Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 15, pp. 2553–2560, 1997

Printed in Great Britain

PII: S0957-4166(97)00310-8

0957-4166/97 $17.00 + 0.00

Stereocontrolled synthesis of 1-oxacepham from 4-vinyloxyazetidin-2-one, a new building block

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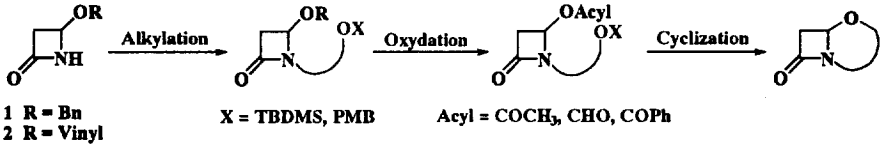
Abstract: A new methodology for 1-oxacepham synthesis is described. Readily available 4-vinyloxyazetidin-2-one **2** is shown to be a useful building block for β-lactam synthesis. N-Alkylation of **2** is followed by oxidation of the vinyloxy group to give 4-acyloxy-N-substituted azetidin-2-ones suitable for nucleophilic displacement at the C-4 carbon atom. The ring closure reaction offers high stereoselectivity. © 1997 Elsevier Science Ltd

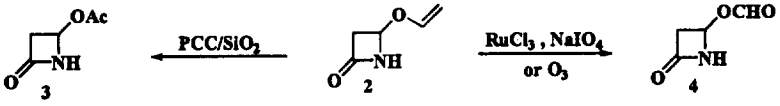
An easy nucleophilic substitution of the acyloxy group at C-4 of 4-acyloxyazetidin-2-ones makes them ideal key intermediates for the synthesis of β-lactam antibiotics.[1,2]

Recently, we have reported a new strategy for β-lactam synthesis employing readily available 4-benzyloxy- and 4-vinyloxyazeditin-2-ones **1** and **2**.[3] The strategy consisted of alkylation of **1** or **2** with a sulfonate bearing a *O*-nucleophilic center, oxidation of the vinyloxy or benzyloxy substituent to the acyloxy group and finally cyclization (Scheme 1). We have assumed that the key step, the ring closure reaction, should offer a better stereodifferentiation at the C-4 carbon atom, than that observed for intermolecular condensation of 4-acetoxyazetidin-2-one **3** with chiral alcohols.[2]



Scheme 1.

For the present study, we selected 4-vinyloxyazetidin-2-one **2** which contains the vinyloxy residue which is easily transformed into formyloxy or acetoxy groups by standard procedures, thus simplifying further steps of the synthesis. For example, oxidation of **2** by PCC afforded the acetate **3** in 36% yield, whereas ruthenium catalyzed oxidation or ozonolysis of **2** gave formate **4** in 82% and 60% yield, respectively (Scheme 2). The preparation of the known acetate **3** is competitive with existing methods.[4] The new formate **4** can play the same role in the synthesis of β-lactams similar to the acetate **3**. 3-Substituted-4-formyloxyazetidin-2-ones were obtained in the past from the respective 4-formyl-β-lactams *via* Baeyer–Villiger oxidation.[5]



Scheme 2.

As recently reported by us cyclization of **5** to 1-oxacepham **8** has been accomplished in 15% yield only (Scheme 3). The yield of the nucleophilic substitution at C-4 of the azetidin-2-one ring, which proceeds *via* the mesomeric cation **7**, depends on the residue at the nitrogen atom. The ability of the

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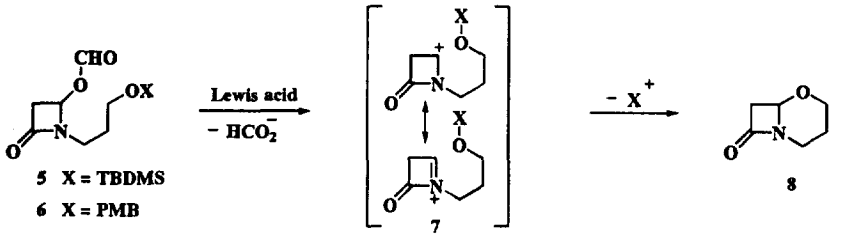
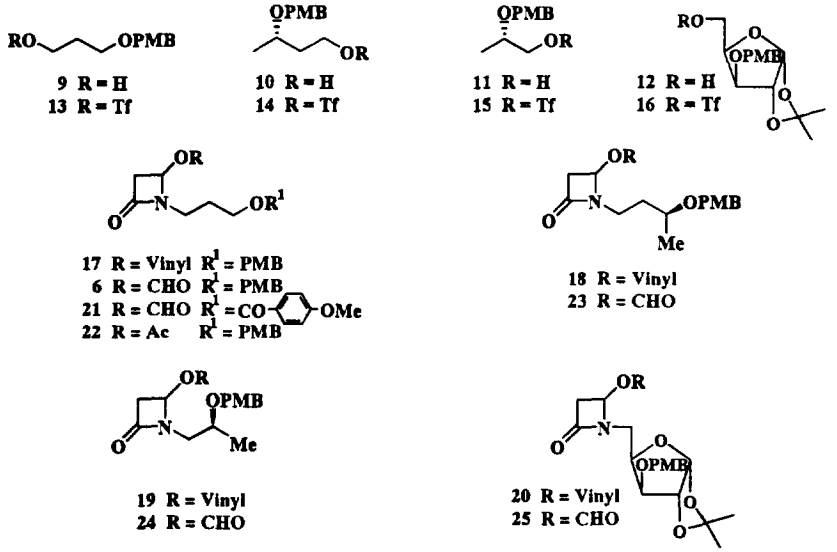
N-substituent to stabilize the positive charge, has been found to be crucial for the reactivity of cation **7**[6] and in consequence it helps to decide on the yield of nucleophilic substitution at C-4. Since our methodology is based on N-alkylated azetidin-2-ones which usually give low yields of substitution, in order to facilitate the reaction progress, we decided to enhance nucleophilicity of the oxygen atom in the side chain by the introduction of the soft cationic substituent to that atom. The 4-methoxybenzyl (PMB) ether is known to be an interesting protecting group for a hydroxyl function, because it is relatively stable and is removable in the presence of a combination of the hard Lewis acid and a soft nucleophile.[7] We expected that the p-methoxybenzyl ether should be more nucleophilic while providing an easily removable substituent under the reaction conditions (Scheme 3).



Scheme 3.

Selected hydroxy compounds **9–12** were easily obtained from 1,3-propandiol,[8] (S)-methyl-2-hydroxy butyrate,[9] (S)-methyl lactate[10] and D-xylose,[11] respectively. Triflation of **9–12** under standard condition Tf_2O/lutydine/CH_2Cl_2 gave respective triflates **13–16**. Attempts of purification of **13–16** on silica gel caused their decomposition, hence, crude triflates were used for the next step. Alkylation of **2** with an active electrophile, for example bromoacetate, proceeded very smoothly under mild, phase-transfer conditions (K_2CO_3, Bu_4NBr, acetonitrile, RT).[3] Alkylation of **2** with triflates **13–16**, however yielded only a minute amount of the desired product.



Recently we have found that 2.2 equiv. of butyllithium in combination with 1.1 equiv of tetrabutylammonium hydrogen sulfate in THF at −78°C yielded an active ammonium salt of deprotonated azetidin-2-one, which could be easily alkylated.[3] Under these conditions N-substituted β-lactams **17–20** were obtained in 50–72% yield. Surprisingly, no N-alkylation product was formed when tetrabutylammonium bromide was used instead of hydrogen sulfate, or when reaction was performed without ammonium salt. The 1:1 diastereomeric mixtures of **18–20** were chromatographically

inseparable. Ruthenium catalyzed periodate oxidation of **17** resulted after 10 minutes in formation of a mixture of the substrate, and formates **6** and **21**. Prolongation of the reaction time to 30 min., yielded only **21** as a result of oxidation of both vinyloxy and p-methoxybenzyl groups.

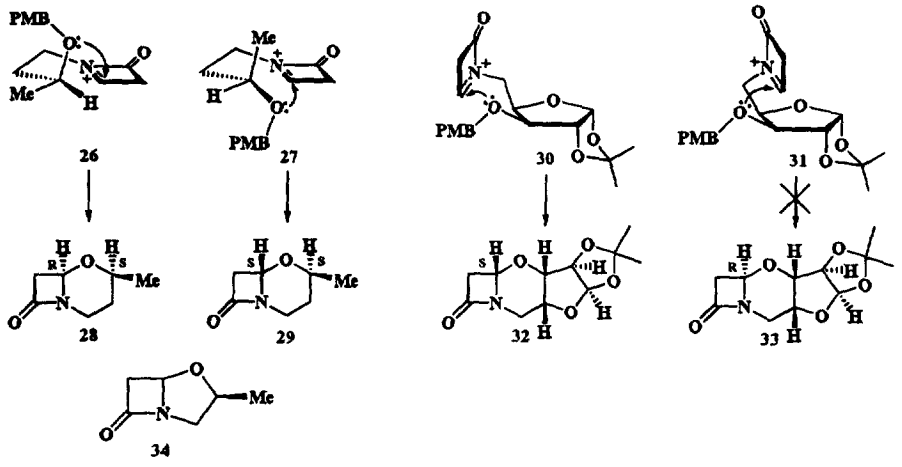
Due to the easy oxidation of primary p-methoxybenzyl ether in **17** we could not apply the ruthenium method for the transformation of the 4-vinyloxy substituent into the 4-formyloxy. Alternatively, the PCC oxidation of **17** in boiling CH_2Cl_2 gave acetate **22** with 62% yield. Under these conditions p-methoxybenzyl remained unchanged. Vinyl ether **17**, exposed to ozone at −78°C, after a reductive workup with dimethyl sulfide gave formate **6** in 68% yield. Prolongation of the ozonolysis time resulted in diminishing the yield of **6**. Ozonolysis of β-lactams **18, 19** and **20** gave the respective formates **23, 24** and **25** in 62–71% yield. In the case of **20** which has a shielded secondary p-methoxybenzyl ether, the ruthenium catalyzed oxidation gave the product **25** of the oxidation of the vinyloxy residue only in 50% yield. 4-Formyloxyazetidin-2-ones **6** and **18–20** were subjected to cyclization to afford bicyclic β-lactams. Compound **6** treated with a catalytic amount of TfOTMS (20% molar equiv.) in CH_2Cl_2 at room temperature after 20 min gave oxacepham **8** in 28% yield. Cyclization of the silyl ether **5** in the presence of the same catalyst, in boiling CH_2Cl_2, required 1.5 h for completion, and yielded **8** in only 15% yield. As we expected, the switch from silyl ether **5** to p-methoxybenzyl ether **6** provided a better yield of **8**. The change of the catalyst gave a further increase in yield. β-Lactam **6** under the influence of BF_3 (20% molar equiv.) in CH_2Cl_2, at rt after 20 min, yielded **8** in 51%. Compound **23** under the same conditions gave an unseparable mixture of oxacephams **28** and **29** in a ratio of 5:1. The relative *cis* configuration of the H-2 and H-6 hydrogens of the major product was proved by a NOE experiment which showed strong spin interaction between both protons.

Recently we have reported the alternative synthesis of 1-oxacephams and clavams by the [2+2]cycloaddition of chlorosulfonyl isocyanate (CSI) to chiral vinyl ethers.[12] Using the cycloaddition methodology, enantiomerically related to **28** and **29**, 2-methyl-1-oxacephams **28** (2R,6S) and **29** (2R,6R) were obtained in the proportion of 1:3 respectively. NOE experiments performed on the major component **29** (2R,6R) of the diastereomeric mixture did not show any spin interactions between H-2 and H-6 consistent with the *trans* configuration of both protons. The results of present and previous NOE experiments are fully consistent and provide unequivocal proof of the absolute configuration of 2-methyl-1-oxacephams obtained in the two alternative ways.

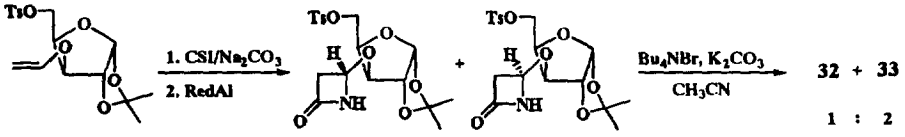
The possible stereochemical model of the cyclization is presented in the Scheme 4. According to the model, the major product **28** is the result of the lower energy transition state **26** in which the methyl group does not interact with the four membered β-lactam ring. The minor product **29** is formed *via* cation **27** which has an unfavorable interaction between the methyl and the β-lactam carbonium ion. The cyclization of **25** carried out in the presence of BF_3 gave exclusively **32** in 52% yield. Compound **32** was found to be identical with the minor diastereomer obtained when the [2+2]cycloaddition method of CSI to sugar-vinyl ether was applied[13] (Scheme 5). High diastereoselectivity of this reaction could be assigned to the low energy transition state **30**, in which the β-lactam ring does not interact with the sugar moiety (Scheme 4). The alternative diastereomer **33** has to be formed *via* the high energy transition state **31**, in which the β-lactam fragment is placed over the sugar ring.

The formation of 1-oxacephams *via* cyclization (Scheme 3) should be classified as *6-endo-trig* process, and according to Baldwin's rules, is favoured.[14] Application of the same procedure for the synthesis of five membered ring analogs (clavams), should proceed *via* disfavored *5-endo-trig* ring closure. Treatment of **24** with a catalytic amount of BF_3 or TfOTMS yielded a complex mixture, which did not contain the desired clavam **34**.

In conclusion, we have developed an attractive new route for the stereocontrolled synthesis of bicyclic β-lactams having the oxacepham skeleton. Readily available 4-vinyloxyazetidin-2-one was shown to be a useful new building block for the β-lactam synthesis. The crucial step in our methodology, which involves a ring closure, is highly diastereoselective. The configuration of a new



Scheme 4.



Scheme 5.

stereogenic center at the C-4 of the azetidin-2-one ring is opposite to that obtained on the alternative [2+2]cycloaddition method.[12,13]

Experimental

Melting points are uncorrected. Optical rotations were measured with a JASCO Dip-360 digital polarimeter. IR spectra were obtained with an FT-IR-1600 Perkin-Elmer spectrophotometer. ^{1}H-NMR spectra were recorded with a Bruker AM 500 spectrometer. Mass spectra were recorded with an AMD 604 mass spectrometer. Column chromatography was performed on Merck Kiesel gel (230–400 mesh). Ozonolysis was performed on Buchi Ozone-Generator OZI.

4-Acetoxyzetidin-2-one 3

Compound **2** (1 mmol,113 mg) was added to the suspension of PCC (2 mmol, 431 mg) and silica gel (431 mg, Merck Kiesel gel) in dichloromethane (7 ml). The mixture was stirred under reflux for 5 h, then filtered through Celite. The precipitate was washed with ethyl acetate (3×10 ml), and the filtrate was concentrated. The crude product was purified on silica gel to give **3** (46 mg, 36%), identical to a commercial sample (Aldrich).

4-Formyloxyazetidin-2-one 4

Method 1

Into a well stirred mixture of H_2O (6 ml), CCl_4 (4 ml) and CH_3CN (4 ml) were added $NaIO_4$ (5 mmol, 1.07g), $CaCO_3$ (2 mmol, 200 mg) and $RuCl_3.xH_2O$ (0.05 mmol, 10 mg). The mixture was cooled to 0°C and the solution of **2** (1 mmol, 113 mg) in CCl_4 (0.5 ml) was added dropwise. Stirring was continued at 0°C for 10 min., subsequently the reaction was quenched by addition of isopropyl alcohol (0.5 ml). The precipitate was filtered off on Celite and washed with ethyl acetate (3×15 ml). The combined filtrates were dried and the solvent was evaporated. Purification on silica gel gave **4** (95 mg, 82%). Colorless crystals, m.p. 39–41°C (ethyl acetate–hexane). IR (CH_2Cl_2): 3411, 1793, 1731 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 8.10 (d, 1H, CHO, J=0.5 Hz); 6.62 (m, 1H, NH); 5.96 (ddd, 1H, H-4,

J=4.0, 1.5, 0.5 Hz); 3.34 (ddd, 1H, H-3a, J=15.3, 4.0, 3.6 Hz); 3.09 (bd, 1H, H-3b, J=15.3 Hz). Anal. calcd for $C_4H_5NO_3$: C, 41.75; H, 4.38; N, 12.17. Found: C, 41.92; H, 4.46; N, 12.04. MS (EI, HR) m/z: $(M+H)^+$ calcd for $C_4H_6NO_3$: 116.03477. Found: 116.03462.

Method 2

The solution of **2** (1 mmol, 113 mg) in CH_2Cl_2 (50 ml) was placed in a three-necked flask, equipped with thermometer, bubbling tube and ozone outlet. The solution was stirred and upon cooling to −78°, ozone was bubbled. After about 15 min., TLC showed the disappearance of substrate, and the solution became light-blue. The ozone generator was switched off, and oxygen was passed through the solution for 5 min. to remove the excess of ozone. Dimethyl sulfide (0.5 ml) was added in one portion, and stirring was continued at −78°C for 20 min. The reaction mixture was brought to r.t. and the solvent was evaporated. Purification on silica gel gave **4** (69 mg, 60%).

*Preparation of triflates **13–16***

2,6-Lutidine (15.7 mmol, 1.83 ml) was dissolved under argon in dry CH_2Cl_2 (30 ml). Upon cooling to −20°C, triflic anhydride (14.3 mmol, 2.41 ml) was added dropwise. The mixture was stirred for 5 min. and a solution of hydroxy compound **9–12** (13 mmol) in CH_2Cl_2 (10 ml) was added dropwise. Stirring was continued at −20°C for 30 min., then the solution was warmed up to 0° and poured into an ice-water mixture (100 ml). The organic phase was separated, washed with cold water (3×50 ml), dried ($MgSO_4$) and evaporated.The crude oil was dissolved in t-butyl-methyl ether (~10 ml) and titrated with hexane (~30 ml). The precipitate was filtered off through Celite and the filtrate was concentrated to give crude triflate, which was promptly used for the next step without any further purification.

*Preparation of β-lactams **17–20***

To a stirred suspention of fine powdered tetrabutylammonium hydrogen sulfate (10.5 mmol, 3.57 g) in dry THF (80 ml) under argon was added **2** (10 mmol, 1.13g). Into this mixture, upon cooling to −78°C butyllithium (21 mmol, 8.4 ml of 2.5 M/hexane) was added and after 20 min. crude triflate (~13 mmol) in a THF solution (10 ml) was added. Stirring was continued at −78°C for 15 min. and subsequently the mixture was slowly warmed up to r.t. (~1 h) and the temperature was maintained for an additional 1 h. The reaction mixture was poured into water (300 ml) and extracted with t-butyl-methyl ether (3×150 ml). The combined extracts were washed with water, dried ($MgSO_4$) and evaporated. The crude product was purified on silica gel.

*1-[1′-(4-Methoxybenzyloxy)propan-3′-yl]-4-vinyloxyazetidin-2-one **17***

Oil, 50% yield. IR (CH_2Cl_2): 1765, 1641, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 6.37 (dd, 1H, OC**H**CH$_2$, J=14.3, J=6.7 Hz); 5.23 (dd, 1H, H-4, J=3.6, 1.1 Hz); 4.42 (bs, 2H, Bn); (4.33, dd, 1H, OCHC**Ha**H**b**, J=14.3, 2.2 Hz); 4.18 (dd, 1H, OCHCH**a**H**b**, J=6.7, 2.2 Hz); 3.80 (s,3H, OMe); 3.53–3.46 (m, 2H, H-1′a, 1′b); 3.40–3.27 (m, 2H, H-3′a, 3′b); 3.06 (dd, 1H, H-3a, J=14.8, 3.6 Hz; 2.83 (dd, 1H, H-3′b, J=14.8, 1.1 Hz); 1.88 (m, 2H, H-2′a, 2′b). Anal. calcd for $C_{16}H_{21}O_4N$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.82; H, 7.28; N, 4.87. MS (EI, HR) m/z: (M^+) calcd for $C_{16}H_{21}NO_4$: 291.14706. Found: 291.14725.

*(4S, 3′S) and (4R, 3′S) 1-[3′-(4-methoxybenzyloxy)butan-1′-yl]-4-vinyloxyazetidin-2-one **18***

Oil, 55% yield. IR (CH_2Cl_2): 1764, 1642, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) selected data for the 1:1 mixture of diastereomer: δ 6.37 and 6.35 (two dd, 2H, OC**H**CH$_2$, J=14.3, 6.7 Hz); 5.22 and 5.17 (two dd, 2H, H-4, J=3.6, 1.1 Hz); 3.07 and 3.01 (two dd, 2H, H-3a, J=14.8, 3.6 Hz); 2.83 and 2.80 (two bd, 2H, H-3b, J=14.8 Hz), 1.84–1.73 (m, 4H, H-2′a, 2′-b). Anal. calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.54; H, 7.54; N, 4.58. MS (EI, HR) m/z: (M^+) calcd for $C_{17}H_{23}NO_4$: 305.162705. Found: 305.16420.

(4S,2'S) and (4R,2'S) 1-[2'-(4-methoxybenzyloxy)propan-1'-yl-4-vinyloxyazetidin-2-one ***19***

Oil, 71% yield. IR (CH_2Cl_2): 1765, 1641, 1613 cm^{-1}. ^{1}H-NMR ($CDCl_3$) selected data for the 1:1 mixture of diastereomer: δ 6.35 and 6.34 (two dd, 2H, OC**H**CH_2, J=14.3, 6.8 Hz); 5.32 and 5.25 (two dd, 2H, H-4, J=3.6, 1.2 Hz); 3.13 and 3.05 (two dd, 2H, H-3a, J=14.8, 3.6 Hz); 2.85 and 2.81 (two bd, 2H, H-3b, J=14.8 Hz); 1.21 and 1.18 (two d, 6H, Me, J=6.3). Anal. calcd for $C_{16}H_{21}NO_4$: C, 65,96; H, 7.27; N, 4.81. Found: C, 66.04; H, 7.35; N, 4.63. MS (EI, HR) m/z: $(M+H)^+$ calcd for $C_{16}H_{22}NO_4$: 292.15488. Found: 292.154614.

(4S) and (4R) 1-[5'-deoxy-1',2'-di-O-isopropylidene-3'-O-(4-methoxybenzylo)-α-D-xylofuranose-5'-yl]-4-vinyloxyazetidin-2-one ***20***

Oil, 65% yield. IR (CH_2Cl_2): 1768, 1642, 1621 cm^{-1}. ^{1}H-NMR ($CDCl_3$) selected data for the 1:1 mixture of diastereomer: δ 6.44 and 6.34 (two dd, 2H, OC**H**CH_2, J=14.2, 6.7 Hz); 5.94 and 5.9 (two d, 2H, H-1', J=3.8 Hz); 5.44 and 5.25 (two dd, 2H, H-4, J=3.7, 1.1 Hz); 3.17 and 3.06 (two dd, H-3a, J=14.8, 3.7 Hz); 2.85 and 2.82 (two bd, 2H, H-3b, J=14.8 Hz). Anal. calcd for $C_{21}H_{27}O_7N$: C, 62.21; H, 6.71; N, 3.45. Found: C, 62.45; H, 6.98; N, 3.24. MS (EI, HR) m/z: (M^+) calcd for $C_{21}H_{27}NO_7$: 405.17875. Found: 405.17934.

Formates **6** and **23–25** were prepared according to the procedure described for **4**, by method 2, formate **21** and **25** were obtained by method 1.

4-Formyloxy-1-[1'-(4-methoxybenzyloxy)propan-3'-yl]azetidin-2-one ***6***

Oil, 68% yield. IR (CH_2Cl_2): 1772, 1731, 1612 cm^{-1}. ^{1}H-NMR (C_6 D_6): δ 7,25 (d, 1H, CHO, J=0.6 Hz); 5.46 (ddd, 1H, H-4, J=4.0, 1.2, 0.6 Hz); 4.26 (bs, 2H, Bn); 3.3 (s, 3H, OMe); 3.23 (t, 2H, H-1'a,1'b,); 3.23–3.17 and 2.99–2.92 (two m, 2H, H-3'a, 3'b); 2.52 (dd, 1H, H-3a, J=14.8, 4.0 Hz); 2.4 (bd, 1H, H-3b, J=14.8 Hz); 1.76–1.56 (m, 2H, H-2'a, 2'b). Anal. calcd for $C_{15}H_{19}O_5N$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.43; H, 6.40; N, 4.64. MS (EI, HR) m/z: (M^+) calcd for $C_{15}H_{19}NO_5$: 293.12632. Found: 293.12619.

4-Formyloxy-1-[1'-(4-methoxybenzoyloxy)propan-3'-yl]azetidin-2-one ***21***

Oil, 55% yield. IR (CH_2Cl_2): 1774, 1731, 1711, 1607 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 8.09 (d, 1H, CHO, J=0.6 Hz); 6.12 (ddd, 1H, H-4, J=3.9, 1.2, 0.6 Hz); 4.34 (t, 2H, 1'a, 1'b, J=6.2); 3.86 (s, 3H, OMe); 3.37–3.0 (m, 2H, H-3'a, 3'b); 3,29 (dd, 1H, H-3a, J=15.2, 3.9 Hz); 2.97 (bd, 1H, H-3b, J=15.2), 2.12–2.05 (m, 2H, H-2'a, 2'b). Anal. calcd for $C_{15}H_{17}O_6N$: C, 58.63; H, 5.54; N, 4.56. Found: C, 58.29; H, 5.70; N, 4.39. MS (EI, HR) m/z: (M^+) calcd for $C_{15}H_{17}NO_6$: 307.10559. Found: 307.10511.

4-Acetoxy-1-[1'-(4-methoxybenzyloxy)propan-3'-yl]azetidin-2-one ***22***

Compound **22** was obtained by PCC oxidation according to the procedure described for **3**.

Oil, 62% yield. IR (CH_2Cl_2): 1788, 1754, 1613 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 5.95 (dd, 1-H, H-4, J=4.0, 1.2 Hz); 4.41 (bs, 2H, Bn); 3.80 (s, 3H, OMe); 3.52–3.44 (m, 2H, H-1'a, 1'b); 3.44–3.39 and 3.22–3.15 (two m, 2H, H-3'a, 3'b); 3.14 (dd, 1H, H-3a, J=15.0, 4.0 Hz); 2.86 (bd, 1H, H-3b, J=15 Hz); 2.09 (s, 3H, Ac); 1.9–1.82 (m, 2H, H-2'a, 2'b). Anal. calcd for $C_{16}H_{21}O_5N$: C, 62.53; H, 6.89; N, 4.53. Found: C, 62.57; H, 7.03; N, 4.39. MS (EI, HR) m/z: (M^+) calcd for $C_{16}H_{21}NO_5$: 307.14197. Found: 307.14201

(4S,3'S) and (4R,3'S) 4-Formyloxy-1-[3'-(4-methoxybenzyloxy)butan-1'-yl]azetidin-2-one ***23***

Oil, 64% yield. IR (CH_2Cl_2): 1771, 1731, 1621 cm^{-1}. ^{1}H-NMR ($CDCl_3$) selected data for the 1:1 mixture of diastereomer: δ 8.06 and 8.07 (two d, 2H, CHO, J=0.4 Hz); 6.04 and 6.00 (two bd, 2H, H-4, J=3.6); 3.20 and 3.11 (two dd, 2H, H-3a, J=15.0, 3.6 Hz); 2.90 and 2.86 (two bd, 2H, H-3b, J=15.0 Hz); 1.84–1.74 (m, 4H, 2'a, 2'b). Anal. calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.46; H, 7.02; N, 4.56. MS (EI, HR) m/z: (M^+) calcd for $C_{16}H_{21}NO_4$: 307.141969. Found: 307.142624.

(4S,2'S) and (4R,2'S) 4-Formyloxy-1-[2'-(4-methoxybenzyloxy)propan-1'-yl]azetidin-2-one ***24***

Oil, 62% yield. IR (CH_2Cl_2): 1773, 1731, 1613 cm^{-1}. ^{1}H-NMR ($CDCl_3$) selected data for the 1:1 mixture of diastereomer: δ 7.97 and 7.92 (two d, 2H, CHO, J=0.6 Hz); 6.11 and 5.95 (two ddd, 2H, H-4, J=3.9, 1.2, 0.6 Hz); 3.23 and 3.22 (two dd, 2H, H-3a, J=15.0, 3.9 Hz); 2.92 and 2.89 (two bd, 2H, H-3b, J=15.0 Hz); 3.78–3.71 (m, 2H. H-2'); 1.20 and 1.18 (two d, 6H, Me, J=6.2 Hz). Anal. calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.20; H, 6.72; N, 4.63. MS (EI, HR) m/z: (M^+) calcd for $C_{15}H_{19}NO_5$: 293.12632. Found: 293.126187.

*(4S) and (4R) 1-[5'-deoxy-1',2'-di-*O*-isopropylidene-3'-*O*-(4-methoxybenzylo)-α-D-xylofuranose-5'-yl]-4-formyloxazetidin-2-one* ***25***

Oil, ruthenium catalyzed oxidation: 50% yield; ozonolysis: 68% yield. IR (CH_2Cl_2): 1774, 1731, 1612 cm^{-1}. ^{1}H-NMR ($CDCl_3$) selected data for the 1:1 mixture of diastereomer: δ 8.5 and 8.04 (two d, 2H, CHO, J=0.6 Hz); 6.16 (ddd, 1H, H-4, J=3.7, 1.1, 0.6 Hz) and 6.13 (ddd, 1H, H-4, J=4.0, 1.2, 0.6 Hz); 5.92 and 5.90 (two d, 2H, H-1', J=3.8 Hz); 3,35 (dd, 1H, H-3a, J=15.0, 3.7 Hz) and 3.23 (dd, 1H, H-3a, J=15.0, 4.0 Hz). Anal. calcd for $C_{20}H_{25}NO_8$: C, 58,96; H, 6.18; N, 3.44. Found: C, 59.07; H, 6.10; N, 3.28. MS (EI, HR) m/z: (M^+) calcd for $C_{20}H_{25}NO_8$: 407.15802. Found: 407.15807.

Preparation of 1-oxacephams ***8, 28, 29 and 31***

To a stirred solution of 4-formyloxy-β-lactam (**6, 23–25**, 0.3 mmol) in CH_2Cl_2 (3 ml) at 0°C was added TfOTMS (0.06 mmol, 11 μl) or $BF_3 \cdot Et_2O$ (0.06 mmol, 7.5 μl). The mixture was brought to r.t. and kept at this temperature for ~20 min. (TLC control). The saturated solution of $NaHCO_3$ (2 ml) was added and stirring was continued for 10 min. The organic phase was separated, washed with water, dried ($MgSO_4$) and evaporated. The crude product was purified on silica gel.

1-Oxacepham ***8***

Obtained according to the procedure described above.
TfOTMS catalysed: 28% yield. $BF_3 \cdot Et_2O$ catalysed: 51% yield.

(2S,6R) and (2S,6S) 2-Methyl-1-oxacephams ***28 and 29***

Obtained according to the procedure described above.
$BF_3 \cdot Et_2O$ catalysed: 49% yield. **28** and **29** were identical as enantiomers of known compounds.[11] **28**:**29**=5:1 (^{1}H-NMR), $[\alpha]_D$=34.5 (c 1.4, CH_2Cl_2).

1-Oxacepham ***32***

Obtained according to the procedure described above.
TfOTMS catalysed: 43% yield. $BF_3 \cdot Et_2O$ catalysed: 52% yield. $[\alpha]_D$=−30 (c 1.1, CH_2Cl_2), (lit.,[13] $[\alpha]_D$=−29.8 (c 0.8, CH_2Cl_2).

Acknowledgements

The authors wish to thank the State Committee for Scientific Research (Grant 3T09A05308) for support of this work.

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(Received in UK 23 May 1997; accepted 15 July 1997)