), and *N*-bromosuccinimide in wet dimethylsulfoxide (14), respectively. In addition, the proton coupling constants (Table 1) were similar to those reported for a closely related model system (20). The structure of **8***a* was verified by reductive debromination of the derived acetate **8***b* with tri-*n*-butyltin hydride followed by hydrogenolytic debenzylation (Pd–C) of **9***a*, thus obtained, to the known (12) diol monoacetate **9***b*.[3]

For the synthesis of the desired prostacyclin derivatives, the bromohydrin **8***a* was converted into the *p*-phenylbenzoate ester **8***c* or the *tert*-butyldimethylsilyl ether **8***d*, which, on reductive debromination (to **9***c* and **9***e*) and subsequent catalytic hydrogenolysis, as described above, gave the primary alcohols **9***d* and **9***f*. Oxidation of these alcohols with Collins reagent (21) and immediate condensation of the crude, unstable aldehydes **13***a* and **13***b* (Scheme 2) with the sodium salts of the appropriate ketophosphonates provided the enones **14***a–d*. In general, considerably better overall yields of the enones **16** were



10 **11** **12**

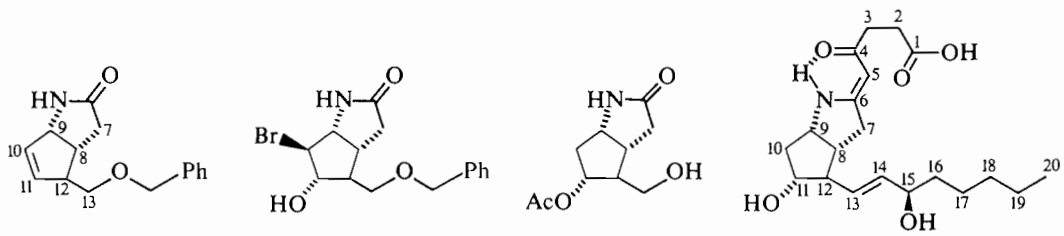
obtained when the silylated alcohol **9***f* was used as the aldehyde precursor for the Wadsworth–Emmons (22) reaction. Reduction of the enones with methanolic sodium borohydride containing cerous chloride (23) produced mixtures of epimeric alcohols, the ratios of which depended on the nature of the alcohol protecting group at C-11 (prostaglandin numbering). The *p*-phenyl benzoate esters **14***a* and **14***c* gave rise to nearly equal amounts of the 15α and 15β isomers[4] **15***a,c* and **15***b,d* whereas a 2:1 ratio of epimers **17***a,c* and **17***b,d* was formed from the silyl ethers **14***b,d*. These alcohols (separable by flash chromatography or preparative tlc on silica gel) were then transformed into the bis-*tert*-butyldimethylsilyl ethers **18***a–f*, either directly, in the case of **17***a–d*, or after conversion into the diols **16***a–d*. Reaction of **18** with Lawesson's reagent (24) in hot benzene provided the thiolactams **19** (Scheme 3) in ca. 70–80% yield. The stage was now set for the introduction of the upper (α) side chain by the sulfide contraction process. Alkylation of the sodium salts of the thiolactams with methyl 5-bromolevulinate gave the unstable thiaimino compounds **20**, which, without purification, were heated with potassium-*tert*-butoxide in a xylene–*tert*-butanol mixture containing triphenylphosphine. The silylated vinylogous amides (**21***a–f*), formed in 55–70% yield, showed the expected infrared absorptions at 3280, 1625, and 1545 cm^{-1} and, in the case of **21***f*, the broad band at 3280 cm^{-1} did not shift on dilution (0.1–0.01 *M*). In addition, the compounds had a singlet nmr absorption at ca. δ 5.0 for the lone olefinic hydrogen atom (at C-5), a broad peak for a strongly H-bonded NH at δ 9.9 ± 0.2, and an intense uv absorption near 306 nm (ε ~ 19 000) for the vinylogous amide chromophore. These spectroscopic properties are virtually identical to those reported (10) for the monocyclic vinylogous amide **24**. Desilylation of **21** was effected with tetra-*n*-butylammonium fluoride in tetrahydrofuran (25) at 40°C and the methyl esters **22**, so produced, were hydrolysed with potassium carbonate in methanol–water solution. Both the methyl esters **22** and the carboxylic acids **23** could be kept for long periods of time at ambient temperature without appreciable decomposition. The carboxylic acids exhibit considerable stability under acidic conditions. Indeed, tlc purification thereof was carried out using an acetic acid containing solvent system.

The carboxylic acids were tested as inhibitors of ADP induced aggregation of human platelet rich plasma in vitro by a modification of the method of Born (26). The 15-cyclopentyl compound **23***e* was the most active member of this series of compounds (see Table 2) with a potency ca. one-quarter that of PGE_1. This low level of activity (~0.01 × prostacyclin sodium salt) was surprising in view of the fact that, where comparisons were possible, the nmr spectral parameters of **23***b* (Table 1), and by implication **23***a*, and prostacyclin (27) showed considerable

[3]We thank Dr. W. Bartmann, Hoechst, A. G. Frankfurt am Main, for providing us with a copy of the nmr spectrum of **9***b*, which was identical to that obtained by us (see Table 1).

[4]The α stereochemistry was assigned to the less polar 15-hydroxy compounds **15***a,c* and **17***a,c* (see Table 3) because, in each case, these gave rise to the azaprostacyclin epimer, which was the more potent inhibitor of adenosine diphosphate (ADP) induced aggregation of human platelet rich plasma (HPRP; see below).

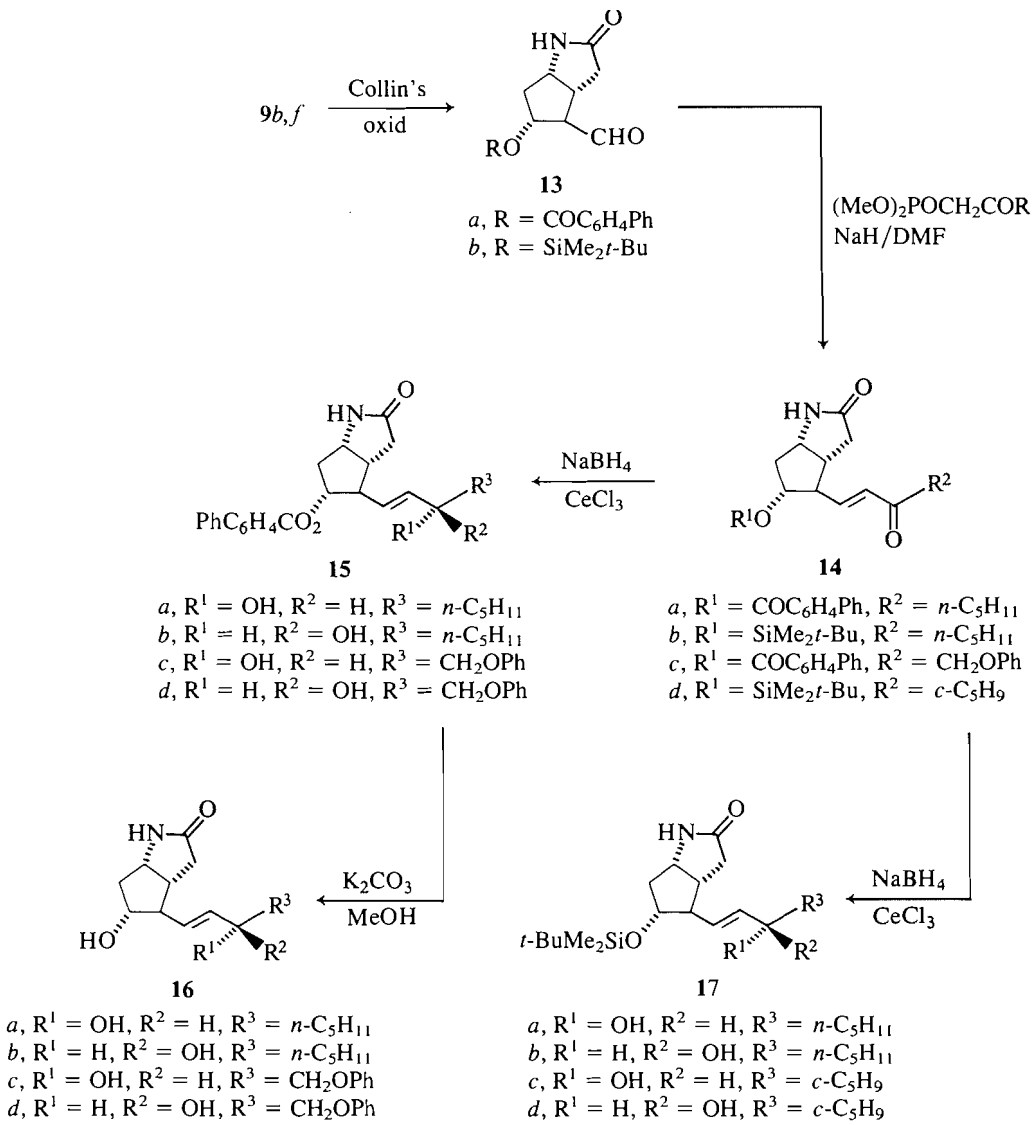
TABLE 1. Chemical shifts and coupling constants of 15-epi-3-oxo-9-deoxy-9-aza PGI_2 and precursors thereof[a]



7 **8***a* **9***b* **23***b*

Proton	δ (ppm)	*J* values (Hz)	Proton	δ (ppm)	*J* values (Hz)	Proton	δ (ppm)	*J* values (Hz)	Proton	δ (ppm)	*J* values (Hz)
7α	2.19	$J(7\alpha-7\beta) = 17.4$	7α	2.23	$J(7\alpha-7\beta) = 17.5$	7α	2.23	$J(7\alpha-7\beta) = -17.1$	2	2.57[b,e]	
		$J(7\alpha-8) = 5.2$			$J(7\alpha-8) = 4.1$			$J(7\alpha-8) = 2.1$	3	2.57[b,e]	
7β	2.65	$J(7\alpha-7\beta) = 17.4$	7β	2.60	$J(7\alpha-8) = 17.5$	7β	2.64	$J(7\alpha-7\beta) = -17.1$	5	5.08[f]	
		$J(7\beta-8) = 10.0$			$J(7\beta-8) = 10.4$			$J(7\beta-8) = 9.6$	7α	2.57[b,e]	
8	2.85[b,c]		8	2.74	$J(7\alpha-8) = 4.1$	8	2.74	$J(7\alpha-8) = 2.1$	7β	2.87	$J(7\alpha-7\beta) = 17.7$
9	4.61	$J(8-9) = 7.8$			$J(7\beta-8) = 10.4$			$J(7\beta-8) = 9.6$			$J(7\beta-8) = 9.3$
10	5.78[d]	$J(10-11) = 5.7$			$J(8-9) = 9.3$			$J(8-9) = 7.6$			$J(5-7\beta) = 0.5$
		$J(9-10) \simeq 1.7$			$J(8-12) = 9.4$			$J(8-12) = 6.9$	8	2.57[b,e]	
		$J(10-12) \simeq 1.7$	9	4.11	$J(8-9) = 9.3$	9	4.10	$J(8-9) = 7.6$	9	4.33	$J(8-9) = 7.5$
11	5.85[d]	$J(10-11) = 5.7$			$J(9-10) = 6.3$			$J(9-10\alpha) = 3.6$			$J(9-10\alpha) = 4.5$
		$J(9-11) \simeq 1.4$	10	3.82	$J(9-10) = 6.3$			$J(9-10\beta) = 7.0$			$J(9-10\beta) = 7.5$
12	2.85[b,c]				$J(10-11) = 9.4$	10α	1.84	$J(9-10\alpha) = 3.6$	10α	1.73	$J(9-10\alpha) = 4.5$
13	3.35	$J(13-13') = 9.05$	11	4.04	$J(10-11) = 9.4$			$J(10\alpha-10\beta) = -14.1$			$J(10\alpha-10\beta) = 3.8$
		$J(12-13) = 6.7$			$J(11-12) = 9.6$			$J(10\alpha-11) = 6.6$			$J(10\alpha-11) = 8.8$
13′	3.45	$J(13-13') = 9.05$			$J(11-OH) = 3.3$	10β	2.38	$J(9-10\beta) = 7.0$	10β	1.57[b,e]	
		$J(12-13') = 5.4$	12	1.97	$J(11-12) = 9.6$			$J(10\alpha-10\beta) = -14.1$	11	3.96	$J(10\alpha-11) = 8.8$
OCH_2	4.52				$J(12-13) = 5.8$			$J(10\beta-11) = 6.6$			$J(10\beta-11) = 7.2$
NH	6.72				$J(12-13') = 5.1$	11	5.06	$J(10\alpha-11) = 6.6$			$J(11-12) = 8.0$
Ph	7.3[b]				$J(8-12) = 9.4$			$J(10\beta-11) = 6.6$	12	2.17	$J(8-12) = 10.0$
			13	3.58	$J(12-13) = 5.8$			$J(11-12) = 6.6$			$J(11-12) = 8.0$
					$J(13-13') = 9.3$	12	2.03	$J(8-12) = 6.9$			$J(12-13) = 8.0$
			13′	3.67	$J(12-13') = 5.1$			$J(11-12) = 6.6$	13	5.58	$J(13-14) = 15.5$
					$J(13-13') = 9.3$			$J(12-13) = 4.9$			$J(12-13) = 8.0$
			OH	3.17	$J(11-OH) = 3.3$			$J(12-13') = 4.7$			$J(13-15) = 0.8$
			OCH_2	4.55		13	3.58	$J(12-13) = 4.9$	14	5.66	$J(13-14) = 15.5$
			Ph	7.3[b]				$J(13-13') = 11.6$			$J(14-15) = 5.7$
						13	3.65	$J(12-13') = 4.7$	15	4.13	$J(15-16) = 6.2$
								$J(13-13') = 11.6$			$J(14-15) = 5.7$
						OH	2.54	$J(13-OH) = 4.5$			$J(13-15) = 0.8$
								$J(13'-OH) = 4.5$	16	1.52	
									17	1.29[b,g]	
									18	1.29[b,g]	
									19	1.29[b,g]	
									20	0.90	$J(19-20) = 6.7$
									NH	10.00	

[a]Spectra measured at 300 MHz. Coupling constants measured to first order.
[b]Centre of multiplet.
[c]H-8 and H-12 overlap.
[d]This assignment could be reversed.
[e]H-2, H-3, H-7α, H-8, and H-10β overlap.
[f]Broad singlet.
[g]H-17, H-18, and H-19 overlap.



SCHEME 2

similarity, indicating a significant conformational congruence between these compounds. It is conceivable that the weak activity of these compounds is a consequence of the rigidity of the vinylogous amide system, which may not permit the carboxyl group to reach the required PGI_2 receptor binding site,[5] but other explanations are possible.

Experimental

The melting points were determined in a Mel-Temp melting point apparatus and are not corrected. The infrared spectra were measured in chloroform solution, unless specified otherwise, with a Perkin–Elmer Model 237 grating spectrophotometer. The ultraviolet spectra were recorded in methanol solution with a Perkin–Elmer Model 402 ultraviolet visible spectrometer. The nmr spectra were obtained with a Varian EM-390 or a Bruker WM 300 nmr spectrometer and are expressed as parts per million (δ) from internal tetramethylsilane. The high resolution mass spectra were measured with a Varian-MAT 311A mass spectrometer.

The terms "worked up in the usual manner" or "the usual work-up" signify that the extract was washed successively with water and saturated sodium chloride solution, then it was dried over magnesium sulfate, and the solvent was removed *in vacuo*.

[5]We thank a referee for this suggestion.

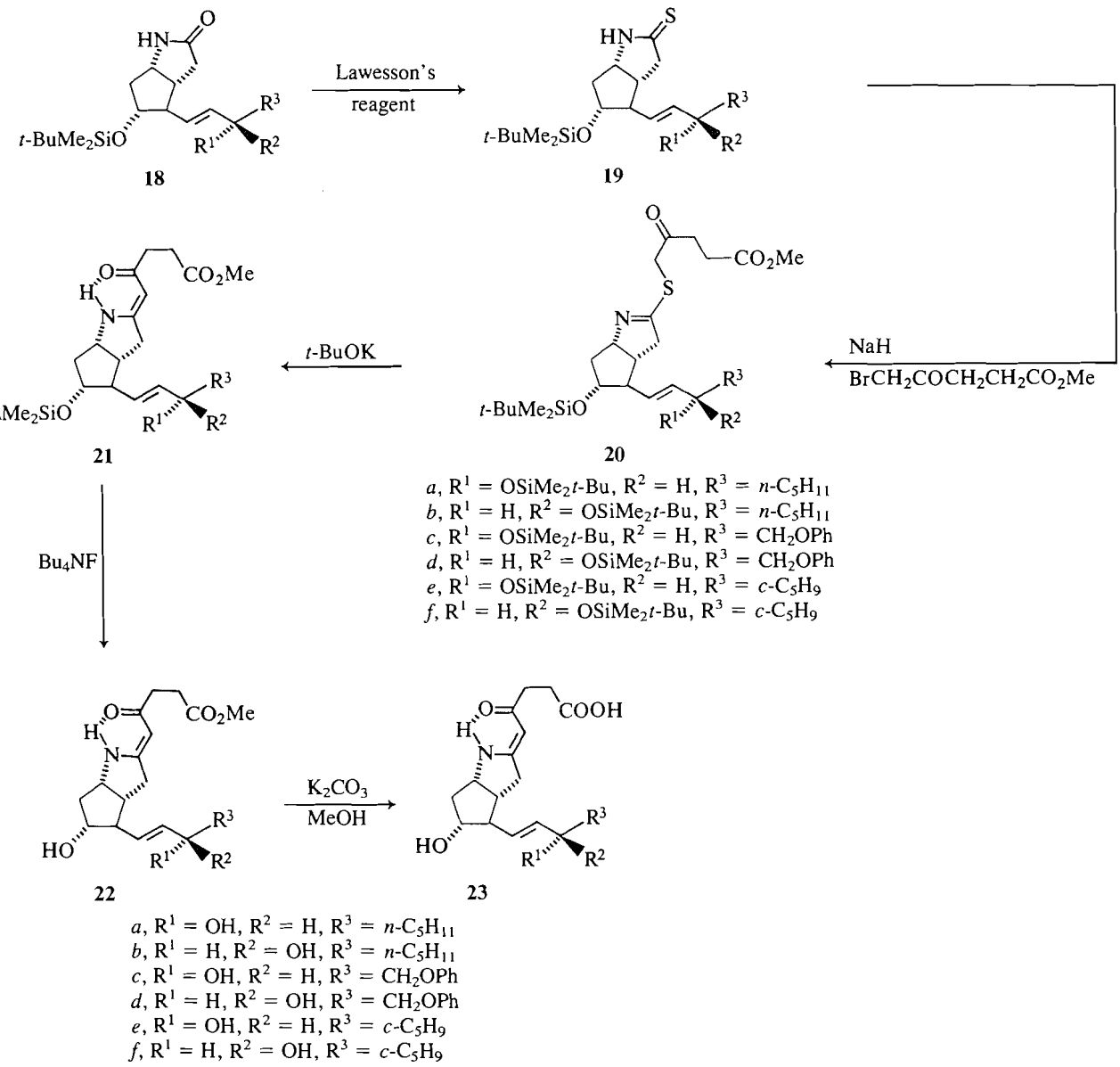
TABLE 2. Inhibition, in vitro, of ADP induced aggregation of HPRP by 3-oxo-9-deoxy-9-azaprostaglandin I_2 derivatives

Compound	Relative potency
PGE_1	1[a]
*23*a	0.032
*23*b	0.0008
*23*c	0.0047
*23*d	0.0007
*23*e	0.24
*23*f	0.0044

[a]$IC_{50} = 5.5 \pm 3.9 \times 10^{-8}$ *M*.

Methyl ω-bromolevulinate

Monomethyl succinate (87 g, 724 mmol) and thionyl chloride (103 mL) were heated together at 40°C for 2 h. The excess thionyl chloride was removed *in vacuo* and the residual oil was distilled at 77–80°C/4 Torr (1 Torr = 133.3 Pa) (95% yield). The acid chloride (6 g) was added dropwise at 0°C to ethereal diazomethane (2.5 equiv. in ether (58 mL)). One half hour after the addition was completed a stream of argon was passed through the solution to remove the excess diazomethane. The solvent was then removed *in vacuo* at room



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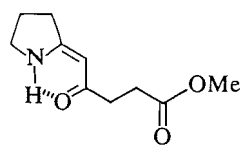

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temperature and the residue was dissolved in ether (85 mL) and cooled to 0°C. An ethereal solution of 1.17 *M* hydrogen bromide (14.2 mL) was added and stirring was maintained for 1 h. The ether was washed with saturated sodium carbonate solution and then worked up as usual. The crude product was distilled at 66–70°C/0.3 Torr (85% yield). This oil solidifies (lit. (10) mp 4°C) in the refrigerator.

Synthesis of the trichloroacetamide **6**

A solution of the unsaturated alcoholic ester **5***a* (12.8 g, 82.6 mmol) in anhydrous ether (100 mL) was added at room temperature to a stirred suspension of sodium hydride (0.328 g, 8.2 mmol; 60% dispersion in mineral oil) in anhydrous ether (90 mL). When hydrogen evolution had terminated (20 min), the solution was cooled to −30°C and a solution of trichloroacetonitrile (8.3 mL, 11.9 g, 82 mmol) in dry ether (15 mL) was added slowly to the stirred solution. The reaction temperature was allowed to reach −10°C and after 25 min at this temperature methanol (1.5 mL) and pentane (750 mL) were added, the mixture was filtered to remove a small amount of a solid, and the filtrate was evaporated *in vacuo*. The crude[6] trichloroacetamidate **5***b* was dissolved in xylene

[6]If the crude trichloroacetamidate was subjected to flash chromatography on silica gel (50 g/g mixture) using hexane – ethyl acetate (4:1) as the eluting solvent, a sample of the pure imidate **5***b* could be isolated, in about 30% yield, as an oil; ir: 3350, 1735, 1665 cm^{-1}; nmr δ: 2.32 (m, 1H, H-12), 2.47 (dd, 1H, $J_{7A,8}$ = 8.0 Hz, $J_{7A,7B}$ = 20.4 Hz, H-7A), 2.57 (dd, 1H, $J_{7B,8}$ = 7.0 Hz, $J_{7A,7B}$ = 20.4 Hz, H-7B), 2.93 (m, 1H, H-8), 3.61 (d, 2H, *J* = 7.5 Hz, 13-CH_2), 3.66 (s, 3H, OMe), 4.54 (s, 2H, OCH_2), 5.66 (m, 1H, H-11), 5.95 (m, 1H, H-10), 6.08 (m, 1H, H-9), 7.32 (m, 5H, C_6H_5), 8.28 (s, 1H, NH); ms *m/e* (CI NH_3): 439, 437 (MNH_4^+), 420 (MH^+), 386 (MH^+ − Cl + H), 352 (386 − Cl + H). This material was not characterized further. Continued elution of the column gave an apparent mixture (3:1) as judged by tlc and nmr (ca. one-half, in weight terms, of the pure imidate), as an oil; ir: 3350, 1735, 1665 cm^{-1}; nmr δ: 2.14, 2.33, 2.46 (multiplets, total 3H), 2.89 (m, 1H), 3.55 (d, 1.5H, *J* = 6.3 Hz), 3.59 (d, 0.5H, *J* = 6.4 Hz), 3.64 (s, 1H, OCH_3), 4.51, 4.53 (singlets, total 2H, OCH_2), 5.54 (bs, 0.75H), 5.66 (bs, 0.25H), 5.75 (m, 0.75H), 5.94 (m, 1H), 6.06 (m, 0.25H), 7.29 (m, 5H, C_6H_5), 8.27

(250 mL) and the solution was heated at reflux temperature (133°C in Mexico City) for 6 h. The solvent was removed *in vacuo* and the residue was dissolved in anhydrous methanol (328 mL) and anhydrous potassium carbonate (18.7 g, 135 mmol) was added thereto. The mixture was stirred at room temperature for 2.5 h, it was then cooled to 0°C and 1 *M* hydrochloric acid was added until a neutral solution was obtained. The methanol was removed *in vacuo* and the aqueous phase was extracted with ethyl acetate. After the usual work-up the crude product was subjected to column chromatography on silica gel. Elution with hexane – ethyl acetate (9:1) gave the crystalline trichloroacetamide **6** (18.7 g). Elution with hexane – ethyl acetate (85:15) gave the starting ester **5***a* (7.1 g, 33%). The yield of the trichloroacetamide, based on trichloroacetonitrile, was 54%. After crystallization from dichloromethane–hexane the amide **6** had mp 81–82°C; ir: 3460, 1730 cm^{-1}; nmr δ: 2.40–3.15 (m, 4H, 7-CH_2, H-8,12[7]), 3.43 (d, 2H, J = 6 Hz, 13-CH_2), 3.63 (s, 3H, OMe), 4.50 (s, 2H, OCH_2), 5.13 (m, 1H, H-9), 5.70 (m, 1H, H-10), 5.98 (m, 1H, H-11), 7.05 (bs, 1H, NH), 7.30 (s, 5H, C_6H_5). *Anal.* calcd. for $C_{18}H_{20}Cl_3NO_4$: C 51.38, H 4.79, Cl 25.28, N 3.33; found: C 51.65, H 4.72, Cl 25.13, N 3.30.

Sodium borohydride induced reductive cyclization of **6** *to bicyclic lactam* **7**

A solution of sodium borohydride (3.39 g, 95 mmol) in anhydrous ethanol (118 mL) was added to a stirred solution of **6** (10.0 g, 23.7 mmol) in ethanol (115 mL) maintained in a heating bath at 60°C in an argon atmosphere. The rate of addition was controlled so that the reaction temperature did not exceed 70°C. When the addition was completed, stirring was continued for a further 0.5 h and then the mixture was cooled to 0°C. Acetone (225 mL) was added and after stirring for 15 min the mixture was evaporated to dryness and the residue was extracted with ethyl acetate. The extract was worked up as usual and the crude product was purified by preparative tlc on silica gel using dichloromethane–ether (1:1) as the developing solvent. The crystalline bicyclic lactam **7** (4.6 g, 80%) was obtained, which after crystallization from ether had mp 56–57°C; ir: 3450, 1690 cm^{-1}; nmr (see Table 1). *Anal.* calcd. for $C_{15}H_{17}NO_4 \cdot 0.33H_2O$: C 72.26, H 7.14, N 5.62; found: C 71.84, H 6.84, N 5.58.

Synthesis of the bromohydrin **8**a

N-Bromosuccinimide (13.2 g, 74 mmol) was added to a cooled (10°C) stirred solution of the unsaturated lactam (9.0 g, 36.9 mmol) in dimethylsulfoxide (162 mL) containing water (18 mL). The reaction mixture was stirred at 20°C for 1 h, the dimethylsulfoxide was removed *in vacuo* (40°/0.4 Torr), and the residue was diluted with saturated aqueous sodium potassium tartarate solution (40 mL). The product was extracted into a 1:1 ether – ethyl acetate solution, the extract was worked up as usual, and the product was purified by tlc on silica gel using ethyl acetate – dichloromethane (9:1) as the developing solvent. The bromohydrin **8***a* was obtained as a solid (5.2 g, 72%) that, after crystallization from ether–hexane, had mp 89–90°C; ir: 3450, 3300, 1700 cm^{-1}; nmr (see Table 1). *Anal.* calcd. for $C_{15}H_{18}BrNO_3 \cdot 0.5H_2O$: C 51.78, H 5.48, Br 22.88, N 4.01; found: C 51.71, H 5.38, Br 22.58, N 4.07.

Conversion of the bromohydrin **8**a *to the diol monoacetate* **9**b

A solution of the bromohydrin **8***a* (0.750 g, 2.2 mmol) in pyridine (1.8 mL) and acetic anhydride (0.8 mL) was stirred at room temperature for 2 h. The solution was diluted with water, the product was extracted into ethyl acetate, and the extract was washed with 2% aqueous sodium bicarbonate solution, dried, and evaporated *in vacuo*. The residue was purified by preparative tlc on silica gel using ethyl acetate – dichloromethane (1:1) as the developing solvent. The acetate **8***b* (0.600 g, 72%) was obtained as an oil; ir: 3430, 1745, 1710 cm^{-1}; nmr δ: 1.90–3.15 (m, 4H), 2.06 (s, 3H, CH_3), 3.36–3.73 (m, 2H, CH_2O), 3.86–4.30 (m, 2H), 4.50 (s, 2H, OCH_2Ph), 5.37 (m, 1H, H-11), 6.80 (bs, 1H, NH), 7.33 (s, 5H, Ph). This material was used without further characterization as follows. A solution of the acetate **8***b* (0.600 g, 1.6 mmol) in toluene (15 mL) containing tri-*n*-butyltin hydride (0.727 g, 2.5 mmol) and azobisisobutyronitrile (0.003 g) was heated at 60°C for 1 h. The solvent was removed *in vacuo*, the residue was dissolved in acetonitrile and this solution was extracted with hexane. The acetonitrile phase was evaporated *in vacuo* and the residue was purified by tlc on silica gel using ethyl acetate as the developing solvent. The debrominated acetate **9***a* (0.370 g, 78%) was isolated as an oil; ir: 3440, 1730, 1690 cm^{-1}; nmr δ: 1.60–2.83 (m, 6H), 2.00 (s, 3H, CH_3), 3.50 (d, 2H, J = 4.5 Hz, CH_2O), 4.50 (s, 2H, OCH_2Ph), 5.03 (m, 1H, H-11), 6.53 (bs, 1H, NH), 7.33 (s, 5H, Ph). This compound was used without further characterization. A solution of **9***a* (0.350 g, 1.15 mmol) in ethyl acetate (20 mL) containing suspended 10% palladium on charcoal catalyst (0.070 g) was stirred under hydrogen at atmospheric pressure until 1 equivalent of hydrogen was absorbed (2.5 h). The mixture was filtered through Celite, the filtrate was evaporated *in vacuo*, and the residue was purified by tlc on silica gel using ethyl acetate – methanol (9:1) as the developing solvent. After crystallization from hexane–dichloromethane the diol monoacetate **9***b* (0.200 g, 82%) had mp 74–76°C; ir: 3400, 1730, 1700 cm^{-1}; nmr δ (see Table 1); *m/e*: 213.1001 (calcd. for $C_{10}H_{15}NO_4$: 213.1000).

Synthesis of the p*-phenylbenzoate* **8**c

4-Phenylbenzoyl chloride (6.65 g, 30.6 mmol) was added to a solution of the bromohydrin **8***a* (8.7 g, 25.6 mmol) in dry pyridine (31 mL). After stirring for 2 h at room temperature water (3 mL) was added and the mixture was stirred for a further 1 h. The pyridine was removed *in vacuo*, dichloromethane was added to the residue, and the mixture was filtered through a pad of Celite. The filtrate was washed with 10% hydrochloric acid and then worked up in the usual way. The crude product was subjected to column chromatography on neutral alumina (Fluka, Act. II) using dichloromethane as the eluant. The pure material (9.5 g, 71%) was obtained as a solid that, after crystallization from dichloromethane, had mp 131–133°C; ir: 3420, 1710 cm^{-1}; nmr δ: 2.10–3.16 (m, 4H, H-8,12), 3.60 (m, 2H, 13-CH_2), 4.00–4.33 (m, 2H, H-9,10), 4.47 (s, 2H, OCH_2Ph), 5.60 (t, 1H, J = 6 Hz, H-11), 6.80 (s, 1H, NH), 7.30 (s, 5H, Ph), 7.33–8.26 (m, 9H, C_6H_4–C_6H_5). *Anal.* calcd. for $C_{28}H_{26}BrNO_4$: C 64.61, H 5.03, Br 15.35, N 2.69, found: C 64.53, H 5.05, Br 15.38, N 2.60.

Synthesis of the tert*-butyldimethylsilyl ether* **8**d

tert-Butyldimethylsilyl chloride (1.60 g, 10.6 mmol) and imidazole (1.86 g, 27.4 mmol) were added to a stirred solution of the bromohydrin (1.00 g, 2.94 mmol) in dry dimethylformamide (14 mL). After 3 h at room temperature the solution was diluted with water and extracted with ethyl acetate. After the usual work-up the crude material was purified by tlc on silica gel using dichloromethane – ethyl acetate (1:1) as the developing solvent. The product (0.866 g, 65%) was obtained as a solid that, after crystallization from dichloromethane–hexane, had mp 106–108°C; ir: 3450, 1700 cm^{-1}; nmr δ: 0.07 (s, 3H, MeSi), 0.16 (s, 3H, MeSi), 0.86 (s, 9H, Me_3CSi), 1.70–3.06 (m, 4H, 7-CH_2, H-8,12), 3.55 (d, 2H, J = 4.5 Hz, 13-CH_2), 3.78 (m, 1H, H-11), 3.96–4.26 (m, 2H, H-9,10), 4.48 (s, 2H, OCH_2Ph), 6.60 (s, 1H, NH), 7.30 (s, 5H, Ph). *Anal.* calcd. for $C_{21}H_{32}BrNO_3Si$: C 55.49, H 7.19, Br 17.58, N 3.08; found: C 55.58, H 7.39, Br 17.69, N 3.06.

Reductive debromination of the p*-phenylbenzoate* **8**c *to* **9**c

A solution of the bromo compound **8***c* (8.50 g, 16.3 mmol) in dry benzene (140 mL) containing tri-*n*-butyltin hydride (5.82 g, 20 mmol) and azobisisobutyronitrile (0.028 g) was heated at 60°C for 4 h. The solvent was removed *in vacuo* and the residue was dissolved in acetonitrile (400 mL). The solution was washed several times with hexane (discarded) and then evaporated *in vacuo*. The residue was subjected to column chromatography on neutral aluminia (Fluka, Act

(s, 0.25H, NH). Meaningful mass spectra could not be obtained for this material. It was not characterized further.

When the pure imidate **5***b* was heated in dry xylene as described in the body of the experimental section, the pure trichloroacetamide **6** was obtained directly in 80% yield. When the above mixture was subjected to the same conditions, it was transformed into the trichloroacetamide **6** (40%) and the starting ester **5***a* (30%), but only after treatment with methanolic potassium carbonate.

[7]Prostaglandin numbering system.

TABLE 3. Purification conditions, yields, and physical constants of 9-azaprostacyclins and precursors thereof

Compd. no.	Purification process[a]	R_f	Yield (%)	Melting point (°C)	Cryst. solvent	Molecular formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
14*a*	tlc;[b] CH_2Cl_2–A[c] (1:1)	0.52	29	150–151	CH_2Cl_2–MeOH	$C_{28}H_{31}NO_4$	73.98	7.09	3.14[d]	74.09	6.80	3.10
14*b*	tlc; CH_2Cl_2–A (7:3)	0.46	59	100–102	CH_2Cl_2–hexane	$C_{21}H_{37}NO_3Si$	66.44	9.82	3.68	66.20	9.87	3.63
14*c*	tlc; EtOAc	0.16	19	166–168	CH_2Cl_2–MeOH	$C_{30}H_{27}NO_5$	73.45	5.75	2.86[d]	73.36	5.72	2.75
14*d*	tlc; CH_2Cl_2–A (3:1)	0.42	68	146–148	CH_2Cl_2–hexane	$C_{21}H_{35}NO_3Si$	66.79	9.34	3.70	66.50	9.40	3.50
15*a*	tlc; CH_2Cl_2–A (1:1)	0.50	38	151–152	Ether–hexane	$C_{28}H_{33}NO_4$	75.13	7.43	3.13	74.97	7.35	3.10
15*b*	tlc; CH_2Cl_2–A (1:1)	0.34	34	181–182	Ether–hexane	$C_{28}H_{33}NO_4$	75.13	7.43	3.13	74.90	7.36	3.10
15*c*	tlc; CH_2Cl_2–A (4:1)	0.54	37	154–156	CH_2Cl_2–hexane	$C_{30}H_{29}NO_5$	73.60	6.11	2.88[e]	73.79	6.35	2.84
15*d*	tlc; CH_2Cl_2–A (4:1)	0.40	32	158–160	CH_2Cl_2–hexane	$C_{30}H_{29}NO_5$	72.71	6.17	2.83[f]	72.87	6.17	3.19
16*a*	tlc; CH_2Cl_2–A (1:1)	0.29	83	146–148	Ether–MeOH	$C_{15}H_{25}NO_3$	67.38	9.42	5.24	67.14	9.20	4.96
16*b*	tlc; A	0.23	83	138–140	Ether–MeOH	$C_{15}H_{25}NO_3$	67.38	9.42	5.24	67.21	9.31	4.98
16*c*	tlc; A	0.38	85	123–125	Ether–hexane	$C_{17}H_{21}NO_4$	67.30	6.98	4.62	66.99	6.98	4.31
16*d*	tlc; A	0.30	83	146–148	CH_2Cl_2–hexane	$C_{17}H_{21}NO_4$	67.30	6.98	4.62	67.00	7.04	4.76
17*a*	tlc; CH_2Cl_2–A (7:3)	0.52	60	86–87	CH_2Cl_2–hexane	$C_{21}H_{39}NO_3Si$	66.09	10.30	3.66	66.15	9.96	3.62
17*b*	tlc; CH_2Cl_2–A (7:3)	0.41	23	146–147	CH_2Cl_2–hexane	$C_{21}H_{39}NO_3Si$	66.09	10.30	3.66	66.14	10.22	3.88
17*c*	fc;[g] EtOAc–hexane (1:1)		68	98–99	Ether–hexane	$C_{21}H_{37}NO_3Si$	66.44	9.82	3.68	66.18	9.66	3.68
17*d*	fc; EtOAc–hexane (1:1)		23	147–148	Ether–hexane	$C_{21}H_{37}NO_3Si$	66.44	9.82	3.68	66.34	9.74	3.59
18*a*	tlc; CH_2Cl_2–EtOAc (95:5)	0.48	72	82–83	Ether–hexane	$C_{27}H_{53}NO_3Si_2$	65.52	10.99	2.82	65.42	11.01	2.72
18*b*	tlc; EtOAc	0.32	68	98–99	Ether–hexane	$C_{27}H_{53}NO_3Si_2$	65.52	10.99	2.82	65.21	10.85	2.69
18*c*	tlc; EtOAc	0.34	76	130–132	CH_2Cl_2–hexane	$C_{29}H_{49}NO_4Si_2$[h]						
18*d*	tlc; EtOAc–CH_2Cl_2 (7:3)	0.21	78	Oil		$C_{29}H_{49}NO_4Si_2$[i]						
18*e*	cc; CH_2Cl_2–EtOAc (9:1)		87	127–128	CH_2Cl_2–hexane	$C_{27}H_{51}NO_3Si_2$	65.66	10.40	2.83	65.61	10.37	2.63
18*f*	cc; CH_2Cl_2–EtOAc (9:1)		88	159–160	CH_2Cl_2–hexane	$C_{27}H_{51}NO_3Si_2$	65.66	10.40	2.83	65.54	10.23	2.63
19*a*	tlc; CH_2Cl_2	0.20	70	Oil		$C_{27}H_{53}NO_2SSi_2$	63.35	10.43	2.73	63.45	10.40	2.57
19*b*	tlc; CH_2Cl_2	0.18	72	85–86	CH_2Cl_2	$C_{27}H_{53}NO_2SSi_2$	63.35	10.43	2.73	63.49	10.49	2.62
19*c*	tlc; CH_2Cl_2–EtOAc (95:5)	0.54	80	Oil		$C_{29}H_{49}NO_3SSi_2$[j]						
19*d*	tlc; CH_2Cl_2–EtOAc (95:5)	0.50	82	Oil		$C_{29}H_{49}NO_3SSi_2$[k]						
19*e*	tlc; hexane–EtOAc (7:3)	0.31	71	146–147	CH_2Cl_2–hexane	$C_{27}H_{51}NO_2SSi_2$	63.59	10.08	2.74	63.41	9.90	2.65
19*f*	tlc; hexane–EtOAc (7:3)	0.31	67	141–142	Ether–hexane	$C_{27}H_{51}NO_2SSi_2$	63.59	10.08	2.74	63.40	9.92	2.85
21*a*	tlc; CH_2Cl_2–ether (95:5)	0.27	64	Oil		$C_{33}H_{61}NO_5Si_2$	65.17	10.11	2.03	65.25	9.82	1.91
21*b*	tlc; CH_2Cl_2–ether (95:5)	0.24	56	Oil		$C_{33}H_{61}NO_5Si_2$	65.17	10.11	2.03	65.16	9.83	2.04
21*c*	tlc; CH_2Cl_2–ether (9:1)	0.26	68	Oil		$C_{35}H_{57}NO_6Si_2$[l]						
21*d*	tlc; CH_2Cl_2–ether (9:1)	0.16	73	Oil		$C_{35}H_{57}NO_6Si_2$	65.27	8.92	2.19	65.20	8.87	2.10
21*e*	cc; CH_2Cl_2–ether (95:5)		66	Oil		$C_{33}H_{59}NO_5Si_2$	65.40	9.81	2.31	65.19	9.60	2.10
21*f*	cc; CH_2Cl_2–ether (95:5)		68	Oil		$C_{33}H_{59}NO_5Si_2$	65.40	9.81	2.31	65.08	9.56	1.71

TABLE 3 (*concluded*)

Compd. no.	Purification process[a]	R_f	Yield (%)	Melting point (°C)	Cryst. solvent	Molecular formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
22*a*	tlc; CH_2Cl_2–A (1:1)	0.34	82	72–73	Ether	$C_{21}H_{33}NO_5$	66.46	8.76	3.68	66.25	8.53	3.61
22*b*	tlc; CH_2Cl_2–A (1:1)	0.30	73	Oil		$C_{21}H_{33}NO_5$[m]						
22*c*	tlc; CH_2Cl_2–A (1:1)	0.26	78	Oil		$C_{23}H_{29}NO_6$[n]						
22*d*	tlc; CH_2Cl_2–A (1:1)	0.16	77	Foam		$C_{23}H_{29}NO_6$[o]						
22*e*	tlc; CH_2Cl_2–A (1:1)	0.30	95	Oil		$C_{21}H_{31}NO_5$	66.81	8.28	3.71	66.91	8.17	3.53
22*f*	tlc; CH_2Cl_2–A (1:1)	0.30	91	Oil		$C_{21}H_{31}NO_5$	66.81	8.28	3.71	66.83	8.11	3.56
23*a*	catlc; B		74	Oil		$C_{20}H_{31}NO_5$[p]	65.73	8.55	3.83			
23*b*	Crystallization		76	118–120	Ether–hexane	$C_{20}H_{31}NO_5$	65.73	8.55	3.83	65.56	8.40	3.64
23*c*	catlc; B		92	Oil		$C_{22}H_{27}NO_6$	65.82	6.78	3.49	65.60	6.78	3.38
23*d*	catlc; B		90	69–70	Ether–hexane	$C_{22}H_{27}NO_6$	65.82	6.78	3.49	65.58	6.63	3.40
23*e*	tlc; B	0.16	60	112–114	Ether–hexane	$C_{20}H_{29}NO_5$	66.09	8.04	3.81	65.90	7.89	3.70
23*f*	tlc; B	0.16	45	Oil		$C_{20}H_{29}NO_5$	66.09	8.04	3.81	66.19	7.90	3.90

[a]Chromatographic separations using silica gel as stationary phase.
[b]tlc = thin-layer chromatography, cc = column chromatography; fc = flash chromatography, catlc = centrifically accelerated tlc.
[c]A = CH_2Cl_2–MeOH – conc. NH_4OH (60:10:1); B = CH_2Cl_2–MeOH–HOAc (60:10:1). The R_f values were measured on 2.5 × 10 cm plates coated with silica gel GF-254 (0.2 mm).
[d]*Anal.* calcd. for hemihydrate.
[e]*Anal.* calcd. for 1/3 H_2O.
[f]*Anal.* calcd. for 2/3 H_2O.
[g]Silica gel, Merck no. 9385.
[h]*m/e* 516.2965 (calcd. for $C_{29}H_{49}NO_4Si_2 - CH_3$: 516.2962).
[i]*m/e* 516.2967 (calcd. for $C_{29}H_{49}NO_4Si_2 - CH_3$: 516.2962).
[j]*m/e* 490.2278 (calcd. for $C_{29}H_{49}NO_3SSi_2 - C_4H_9$: 490.2267).
[k]*m/e* 490.2287 (calcd. for $C_{29}H_{49}NO_3SSi_2 - C_4H_9$: 490.2267).
[l]*m/e* 643.3724 (calcd. for $C_{35}H_{57}NO_6Si_2$: 643.3717).
[m]*m/e* 379.2358 (calcd. for $C_{21}H_{33}NO_5$: 379.2358).
[n]*m/e* 415.1993 (calcd. for $C_{23}H_{29}NO_6$: 415.1995).
[o]*m/e* 415.1997 (calcd. for $C_{23}H_{29}NO_6$: 415.1995).
[p]*m/e* 365.2200 (calcd. for $C_{20}H_{31}NO_5$: 365.2202).

II) using dichloromethane as the eluant. The product **9***c* was isolated as a solid (6.10 g, 85%) that on crystallization from dichloromethane–hexane, had mp 145–146°C; ir: 3460, 1695 cm^{-1}; nmr δ: 2.10–2.86 (m, 4H, 7-CH_2, H-8,12), 3.51 (d, 2H, J = 6 Hz, 13-CH_2), 4.13 (m, 1H, H-9), 4.50 (s, 2H, OCH_2Ph), 5.35 (dd, 1H, $J \simeq 4.5$ Hz, H-11), 6.50 (s, 1H, NH), 7.28 (s, 5H, Ph), 7.20–8.50 (m, 9H, $C_6H_4C_6H_5$). *Anal.* calcd. for $C_{28}H_{27}NO_4$: C 76.06, H 6.16, N 3.17; found: C 75.88, H 6.17, N 3.08.

Reductive debromination of the tert*-butyldimethylsilyl ether* **8**d *to* **9**e

The debromination of **8***d* was effected in the same manner as described for **8***c* except that the reaction was carried out at 70°C for 2 h and the product, obtained in 95% yield, was purified by crystallization from dichloromethane–hexane. It had mp 108–110°C; ir: 3460, 1695 cm^{-1}; nmr δ: 0.10 (s, 6H, Me_2Si), 0.86 (s, 9H, Me_3CSi), 1.20–2.73 (m, 4H, 7-CH_2, H-8,12), 3.44 (d, 2H, J = 4.5 Hz, 13-CH_2), 3.80–4.20 (m, 2H, H-9,11), 4.46 (s, 2H, OCH_2Ph), 5.53 (s, 1H, NH), 7.30 (s, 5H, Ph). *Anal.* calcd. for $C_{21}H_{33}NO_3Si$: C 67.15, H 8.85, N 3.72; found: C 67.03, H 8.71, N 3.60.

Hydrogenolysis of **9**c *to* **9**d

A stirred solution of the benzyl ether **9***c* (8.70 g, 19.7 mmol) in dimethyoxyethane (75 mL) containing 70% perchloric acid (1.3 mL) and suspended 10% palladium on charcoal catalyst (3.1 g) was hydrogenated at room temperature and atmospheric pressure until hydrogen absorption ceased (10 h). The mixture was filtered through Celite, the filtrate was evaporated *in vacuo*, and the residue was dissolved in dichloromethane. This solution was worked up in the usual way to give the alcohol **9***d* as a solid (6.50 g, 94%) that, on crystallization from ethyl acetate – methanol, had mp 175–178°C; ir: 3480, 1695 cm^{-1}; nmr δ: 2.00–2.96 (m, 6H), 3.60 (m, 2H, 13-CH_2), 4.20 (m, 1H, H-9), 5.36 (q, $J \simeq 6$ Hz, H-11), 5.80 (s, 1H, NH), 7.33–7.66 (m, 5H, Ph), 7.89 (q, 4H, J_o = 7.5 Hz, C_6H_4). *Anal.* calcd. for $C_{21}H_{21}NO_4 \cdot 0.5H_2O$: C 69.98, H 6.15, N 3.89; found: C 70.00, H 5.87, N 3.89.

Hydrogenolysis of **9**e *to* **9**f

A stirred solution of the benzyl ether **9***e* (0.750 g, 2 mmol) in ethyl acetate (40 mL) containing suspended 10% palladium on carbon catalyst (0.15 g) was hydrogenated as described for the synthesis of **9***d* (18 h). After filtration of the mixture through Celite and evaporation of the filtrate *in vacuo*, the residue was purified by tlc on silica gel using ethyl acetate – methanol (98:2) as the developing solvent. The solid product (0.432 g, 76%), on crystallization from dichloromethane–hexane, had mp 80–82°C; ir: 3440, 3250, 1690 cm^{-1}; nmr δ: 0.07 (s, 6H, Me_2Si), 0.86 (s, 9H, Me_3CSi), 1.20–2.73 (m, 4H), 3.55 (d, 2H, J = 6 Hz, 13-CH_2), 3.80–4.20 (m, 2H, H-9,11). *Anal.* calcd. for $C_{14}H_{27}NO_3Si$: C 58.90, H 9.53, N 4.90; found: C 58.65, H 9.86, N 4.72.

Synthesis of the enones **14**

(a) n*-Amyl enone* **14**a

Collins reagent (22.7 g) and a suspension of the alcohol **9***d* (3.50 g, 10 mmol) in dry dichloromethane (100 mL) were added successively to a stirred suspension of Celite (45.4 g, dried at 125°C for 24 h) in anhydrous dichloromethane (300 mL) at 0°C. The reaction mixture was stirred at 5°C for 15 min, sodium bisulfate dihydrate (45.4 g) was added, and agitation was continued for a further 10 min at 5°C. The mixture was filtered through a pad of anhydrous magnesium sulfate, the filtrate was evaporated *in vacuo*, and the residual aldehyde **13***a* (~3.5 g) was used directly as follows. Dimethyl 2-oxoheptylphosphonate (2.09 g, 9.4 mmol) dissolved in dry dimethoxyethane (47 mL) was added to a stirred suspension of sodium hydride (obtained from a 60% dispersion in mineral oil (0.378 g, 9.4 mmol) washed with dry hexane) in anhydrous dimethoxyethane (112 mL). After 0.5 h at room temperature a solution of the above aldehyde (3.5 g) in dry dimethoxyethane (50 mL) was added and the mixture was stirred at room temperature for 2.5 h. Acetic acid (0.54 mL) was added, the solvent was removed *in vacuo*, and ethyl acetate was added to the residue. The mixture was filtered through Celite, the filtrate was dried, and the solvent was removed *in vacuo*. The residue was purified by the process indicated in Table 3. The yield, mp, solvent of crystallization, and elemental analysis are also found in this table.

(b) Silylated enone **14**b

The synthesis of this compound was carried out as described for **14***a* except that the quantities of the phosphonate (0.490 g, 1.9 mmol), 60% sodium hydride (0.070 g, 1.75 mmol), and the crude aldehyde **13***b* (derived from 1.4 mmol (0.400 g) of the alcohol **9***f*) were slightly different and the reaction time was 1 h. See Table 3 for purification and physical constants; uv: 236 (10 700) nm; ir: 3460, 1700, 1670 cm^{-1}; nmr δ: 0.03 (s, 6H, Me_2Si), 0.73–1.03 (m, 12H), 1.16–2.80 (m, 14H), 3.77–4.20 (m, 2H, H-9,11), 6.15 (d, 1H, $J_{13,14}$ = 16 Hz, H-14), 6.63 (dd, 1H, $J_{12,13}$ = 7.5 Hz, $J_{13,14}$ = 16 Hz, H-13), 6.80 (s, 1H, NH).

(c) 16-Phenoxy enone **14**c

The synthesis of this enone was carried out as described for **14***b* except that the phosphonate was dimethyl-2-oxo-3-phenoxypropylphosphonate and the reaction time was 3 h.

(d) Cyclopentyl enone **14**d

This enone was prepared in the same manner as described for **14***b* except that dimethyl 2-oxo-2-cyclopentylethylphosphonate was used and the reaction time was 1.5 h.

Sodium borohydride reduction of the enones **14**

(a) Synthesis of **15**a *and* **15**b

Methanolic cerous chloride hexahydrate (1.35 mL of a 0.4 *M* solution; 0.54 mmol) was added, at 0°C, to a stirred solution of the enone **14***a* (1.30 g, 2.9 mmol) in tetrahydrofuran (25 mL). Immediately thereafter, sodium borohydride (0.133 g, 3.5 mmol) was added in four equal portions at 1-min intervals. Stirring was continued for 7 min and then water (15 mL) was added and the reaction mixture was extracted with ethyl acetate. After the usual work-up, the crude product was purified as indicated in Table 3. The physical constants of the less polar 15α alcohol **15***a* and the more polar **15**β alcohol **15***b* are also found in Table 3.

(b) Synthesis of **17**a *and* **17**b *from* **14**b

This reduction was effected as described above for **14***a* except that the enone (0.300 g, 0.79 mmol) was dissolved in methanol (28 mL) and was reacted with 0.4 *M* methanolic cerous chloride hexahydrate (0.3 mL) and sodium borohydride (0.030 g, 0.79 mmol). The mixture was separated by tlc as indicated in Table 3 to give the 15α (less polar) and 15β (more polar) alcohols **17***a* and **17***b*. Compound **17***a* had the following spectroscopic properties: ir: 3610, 3460, 1695 cm^{-1}; nmr δ: 0.03 (s, 6H, Me_2Si), 0.73–1.00 (m, 12H), 1.13–2.66 (m, 14H), 3.66–4.23 (m, 3H, H-9,11,15), 5.40–5.63 (m, 2H, H-13,14), 6.73 (bs, 1H, NH).

(c) Synthesis of **15**c *and* **15**d *from* **14**c

This reduction was carried out as described for **14***a* except that the enone was dissolved in a tetrahydrofuran (30 mL/g enone) – methanol (10 mL/g enone) solvent mixture. The mixture of alcohols produced was separated by tlc on silica gel using the solvent system indicated in Table 3.

(d) Reduction of **14**d *to* **17**c *and* **17**d

This reduction was carried out as described for **14***c* except that the enone **14***d* (3.6 g, 9.65 mmol) in methanol (100 mL) was reacted with 0.4 *M* methanolic cerous chloride hexahydrate (25 mL, 10 mmol) and sodium borohydride (0.377 g, 9.9 mmol). The mixture of alcohols obtained was separated by flash chromatography on silica gel (Merck, no. 9385) using hexane – ethyl acetate (1:1) as the eluting solvent.

Hydrolysis of the esters **15** *to the diols* **16**

The conversion of **15***a* to **16***a* was typical. A solution of the *p*-phenylbenzoate **15***a* (0.500 g, 1.12 mmol) in absolute methanol (10 mL) containing anhydrous potassium carbonate (0.154 g, 1.12 mmol) was stirred at room temperature for 3 h. The solution was cooled

to 0°C, neutralized with 1 *M* hydrochloric acid (2.2 mL), and the methanol was removed *in vacuo*. The residue was mixed with ethyl acetate, and the organic phase was washed with 10% sodium bicarbonate solution and then worked up in the usual way. The crude diol was purified as indicated in Table 3. After crystallization, the less polar diol **16***a* had the following spectroscopic properties: ir: 3620, 3450, 1680 cm^{-1}; nmr δ: 0.88 (t, 3H, J = 6 Hz, 20-CH_3), 1.03–2.66 (m, 14H), 3.97 (m, 3H, H-9,11,15), 5.53 (m, 2H, H-13,14), 7.04 (bs, 1H, NH).

The diols **16***b*, **16***c*, and **16***d* were prepared as described above for **16***a* except that a mixture of methanol (10 mL) and tetrahydrofuran (2 mL) was used as the solvent for a reaction carried out on a 1-mmol scale.

*Synthesis of the bis-*tert*-butyldimethylsilyl compounds **18***

Imidazole (10 mmol) and *tert*-butyldimethylsilyl chloride (5 mmol) were added to a stirred solution of the diol **16** or monosilylated diol **17** (1 mmol) in anhydrous DMF (25–35 mL/g alcohol). After reaction for 1–3 h, the solution was diluted with water and the product was extracted with ethyl acetate or a 1:1 benzene – ethyl acetate mixture (for **18***e* and **18***f*). After the usual work-up, the crude products were purified as indicated in Table 2. Compound **18***a* had the following spectroscopic properties: ir: 3450, 1698 cm^{-1}; nmr δ: 0.03 (s, 12H, Me_2Si), 0.86 (m, 21H, Me_3CSi, 20-CH_3), 1.13–2.60 (m, 14H), 3.93 (m, 3H, H-19,11,15), 5.43 (m, 2H, H-13,14), 6.50 (s, 1H, NH).

*Synthesis of the thiolactams **19***

A solution of the lactam (2 mmol) and Lawesson's reagent (1–1.4 mmol); 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide, Aldrich Chem. Co.) in anhydrous benzene (25–50 mL/g of lactam) was heated at reflux temperature for 0.5–1 h. The solvent was removed *in vacuo*, the residue was mixed with dichloromethane, and the mixture was filtered. The filtrate was evaporated *in vacuo* and the residue was purified by preparative tlc on silica gel using the solvent system indicated in Table 3. The tlc pure 15α compound **19***a* had the following spectroscopic properties: ir: 3420, 1500 cm^{-1}; nmr δ: 0.03 (s, 12H, Me_2Si), 0.88 (m, 21H, 20-Me, Me_3CSi), 1.06–3.26 (m, 14H), 4.05 (m, 3H, H-9,11,15), 5.43 (m, 2H, H-13,14), 8.72 (s, 1H, NH).

*Synthesis of the bis-*tert*-butyldimethylsilyl vinylogous amides **21***

Sodium hydride in mineral oil (50% suspension, 1 mmol) was washed with dry hexane, layered with anhydrous tetrahydrofuran (10–20 mL), and the thiolactam (1 mmol) dissolved in dry tetrahydrofuran (10–20 mL) was added thereto with stirring. After 1 h at room temperature the mixture was cooled to 0°C and a solution of methyl 5-bromolevulinate (1.1 mmol) in dry tetrahydrofuran (10–20 mL) was added slowly and then the reaction mixture was stirred for 0.25–0.5 h. Ethyl acetate, or ethyl acetate – ether (1:1) in the case of **20***e* and **20***f*, and water were added and the reaction was then worked up as usual to give the thioimidates **20**. The crude thioimidates (ir absorption of 1740–1750 cm^{-1}) were used immediately in the next step.

*(a) Synthesis of **21**a–d*

Triphenylphosphine (1.5 mmol) and potassium-*tert*-butoxide (0.2 mmol) were added to the crude thioimidate dissolved in 1:1 xylene–*tert*-butanol solution (7 mL, anhydrous) and the mixture was heated at reflux temperature for 2–3 h. The mixture was diluted with water and worked up in the usual way. The crude products were purified in the manner described in Table 3. The tlc-pure, oily **21***a* had the following spectroscopic properties: uv: 270 (1590), 308 (20 000) nm; ir: 3260, 1740, 1625, 1540 cm^{-1}; nmr δ: 0.03 (s, 12H, Me_2Si), 0.66 (m, 21H, 20-Me_3CSi), 1.03–3.00 (m, 14H), 2.56 (s, 4H, 2-CH_2, 3-CH_2), 3.93 (m, 3H, H-9,11,15), 3.63 (s, 3H, OMe), 4.96 (s, 1H, H-5), 5.24 (m, 2H, H-13,14), 9.88 (bs, 1H, NH).

*(b) Synthesis of **21**e,f*

Triphenylphosphine (0.16 mmol) and potassium-*tert*-butoxide (0.2 mmol) were added to the crude thioimidate from above dissolved in 10:1 xylene–*tert*-butanol (10 mL) and the reaction was effected as described for **21***a–d*.

*Hydrolysis of the bis-*tert*-butyldimethylsilyl ethers **21** to the 11,15-diols **22***

A solution of tetra-*n*-butylammonium fluoride (4 mmol) in anhydrous tetrahydrofuran (5 mL) was added to a stirred solution of the disilyl ether (1 mmol) in the same solvent (10–25 mL). The resulting solution was heated at 40°C for 18–24 h and the solvent was then removed *in vacuo*. The residue was partitioned between water and ethyl acetate and worked up in the usual way. The product was purified in the manner described in Table 3. Pure **22***a* had the following spectroscopic properties: uv: 215 (1660), 317 (19 600) nm; ir: 3620, 3390 (br) 1740, 1625, 1540 cm^{-1}; nmr δ: 0.88 (m, 3H, 20-CH_3), 1.16–3.33 (m, 18H), 3.95 (m, 3H, H-9,11,15), 5.01 (s, 1H, H-5), 5.46 (m, 2H, H-13,14), 9.77 (bs, 1H, NH).

*Hydrolysis of the azaprostacyclin methyl esters **22** to the carboxylic acids **23***

A solution of the ester (1 mmol) in methanol (15 mL) containing water (1 mL) and potassium carbonate (3 mmol) was stirred at room temperature for 38–64 h. The methanol was removed *in vacuo*, water was added to the residue, and the solution was extracted with dichloromethane. The aqueous phase was cooled to 0°C and brought to pH 4 by the addition of a saturated aqueous oxalic acid solution. The product was extracted into ethyl acetate and worked up in the usual way.

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