THE ENANTIOMERICALLY PURE BICYCLIC β-LACTAMS DERIVED FROM SUGARS

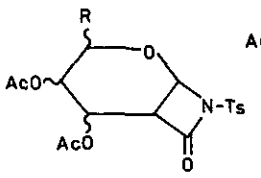
MAREK CHMIELEWSKI,* ZBIGNIEW KAŁUZA, CZESŁAW BEŁZECKI, PIOTR SAŁANSKI, AND JANUSZ JURCZAK

Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warsaw, Poland

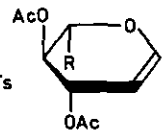
Abstract - Trichloroacetyl isocyanate reacts with glycals 2 and 3 under 10 kbar pressure to give (4+2) adduct 7 or 16, β-lactams 8 and 9 or 17 and 18, respectively. Treatment of the post-reaction mixtures with *Florisil* enabled to obtain the N-unsubstituted β-lactam 10 in case of products derived from 2, and 19 in case of those derived from 3.

Application of 10 kbar pressure enabled the (2+2) cycloaddition of tosyl isocyanate to glycals.[1,2] The reaction proceeded with high stereoselectivity to afford a four-membered β-lactam ring, which was *trans* with respect to the acetoxy group at C-3. Adducts 1 are thermodynamically unstable, and upon standing at room temperature under normal pressure they undergo retro-addition. When treated with alcohols, 1 gave the respective glycosides with the relative *trans* configuration of substituents at the C-1 and C-2 carbon atoms.[1,2]

Our goal was to synthesize suitably functionalized bicyclic β-lactam 1, which might serve as a convenient precursor for the synthesis of oxapenams and oxacephams. Therefore we selected di-O-acetyl-L--rhamnal (2) and di-O-acetyl-L-xylal (3) as our glycals, as they should produce adducts having R-configuration[1,2] of the anomeric carbon atom crucial for the biological activity of β-lactam antibiotics.

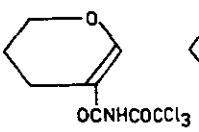


1. R=H, CH_3, CH_2OAc



2: R=CH_3

3: R=H



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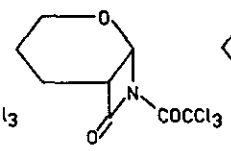

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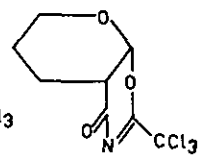

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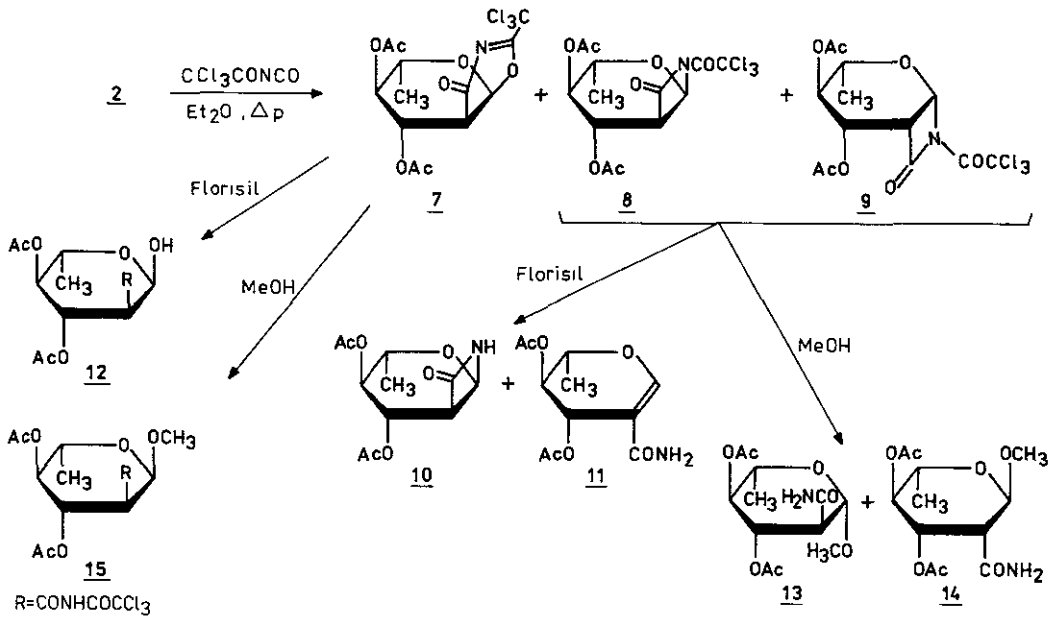
Our choice of the isocyanate was dictated by the fact that while an electrowithdrawing group is necessary for the cycloaddition, it is also responsible for the instability of the four-membered ring in 1.[2] Therefore we had to chose a group which both promoted the cycloaddition reaction, and was readily removeable under mild conditions. Trichloroacetyl isocyanate offers such an electrowithdrawing group, because it is labile in the presence of Florisil,[3] and can be easily removed before the other chemical transformations of 1 are undertaken.

Trichloroacetyl isocyanate reacted with 3,4-dihydro-2H-pyran at room temperature under normal pressure to give unsaturated amide 4 by the intermediary formation of the bicyclic β-lactam 5 and the (4+2) cycloadduct 6.[4] Under the same conditions glycals 2 and 3 remained unreactive.

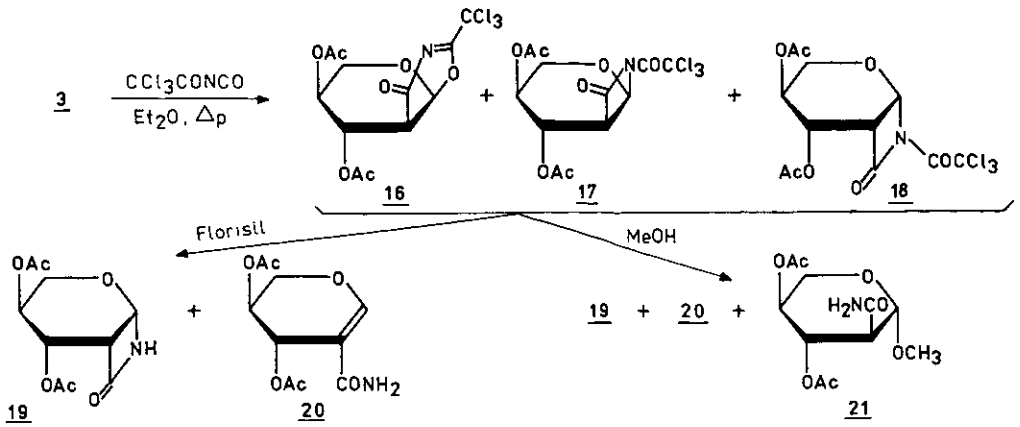
Under 10 kbar pressure the isocyanate (1.5 equiv) was condensed with glycals 2 or 3 (1 equiv) in ether solution at room temperature for 18 h. The cycloaddition reaction of 2 and trichloroacetyl isocyanate afforded three products 7, 8 and 9 (Scheme 1) in a ratio of about 4 : 1.4 : 1 (according to ^{13}C NMR of the crude reaction mixture). The adduct 7 crystallized from the reaction mixture (43%) and could be purified by recrystallization from benzene-hexane mixture. After separation of 7, the mother liquor was evaporated and passed through a column of Florisil. The oily residue was subsequently separated on a silica-gel column by flash chromatography to give 10 (12%) and 11 (9%).

Scheme 1



On the other hand, 7 treated with Florisil gave free sugar 12 with α-*gluco* configuration. The mixture of 8 and 9 underwent the opening of the β-lactam ring in methanol solution yielding glycosides 13 and 14 with β-*gluco* and α-*manno* configuration, respectively. Interestingly, 7 subjected to methanolysis furnished 15 with α-*gluco* configuration as the result of the opening of the six-membered ring with retention of configuration at C-1 carbon atom. Alternatively, subjection of L-xylal 3 to the same reaction followed the same general scheme to give the three products 16, 17 and 18 (Scheme 2) in the approximate proportions 1.3 : 1 : 1.3 (^{13}C NMR). The mixture was not separated into pure components. The crude product was passed through a Florisil column affording 19 (16%) and 20 (5.5%), which were subsequently separated on silica gel. When the cycloadducts 16 - 18 were treated with methanol, the bicyclic β-lactam 19, the open-chain amide 20 and the β-*xylo* glycoside 21 were obtained.

Scheme 2



The structures of compounds 7 - 21 were assigned on the basis of their spectral data.[5] Products 8, 9, 13, 14, 16 - 18 and 21 were characterized as mixtures, whereas 7, 10 - 12, 15, 19 and 20 as pure compounds.[5]

Cycloadducts 7 - 9 and 16 - 18 slowly undergo the retro-reaction upon heating to 60°C to give starting glycals 2 and 3. Adducts derived from 3 (16 - 18) however, differ in other chemical behaviour in comparison to the corresponding compounds 7 - 9 which were obtained when 2 was used as the substrate of the cycloaddition. In particular, the stability of the β-lactam ring does not depend upon the relative configuration of substituents within the bicyclic skeleton. This is clearly visible by the comparison of stability of 8 *versus* 9, and 18 *versus* 17. The different reactivity of the cycloadduct 7 with that of 16 is also worth of notice.

In conclusion, we have demonstrated a means to prepare new enantiomerically pure bicyclic β-lactam skeletons which can be used as the intermediates for the further transformations leading to optically pure antibiotics.[6] It should be underlined that the stability of 10 and 19 follows our earlier expectations mentioned above.

ACKNOWLEDGMENTS

The Authors are kindly indebted to Dr. Klaus Bock (the Technical University of Denmark) for recording the ^{1}H NMR spectra. This work was supported by the Polish Academy of Sciences MR-I-12 grant.

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4. J. L. Chitwood, P. G. Gott, and J. C. Martin, *J. Org. Chem.*, 1971, 36, 2228.

5. The selected data of compounds 7 - 21. The ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ with TMS as a standard (TMS = 0 ppm). The assignments of ^{13}C NMR signals of cycloadducts 7 - 9 and 16 - 18 are based on ^{13}C line intensities and should be considered as tentative.

7: mp 92-97°C (decomp.); $[\alpha]_D$ +9.8° (c 2, CH_2Cl_2); ^{1}H NMR: 6.03(d,1H,J_{12}=3.8Hz,H-1), 3.13(dd,1H, J_{23}=11.2Hz,H-2), 5.25(dd,J_{34}=9.5Hz,H-3); ^{13}C NMR: 100.62(C-1), 47.27(C-2), 67.83(C-3), 71.41, 70.32(C-4,C-5), 17.19(C-6).

8: ^{1}H NMR: 6.08(d,1H,J_{12}=5.8Hz,H-1), 3.73(dd,1H,J_{23}=2.2Hz,H-2); ^{13}C NMR: 79.40(C-1), 52.21(C-2), 67.68(C-3), 72.26(C-4), 71.21(C-5), 18.68(C-6).

9: ^{1}H NMR: 5.81(d,1H,J_{12}=5.7Hz,H-1); ^{13}C NMR: 77.85(C-1), 50.13(C-2), 67.13(C-3), 67.40(C-4), 72.54(C-5), 18.68(C-6).

10: mp 123-125°C; $[\alpha]_D$ -101.4° (c 1.5, CH_2Cl_2); ^{1}H NMR: 5.53(d,1H,J_{12}=4.3Hz,H-1), 3.42(dd,1H,J_{23}= =2.2Hz,H-2), 5.33(dd,1H,J_{34}=6.5Hz,H-3).

11: mp 151-152°C; $[\alpha]_D$ +96.6° (c 2, CH_2Cl_2); ^{1}H NMR: 7.74(s,1H,H-1), 5.64(bs,1H,H-3), 4.99(s,1H,H-4).

12: mp 135-136°C; $[\alpha]_D$ -137.0° (c 2.5, CH_2Cl_2); ^{1}H NMR: 5.78(d,1H,J_{12}=3.2Hz,H-1), 2.84(dd,1H,J_{23}= =10.8Hz,H-2); ^{13}C NMR: 95.61(C-1), 51.15(C-2), 68.37(C-3), 73.67(C-4), 69.00(C-5), 17.34(C-6).

13: ^{1}H NMR: 4.58(d,1H,J_{12}=8.4Hz,H-1), 2.63(dd,1H,J_{23}=11.0Hz,H-2).

14: ^{1}H NMR: 5.07(d,1H,J_{12}=1.6Hz,H-1), 3.22(dd,1H,J_{23}=6.2Hz,H-2).

15: mp 181-182°C; $[\alpha]_D$ -139.0° (c 2, CH_2Cl_2); ^{1}H NMR: 5.62(d,1H,J_{12}=3.3Hz,H-1), 2.85(dd,1H,J_{23}= =10.7Hz,H-2), 5.76(dd,1H,J_{34}=9.6Hz,H-3).

16: ^{1}H NMR: 6.05(d,1H,J_{12}=4.0Hz,H-1), 3.21(dd,1H,J_{23}=7.5Hz,H-2); ^{13}C NMR: 99.64(C-1), 45.06(C-2), 66.85(C-3), 65.72(C-4), 61.62(C-5).

17: ^{1}H NMR: 6.04(d,1H,J_{12}=5.8Hz,H-1), 3.75(ddd,1H,J_{23}=5.0,J_{24}=0.8Hz,H-2), 5.40(dd,1H,J_{34}=4.6Hz,H-3); ^{13}C NMR: 78.21(C-1), 48.17(C-2), 66.69(C-3), 65.42(C-4), 60.91(C-5).

18: ^{1}H NMR: 6.01(d,1H,J_{12}=5.8Hz,H-1),4.11(dd,1H,J_{23}=8.8Hz,H-2), 5.23(ddd,1H,J_{34}=5.2,J_{35}=0.8Hz, H-3); ^{13}C NMR: 77.91(C-1), 51.01(C-2), 67.40(C-3), 66.31(C-4), 61.24(C-5).

19: mp 112-113°C; $[\alpha]_D$ +97.5° (c 1, CH_2Cl_2); ^{1}H NMR: 5.45(d,1H,J_{12}=4.6Hz,H-1), 3.78(dd,1H,J_{23}=8.1Hz, H-2), 5.19(ddd,1H,J_{34}=5.4,J_{35}=0.9Hz,H-3).

20: mp 117-118°C; $[\alpha]_D$ +277.5° (c 2, CH_2Cl_2); ^{1}H NMR: 7.87(s,1H,H-1), 5.55(dd,1H,J_{34}=3.3,J_{35}=1.7Hz, H-3), 4.95(dt,1H,J_{45}=$J_{45'}$=1.7Hz,H-4); ^{13}C NMR: 157.99(C-1), 104.42(C-2), 65.37(C-3), 64.10(C-4), 61.47(C-5).

21: ^{1}H NMR: 4.53(d,1H,J_{12}=8.0Hz,H-1), 2.56(dd,1H,J_{23}=10.5Hz,H-2), 5.46(dd,1H,J_{34}=9.2Hz,H-3).

6. Preliminary experiments showed that the NH group in 10 and 19 can be silylated with $^{t}BuMe_2SiCl$ in the presence of DMAP. On the other hand, 10 and 19 deacetylated with MeONa in methanol gave relatively stable, water soluble β-lactam.

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