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TETRAHEDRON: *ASYMMETRY*

Stereocontrolled formation of cephams from 1,3-*O*-ethylidene-L-erythritol†

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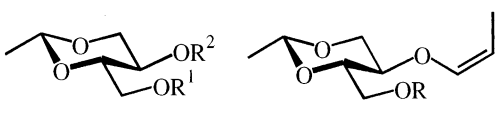
Abstract—[2+2]Cycloaddition of chlorosulfonyl isocyanate to (*Z*)-1,3-*O*-ethylidene-2-*O*-propenyl-4-*O*-trityl-L-erythritol proceeds with excellent stereoselectivity to afford the corresponding (*R*)-4′-alkoxy-azetidin-2-one which can be transformed into 5-oxacepham by intramolecular alkylation of the β-lactam nitrogen atom. Cepham having the alternative (*S*) configuration at the bridgehead carbon atom can be achieved by another methodology based on alkylation of the nitrogen atom in 4-vinyloxy-azetidin-2-one by the suitably protected 1,3-ethylidene-L-erythritol followed by intramolecular displacement of the vinyloxy group.

Recently we have shown that [2+2]cycloaddition of chlorosulfonyl isocyanate (CSI) to 3-*O*- and 5-*O*-vinyl ethers of 1,2-*O*-isopropylidene-D-glycofuranose proceeds in many cases with excellent stereoselectivity and allows control of the configuration at C-(4) of the 4-alkoxy-azetidin-2-one.[1–3] The cycloadducts offer an entry to 5-oxacephams and clavams via suitable transformation of the sugar auxiliary.[4,5] Due to the specific multifunctional character of the 1,2-*O*-isopropylidene-D-glycofuranose residue, previously presented syntheses[4,5] are of limited practical value.

Herein, we demonstrate that the stereochemical [2+2]-cycloaddition model proposed by us recently[6] has a general applicability and that alternative strategies for the formation of 5-dethia-5-oxa-cephams[7] offer full control of the configuration at the bridgehead carbon atom of the antibiotic, C-(6).

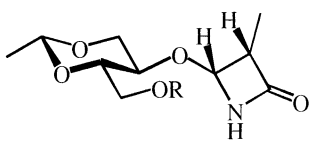
For these model studies we selected 1,3-*O*-ethylidene-L-erythritol **1**, which is readily synthesized from D-glucose.[8] The terminal hydroxymethyl group in **1** was protected as a trityl[9] or *tert*-butyldimethylsilyl (TBS)[10] ether and the secondary hydroxyl was protected as its allyl ether. The allyl substituent in compound **3** was then transformed into the corresponding (*Z*)-propenyl ether **6**,[11] by the standard potassium *tert*-butoxide isomerization.[12] In the case of **5**, isomerization of the allyl ether caused concomitant deprotection of the silyl ether, yielding **7**. The hydroxyl group in **7** was mesylated or tosylated under standard conditions to afford the corresponding sulfonates **8** and **9**.

It has been shown that both vinyl and (*Z*)-propenyl ethers display the same direction of asymmetric induction in [2+2]cycloadditions with CSI.[12] Since the formation of vinyl ethers requires acid catalysis, which could

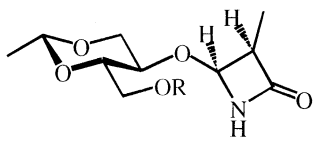


1: $R^1 = R^2 = H$
2: $R^1 = Tr$, $R^2 = H$
3: $R^1 = Tr$, $R^2 = Allyl$
4: $R^1 = TBS$, $R^2 = H$
5: $R^1 = TBS$, $R^2 = Allyl$

6: R = Tr
7: R = H
8: R = Ms
9: R = Ts



10: R = Tr
11: R = H
12: R = Ts
13: R = Ms



14: R = Ms
15: R = Ts

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† Dedicated to Professor Dr. Joachim Thiem in the year of his 60th birthday.

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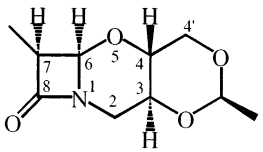
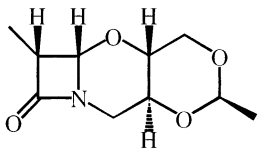
have effected migration or rearrangement of the ethylidene fragment in **2**–**5**, we decided to use propenyl ethers in this study. The [2+2]cycloaddition of CSI to **6**, followed by reduction of the *N*-chlorosulfonyl group with Red-Al,[1–6,13] afforded the β-lactam **10** as a single *cis*-diastereomer in 82% yield.[11] The trityl protecting group of **10** was then removed cleanly by treatment with sodium in liquid ammonia to give **11** in 74% yield and the hydroxy group was subsequently tosylated under standard conditions. The intramolecular alkylation of the β-lactam nitrogen in **12** using a two-phase system (anhydrous potassium carbonate/tetrabutylammonium bromide) in acetonitrile led[1,2] to formation of 5-oxacepham **16**[11] in 60% yield. The structure and (6*R*) configuration of **16** was confirmed by X-ray crystallography (Fig. 1).[14]



16



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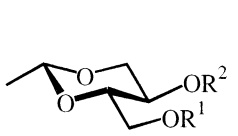
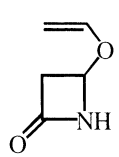
The cycloaddition performed on **8** and **9** afforded two corresponding *cis* azetidin-2-ones in each case: **13** and **14** in a ratio of 2:1, respectively, in 69% yield and **12** and **15** in a ratio of 3:1, respectively, in 52% yield. The **13**/**14** and **12**/**15** mixtures were separated into pure components, which were independently subjected to cyclization to afford **16** and **17**. The structure and (6*S*) configuration of **17**[11] was again established by X-ray crystallography (Fig. 1).[14]

The results of the cycloadditions indicate an *s-trans* conformation of the olefin[6] in the transition state and steric control of the reaction. The bulky trityl group blocks the approach of CSI to the *re*-face, whereas substituents smaller than trityl (i.e. tosyl or mesyl) allow access of CSI to either side of the olefin.

Stereocontrolled formation of the (6*S*) configuration in cepham **23** of the same tricyclic skeleton as **16** and **17** can be achieved by a different methodology.[7,15] The crucial substrate for the synthesis of compound **23** was obtained from **4** by a standard reaction sequence involving protection of **4** as its *p*-methoxybenzyl ether, removal of the silyl protecting group of **18** and formation of the corresponding triflate **20**. Alkylation of the β-lactam nitrogen atom in **21** with **20** in the presence of tetrabutylammonium hydrogen sulfate/*n*-BuLi in THF[15] afforded a mixture of diastereoisomers **22**, that could be easily separated by chromatography. Subsequently, BF_3–etherate-catalysed transformation of each stereoisomer of **22** afforded the same (6*S*)-cepham **23** from either compound.[16] The (6*S*) configuration of **23** was established by X-ray crystallography (Fig. 1).



18: R^1 = TBS, R^2 = PMB
19: R^1 = H, R^2 = PMB
20: R^1 = Tf, R^2 = PMB



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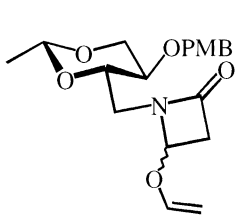

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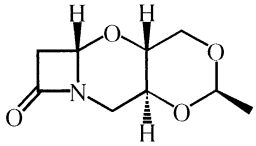
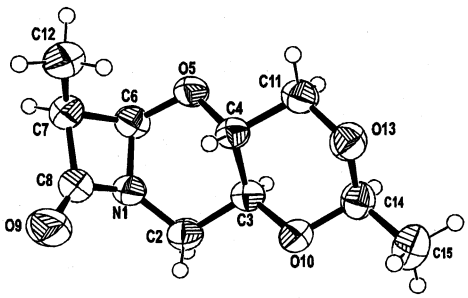
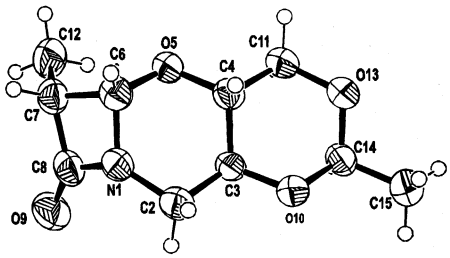


23



16



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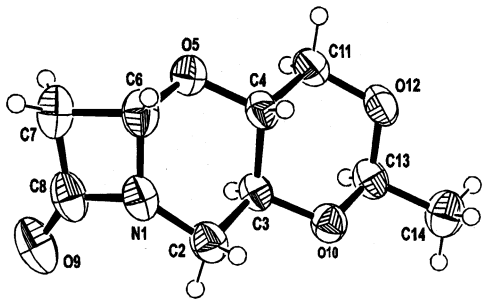

23

Figure 1. X-Ray structures of cephams **16**, **17** and **23** with crystallographic numbering scheme.

Thus, it was demonstrated that the configuration at C-(6), which is crucial for biological activity of β-lactam antibiotics, can be controlled by selection of the strategy for cepham formation. The *trans* fused ring system provides a rigid template which could induce an alteration of geometry of the β-lactam nitrogen atom in isomers **16** and **17**. The crystal structures displayed in Fig. 1 show that there are some changes in geometry of the 'decalin' system between **16** and **17**/**23**, but irrespective of the relative configuration at C-(3), C-(4) and C-(6) the environment of the nitrogen atom is only slightly pyramidal in all cephams obtained. The distance of the nitrogen atom from the plane formed by C-(2), C-(6) and C-(8) carbon atoms amounts to only 0.250 (2), 0.260 (3) and 0.256 (2) Å, respectively.

Acknowledgements

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References

1. Kałuża, Z.; Furman, B.; Patel, M.; Chmielewski, M. *Tetrahedron: Asymmetry* **1994**, *5*, 2179–2186.
2. Kałuża, Z.; Furman, B.; Chmielewski, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1719–1730.
3. Furman, B.; Kałuża, Z.; Chmielewski, M. *J. Org. Chem.* **1997**, *62*, 3135–3139.
4. Neuß, O.; Furman, B.; Kałuża, Z.; Chmielewski, M. *Heterocycles* **1997**, *45*, 265–270.
5. Furman, B.; Molotov, S.; Thürmer, R.; Kałuża, Z.; Voelter, W.; Chmielewski, M. *Tetrahedron* **1997**, *53*, 5883–5890.
6. Furman, B.; Krajewski, P.; Kałuża, Z.; Thürmer, R.; Voelter, W.; Williamson, M. P.; Chmielewski, M. *J. Chem. Soc., Perkin Trans. 2* **1999**, 217–224.
7. Kałuża, Z.; Furman, B.; Krajewski, P.; Chmielewski, M. *Tetrahedron* **2000**, *56*, 5553–5562.
8. (a) Barker, S. A.; Foster, A. B.; Haines, A. H.; Lehmann, J.; Webber, J. M.; Zweifel, G. *J. Am. Chem. Soc.* **1963**, *85*, 4161–4167; (b) Barker, R.; MacDonald, D. L. *J. Am. Chem. Soc.* **1960**, *82*, 2301–2303.
9. Hartman, F. C.; Barker, R. *J. Org. Chem.* **1963**, *28*, 1004–1008.
10. Marusawa, H.; Setoi, H.; Kuroda, A.; Sewada, A.; Seki, J.; Motoyama, Y.; Tanaka, H. *Bioorg. Med. Chem.* **1999**, *7*, 2635–2645.
11. All new compounds were fully characterized by spectral and analytical data. Selected data of representative compounds **6**, **10**, **16**, **17** and **23** are given below:
6: mp 59–61°C; $[\alpha]_D=-3.1$ (*c* 0.4, CH_2Cl_2); IR ($CHCl_3$) 1669 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.85 (dq, 1H, $J=1.7$, 6.1 Hz, H-1′), 4.71 (q, 1H, $J=5.0$ Hz, H-1″), 4.21 (dq, 1H, $J=6.1$, 6.8 Hz, H-2′). HRMS (ESI) m/z $(M+Na)^+$ found: 453.2048, calcd for $C_{28}H_{30}O_4Na$: 453.2036.
10: mp 136–138°C; $[\alpha]_D=-19.2$ (*c* 0.4, CH_2Cl_2); IR (film) 1774 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.84 (d, 1H, $J=4.5$ Hz, H-4′), 4.72 (q, 1H, $J=5.0$ Hz, H-1″), 2.88 (qdd, 1H, $J=2.5$, 4.5, 7.5 Hz, H-3′), 1.44 (d, 3H, $J=5.0$ Hz, CH_3'′), 0.85 (d, 3H, $J=7.5$ Hz, CH_3'). HRMS (EI) m/z M^+ found: 473.2206, calcd for $C_{29}H_{31}O_5N$: 473.2202.
16: mp 59–61°C; $[\alpha]_D=+111.5$ (*c* 0.6, CH_2Cl_2); IR (film) 1769 cm^{-1}; ^1H NMR (C_6D_6) δ 4.54 (d, 1H, $J=3.3$ Hz, H-6), 2.70 (qdd, 1H, $J=1.8$, 3.3, 7.6 Hz, H-7), 1.22 (d, 3H, $J=5.1$ Hz, CH_3), 0.92 (d, 3H, $J=7.6$ Hz, CH_3). HRMS (ESI) m/z $(M+Na)^+$ found: 236.0891, calcd for $C_{10}H_{15}NO_4Na$: 236.0893.
17: mp 68–71°C; $[\alpha]_D=-16.0$ (*c* 0.5, CH_2Cl_2); IR (film) 1769 cm^{-1}; ^1H NMR (C_6D_6) δ 4.17 (d, 1H, $J=3.8$ Hz, H-6), 2.76 (qdd, 1H, $J=1.5$, 3.8, 7.5 Hz, H-7), 1.20 (d, 3H, $J=5.1$ Hz, CH_3), 1.05 (d, 1H, $J=7.5$ Hz, CH_3). HRMS (ESI) m/z $(M+Na)^+$ found: 236.0886, calcd for $C_{10}H_{15}NO_4Na$: 236.0893.
23: mp 94–96°C; $[\alpha]_D=-71.9$ (*c* 0.3, CH_2Cl_2); IR (film) 1771 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.06 (d, 1H, $J=3.3$ Hz, H-6), 2.76 (ddd, 1H, $J=1.7$, 3.3, 15.1 Hz, H-7a), 2.81 (dd, 1H, $J=0.5$, 15.1 Hz, H-7b), 1.33 (d, 3H, $J=5.1$ Hz, CH_3). HRMS (ESI) m/z $(M+Na)^+$ found: 222.0739, calcd for $C_9H_{13}NO_4Na$: 222.0737.
12. Łysek, R.; Furman, B.; Kałuża, Z.; Chmielewski, M. *Polish J. Chem.* **2000**, *74*, 51–60.
13. Chmielewski, M.; Kałuża, Z.; Abramski, W.; Bełżecki, C.; Grodner, J.; Mostowicz, D.; Urbański, R. *Synlett* **1994**, 539–541.
14. Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre, Cambridge, UK, as a supplementary publication: **16**, CCDC 159585; **17**, CCDC 159584; **23**, CCDC 159586.
15. (a) Kałuża, Z.; Park, S.-H. *Synlett* **1996**, 895–896; (b) Kałuża, Z.; Łysek, R. *Tetrahedron: Asymmetry* **1997**, *8*, 2553–2560.
16. Kałuża, Z. *Tetrahedron Lett.* **1999**, *40*, 1025–1026.