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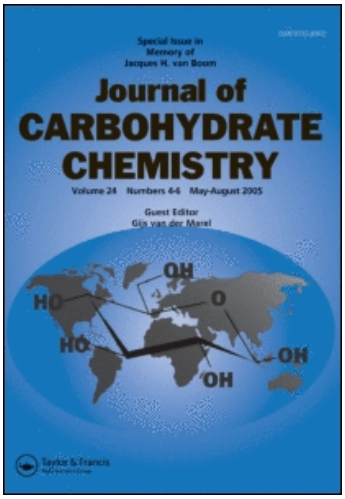


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# An Approach to A 1-Oxacephem Skeleton from D-Galactose

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# AN APPROACH TO A 1-OXACEPHEM SKELETON FROM D-GALACTOSE

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## ABSTRACT

2,4,6-Tri-*O*-benzyl-D-galactal (**1**) was transformed into a 1-oxacephem skeleton. The sequence of reaction involved: [2+2]cycloaddition, *N*-alkylation, glycolic cleavage of the *vic*-diol grouping, reduction of dialdehyde and cyclization to the title skeleton.

Recently we have reported that the [2+2]cycloaddition of isocyanates to glycals proceeds with high stereoselectivity to afford a 2-*C*:1-*N*-carbonyl-2-deoxy-glycopyranosylamine skeleton having a four - membered azetidinone ring located exclusively *anti* to the substituent at the C-3 carbon atom of a sugar ring.[1] Glycolic cleavage of the *vic*-diol group present in *N*-protected 2-*C*:1-*N*-carbonyl-2-deoxypento- and hexopyranosylamine leads to the formation of reactive dialdehydes which can be stabilized by reduction or oxidation of both aldehyde groups to a diol or dicarboxylic acid, respectively. The dialdehyde can also be epimerized at the C-3 azetidinone carbon atom to the respective *trans* dialdehyde and then stabilized in the same way as the *cis* isomer. Owing to the stereospecificity of cycloaddition this methodology opens fully stereocontrolled access to 1-oxa-bicyclic β-lactams having the desired configuration at the carbon atom bearing the nitrogen and oxygen atoms. Moreover, epimerization at the C-3 of the azetidinone ring at the dialdehyde stage offers stereocontrol also at that atom (Scheme 1).[2]



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The first exemplification of a synthetic project leading from glycals to 1-oxa-bicyclic β-lactams has been recently reported and involved the synthesis of a clavam skeleton from 3,4,6-tri-*O*-benzyl-D-galactal (**1**).[3] The present paper deals with the synthesis of a 1-oxacephem skeleton from the same sugar substrate **1**. We would like to demonstrate the usefulness of our approach to bicyclic β-lactams, rather than the synthesis of any particular antibiotic structure. Owing to the stereochemical consequences of [2+2]cycloaddition to the D-galactal, the configuration at the carbon atom bearing oxygen and nitrogen atoms is opposite to that found in active antibiotics. It is obvious, however, that the synthesis could be repeated from 2-*C*:1-*N*-carbonyl-β-D-*altro*-pyranosylamine easily available from D-allal,[4] and in this way it would complete the 1-oxacephem skeleton having the proper configuration at the bridge - head carbon atom, which is known to be decisive for the biological activity of β-lactam antibiotics (Scheme 1).

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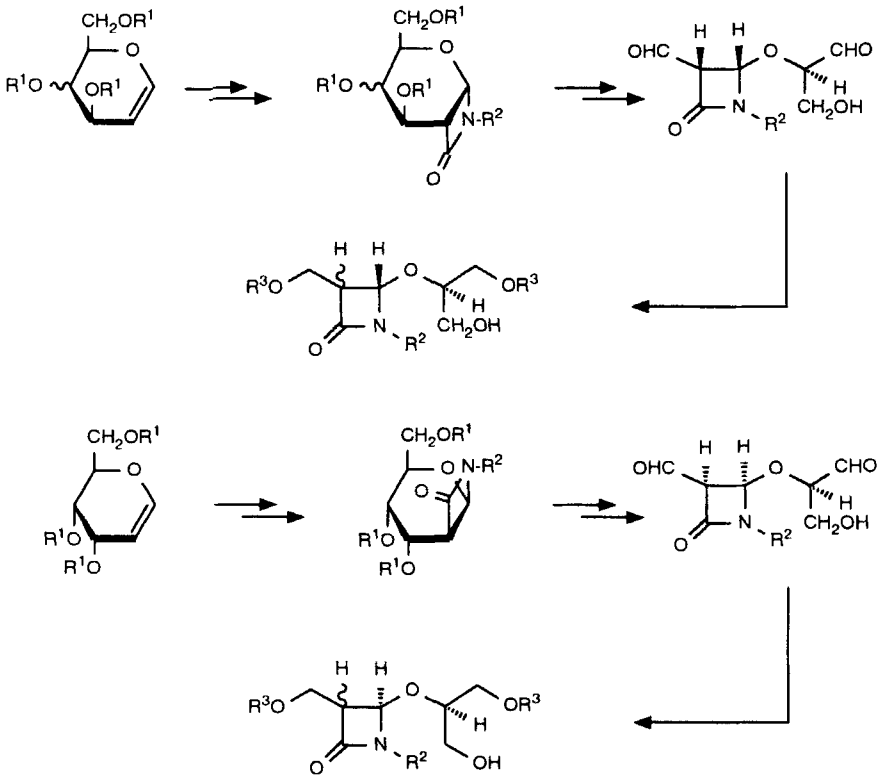
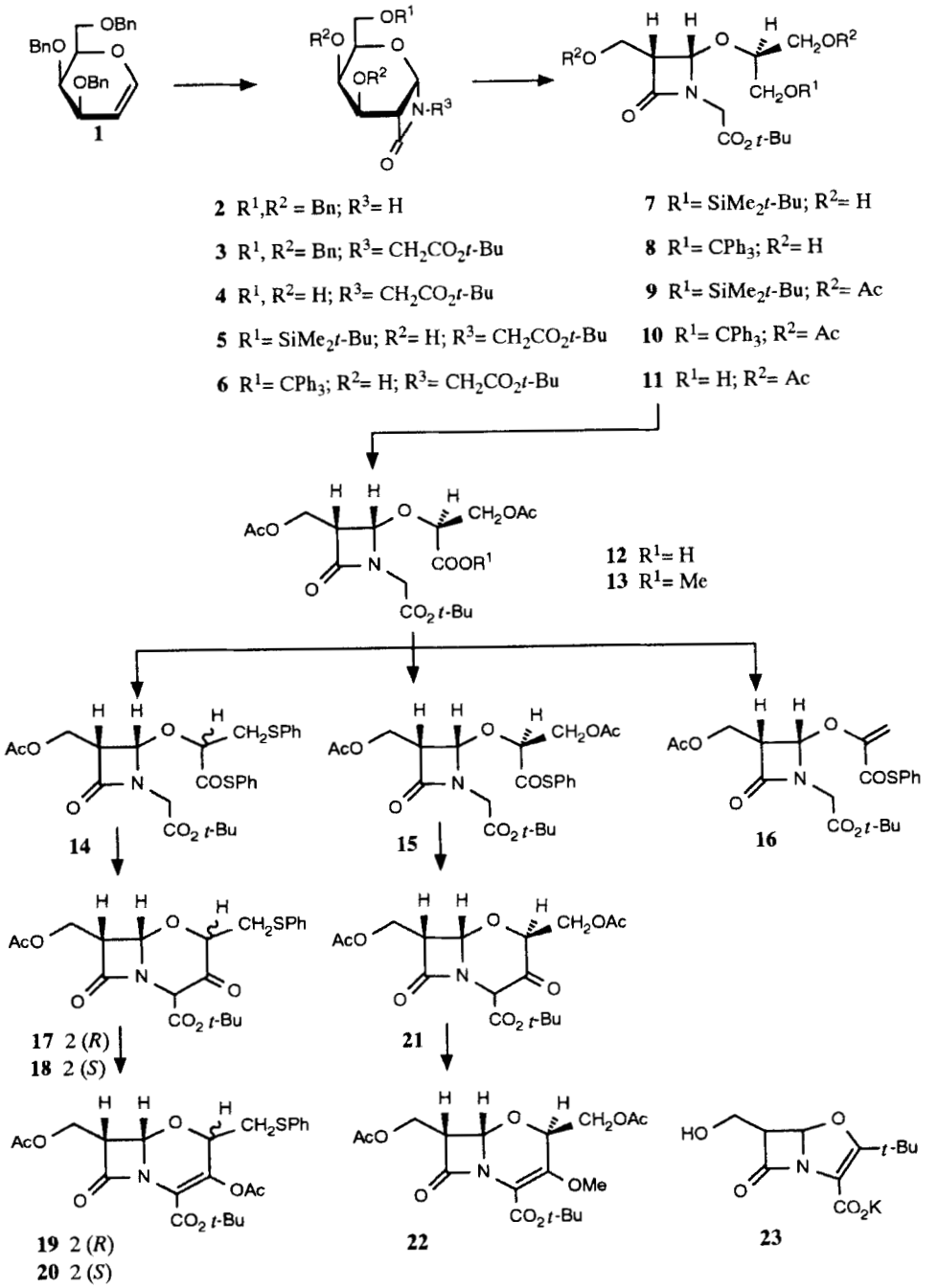
Scheme 1



$R^1$, $R^2$ = Silyl, Benzyl; $R^3$= H, Ac

Scheme 2

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Bicyclic β-lactam **2** obtained from **1** was alkylated with *t*-butyl bromoacetate under PTC conditions to afford **3** in 80% yield (Scheme 2). Subsequently the *O*-benzyl groups were removed by hydrogenolysis and compound **4** was protected at C-6 either with a *t*-butyldimethylsilyl or trityl group to give **5** and **6**, respectively. Compounds **5** and **6** were independently subjected to glycolic cleavage and the respective dialdehydes were immediately reduced with sodium borohydride in order to retain a *cis* substitution of the azetidinone ring, affording **7** and **8**, respectively. Hydroxyl groups in **7** and **8** were acetylated. Silyl protection in **7** was removed with hydrogen fluoride in a pyridine solution whereas the trityl substituent in **8** was removed by hydrogenolysis, giving in both cases the same product **11**. *t*-Butyldimethylsilyl protection was found to be more efficient, affording the final product in a better overall yield. The deprotected hydroxymethyl group was oxidized to the carboxyl function using ruthenium trichloride and sodium metaperiodate.[5] The acid **12** was treated with thiophenol in the presence of DCC and DMAP. In the presence of a trimolar excess of reagents the thiophenyl ester was produced and the acetoxy substituent was replaced by the second thiophenyl residue to yield **14** (Scheme 2). The addition - elimination mechanism of the acetoxyl displacement caused epimerization at the carbon atom next to the thiophenyl ester group. The expected thiophenyl ester **15** was found to be only a by-product. The ester **15** could be obtained when equimolar amounts of the acid **12**, thiophenol, and DCC were used, without DMAP catalysis. When a large excess of DCC was applied, the unsaturated ester **16** was produced. Thioesters **14** and **15** were subjected to cyclization using lithium bis-(trimethylsilyl)amide in THF at -78 °C.[6] From the ester **14**, a mixture of two diastereomers **17** and **18** in a 4:3 proportion was obtained. The unstable mixture of **17** and **18** was acetylated to give enol acetates **19** and **20**. Under the same conditions ester **15** afforded 1-oxacephem **21** which was methylated to give the more stable compound **22** as a single diastereomer. Unsaturated ester **16** subjected to cyclization failed to give the expected 1-oxacephem skeleton. The final products **21** and **22** possess two additional acetoxymethyl groups which do not represent any special synthetic target. The configuration of all stereogenic centers present in compound **22**, originating from galactal and being a consequence of the stereochemical course of [2+2]cycloaddition, was controlled during the performed reaction sequence.

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It should be noted that recently two enantiomeric potassium *trans*-2-*tert*-butyl-6-hydroxymethyloxapenem-3-carboxylates (**23**) have been obtained , and surprisingly, both forms have been found to display effective antibacterial and β-lactamase inhibitory activities.[7] Enantiomeric clavams **23** resemble compounds **19**, **20**, **22**, and clavams obtained previously.[3]

## EXPERIMENTAL

Melting points are uncorrected. Optical rotations were measured with a JASCO Dip-360 digital polarimeter. IR spectra were taken with a Perkin - Elmer spectrophotometer. $^1$H NMR spectra were recorded with Varian Gemini 200 and Bruker AM 500 spectrometers. Column chromathography was performed on Merck Kieselgel 60 (230-400 mesh).

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β-Lactam **2** was obtained according to the known procedure.[2,8]

**3,4,6-Tri-*O*-benzyl-*N*-*tert*-butoxycarbonylmethyl-2-*C*:1-*N*-carbonyl-2-deoxy-α-D-galactopyranosylamine (3).** To a stirred suspension of finely pulverized KOH (1.14 g, 20 mmol) and tetrabutylammonium bromide (0.032 g, 0.1 mmol) in anhyd benzene (30 mL) a solution of *t*-butyl bromoacetate (1.95 g, 10 mmol) and β-lactam **2** (4.59, 10 mmol) in anhyd benzene (10 mL) were added in portions during 1 h. Stirring was continued for 1 h and then the mixture was filtered through Celite, washed with water, dried, and concentrated. The product was crystallized from hexane. The residue was purified by chromatography using AcOEt-Hexane 1:6 $^{v}/_{v}$ as an eluent to give additional amount of product. Total yield 4.58 g (80%), mp 78-79 °C; $[\alpha]_D$ +5.1° (*c* 1, $CHCl_3$) IR ($CHCl_3$) 1770 and 1740 cm$^{-1}$; $^1$H NMR ($CDCl_3$) 1.44 (s, 9H, *t*-Bu), 3.44 (m, 1H, H-2), 3.50 (m, 2H, H-6,6'), 3.74 and 3.92 (2d, 2H, *J* 17.9 Hz, $CH_2CO_2t$-Bu), 3.87 (m, 3H, H-3,4,5), 4.3-4.6 (6d, 6H, Benzyl), 5.53 (d, 1H, *J* 4.6 Hz, H-1).

Anal. Calcd for $C_{34}H_{39}NO_7$: C, 71.18; H, 6.85; N, 2.44. Found C, 71.20; H, 6.85; N, 2.57.

***N*-*tert*-Butoxycarbonylmethyl-2-*C*:1-*N*-carbonyl-2-deoxy-α-D-galacto-pyranosylamine (4).** Compound **3** (5.79 g, 10 mmol) was hydrogenated in ethanol (200 mL) over 10% Pd/C palladium Degussa type (0.5 g) 5 h. The catalyst was filtered off and

the solvent was evaporated. The residue was crystallized from AcOEt to give **4** (3.0 g, 97%); mp 62-63 °C; $[\alpha]_D$ +58.1° (*c* 1, $CHCl_3$); IR ($CHCl_3$) 3400, 1740, 1670 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.48 (s, 9H, *t*-Bu), 3.26 (t, 1H, *J* 4.9 and 4.5 Hz, H-2), 3.7-4.0 (m, 4H, H-4, 5,6,6'), 4.01 (m, 2H, $CH_2CO_2t$-Bu), 4.13 (dd, 1H, *J* 4.9 and 4.1 Hz, H-3), 5.53 (d, 1H, *J* 4.5 Hz, H-1).

Anal. Calcd for $C_{13}H_{21}NO_7$: C, 51.49; H, 6.98; N, 4.62. Found: C, 51.76; H, 6.76; N, 4.52.

***N-tert*-Butoxycarbonylmethyl-6-*O*-*tert*-butyldimethylsilyl-2-*C*:1-*N*-carbonyl-2-deoxy-α-D-galactopyranosylamine** (**5**). Compound **4** (0.60 g, 2 mmol) in anhyd $CH_2Cl_2$ (20 mL) was treated with imidazole (0.075 g, 2.4 mmol) and *tert*-butyldimethylsilyl chloride (0.33 g, 2.2 mmol) and the mixture was left overnight. Subsequently methanol (0.2 mL) was added and after 1 h the solution was diluted with $CH_2Cl_2$ (20 mL), washed with water, dried and concentrated. The crude product was purified on silica gel using AcOEt : Hexane 2:3 $^v/_v$ as an eluent to give **5** (0.71 g, 85%); mp 129-130 °C, $[\alpha]_D$ +48.7° (*c* 1, $CHCl_3$); IR ($CHCl_3$) 3450, 1760, 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 0.10, 0.91 (2s, 15H, *t*-Bu$Me_2$Si), 1.46 (s, 9H, *t*-Bu), 3.27 (t, 1H, *J* 4.5 and 3.8 Hz, H-2), 3.78, 3.89 (2d, 2H, *J* 17.9 Hz, $CH_2CO_2t$-Bu), 3.87 (m, 3H, H-5,6,6'), 4.04 (dd, 1H, H-4), 4.08 (t, 1H, *J* 3.9 and 3.8 Hz, H-3), 5.51 (d, 1H, *J* 4.5 Hz, H-1).

Anal. Calcd for $C_{19}H_{35}NO_7Si$: C, 54.65; H, 8.45; N, 3.35. Found: C, 54.53; H, 8.78; N, 3.29.

***N-tert*-Butoxycarbonylmethyl-6-*O*-triphenylmethyl-2-*C*:1-*N*-carbonyl-2-deoxy-α-D-galactopyranosylamine** (**6**). Compound **4** (0.61 g, 2 mmol) in anhyd pyridine (20 mL) was treated with triphenylmethyl chloride (0.65 g, 2.4 mmol) and DMAP (0.01 g), and was left for 2 days. Subsequently the mixture was poured into water and extracted with toluene. The extract was washed, dried, and concentrated. The crude product was purified by chromatography using AcOEt : Hexane 1:2 $^v/_v$ as an eluent to afford **6** (0.77 g, 71%), syrup; $[\alpha]_D$ +36.2° (*c* 1, $CHCl_3$); IR ($CHCl_3$) 3400, 1760, 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.42 (s, 9H, *t*-Bu), 3.23 (t, 1H, *J* 4.5 and 4.1 Hz, H-2), 3.33 (dd, 1H, *J* 9.6 and 5.7 Hz, H-6'), 3.73, 3.87 (2d, 2H, *J* 17.9 Hz, $CH_2CO_2t$-Bu), 3.83 (m, 1H, H-5, 3.98 (bd, 1H, H-4), 4.07 (t, 1H, *J* 4.1 Hz, H-3), 5.51 (d, 1H, *J* 4.5 Hz, H-1).

Anal. Calcd for $C_{32}H_{35}NO_7$: C, 70.44; H, 6.47; N, 2.57. Found: C, 69.42; H, 6.42;

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N, 2.48.

**(3*R*, 4*S*, 1'*S*)-1-*tert*-Butoxycarbonylmethyl-3-hydroxymethyl-4-(1'-hydroxymethyl-2'-*tert*-butyldimethylsilyloxy)ethoxy-azetidinone-2 (7)**. Compound **5** (0.42 g, 1 mmol) dissolved in *tert*-butyl alcohol (20 mL) and 4% aqueous solution of ammonium sulfate (20 mL) was cooled to 0 °C and, with stirring, treated with sodium metaperiodate (0.24 g, 1.1 mmol). Stirring and cooling were continued for 30 min and then sodium borohydride (0.1 g, 2.5 mmol) was added. The temperature was allowed to rise to room temperature. The mixture was saturated with ammonium sulfate and extracted with chloroform. The extract was dried, concentrated and purified by chromatography using AcOEt : Hexane 1:2 $^{v}/_{v}$ as an eluent to give **7** (0.3 g, 71%), syrup; $[\alpha]_D$ +10.6 (*c* 1, $CHCl_3$); IR (film) 3400, 1760, 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 0.09, 0.91 (2s, 15H, *t*-Bu$Me_2$Si), 1.49 (s, 9H, *t*-Bu), 3.5-4.1 (m, 8H, H-3, 3x$CH_2$-, OCH=), 3.87, 4.07 (2d, 2H, *J* 17.7 Hz, $CH_2CO_2$*t*-Bu), 5.47 (d, 1H, *J* 3.9 Hz, H-4).

Anal. Calcd for $C_{19}H_{37}NO_7Si$:C, 54.40; H, 8.88; N, 3.34. Found: C, 54.22; H, 8.87; N, 3.34.

**Di-acetate 9**: mp 55-56 °C; $[\alpha]_D$ +7.8° +7.8 (*c* 1, $CHCl_3$); IR ($CHCl_3$) 1780, 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 0.07, 0.89 (2s, 15H, *t*-Bu$Me_2$Si), 1.47 (s, 9H, *t*-Bu), 2.06, 2.09 (2s, 6H, 2Ac), 3.65-3.84 (m, 4H, H-3, $CH_2$OSi, OCH=), 3.66, 4.18 (2d, 2H, *J* 17.9 Hz, $CH_2CO_2$*t*-Bu), 3.98-4.50 (m, 4H, 2$CH_2$OAc), 5.50 (d, 1H, *J* 4.0 Hz, H-4).

Anal. Calcd for $C_{23}H_{41}NO_9Si$: C, 54.85; H, 8.21; N, 2.78. Found: C, 54.92; H, 8.09; N, 2.82.

**(3*R*, 4*S*, 1'*S*)-1-*tert*-Butoxycarbonylmethyl-3-hydroxymethyl-4-(1'-hydroxymethyl-2'-triphenylmethoxy)ethoxy-azetidinone-2 (8)**. Glycolic cleavage of compound **6** was performed according to the procedure described for **5** to afford **7**. Crude compound was purified by chromatography using AcOEt : Hexane 1:2 $^{v}/_{v}$ as an eluent (73%); syrup; $[\alpha]_D$ +6.5° (*c* 1, $CHCl_3$); IR (film) 3500, 1765, 1730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.46 (s, 9H, *t*-Bu), 3.17 (dd, 1H, *J* 10.4 Hz, $CH_AH_BOTr$), 3.28 (dd, 1H, *J* 10.4 and 3.8 Hz, $CH_AH_BOTr$), 3.4-3.7 (m, 3H, H-3, $CH_2OH$), 3.7-4.2 (m, 3H, OCH=, $CH_2OH$), 3.88, 4.06 (2d, 2H, *J* 17.9 Hz, $CH_2CO_2$*t*-Bu), 5.52 (d, 1H, *J* 4.2 Hz, H-4).

Anal. Calcd for $C_{32}H_{37}NO_7$: C, 70.20; H, 6.81; N, 2.56. Found: C, 70.74; H, 6.84; N, 2.48.

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**Acetate 10**: syrup; $[\alpha]_D$ +6.9° (*c* 1, $CHCl_3$); IR (film) 1760, 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.47 (s, 9H, *t*-Bu), 1.86, 2.03 (2s, 6H, 2Ac), 3.19 (dd, 1H, *J* 10.1 and 5.9 Hz, $CH_AH_BOTr$), 3.26 (dd, 1H, *J* 10.1 and 5.4 Hz, $CH_AH_BOTr$), 3.58 (m, 1H, H-3), 3.64, 4.18 (2d, 2H, *J* 17.9 Hz, $CH_2CO_2t$-Bu), 3.74 (m, 1H, OCH=), 4.00-4.42 (m, 4H, 2 $CH_2OAc$), 5.44 (d, 1H, *J* 4.1 Hz, H-4).

Anal. Calcd for $C_{36}H_{41}NO_9$: C, 68.46; H, 6.54; N, 2.22. Found: C, 68.22; H, 6.59; N, 2.10.

**(3*R*, 4*S*, 1'*R*)-1-*tert*-Butoxycarbonylmethyl-3-hydroxymethyl-4-(1'-acetoxymethyl-2'-hydroxy)ethoxy-azetidinone-2 (11)** from **9**. Compound **9** (0.50 g, 1.0 mmol) in anhyd pyridine (1 mL) was cooled to 5-10 °C and treated with a 70% solution of hydrogen fluoride in pyridine (2 mL), whereupon the mixture was left overnight. Subsequently it was poured into an aqueous solution of sodium bicarbonate, extracted with toluene, dried, and concentrated. The crude product was purified by chromathography using AcOEt : Hexane 1:4 $^v/_v$ and 1:1 $^v/_v$ as an eluent to give **11** (0.36 g, 93%); syrup; $[\alpha]_D$ -8.2° (*c* 1, $CHCl_3$) IR (film): 3500, 1770, 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.47 (s, 9H, *t*-Bu), 2.08, 2.09 (2s, 6H, 2Ac), 3.68-3.75 (m, 3H, H-3, $CH_2OH$), 3.83 (m, 1H, OCH=), 3.67-4.18 (2d, 2H, *J* 17.9 Hz, $CH_2CO_2t$-Bu), 4.10 (dd, 1H, *J* 12.0 and 6.0 Hz, $CH_AH_BOAc$), 4.19 (dd, 2H, *J* 12.0 and 4.5 Hz, $CH_AH_BOAc$), 4.34, 4.64 (2dd, 2H, *J* 11.9, 8.7, and 3.9 Hz, $CH_2OAc$), 5.60 (d, 1H, *J* 4.0 Hz, H-4).

Anal. Calcd for $C_{17}H_{27}NO_9$: C, 52.44; H, 6.99; N, 3.60. Found: C, 52.44; H, 7.01; N, 3.68.

From **10**. Compound **10** (0.63 g, 1.0 mmol) dissolved in ethanol (30 mL) was hydrogenated over 10% Pd/C Degussa type for 7 h. Subsequently the mixture was filtered and concentrated to give **11** (0.24 g, 62%) identical with that obtained from **9**.

**(3*R*, 4*S*, 1'*S*)-1-*tert*-Butoxycarbonylmethyl-3-acetoxymethyl-4-(1'-carboxy-2'-acetoxy)ethoxy-azetidinone-2 (12)**. Compound **11** (0.78 g, 2 mmol) in a 70% aqueous solution of acetone (15 mL) was treated with sodium metaperiodate (1.73 g, 8 mmol) and a catalytic amount of ruthenium trichloride. The mixture was stirred at room temperature for 4 h. Subsequently it was diluted with acetone, filtered through Celite and concentrated *in vacuo*. The crude product was purified by chromatography using AcOEt : Hexane 1:2 $^v/_v$ and 1:1 $^v/_v$ as eluent to afford **12** (0.5 g, 67%), syrup; $[\alpha]_D$ +11.3° (*c* 1, $CHCl_3$); IR

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($CHCl_3$) 3450, 1770, 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.48 (s, 9H, *t*-Bu), 2.06, 2.10 (2s, 6H, 2Ac), 3.68, 4.21 (2s, 2H, *J* 18.0 Hz, $CH_2CO_2$*t*-Bu), 3.71 (m, 1H, H-3), 4.26-4.63 (m, 5H, OCH=, $2CH_2OAc$), 5.52 (d, 1H, *J* 4.0 Hz, H-4).

Anal. Calcd for $C_{17}H_{25}NO_{10}$: C, 50.62; H, 6.25; N, 3.47. Found: C, 50.91; H, 6.31, N, 3.55.

Methyl ester **13**: syrup; $[\alpha]_D$ +22.5° (*c* 1, $CHCl_3$); IR (film) 1778, 1740 $cm^{-1}$, $^1H$ NMR ($CDCl_3$) 1.47 (s, 9H, *t*-Bu), 2.05, 2.09 (2s, 6H, 2Ac), 3.65, 4.20 (2d, 2H, *J* 17.8 Hz, $CH_2CO_2$*t*-Bu), 3.67 (dt, 1H, H-3), 3.78 (s, 3H, $OCH_3$), 4.21-4.57 (m, 5H, OCH=, $2CH_2OAc$), 5.50 (d, 1H, *J* 3.9 Hz, H-4).

Anal. Calcd for $C_{18}H_{27}NO_{10}$: C, 51.79; H, 6.52; N, 3.35. Found: C, 51.92; H, 6.51; N, 3.23.

**(3*R*, 4*S*)-1-*tert*-Butoxycarbonylmethyl-3-acetoxymethyl-4-(1'-thiophenoxycarbonyl-2'-thiophenoxy)ethoxy-azetidinone-2 (14)**. To a solution of acid **12** (0.80 g, 2 mmol) in anhyd $CH_2Cl_2$ (10 mL) DMAP (0.024 g, 0.2 mmol) and thiophenol (0.66 g, 6.0 mmol) were added and the mixture was stirred at room temperature for 3 h. Subsequently the precipitate was filtered off and the solution was washed with an aqueous solution of sodium bicarbonate, dried and concentrated. The crude product was purified by chromatography using AcOEt : Hexane 1:8 $^v/_v$ as an eluent to give **14** (0.70 g, 65%) as a mixture of two diastereomers in a 5.5:4.5 proportion; syrup; IR (film) 1777, 1738, 1698 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) signals of both isomer: 1.38, 1.43 (2s, 9H, *t*-Bu), 2.01-2.03 (2s, 3H, Ac), 3.21, 3.23 (2dd, 1H, H-2'a), 3.44 (2m, 1H, H-2'b), 3.66 (m, 1H, H-3), 4.20-4.60 (m, 5H, OCH=, $2xCH_2OAc$), 5.51 (d, 0.55H, *J* 4.1 Hz, H-4 major), 5.64 (d, 0.44H, *J* 3.9 Hz, H-4 minor).

Anal. Calcd for $C_{27}H_{31}NO_7S_2$: C, 59.43; H, 5.72; N, 2.56; S, 11.75. Found: C, 59.97; H, 5.93; N, 2.72; S, 10.88.

**(3*R*, 4*S*, 1'*S*)-1-*tert*-Butoxycarbonylmethyl-3-acetoxymethyl-4-(1'-thiophenoxycarbonyl-2'-acetoxy)ethoxy-azetidinone-2 (15)** and **(3*R*, 4*S*)-1-*tert*-Butoxycarbonylmethyl-3-acetoxymethyl-4-(1'-thiophenoxycarbonyl)vinyloxy-azetidinone-2 (16)**. Dicyclohexylcarbodiimide (0.25 g, 1.2 mmol) in anhyd $CH_2Cl_2$ (2 mL) was treated with a solution of thiophenol (0.11 g, 1.0 mmol) and acid **12** (0.40 g, 1.0 mmol) in anhyd $CH_2Cl_2$ (3 mL). The mixture was left at room temperature for

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16 h. Subsequently the precipitate was filtered off and the solution was washed with water, dried, concentrated, and separated on a silica gel column using AcOEt : Hexane 1:8 $^{v}/_{v}$ as an eluent to give **15** (0.39 g, 80%) and **16** (0.04 g, 10%) **15**; syrup; $[\alpha]_D$ -11.7° (*c* 1, $CHCl_3$); IR (film) 1779, 1742, 1700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.48 (s, 9H, *t*-Bu), 2.02, 2.13 (2s, 6H, 2Ac), 3.71, 4.26 (2d, 2H, *J* 17.9 Hz, $CH_2CO_2t$-Bu), 3.78 (m, 1H, H-3), 4.27-4.61 (m, 5H, OCH=, $2CH_2OAc$), 5.64 (d, 1H, *J* 3.9 Hz, H-4).

Anal. Calcd for $C_{23}H_{29}NO_9S$: C, 55.76; H, 5.90; N, 2.83. Found: C, 55.69; H, 5.76; N, 3.00.

**16**: Using two equivalents of DCC under the same reaction conditions as for **15**, the yield of **16** was 66% and for **15**, 24%. Rf (AcOEt : Hexane 1:1) for **15** and **16** are 0.41 and 0.50; syrup; $[\alpha]_D$ +24.4° (*c* 1, $CHCl_3$); IR (film) 1785, 1741, 1697, 1654, 1618 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.49 (s, 9H, *t*-Bu), 2.07 (s, 3H, Ac), 3.74, 4.32 (2d, 2H, *J* 18.2 Hz, $CH_2CO_2t$-Bu), 3.88 (dt, 1H, H-3), 4.51 (d, 2H, $CH_2OAc$), 4.69, 5.47 (2d, 2H, *J* 3.3 Hz, $=CH_2$), 5.58 (d, 1H, *J* 3.8 Hz, H-4).

Anal. Calcd for $C_{21}H_{25}NO_7S$: C, 57.93; H, 5.79; N, 3.22. Found: C, 57.86; H, 6.02; N, 3.12.

**(6*S*, 7*R*, 2*R*) and (6*S*, 7*R*, 2*S*) 7-Acetoxymethyl-4-*tert*-butoxycarbonyl-1-oxa-3-hydroxy-2-thiophenoxymethyl-cephem-3 (17** and **18)**. To a solution of **14** (0.14 g, 0.26 mmol) in anhyd THF (3 mL), at -78 °C LiN $(TMS)_2$, a (1.0 M solution in hexane; 1.16 mL, 1.16 mmol) was added. After 8 min acetic acid (0.072 g, 1.2 mmol) was added, and reaction temperature was allowed to rise to room temperature. Subsequently $CH_2Cl_2$ (20 mL) was added and the solution was washed with water, dried and concentrated to give a mixture of two unstable diastereomers **17** and **18** in a 6:4 ratio, respectively (0.063 g, 56%). The major, less polar diastereomer **17** can be separated by chromatography. Column chromatography (AcOEt : Hexane 1:8 $^{v}/_{v}$) yields pure less polar product **17** and a mixture of diastereomers **17** and **18**. A sample of this mixture was separated by prep. TLC using AcOEt : Hexane 1:1 $^{v}/_{v}$ as an eluent; Rf for **17** and **18** are 0.32 and 0.23 respectively.

**17**: syrup; $[\alpha]_D$ -39.1° (*c* 1, $CHCl_3$); IR (film) 3435, 1783, 1732, 1661, 1630 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.55 (s, 9H, *t*-Bu), 2.08 (s, 3H, Ac), 3.35 (dd, 1H, *J* 14.4 and 8.8 Hz, $CH_AH_BSPh$), 3.44 (dd, 1H, *J* 14.4 and 3.5 Hz, $CH_AH_BSPh$), 3.68 (ddd, 1H, H-7), 4.33

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(dd, 1H, *J* 11.7 and 6.0 Hz, C**H**$_A$H$_B$OAc), 4.39 (dd, 1H, *J* 11.7 and 8.4 Hz, CH$_A$**H**$_B$OAc), 4.59 (dd, 1 H, *J* 8.8 and 3.5 Hz, H-2), 5.22 (d, 1H, *J* 3.8 Hz, H-6). MS *m/z* : $M^{+\cdot}$ 385.

Anal. Calcd for $C_{21}H_{25}NO_7S$: C, 57.93; H, 5.79; N, 3.22. Found: C, 57.86; H, 6.21; N, 3.09.

More polar isomer **18**: syrup; $[\alpha]_D$ -19.0° (*c* 1, $CHCl_3$); IR (film) 3432, 1787, 1728, 1661 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.57 (s, 9H, *t*-Bu), 2.05 (s, 3H, Ac), 3.28 (dd, 1H, *J* 14.3 and 6.2 Hz, C**H**$_A$H$_B$SPh), 3.35 (dd, 1H, *J* 14.3 and 3.2 Hz, CH$_A$**H**$_B$SPh), 3.70 (m, 1H, H-7), 4.21 (dd, 1H, *J* 11.8 and 8.5 Hz, C**H**$_A$H$_B$OAc), 4.27 (dd, 1H, *J* 11.8 and 8.5 Hz, CH$_A$**H**$_B$OAc), 4.73 (dd, 1H, *J* 6.2 and 3.2 Hz, H-2), 5.09 (d, 1H, *J* 3.8 Hz, H-6).

Anal. Calcd for $C_{21}H_{25}NO_7S$: C, 57.93; H, 5.79; N, 3.22. Found: C, 57.75; H, 6.18; N, 3.43.

**(2*R*, 6*S*, 7*R*) and (2*S*, 6*S*, 7*R*) 3-Acetoxy-7-acetoxymethyl-4-*tert*-butoxycarbonyl-1-oxa-2-thiophenoxymethyl-cephem-3** (**19**) and (**20**). A mixture of **17** and **18** was acetylated with an acetic anhydride - pyridine mixture. After a standard work up a mixture of **19** and **20** in a 3:2 ratio was obtained (0.35 g, 73%). The crude product was purified and separated by chromatography using AcOEt : Hexane 1:8 $^v/_v$ as an eluent, yielding pure **19** and a mixture of **19** and **20** which was subsequently separated by prep. TLC using AcOEt : Hexane 1:1 $^v/_v$ as an eluent; Rf values for **19** and **20** are 0.82 and 0.73 respectively.

**19**: mp 163-165 °C, $[\alpha]_D$ -11.8° (*c* 1, $CHCl_3$); IR ($CHCl_3$) 1792, 1724 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.50 (s, 9H, *t*-Bu), 2.08, 2.20 (2s, 6H, 2Ac), 3.22 (m, 2H, $CH_2SPh$), 3.73 (m, 1H, H-7), 4.36 (dd, 1H, *J* 11.8 and 6.0 Hz, C**H**$_A$H$_B$OAc), 4.41 (dd, 1H, *J* 11.8 and 8.2 Hz, CH$_A$**H**$_B$OAc), 4.60 (m, 1H, H-2), 5.15 (dd, *J* 4.1 and 0.6 Hz, H-6).

Minor, more polar component **20**: syrup; $[\alpha]_D$ -33.6° (*c* 1, $CHCl_3$), IR ($CHCl_3$) 1793, 1724 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.50 (s, 9H, *t*-Bu), 2.06, 2.21 (2s, 6H, 2Ac), 3.19 (dd, 1H, *J* 14.3 and 6.3 Hz, C**H**$_A$H$_B$SPh), 3.41 (dd, 1H, *J* 14.3 and 3.7 Hz, CH$_A$**H**$_B$SPh), 3.75 (ddd, 1H, H-7), 4.22 (dd, 1H, *J* 11.8 and 8.4 Hz, C**H**$_A$H$_B$OAc), 4.28 (dd, 1H, *J* 11.8 and 5.7 Hz, CH$_A$**H**$_B$OAc), 4.64 (dd, 1H, *J* 6.3 and 3.7 Hz, H-2), 5.19 (d, 1H, *J* 4.0 Hz, H-6). MS *m/z* : $M^{+\cdot}$ 477.

**(2*S*, 6*S*, 7*S*) 2,7-Diacetoxymethyl-4-*tert*-butoxycarbonyl-1-cephem-3-hydroxy-oxa-3** (**21**) and **(2*S*, 6*S*, 7*S*) 2,7-diacetoxymethyl-4-*tert*-butoxycarbonyl-3-methoxy-1-**

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**oxacephem-3** (**22**). Cyclization of **15** was performed according to the procedure described for **14**. The crude product was purified by chromatography to give unstable **21** in 45% yield. The crude product **21** was methylated with diazomethane in ethyl ether solution to afford compound **22**. The crude product was purified by column chromatography using AcOEt : Hexane 1:8 $^{v}/_{v}$ as an eluent, yield 42%; syrup $[\alpha]_D$ +18.7° (*c* 0.4, $CHCl_3$); IR ($CHCl_3$) 1788, 1746, 1714, 1634 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.55 (s, 9H, *t*-Bu), 2.07, 2.12 (2s, 6H, 2Ac), 3.77 (m, 1H, H-7), 3.81 (s, 3H, $OCH_3$), 4.21 (2d, 1H, *J* 12.0 and 2.3 Hz, $CH_AH_BOAc$), 4.35 (dd, 1H, *J* 11.7 and 5.8 Hz, $CH_AH_BOAc$), 4.42 (dd, 1H, *J* 12.0 and 8.7 Hz, $CH_AH_BOAc$), 4.58 (dd, 1H, *J* 11.7 and 6.7 Hz, $CH_AH_BOAc$), 4.63 (m, 1H, H-2), 5.32 (dd, 1H, *J* 3.9 and 0.4 Hz, H-6).

Ms *m/z* : $M^{+\cdot}$ calcd for $C_{18}H_{25}NO_9$ 399.15293; found 399.15240.

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