Synthesis of a Novel, Optically Active 15-Nonstereogenic Carbaprostacyclin

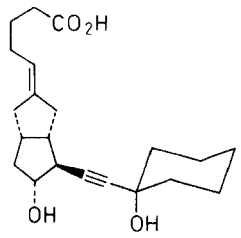
Tõnis Kanger,[a] Margus Lopp,*[a] Anne Müraus,[a] Madis Lõhmus,[a] Gennadi Kobzar,[a] Tõnis Pehk,[b] Ülo Lille[a]

[a] Institute of Chemistry, Estonian Academy of Sciences, Akadeemia tee 15, 200108 Tallinn, Estonia
[b] Institute of Chemical and Biological Physics, Estonian Academy of Sciences, Rävala pst. 10, 200001 Tallinn, Estonia

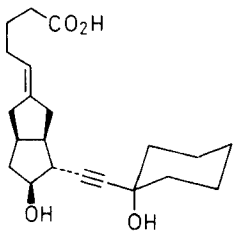
Received 11 November 1991; revised 19 February 1992

Novel, optically active carbacyclin analogues (+)-**1** and (−)-**1** with an achiral ω-chain were synthesized from homochiral bromohydrins **3a** and **4a**, respectively.

The analogues of natural prostacyclin PGI_2, especially its 9a-carbon analogues (carbacyclins), are of particular importance in organic synthesis due to their chemical stability and high biological activity.[1] It has been shown that in all cases, the *S*-configuration of the chiral carbon atom at position 15 is important in determining the activity of the analogue.[2,3] Unfortunately, most of the methods used in the synthesis of prostaglandins lead to a mixture of 15-(*S*)/(*R*)-isomers that require their troublesome separation. This problem may be completely avoided by construction of an achiral ω-chain. For this purpose, the cyclohexanol derivatives, in which the hydroxy function is located at the symmetrically substituted carbon atom may be used. In our previous reports,[4] we have dealt with the synthesis and properties of racemic 13,14-didehydro-15,16,17,18,19,20-hexanor-14-(1-hydroxycyclohexyl)carbacyclin (**1**). In this paper we report the synthesis of enantiomeric (+)-**1** and (−)-**1**.

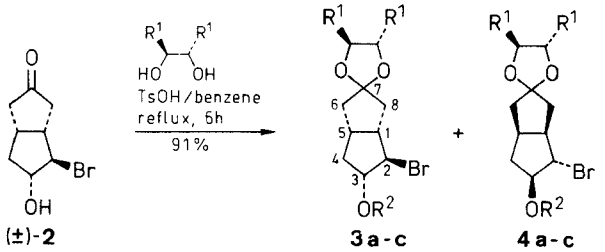


(+)-**1**



(−)-**1**

The synthesis starts from diastereomeric bromohydrins **3a** and **4a** obtained from the racemic bicyclic ketone **2**[5] via acetalization with (*S,S*)-(−)-1,4-bis(benzyloxy)-2,3-butanediol (derived from (*R,R*)-tartaric acid ester)[6] (Scheme 1).



(±)-**2** **3a-c** **4a-c**

3, 4	R^1	R^2
a	CH_2OCH_2Ph	H
b	$CH_2OCH_2C_6H_4Cl$-4	H
c	CH_2OCH_2Ph	COCH(OMe)Ph

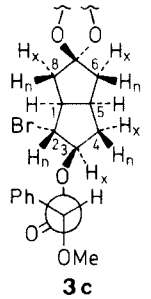
Scheme 1

Compounds **3** and **4a** were separated by preparative HPLC on silica gel (hexane/ethylacetate 4:1) to afford homochiral diastereoisomers with optical purity more than 99% (ee was determined by HPLC). The absolute configuration of bromohydrins **3a** and **4a** were determined by detailed ^1H and ^{13}C NMR analysis by 2D ^1H-^1H and ^1H-^{13}C COSY correlations of their (R)-*O*-methylmandelic acid (MPA) esters **3c** and **4c**. In preferred conformations of these esters, the phenyl ring must shield in **3c** protons at C-1,2,8 and in **4c** at C-4,5,6.[7] These trends are observed in both ^1H and ^{13}C spectra, if one compares the corresponding chemical shifts from esters of **3c** and **4c** (Table).

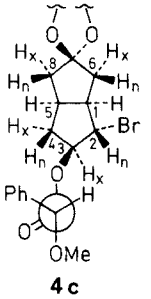
Table. Differential Shieldings of ^{13}C and ^1H Nuclei from (R)-*O*-Methylmandelates **3c** and **4c**[a] ($\Delta\delta$ **3c**–**4c** in ppm)

Atoms	1	2	8	4	5	6
$\Delta\delta$ ^{13}C	−0.03	−0.12	−0.18	0.15	0.12	0.13
$\Delta\delta$ ^1H	−0.03	−0.11	−0.08 (x)	0.12 (x)	0.04	0.07 (x)
			−0.16 (n)	0.25 (n)		0.17 (n)

[a]



3c
(1*S*, 2*R*, 3*R*, 5*R*)-R-MPA ester



4c
(1*R*, 2*S*, 3*S*, 5*S*)-R-MPA ester

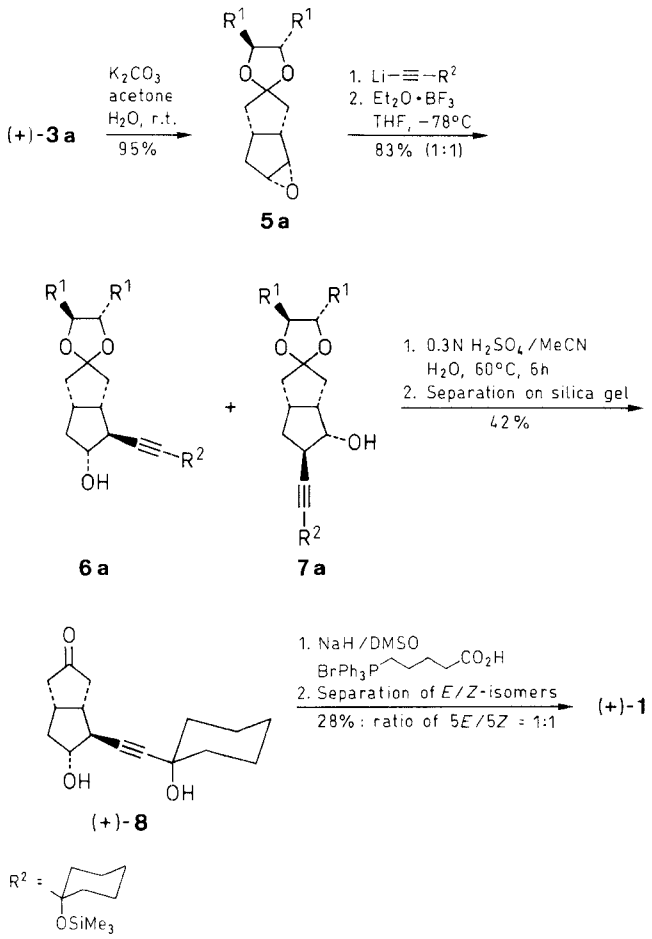
x = exo, n = endo

Absolute configuration of the bromohydrins were also confirmed by biological activities of the enantiomeric target carbacyclins **1**. It should be mentioned that the chromatographed behaviour of compounds **3a** and **4a**, as compared with the corresponding bromohydrins with the bicyclo[3.2.0]heptane framework,[8] is different (the eluting order is reversed) and therefore this kind of analogy cannot be used to suggest the configuration of bicyclic systems.

Although, it is known that the cyclic diastereomeric acetals derived from *p*-chlorobenzyloxybutanediol have good crystallizing properties,[9] we failed to separate the corresponding diastereomers **3b** and **4b** by crystallization from various binary solvent systems.

The preparation of carbacyclins from bromohydrin **3a** followed the known reaction sequence (Scheme 2).

Bromohydrin **3a** was epoxidized under the basic conditions in high yield (95%). The oxirane ring was opened



Scheme 2

smoothly using the lithiumalkynide/boron trifluoride reagent[10] in tetrahydrofuran at −78 °C to afford a 1:1 mixture of regioisomers **6a** and **7a**. The trimethylsilyl protected 1-ethynyl-1-cyclohexanol required for forming the reagent with boron trifluoride was synthesized from cyclohexanone and ethynyl magnesium bromide followed by protection of the hydroxyl group. Regioisomers **6a** and **7a** were easily separated by column chromatography on silica gel after removing the protective groups. The treatment of ketone **8** with the ylide derived from (4-carboxybutyl)triphenylphosphonium bromide and sodium hydride in dimethyl sulfoxide led to a 1:1 mixture of (5*E*)/(5*Z*)-isomers of compound (+)-**1** in 56% yield. After chromatographic separation of (5*E*)/(5*Z*)-isomers on silica gel, a single homochiral isomer (+)-**1** was obtained. Its enantiomer (−)-**1** was synthesized from the diastereomeric acetal **4a** in the same way.

The platelet antiaggregating activity (IC_{50}) of compound (+)-**1** on human platelet-rich blood plasma with ADP as an inducer of aggregation was found to be almost equal to that of natural prostaglandin E_1 ($IC_{50} = 4.0 \times 10^{-8}$ M). The activity of (−)-**1** was by about two orders of magnitude lower.

IR spectra were measured with a Specord IR-75 spectrometer. ^1H and ^{13}C NMR spectra were obtained on a Brucker AM-500 spectrometer in $CDCl_3$. The chemical shifts are reported in relative to TMS from solvent ($CDCl_3$) signal ($\delta_H = 7.27$, $\delta_C = 77.0$). Preparative HPLC was done using a PVK-31 system (Special Designing Bureau, Estonian Academy of Sciences, column: 300 × 30 mm, 5 μm Separon SGX, flow rate 35 mL/min, detector UV-260 nm). Optical rotations were obtained at 20 °C using a Polamat A polarimeter. Microanalyses were obtained using Hewlett-Packard 178 element analyser.

(1*S*,2*R*,3*R*,5*R*,4′*S*,5′*S*)-2-Bromo-3-hydroxy-4′,5′-bis(benzyloxymethyl)spiro{bicyclo[3.3.0]octane-7,2′(1,3)-dioxolane} (3a) and its Diastereoisomer 4a:

A solution of racemic bromohydrin **2** (1.50 g, 6.8 mmol), (*S,S*)-(−)-1,4-bis(benzyloxy)-2,3-butanediol (3.08 g, 10.2 mmol) and a catalytic amount of TsOH in benzene (20 mL) was refluxed under the conditions of azeotropic water distillation by the Dean-Stark trap for 6 h. The solution was washed with aq 9% $NaHCO_3$ solution and the organic phase was dried ($MgSO_4$). The solvent was evaporated and the mixture of isomers **3a** and **4a** was purified on a short silica gel column. Diastereoisomers were separated by means of preparative HPLC using hexane EtOAc as eluent to give 1.37 g of **3a** as a less polar compound, 1.43 g of **4a** as a more polar compound and 0.3 g of the mixture of isomers in 91% overall yield.

3a: $[\alpha]_D^{20}$ +26.15° (*c* = 4.02, $CHCl_3$)

$C_{26}H_{31}BrO_5$	calc.	C 62.02	H 6.22
(503.5)	found	62.09	6.27

IR (film): *v* = 3550, 3050, 1510, 1465, 1020 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.54 (H-4n), 1.76 (H-6n), 1.87 (H-8n), 2.07 (2H, H-6x, H-6x), 2.27 (H-4x), 2.62 (H-5), 2.76 (H-1), 3.97 (H-2), 4.12 (H-3).

^{13}C NMR ($CDCl_3$): δ = 35.45 (C-5), 37.47 (C-4), 40.00 (C-8), 42.75 (C-6), 47.53 (C-1), 62.69 (C-2), 79.66 (C-3), 118.94 (C-7).

(R)-O-Methylmandelic Acid Ester **3c**:

^1H NMR ($CDCl_3$): δ = 1.54 (H-4n), 1.69 (H-8n), 1.73 (H-6n), 1.98 (H-8x), 2.06 (H-6x), 2.44 (H-4x), 2.68 (H-5), 2.75 (H-1), 4.00 (H-2), 5.17 (H-3).

^{13}C NMR ($CDCl_3$): δ = 35.48 (C-4), 36.03 (C-5), 40.14 (C-8), 42.91 (C-6), 47.82 (C-1), 55.74 (C-2), 81.57 (C-3), 118.71 (C-7).

4a: $[\alpha]_D^{20}$ −28.61° (*c* = 5.11, $CHCl_3$).

$C_{26}H_{31}BrO_5$	calc.	C 62.02	H 6.22
(503.5)	found	61.91	6.30

IR (film): *v* = 3550, 3060, 1520, 1480, 1020 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.52 (H-4n), 1.72 (H-6n), 1.92 (H-8n), 2.06 (H-6x), 2.08 (H-8x), 2.28 (H-4x), 2.63 (H-5), 2.75 (H-1), 3.99 (H-2), 4.12 (H-3).

^{13}C NMR ($CDCl_3$): δ = 35.45 (C-5), 37.62 (C-4), 40.00 (C-8), 42.68 (C-6), 47.49 (C-1), 62.53 (C-2), 79.67 (C-3), 118.89 (C-7).

(R)-O-Methylmandelic Acid Ester **4c**:

^1H NMR ($CDCl_3$): δ = 1.29 (H-4n), 1.56 (H-6n), 1.85 (H-8n), 1.99 (H-6x), 2.06 (H-8x), 2.32 (H-4x), 2.64 (H-5), 2.78 (H-1), 4.11 (H-2), 5.22 (H-3).

^{13}C NMR ($CDCl_3$): δ = 35.33 (C-4), 35.91 (C-5), 40.32 (C-8), 42.78 (C-6), 47.85 (C-1), 55.86 (C-2), 81.48 (C-3), 118.69 (C-7).

(1*S*,2*S*,3*R*,5*R*,4′*S*,5′*S*)-2,3-Epoxy-4′,5′-bis[(benzyloxy)methyl]spiro-{bicyclo[3.3.0]octane-7,2′(1,3)-dioxolane} (5a):

The solution of bromohydrin **8** (335 mg, 0.67 mmol) and K_2CO_3 (145 mg, 1 mmol) in acetone/water (2:1, 30 mL) was stirred at room temperature for 4 h. Acetone was evaporated at reduced pressure, the residue was extracted with EtOAc (3 × 30 mL). The organic layer was washed with brine and dried ($MgSO_4$). The solvent was evaporated to give **5a** as oil; yield: 269 mg (95%); $[\alpha]_D^{20}$ −6.30° (*c* = 3.55, $CHCl_3$).

$C_{26}H_{30}O_5$	calc.	C 73.90	H 7.17
(422.6)	found	74.02	7.13

IR (film): *v* = 3070, 1530, 1490, 1120, 870 cm^{-1}.

^{13}C NMR ($CDCl_3$): δ = 32.3 (C-4), 36.3 (C-8), 38.9 (C-5), 40.9 (C-1), 44.1 (C-6), 62.0 (C-3), 62.4 (C-2), 70.5 and 70.7 (CH_2O), 73.4 (2 CH_2OBn), 77.2 and 77.6 (ketal ring), 120.1 (C-7), 127.5 and 127.6 (C_p), 127.5 and 127.6 (C_o), 128.3 (C_m), 137.9 and 138.0 (C_s).

(1*S*,2*S*,3*R*,5*R*)-2-[(1-Hydroxycyclohexyl)ethynyl]-3-hydroxybicyclo-[3.3.0]octane-7-one (8):

In a dried, Ar filled flask 2-(1-trimethylsilyloxycyclohexyl)-1-ethyne (244 mg, 1.25 mmol) was dissolved in THF (2.5 mL) distilled from $LiAlH_4$. The solution was cooled to −78 °C and BuLi (1.6 M, 1.28 mL) was added under Ar and the mixture was stirred for 10 min. Then $Et_2O \cdot BF_3$ (157 μL, 1.25 mmol) was added and the mixture was stirred for another 10 min. A solution of epoxide **5a** (350 mg, 0.83 mmol) in THF (3.5 mL) was added dropwise and the stirring was continued at −78 °C for 1 h. The reaction was quenched with aq 9% $NaHCO_3$ solution (10 mL) and allowed to warm up to r.t. EtOAc (15 mL) was added and the organic phase was separated. The water phase was extracted with EtOAc (3 × 30 mL) and the organic layers were washed with brine, dried ($MgSO_4$) and evaporated affording regioisomers **6a** and **7a**. The mixture of isomers was subjected to acidic deprotection without any purification. 0.3 N H_2SO_4 (3 mL) was added to a solution of the crude mixture of **6a**/**7a** (600 mg) in MeCN (20 mL) and stirred at 60 °C for 6 h. The mixture was neutralized with aq 9% $NaHCO_3$ solution and extracted with EtOAc (3 × 50 mL). The organic layers were washed with brine and dried ($MgSO_4$). The solvent was evaporated and the products were separated on a silica gel column using hexane/EtOAc (3:2 to 1:1) as eluent affording **8**; yield: 91 mg (42%); $[\alpha]_D^{20}$ +1.83 (c = 3.31, CH_2Cl_2)

$C_{16}H_{22}O_3$	calc.	C 73.24	H 8.47
(262.4)	found	73.31	8.42

IR (film): ν = 3550, 2980, 2190, 1760, 1460, 1065, 960 cm^{-1}.

^{13}C NMR ($CDCl_3$): δ = 23.6 (C-3,5 of cyclohexyl), 25.2 (C-4 of cyclohexyl) 35.4 (C-5), 40.1 (C-2,6 of cyclohexyl), 40.8 (C-4), 43.3 (C-8), 44.7 (C-2), 45.6 (C-8), 45.9 (C-1), 68.7 (C-1 of cyclohexyl), 78.7 (C-3), 84.6 and 86.4 (C≡C), 220.3 (C-7).

(3a*S*,4*S*,5*R*,6a*S*)-2(*E*)-(+)-5-{Octahydro-5-hydroxy-4-[(1-hydroxy-cyclohexyl)ethynyl]-2-(1*H*)-pentalenylidene}pentanoic Acid [(+)-1] [(8*S*,9*S*,11*R*,12*S*) (5*E*)-13,14-Didehydro-ω-hexanor(1-hydroxycyclo-hexyl)-9a-carbaprostacyclin (+)-1]:

Compound (+)-**1** was prepared from **8** (75 mg, 0.29 mmol) according to procedure described in Ref. 4. *E*- and *Z*-Isomers (ratio ~1:1) were separated on silica gel using hexane/EtOAc (1:1 to 1:2) as eluent; yield: 27 mg (28%); $[\alpha]_D^{20}$ +78 (c = 0.68, CH_2Cl_2).

$C_{21}H_{30}O_4$	calc.	C 72.79	H 8.74
(346.5)	found	72.89	8.61

IR (film): ν = 3360, 2240, 1700, 1060, 960 cm^{-1}.

^{13}C NMR ($CDCl_3$): δ = 23.5 (C-17, 19), 24.7 (C-3), 25.2 (C-18), 28.5 (C-4), 33.3 (C-2), 35.4 (C-7), 37.5 (C-9), 38.6 (C-9a), 40.1 (C-16, 20), 40.9 (C-10), 44.8 (C-12), 46.5 (C-8), 68.7 (C-15), 78.0 (C-11), 85.3 (C-13), 85.7 (C-14), 121.5 (C-5), 141.8 (C-6), 177.9 (C-1).

Compound (−)-**1** was synthesized from **4a** using the same sequence: (+)-**5a**: $[\alpha]_D^{20}$ +1.16 (c = 4.88, $CHCl_3$); (−)-**8**: $[\alpha]_D^{20}$ −1.90 (c = 2.78, CH_2Cl_2); (−)-**1**: $[\alpha]_D^{20}$ −80° (c = 0.48, CH_2Cl_2).

We thank Mrs. V. Maidla for the pharmacological studies.

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