Tetrahedron Letters,Vol.30,No.38,pp 5171-5172,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

SYNTHESIS OF β-LACTAMS FROM SUGAR VINYL ETHERS AND ISOCYANATES

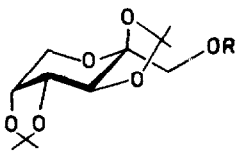
Zbigniew Kałuża, Wang Fudong, Czesław Bełżecki, and Marek Chmielewski*
Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warsaw, POLAND.

Abstract: [2+2] Cycloaddition of tosyl isocyanate to sugar vinyl ethers followed by N-deprotection affords β-lactams with fairly good asymmetric induction.

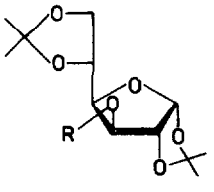
Among many reports on the synthesis of β-lactam antibiotics from carbohydrate precursors[1,2], only one has not used sugar for construction of a four-membered azetidinone fragment, using it instead to form a five-membered oxazolidine ring and side chain of the antibiotic. Commercially available 4-acetoxyazetidinone has afforded the β-lactam portion[2]. The present paper reports preliminary studies directed toward an alternative idea to that published by the Hoffmann - La Roche group[2]. Our approach is based on [2+2] cycloaddition of isocyanates to sugar vinyl ethers.

For the model studies of cycloaddition, asymmetric induction, and deprotection of the nitrogen atom, we selected three vinyl ethers **4**, **5**, and **6** which can readily be prepared from the respective sugar precursors **1**, **2**, and **3** by the known transetherification method[3].

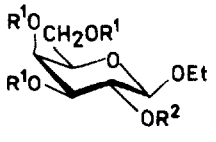
Compounds **4**, **5**, or **6** were condensed with tosyl isocyanate affording the respective cycloadducts **7**, **8**, and **9** which were subsequently deprotected at the nitrogen atom with sodium in liquid ammonia to give stable compounds **10**, **11**, and **12**[4] in about 35% yield. In each case the product also contained the respective starting sugar **1**, **2**, or **14** (ca 45%). The ratio of diastereomers at C-4 of the azetidinone ring was found to be 7:3 for **10** with predominance of S isomer, 6:1 for **11** with predominance of R isomer, and 7:3 for **12** with predomominance of S isomer. The absolute configuration of the C-4 atom of the azetidinone ring in the main diastereomer was determined on the basis of the octant rule of Rehling and Jensen[5], which expects a strongly positive Cotton effect at 214 nm for 4S-substituted-2-azetidinones, whereas a negative one for the 4R-isomer. The relatively high asymmetric induction, despite of a long distance from the sugar chirality center should be underlined. Only vinyl ether **5** provides the β-lactam with R-configuration , which is crucial for biological activity of bicyclic antibiotics[6].



1: R=H
4: R=CH=CH$_2$
7: R= (S)-Ts-azetidinone
10: R= (S)-H-azetidinone

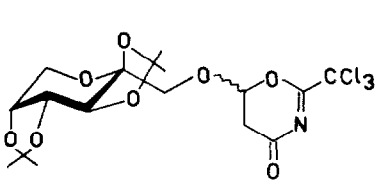


2: R=H
5: R=CH=CH$_2$
8: R= (R)-Ts-azetidinone
11: R= (R)-H-azetidinone

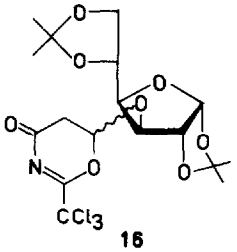


3: R^1=Bn, R^2=H
6: R^1=Bn, R^2=CH=CH$_2$
9: R^1=Bn, R^2= (S)-Ts-azetidinone
12: R^1=H, R^2= (S)-H-azetidinone
13: R^1=Ac, R^2= (S)-H-azetidinone
14: R^1=R^2=H

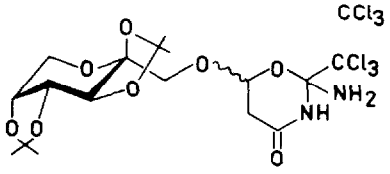
The high content of sugars **1**, **2**, and **14** was the result of low stability of adducts **7** - **9** in the presence of liquid ammonia, while compounds **10**, **11**, and **12**, each having a free NH



15



16



17

group, were found to be resistant to liquid ammonia.

Cycloaddition of acyl isocyanates proceeds in a different manner. As would be expected from literature data[7], compounds **4** and **5** treated with trichloroacetyl isocyanate significantly prefer formation of the [4+2] over the [2+2] cycloadduct; in the case of addition to **4**, 93% of **15**[8] was found, whereas in the case of **5**, only **16**[8] was found. Stereoselectivity in formation of [4+2] cycloadducts **15** and **16** was lower than that found for [2+2] cycloaddition of tosyl isocyanate and amounts to 1.8:1 for **15** and 1:1 for **16**. The structure of the [4+2] cycloadducts was proved by transformation of one of them (**15**) to **17**, by treatment with ammonia[9].

Acknowledgments. This work was supported by the Polish Academy of Sciences grant CPBP 01.13. We thank Dr. J. Gawronski for the CD measurements.

References and notes

1. P.L. Durette, *Carbohydr. Res.*, 100, 27 1982); K. Koga, N. Ikata, O. Toshino, *Chem. Pharm. Bull.*, 30, 1929 (1982); S. Hanessian, D. Desilets, G. Rancourt, R. Fosfin, *Can. J. Chem.*, 60, 2292 (1982); A. Yoshikoshi, M. Miyashita, N. Chida, *J. Chem. Soc., Chem. Commun.*, 1354 (1982); T. Tamada, H. Matsunga, T. Sakamahi, H. Nagaoka, *Tetrahedron Lett.*, 24, 3009 (1983); A. Knierzinger, A. Vasella, *J. Chem. Soc., Chem. Commun.*, 9 (1984); C. Hubschwerden, *Synthesis*, 962 (1986).
2. S. De Bernardo, J.P. Tengi, G.J. Sasso, M. Weigele, *J. Org. Chem.*, 50, 3457 (1985).
3. W.H. Watanabe, L.E. Coulon, *J. Am. Chem. Soc.*, 79, 2828 (1957).
4. Compound **4**, **5**, or **6** (2 mmol) in abs. ether (3 mL) was treated with tosyl isocyanate (4 mmol) and the mixture was left overnight. Subsequently the reaction mixture was added rapidly to the solution of sodium (0.5 g) in liquid ammonia (50 mL) at -50 °C. The standard work-up and chromatographic separation led in each case to the mixture of diastereomeric adducts **10**, **11**, or **12** and the sugar **1**, **2**, **14** respectively.
10: IR ($CHCl_3$): 1800 cm^{-1}; ^1H NMR ($CDCl_3$), azetidinone ring, (S) isomer: 2.93 (ddd, 0.7 H, H-3), 3.11 (ddd, 0.7 H, H-3'), 5.21 (dd, 0.7 H, J 1.4, 3.9 Hz, H-4); (R) isomer: 2.92 (ddd, 0.3 H, H-3), 3.10 (ddd, 0.3 H, H-3'), 5.13 (dd, 0.7 H, J 1.4, 3.9 Hz, H-4). **11**: IR ($CHCl_3$): 1785 cm^{-1}; ^1H NMR ($CDCl_3$), azetidinone ring, (R) isomer: 2.98 (ddd, 0.85 H, H-3), 3.14 (ddd, 0.85 H, H-3'), 5.31 (ddd, 0.85 H, J 1.4, 3.9 Hz, H-4); (S) isomer: 2.88 (dt, 0.15 H, H-3), 3.17 (ddd, 0.15 H, H-3'), 5.17 (dd, 0.15 H, J 1.4, 4.0 Hz, H-4). **12**: characterized as the acetate **13**; IR ($CHCl_3$): 1780 cm^{-1}; ^1H NMR ($CDCl_3$), azetidinone ring, (S) isomer: 2.85 (bd, 0.7 H, H-3), 3.11 (m, 0.7 H, H-3'), 5.16 (dd, 0.7 H, J 1.3, 3.9 Hz, H-4); (R) isomer: 2.89 (bd, 0.3 H, H-3), 3.12(m, 0.3 H, H-3'), 5.34 (dd, 0.3 H, J 1.4, 3.9 Hz, H-4).
5. H. Rehling, H. Jensen, *Tetrahedron Lett.*, 2793 (1972).
6. R.B. Morin and M. Gorman Ed., *Chemistry and Biology of β-Lactam Antibiotics.* Academic Press, 1982, New York.
7. J.L. Chitwood, P.G. Gott, J.C. Martin, *J. Org. Chem.* 36, 2228 (1971).
8. **15**: ^1H NMR ($CDCl_3$), 1,3-oxazine ring, major componenent: 2.91 (dd, 0.66 H, J 2.0, 16.2 Hz, H-3), 3.20 (dd, 0.66 H, J 4.2 Hz, H-3'); 6.09 (dd, 0.66 H, H-4); minor component: 2.95 (dd, 0.34 H, J 1.9, 16.2 Hz, H-3), 3.19 (dd, 0.34 H, 4.2 Hz, H-3'), 6.07 (dd, 0.34 H, H-4). **16**: ^1H NMR ($CDCl_3$), 1,3-oxazine ring: 2.89 (dd, 0.5 H, J 1.9, 15.7 Hz, H-3A), 2.92 (dd, 0.5 H, J 2.1, 16.0 Hz, H-3B), 3.03 (dd, 0.5 H, J 4.1 Hz, H-3'A), 3.04 (dd, 0.5 H, J 4.2 Hz, H-3'B), 6.06 (dd, 0.6 H, H-4B), 6.11 (dd, 0.5 H, H-4A). **17**: ^1H NMR ($CDCl_3$), 1,3-oxazine ring: 2.65 (bdd, 1 H, H-3A, 3B), 2.85 (dd, 0.5 H, J 4.1, 16.9 Hz, H-3'A), 2.89 (dd, 0.5 H, J 4.4, 16.9 Hz, H-3'B), 5.39 (dd, 0.5 H, J 0.9 Hz, H-4A), 5.44 (dd, 0.5 H, J 1.1 Hz, H-4B).
9. M. Chmielewski, Z. Kałuża, *Carbohydr. Res.*, 167, 143 (1987).

(Received in UK 28 July 1989)