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Stereospecific Synthesis of Intermediates for 11-Aza-11-deoxy and 11-Azaprostaglandin Analogues from L-Arabinose

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STEREOSPECIFIC SYNTHESIS OF INTERMEDIATES FOR 11–AZA–11–DEOXY AND 11–AZAPROSTAGLANDIN ANALOGUES FROM *L*–ARABINOSE

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Abstract: The syntheses of chiral synthons for 11–aza–11–deoxy and 11–azaprostanoids are described. The key intermediate in both routes was 5–*O*–benzoyl–3*C*–(carboxymethyl–2,3–γ–lactone)–3–deoxy–α–*L*–lyxo–furanose which is readily available from *L*–arabinose.

Prostaglandins have been targets of biological and chemical research for many years. Thousands of synthetic analogues have been prepared in the quest for efficient pharmaceutical agents which are more specific in their physiological applications.[1] This research has often resulted in the development of new synthetic methodology which could also be applied in other fields of synthetic organic chemistry.[2] Several stereoselective routes for the synthesis of heterocyclic prostanoids were developed in our laboratories[3-8] and we now report two new and efficient routes for the preparation of

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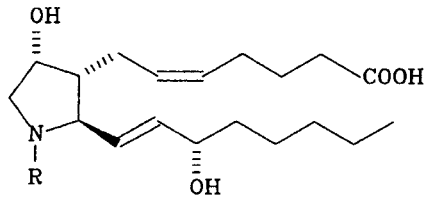
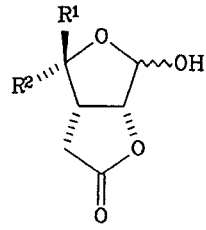
synthons for the synthesis of 11–aza–11–deoxy and 11–azaprostaglandin analogues, e.g. 1 and 2, respectively. Several syntheses of pyrrolidine analogues of prostaglandins have been reported, including several non–stereoselective and stereoselective routes.[9-18] Carbohydrates proved to be useful chiral templates in stereoselective routes[3-5,18-20] and were chosen for their array of functional groups and chiral centra which could be incorporated into the target molecules.



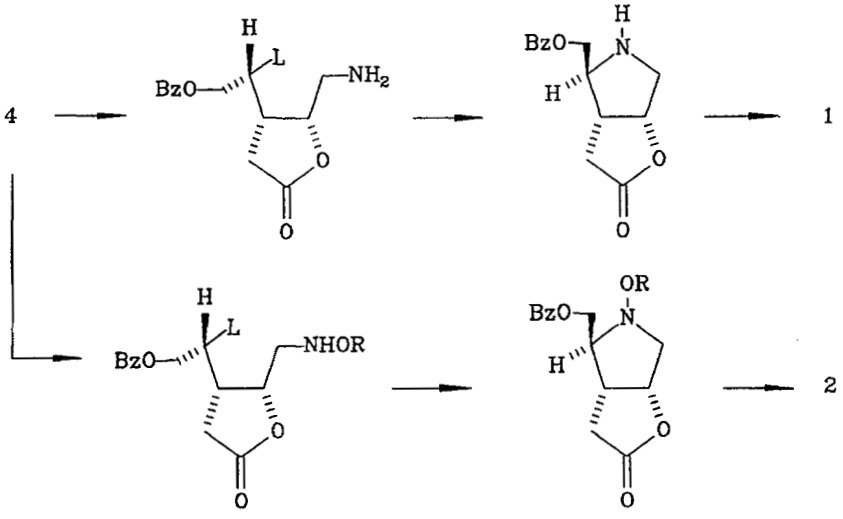
1 R = H

2 R = OH



	R^1	R^2
3		H
4	H	CH_2OBz

The bicyclic lactones (3) and (4) are versatile intermediates in the synthesis of oxaprostanoids[6] and thiaprostanoids.[7] Lactone (4), which is derived from from *L*–arabinose[21], was recognized as a suitable precursor for the preparation of 11–aza and 11–aza–11–deoxyprostaglandins. Introduction of an amine moiety at C–1, followed by S_N2 displacement of a leaving group at C–4, would result in the inversion of the C–4 absolute configuration to afford a product with the correct stereochemistry for further elaboration to an 11–aza–11–deoxyprostaglandin (Scheme 1). Using a hydroxylamine moiety instead of an amine at C–1 would result in the formation of an 11–azaprostanoid in which the C–11 carbon atom is isosterically replaced by



L = leaving group

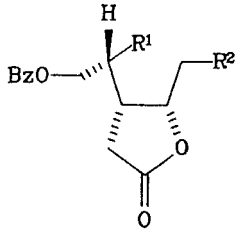
Scheme 1

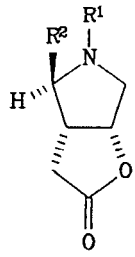
nitrogen (Scheme 1). Prostaglandin analogues in which the C–11 carbinol is replaced by a hydroxylamine group have not been reported in the literature before.

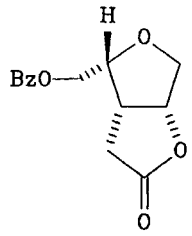
Synthesis of pyrrolidine (17), a chiron for 11–aza–11–deoxyprostaglandins.

The primary hydroxyl group of diol (5), which was prepared by sodium borohydride reduction[7] of 4, was selectively reacted with tosyl chloride in pyridine to afford the monotosylate (6). However, during work–up, the basic conditions of the reaction mixture resulted in the intramolecular substitution of the tosylate by the C–4 hydroxyl group to give quite a significant quantity of the deoxygenated compound (7). This undesired reaction could be suppressed by working up under acidic conditions at low temperature and the product (6) could be isolated in an 88% yield. The alcohol group of 6 was

subsequently reacted with 3,4–dihydro–2H–pyran under acid catalyzed conditions to afford a mixture of the *R* and *S* tetrahydropyranyl ethers (8). Introduction of the nitrogen atom at C–1 was effected by displacement of the tosylate with an azide group. It was found that the use of tetra–*n*–butyl ammonium azide[22] in dry 1,2–dimethoxyethane (DME) at 80° C resulted in excellent conversion to the C–1 azide (9) and afforded the product in a quantitative yield.







	R^1	R^2
5	OH	OH
6	OH	OTs
8	OTHP	OTs
9	OTHP	N_3
10	OH	N_3
11	OMs	N_3
12	OMs	NH_2

	R^1	R^2
13	H	CH_2OBz
14	CO^tBut	CH_2OBz
15	CO^tBut	CH_2OH
16	CO^tBut	CHO
17	CO^tBut	$CH\overset{t}{=}CHCOC_5H_{11}$

7

Acid catalyzed hydrolysis of the THP ethers (9) gave the alcohol (10) which was readily converted into the mesylate (11) in a high yield. Drastic conditions for the reduction of the azide group, such as lithium aluminium hydride, was incompatible with the two ester moieties in the molecule and therefore necessitated the use of a milder reducing agent. The azide (11) in MeOH/DME (30:10) was reduced under 20 psi hydrogen with Raney–Nickel as catalyst. Cyclization occurred immediately upon formation of the amine

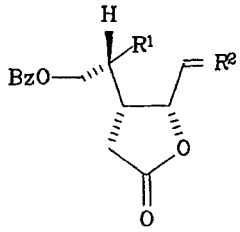
(12) and the resultant pyrrolidine (13) was directly treated with pivaloyl chloride to give the amide (14). This procedure allowed the conversion of 11 into 14 in a one–pot reaction in an overall yield of 69%. In the ^{1}H NMR spectrum of 14, H–2 appeared as an eight signal multiplet at δ 4.63 with $J_{2,3}$ = 3.2 Hz. A similar $J_{2,3}$ value of 2.9 Hz was observed for the sulfur analogue[21] of 14 which had the benzoyloxymethyl substituent in the β–position relative to the lactone ring. Given these data and the probability that the displacement reaction occurred *via* a S_N2 mechanism, it could be assumed that the C–2 substituent was in the β–position.

Sodium methoxide treatment of 14 resulted in saponification of the benzoate ester and the resultant primary alcohol (15) was oxidized using pyridinium chlorochromate and anhydrous molecular sieves[23] in CH_2Cl_2. It was important to terminate the reaction after 20 minutes to prevent decomposition of the aldehyde (16). Condensation of the crude aldehyde (16) with the anion of dimethyl 2–(oxoheptyl)phosphonate gave (2*S*,3*R*,4*R*)–*N*–pivaloyl–3–(carboxymethyl–3,4–γ–lactone)–4–hydroxy–2–[3–oxo–(*E*)–1–octenyl]pyrrolidine (17). This compound can easily be converted into 11–aza–11–deoxyprostaglandin analogues by a sequence of standard procedures.[6]

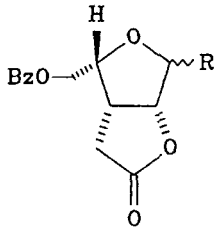
Synthesis of (2S,3R,4R)–N–benzyloxy–2–benzoyloxymethyl–3–(carboxymethyl–3,4–γ–lactone)–4–hydroxypyrrolidine (24) and (2S,3R,4R)–N–allyloxy–2–benzoyloxymethyl–3–(carboxymethyl–3,4–γ–lactone)–4–hydroxypyrrolidine (25) as chirons for 11–azaprostaglandins.

Condensation with an *O*–alkyl oxime ether was considered as a viable method of introducing a hydroxylamine moiety into the furanose (4). Oxime

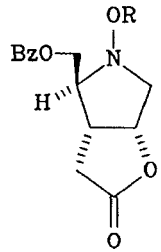
ethers of natural aldoses have been prepared before by the reaction of the aldoses with *O*–benzyl or *O*–methyl hydroxylamine hydrochloride.[24,25] These reactions were fast and gave the corresponding aldoxime ethers in good yields. It was therefore decided to prepare several *O*–alkyloxime derivatives of 4 containing different *O*–protecting groups for removal at a later stage in the synthesis.



	R^1	R^2
18	OH	=NOBn
20	OMs	=NOBn
21	OH	$=NOCH_2CH=CH_2$
22	OMs	$=NOCH_2CH=CH_2$
23	OMs	H,–NHOBn



	R
19	NHOBn



	R
24	Bn
25	$CH_2CH=CH_2$

Reaction of the hemi–acetal (4) with commercially available *O*–benzylhydroxylamine hydrochloride in pyridine, proceeded smoothly and two compounds were obtained upon chromatography of the crude product. NMR analysis showed that the major product was a mixture of the *syn*– and *anti*–isomers of the required acyclic oxime ether (18). The minor product was identified as the *N*–substituted tetrahydrofuran (19) which resulted from intramolecular condensation of the C–4 hydroxyl group with the sp^2–carbon of the oxime ether moiety. Subsequent experiments indicated that only the oxime ether (18) was formed in the reaction and that cyclization was catalyzed by the acidic silica gel during column chromatography.

Crystallization of (18) from diethyl ether also resulted in the undesired cyclization reaction. To circumvent this problem, the crude product was extracted from the reaction mixture with ethyl acetate, concentrated and added to a solution of 5 molar equivalents of mesyl chloride in pyridine. This procedure allowed isolation of the mesylate (20) in 87% yield from (4) without products arising from the competing cyclization reaction.

In a similar procedure, *O*–allylhydroxylamine hydrochloride reacted with 4 in pyridine and the resultant (21) was directly mesylated without isolation and purification to afford the acyclic oxime ether (22) in good overall yield.

Reduction of oxime double bonds can be accomplished in many ways. Attempted reduction of 20 to the *O*–benzylhydroxylamine (23) with sodium cyanoborohydride in acidic medium[26] resulted in the formation of a small quantity of a highly polar compound (TLC) which was eventually transformed into a less polar compound. The resultant product, albeit in low yield, was isolated and characterized as the pyrrolidine (24). Intramolecular cyclization took place directly after reduction of the double bond and thus afforded the required precursor (24) for 11–azaprostanoids. In view of the low yield of 10% of this reaction, a method developed by Fujita *et al.*[27] was used to reduce 20. This method involves the reaction of dimethylphenylsilane (DMPS) with oximes in trifluoroacetic acid (TFA) to give the corresponding hydroxylamines. The compounds (20 and 22) are stable under acidic conditions and this method proved to be excellent in the conversion of the oxime ethers into their corresponding pyrrolidines. For example, 20 was dissolved in TFA at room temperature and treated with three molar equivalents of DMPS for one hour resulting in complete

reduction of the oxime to the hydroxylamine (23). Stirring of the crude product (23) in ethyl acetate in the presence of silica gel, resulted in cyclization and the pyrrolidine (24) could be isolated in a yield of 72% from the oxime ether (20). Using the same procedure with the oxime ether (22), the corresponding pyrrolidine (25) was obtained in a good yield.

The *N*–alkoxypyrrolidines (24 and 25) are useful intermediates with the correct relative stereochemistry of all chiral centra for direct incorporation into the target molecule (2) in which the C–11 carbinol is isosterically replaced by a hydroxylamine group. The γ–lactone serves as connection point for the α–side chain whereas deprotection of the primary hydroxyl group, followed by oxidation and Wittig condensation, would furnish the aliphatic side chain. A variety of 11–azaprostaglandin analogues can be synthesized from these bicyclic pyrrolidines by incorporating different side chains in the molecules. Methods for the removal of the benzyl and allyl protecting groups are described in the literature.[28,29]

EXPERIMENTAL SECTION

Melting points were determined with a Kofler hot–stage apparatus and are uncorrected. Optical rotations were measured with a Jasco DIP–370 digital polarimeter and IR spectra were recorded on a Perkin Elmer 881 spectrophotometer. NMR spectra were recorded on Bruker WP 80, Bruker 500 and Varian VXR 200 instruments in the solvents stated using the $CHCl_3$ or TMS signals as references. A Finnigan–Matt 8200 mass spectrometer was

used for the recording of mass spectra. Thin layer chromatography was performed on pre–coated silica gel PF_{254} plates and column chromatography was done using Merck 60 – 230 mesh silica gel with eluents mixed on volume per volume basis. Solvents were distilled prior to use.

Synthesis of (2S,3R,4R)–N–pivaloyl–3–(carboxymethyl–3,4–γ–lactone)–4–hydroxy–2–[3–oxo–(E)–1–octenyl]pyrrolidine (17).

Preparation of 6 and 7 from 5.

The diol (5)[7] (1.315 g) in dry pyridine (7 ml) was stirred for 20 hours in the presence of tosyl chloride (3 equiv) and dimethylaminopyridine (DMAP) (1 equiv). After removal of the solvent *in vacuo* below 40^{o} C, the residue was dissolved in ethyl acetate, washed with cold 1N HCl, dried (Na_2SO_4) and evaporated. Crystallization from $CHCl_3$ afforded the monotosylate (6) in 88% yield. Mp. 138 – 141^{o} C; $[\alpha]_D^{18}$ –41^{o} (*c* 1.4, MeOH/DME 1:1), ν_{max} 3500 (OH), 1785 (lactone C=O), 1720 (ester C=O), 1370 and 1190 (sulfonate) cm^{-1}; δ (300 MHz, DMSO–d_6) 7.44 – 7.97 (9H, arom. H's), 4.79 (1H, *dt*, $J_{1a,2}$ = 2.7 and $J_{1b,2} = J_{2,3}$ = 8 Hz, H–2), 4.45 (1H, *dd*, $J_{1a,1b}$ = 11 and $J_{1a,2}$ = 2.7 Hz, H–1a), 4.35 (1H, *dd*, $J_{1a,1b}$ = 11 and $J_{1b,2}$ = 8 Hz, H–1b), 4.11 (1H, *dd*, $J_{4,5a}$ = 7.1 and $J_{5a,5b}$ = 11.3 Hz, H–5a), 4.09 (1H, *dd*, $J_{4,5b}$ = 4.8 and $J_{5a,5b}$ = 11.3 Hz, H–5b), 3.92 (1H, *ddd*, $J_{3,4}$ = 3, $J_{4,5a}$ = 7.1 and $J_{4,5b}$ = 4.8 Hz, H–4), 2.82 (1H, *dddd*, $J_{2,3}$ = 8 Hz, $J_{3,3'a}$ = 9.1, $J_{3,3'b}$ = 6.3 and $J_{3,4}$ = 3 Hz, H–3), 2.57 (1H, *dd*, $J_{3,3'a}$ = 9.1 and $J_{3'a,3'b}$ = 17.5 Hz, H–3'a), 2.54 (1H, *dd*, $J_{3,3'b}$ = 6.3 and $J_{3'a,3'b}$ = 17.5 Hz, H–3'b), 2.41 (1H, *d*, *J* = 4.7 Hz, OH) 2.37 (3H, *s*, CH_3); m/z 262 $[M - TsOH]^+$, 140 $[M - TsOH - BzOH]^+$.

The mother liquor was subjected to column chromatography (EtOAc:Hex; 3:2) to afford 7 (12%), mp. 83 – 85° C, $[\alpha]_D^{21}$ 3.3° (*c* 4.5, $CHCl_3$), δ (80 MHz, $CDCl_3$) 5.61 (1H, *dd*, $J_{1b,2}$ = 4 and $J_{2,3}$ = 7.1 Hz, H–2), 4.21 (1H, *d*, $J_{1a,1b}$ = 11.2 Hz, H–1a), 4.14 (1H, *q*, $J_{3,4} = J_{4,5a} = J_{4,5b}$ = 5.9 Hz, H–4), 3.72 (1H, *dd*, $J_{1a,1b}$ = 11.2 and $J_{1b,2}$ = 4 Hz, H–1b); m/e 262 $[M]^+$, 140 $[M - BzOH]^+$.

Conversion of 6 into the azido mesylate (11).

The alcohol (6) (15 g) in dry DME (60 ml) and dihydropyran (1.5 equiv) was stirred at 0° C in the presence of *p*–toluene sulfonic acid (0.05 equiv) for 2 hours. Neutralization with pyridine, evaporation and column chromatography (EtOAc:Hex; 2:3) gave 8 (95%) as an oil, $[\alpha]_D^{20}$ –8° (*c* 3, $CHCl_3$), δ 1.2 – 2.0 (6H, *m*, OTHP); m/z 434 $[M - DHP]^+$. A solution of 8 (9.438 g) and tetra–*n*–butylammonium azide (3 equiv) in dry DME (50 ml) was stirred at 80° C for 3 hours. Evaporation of the solvent and chromatography (EtOAc:Hex; 2:3) gave the azide (9) (100%), $[\alpha]_D^{20}$ –13° (*c* 1.3, $CHCl_3$), ν_{max} 2115 (N_3) cm^{-1}. The azide (9) (7 g) was stirred in 70% acetic acid (75 ml) at 40° C for 4 hours and the solvent was removed *in vacuo*. A solution of the residue in pyridine (50 ml) was treated with methanesulfonylchloride (3 equiv) and DMAP (1 equiv) for 80 hours at room temperature. After concentration, the crude product was washed with 1N HCl, water and saturated $NaHCO_3$ solution. Chromatography (EtOAc:Hex; 2:3) gave the mesylate (11) as an oil, $[\alpha]_D^{20}$ –27° (*c* 1.2, $CHCl_3$), ν_{max} 2120 (N_3), 1270 (sulfonate) cm^{-1}; δ (80 MHz, $CDCl_3$) 7.2 – 8.1 (5H, *m*, arom. H's), 5.26 (1H, *ddd*, $J_{3,4}$ = 6.3, $J_{4,5a}$ = 3.7 and $J_{4,5b}$ = 6.1 Hz, H–4), 4.70 (1H, *ddd*, $J_{1a,2}$ = 4.1, $J_{1b,2}$ = 5.2 and $J_{2,3}$ = 6 Hz, H–2), 4.59 (1H, *dd*, $J_{4,5a}$ = 3.7

and $J_{5a,5b}$ = 12.7 Hz, H–5a), 4.43 (1H, $J_{4,5b}$ = 6.1 and $J_{5a,5b}$ = 12.7 Hz, H–5b), 3.89 (1H, *dd*, $J_{1a,1b}$ = 13.7 and $J_{1a,2}$ = 4.1 Hz, H–1a), 3.80 (1H, *dd*, $J_{1a,1b}$ = 13.7 and $J_{1b,2}$ = 5.2 Hz, H–1b), 3.11 (1H, *dd*, $J_{3,3'a}$ = 7.4 and $J_{3'a,3'b}$ = 14.4 Hz, H–3'a), 3.08 (3H, *s*, OMs), 2.88 (1H, *ddt*, $J_{2,3}$ = 6, $J_{3,3'a}$ = $J_{3,3'b}$ = 7.4 and $J_{3,4}$ = 6.3 Hz, H–3), 2.74 (1H, *dd*, $J_{3'a,3'b}$ = 14.4 and $J_{3,3'b}$ = 7.4 Hz, H–3'b); m/z 205 $[M - BzO - CH_2{=}NH - N_2]^+$; calc. for $C_{15}H_{17}N_3O_7S$: 383.07881; found: 383.07876.

Hydrogenation of 11 and conversion to 14.

The azide (**11**) (3.525 g) in MeOH/DME (3:1) (40 ml) was reduced under 20 psi H_2 in the presence of Raney–Nickel (3.5 g). The reduction was complete after 3 hours and the suspension was filtered through celite. Evaporation of the solvent gave an oil which was directly treated with pivaloyl chloride (2 equiv) and DMAP (0.5 equiv) in pyridine–triethylamine (1:1) for 24 hours. After removal of the solvents, the crude product was purified by column chromatography (EtOAc:Hex; 1:1) to give (2*S*,3*R*,4*R*)–*N*–pivaloyl–2–benzoyloxymethyl–3–(carboxymethyl–3,4–γ–lactone)–4–hydroxypyrrolidine (**14**) in a yield of 71%. The product was crystallized from ether–hexane, mp. 128 – 130° C; $[\alpha]_D^{21}$ +77° (*c* 2.2, $CHCl_3$); ν_{max} 1780 (lactone), 1720 (ester C=O), 1630 (amide C=O) cm^{-1}; δ (500 MHz, $CDCl_3$) 7.4 – 8.0 (5H, *m*, arom. H's), 5.09 (1H, *dd*, $J_{3,4}$ = 6.6 and $J_{4,5a}$ = 4.3 Hz, H–4), 4.63 (1H, *ddd*, $J_{1'a,2}$ = 5.1, $J_{2,3}$ = 3.2 and $J_{1'b,2}$ = 4 Hz, H–2), 4.56 (1H, *dd*, $J_{1'a,1'b}$ = 11.3 and $J_{1'a,2}$ = 5.1 Hz, H–1'a), 4.51 (1H, *dd*, $J_{1'a,1'b}$ = 11.3 and $J_{1'b,2}$ = 4 Hz, H–1'b), 4.33 (1H, *d*, $J_{5a,5b}$ = 12.9 Hz, H–5a), 3.72 (1H, *dd*, $J_{4,5a}$ = 4.3 and $J_{5a,5b}$ = 12.9 Hz, H–5b), 3.05 (1H, *dddd*, $J_{1''a,3}$ = 9.7, $J_{1''b,3}$ = 2.8, $J_{2,3}$ = 3.2 and $J_{3,4}$ = 6.6 Hz, H–3), 2.89 (1H, *dd*, $J_{1''a,1''b}$ = 18.3 and $J_{1''a,3}$ = 9.7

Hz, H–1''a), 2.56 (1H, *dd*, $J_{1''a,1''b}$ = 18.3 and $J_{1''b,3}$ = 2.8 Hz, H–1''b), 1.23 (9H, *s*, $C(CH_3)_3$); m/z 260 $[M - (CH_3)_3CCO]^+$, 223 $[M - BzOH]^+$; calc. for $C_{19}H_{23}NO_5$: 345.15769; found: 345.15749.

(2S,3R,4R)–N–Pivaloyl–3–(carboxymethyl–3,4–γ–lactone)–4–hydroxy–2–[3–oxo–(E)–1–octenyl]pyrrolidine (17).

A solution of the benzoate (**14**) (260 mg) in methanol (2 ml) was treated with sodium methoxide (750 μl of a 10 mg/ml Na in MeOH) at room temperature for 3 hours. Neutralization with solid CO_2 followed by filtration and evaporation, gave an oil which was subjected to column chromatography (EtOAc:Hex; 1:1) to afford the alcohol (**15**) in 55% yield. $[\alpha]_D^{19}$ –47° (*c* 5.3, $CHCl_3$); ν_{max} 3400 (OH) cm^{-1}; δ (80 MHz, $CDCl_3$) 3.3 (1H, *m*, OH), m/z 223 $[M - H_2O]^+$. The alcohol (**15**) (40 mg) in CH_2Cl_2 (4 ml) was stirred in the presence of anhydrous 4Å molecular sieves (160 mg) and piridinium chlorochromate (4 equiv) for 20 minutes. The reaction mixture was diluted with EtOAc (20 ml) and filtered through a mixture of $CaSO_4$ and silica gel (1:10). The solvent was evaporated and the crude aldehyde (**16**) was used without purification in the subsequent condensation reaction. A suspension of dimethyl (2–oxoheptyl)phosphonate (37 mg, 2.5 equiv) and NaH (2.5 equiv) in dry DME (2 ml) was stirred for 30 minutes and the crude aldehyde (**16**) in DME (2 ml) was added to it. After 20 minutes, the reaction mixture was neutralized with acetic acid and the crude product was purified by column chromatography (EtOAc:Hex; 1:1). The product (**17**) (56%) had $[\alpha]_D^{21}$ –56° (*c* 0.3 $CHCl_3$), ν_{max} 1785 (lactone C=O), 1730 (enone C=O), 1630 (amide C=O) cm^{-1}; δ (80 MHz, $CDCl_3$) 6.64 (1H, *dd*, $J_{1',2'}$ = 15.8 and $J_{1',2}$ = 5.8 Hz, H–1'), 6.10 (1H, *dd*, $J_{1',2'}$ = 15.8 and $J_{2,2'}$ = 1.3 Hz, H–2'),

5.07 (1H, *dd*, $J_{3,4}$ = 5.4 and $J_{4,5b}$ = 4.3 Hz, H–4), 4.8 – 5.0 (1H, *m*, H–2), 4.40 (1H, *d*, $J_{5a,5b}$ = 13.1 Hz, H–5a), 3.16 (1H, *dd*, $J_{4,5b}$ = 4.3 and $J_{5a,5b}$ = 13.1 Hz, H–5b), 2.4 – 3.2 (5H, *m*, H–1''a, H–1''b, H–3, H–4'a and H–4'b), 1.28 (9H, *s*, $C(CH_3)_2$), 1.1 – 1.4 (6H, *m*, $(CH_2)_3$), 0.89 (3H, *t*, CH_3); m/z 335 $[M]^+$; calc. for $C_{19}H_{29}NO_4$: 335.20977; found: 335.20986.

Synthesis of (2S,3R,4R)–N–benzyloxy–2–benzoyloxymethyl–3–(carboxymethyl–3,4–γ–lactone)–4–hydroxypyrrolidine (24) and (2S,3R,4R)–N–allyloxy–2–benzoyloxymethyl–3–(carboxymethyl–3,4–γ–lactone)–4–hydroxypyrrolidine (25).

Conversion of 4 into 20 and 22.

O–Benzylhydroxylamine hydrochloride (631 mg, 1.1 equiv) was added to a solution of **4** (1 g) in dry pyridine. After stirring overnight, the solvent was removed *in vacuo* and the resultant residue dissolved in ethyl acetate. The solution was washed with water, dried (Na_2SO_4) and concentrated. Crystallization from EtOAc–Hex afforded the *syn*–isomer of **18**. Mp. 114 – 116° C; $[\alpha]_D^{21}$ +100° (*c* 1, $CHCl_3$); ν_{max} 1790 (lactone C=O), 1720 (ester C=O) cm^{-1}; δ (200 MHz, $CDCl_3$) 7.22 – 7.98 (10H, *m*, arom. H's), 6.79 (1H, *d*, $J_{1,2}$ = 4.3 Hz, H–1), 5.10 (1H, *m*, H–2), 5.06 (2H, *s*, OCH_2Ph), 4.79 (1H, *m*, H–4), 4.12 (2H, *m*, H–5a and H–5b), 2.90 (1H, *m*, H–3), 2.82 (1H, *s*, OH), 2.63 (2H, *m*, H–3'a and H–3'b); m/e 383 $[M]^+$. The alcohol (**18**) was dissolved in pyridine and treated with a solution of methanesulfonyl chloride (5 equiv) in pyridine for 18 hours. Extraction, evaporation and chromatography gave the mesylate (**20**) in 90% yield, $[\alpha]_D^{21}$ +24° (*c* 1.1, $CHCl_3$); δ (200 MHz, $CDCl_3$) 4.97 (1H, *m*, H–4), 3.14 (1H, *m*, H–3); m/z

461 $[M]^+$, 365 $[M - MsOH]^+$; calc. for $C_{22}H_{23}NO_8S$: 461.11449; found: 461.11454.

In a similar fashion the mesylate (23) of *O*–allyloxime ether (22) was prepared from 4. The mesylate (23) had $[\alpha]_D^{21}$ -3^o (*c* 1, $CHCl_3$); δ (200 MHz, $CDCl_3$) 7.40 – 8.03 (5H, *m*, arom. H's), 7.11 (1H, *d*, $J_{1,2}$ = 4.2 Hz, H–1), 5.93 (1H, *m*, $CH{=}CH_2$), 5.53 (1H, *dd*, $J_{1,2}$ = 4.2 and $J_{2,3}$ = 6.7 Hz, H–2), 5.23 (2H, *m*, $CH{=}CH_2$), 5.07 (1H, *dd*, $J_{3,4}$ = 2.3 and $J_{4,5}$ = 5.6 Hz, H–4), 4.60 (2H, *m*, $CH_2CH{=}CH_2$), 4.46 (2H, *m*, H–5a and H–5b), 3.16 (1H, *m*, H–3), 3.07 (3H, *s*, SO_2CH_3), 2.77 (2H, *m*, H–3'a and H–3'b); m/z 411 $[M]^+$; calc. for $C_{18}H_{21}NO_8S$; 411.09883; found: 411.09894.

Conversion of 20 and 23 into 24 and 25.

Dimethylphenylsilane (765 μl, 2.3 equiv) was added to a solution of 20 (1 g) in TFA (10 ml). After 1 hour the solvent was evaporated, the residue dissolved in ethyl acetate and silica gel was added. Stirring overnight resulted in the complete conversion of the starting material. The suspension was filtered and the filtrate was evaporated. Chromatography (EtOAc:Hex; 1:1) gave the crystalline pyrrolidine (24) (65%). Mp. 81 – 82.5° C; $[\alpha]_D^{21}$ -3^o (*c* 1, $CHCl_3$), ν_{max} 1779 (lactone C=O), 1722 (ester C=O) cm^{-1}; δ (200 MHz, $CDCl_3$) 8.00 – 7.24 (10H, *m*, arom. H's), 5.02 (1H, *m*, H–4), 4.68 (2H, *s*, CH_2Ph), 4,46 (1H, *dd*, $J_{1'a,1'b}$ = 11.5 and $J_{1'a,2}$ = 5.9 Hz, H–1'a), 4.35 (1H, *dd*, $J_{1,1'b}$ = 5.9 and $J_{1'a,1'b}$ = 11.5 Hz, H–1'b), 3.61 (1H, *dd*, $J_{4,5a}$ = 6.1 and $J_{5a,5b}$ = 13.4 Hz, H–5a), 3.36 (1H, *dd*, $J_{1'a,2}$ = 5.9 and $J_{1'b,2}$ 5.6 Hz, H–2), 3.23 (1H, *dd*, $J_{4,5b}$ = 3.4 and $J_{5a,5b}$ = 13.4 Hz, H–5b), 2.90 (2H, *m*, H–1''a and H–3), 2.57 (1H, *d*, $J_{1''a,1''b}$ = 15.8 Hz, H–1''b); m/z 367 $[M]^+$,

276 $[M - OBn]^+$, 245 $[M - BzOH]^+$; calc. for $C_{21}H_{21}NO_5$: 367.14203; found: 367.14218.

DMPS (5 μl, 2.3 equiv) was added to a solution of the oxime (**23**) (101 mg) in TFA (1.5 ml). Quantitative conversion occurred within one hour and the solvent was removed *in vacuo*. The residue was dissolved in EtOAc (10 ml), silica gel (250 mg) was added and the suspension was stirred overnight. Removal of the solvent and chromatography (EtOAc: Hex; 1:1) afforded **25** (55%) as a colourless oil, $[\alpha]_D^{21}$ -4^o (*c* 1, $CHCl_3$); ν_{max} 1724 (ester C=O), 1779 (lactone C=O) cm^{-1}; δ (200 MHz, $CDCl_3$) 8.05 –7.41 (5H, *m*, arom. H's), 5.90 (1H, *m*, $CH{=}CH_2$), 5.18 (2H, *m*, $CH{=}CH_2$), 5.06 (1H, *m*, H–4), 4.81 (2H, *m*, $CH_2CH{=}CH_2$), 4.51 (1H, *dd*, $J_{1'a,1'b}$ = 11.5 and $J_{1'a,2}$ = Hz, H–1'a), 4.39 (1H, *dd*, $J_{1'a,1'b}$ = 11.5 and $J_{1'b,2}$ = 5.8 Hz, H–1'b), 3.71 (1H, *dd*, $J_{4,5a}$ = 6.1 and $J_{5a,5b}$ = 13.4 Hz, H–5a), 3.40 (1H, *m*, H–2), 3.27 (1H, *dd*, $J_{4,5b}$ = 3.4 and $J_{5a,5b}$ = 13.4 Hz, H–5b), 2.75 (3H, *m*, $CH_2C{=}O$ and H–3); m/z 317 $[M]^+$, 276 [M – isoprene]$^+$, 260 [M – O–allyl]$^+$; calc. for $C_{17}H_{19}NO_5$: 317.12637; found: 317.12624.

REFERENCES

1. Bindra, J.S. and Bindra, R., *Prostaglandin Synthesis*, Academic Press, 1977; pp. 469 – 510.
2. Holzapfel, C.W., Koekemoer, J.M. and Verdoorn, G.H., *S. Afr. J. Chem.*, 1986, **39**, 151.
3. Coetzee, I., Holzapfel, C.W., Koekemoer, J.M. and von Platen, A.E., *S. Afr. J. Chem.*, 1984, **37**, 11.
4. Holzapfel, C.W., Jina, A.N., Koekemoer, J.M. and von Platen, A.E., *S. Afr. J. Chem.*, 1985, **38**, 65.
5. Holzapfel, C.W., Koekemoer, J.M. and Verdoorn, G.H., *S. Afr. J. Chem.*, 1987, **40**, 87.

6. Verdoorn, G.H. Holzapfel, C.W. and Koekemoer, J.M., *S. Afr. J. Chem.*, 1987, **40**, 134.
7. Verdoorn, G.H., Holzapfel, C.W. and Swanepoel, A.D., *Synth. Comm.*, 1989, **19**, 1771.
8. Basson, M.M., Holzapfel, C.W. and Verdoorn, G.H., *Heterocycles*, 1989, **29**, 2261.
9. Zoretic, P.A., Bhakta, C., Sinha, N.D. and Jardin, J., *J. Heterocyclic Chem.*, 1981, **17**, 1643.
10. Bruin, J.W., de Koning, H and Huisman, H.O., *Tetrahedron Lett.*, 1975, 4599.
11. Bollinger, G. and Muchowski, J.M., *Tetrahedron Lett.*, 1975, 2931.
12. Zoretic, P.A., Bhakta, C. and Jardin, J., *J. Heterocyclic Chem.*, 1983, **20**, 465.
13. Wang, C.J., *Tetrahedron Lett.*, 1982, 1067.
14. Scribner, R.M., *Tetrahedron Lett.*, 1976, 3853.
15. Deprés, J–P., Greene, A.E. and Crabbé, P., *Tetrahedron*, 1981, 621.
16. Barco, A., Benetti, S., Pollini, G.P., Baraldi, P.G., Guarneri, M., Gandolfi, C., Ceserani, R. and Longiave, D., *J. Med. Chem.*, 1981, **24**, 625.
17. King, R.W., *Tetrahedron Lett.*, 1981, 2837.
18. Morin, C., *Ph.D. Thesis*, Univ. Paris–Sud, 1980.
19. Blondet, D. and Morin, C., *Tetrahedron Lett.*, 1982, 3681.
20. Blondet, D. and Morin, C., *J. Chem. Soc. Perkin Trans. I*, 1984, 1085.
21. Lourens, G.J. and Boessenkool, I.K., *S. Afr. J. Chem.*, 1980, **33**, 112.
22. Brandström, A., Lamm, B., and Palmertz, I., *Acta Chem. Scand. B*, 1974, **28**, 699.
23. Hersovici, J., Egron, M–J. and Antonakis, K., *J. Chem. Soc. Perkin Trans. I*, 1982, 1967.
24. Plienkiewicz, J. and Szarek, W.A., *Synthesis*, 1974, 56.
25. Funke, W. and von Sontag, C., *Carb. Res.*, 1979, 247.
26. Borch, R.F., Bernstein, M.D. and Durst, H.D., *J. Am. Chem. Soc.*, 1971, **93**, 2897.
27. Fujita, M., Oisha, H. and Hiyama, T., *Chem. Lett.*, 1986, 837.
28. Greene, T.W. and Wuts, P.G.M., *Protective Groups in Organic Synthesis*, John Wilye & Sons, Inc., 1991, 44 – 53.

29. Shimizu, I., Oshima, M., Nagasawa, J., Tsuji, T. and Mandai, T., *J. Synth. Org. Chem., Jpn.*, 1991, **49**, 526.

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