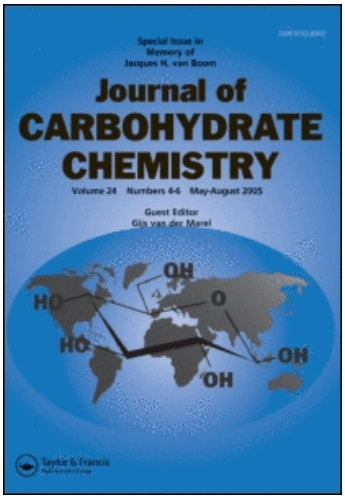


Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

An Entry to the Optically Pure β-Lactam Skeleton Based on 1,3-Dipolar Cycloaddition of Nitrones to 4,6-Di-O-Acetyl-2,3-Dideoxy-D-Threo-Hex-2-Enono-1,5-Lactone

Irma Panfil[a]; CzesLaw Belzecki[a]; Marek Chmielewski[a]
[a] Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw, Poland

To cite this Article Panfil, Irma , Belzecki, CzesLaw and Chmielewski, Marek(1987) 'An Entry to the Optically Pure β-Lactam Skeleton Based on 1,3-Dipolar Cycloaddition of Nitrones to 4,6-Di-O-Acetyl-2,3-Dideoxy-D-Threo-Hex-2-Enono-1,5-Lactone', Journal of Carbohydrate Chemistry, 6: 3, 463 — 470
To link to this Article: DOI: 10.1080/07328308708057933
URL: http://dx.doi.org/10.1080/07328308708057933

J. CARBOHYDRATE CHEMISTRY, 6(3), 463-470 (1987)

AN ENTRY TO THE OPTICALLY PURE β-LACTAM SKELETON BASED ON 1,3-DIPOLAR CYCLOADDITION OF NITRONES TO 4,6-DI-O-ACETYL-2,3-DIDEOXY-D-THREO--HEX-2-ENONO-1,5-LACTONE

Irma Panfil, Czesław Bełzecki, and Marek Chmielewski*

Institute of Organic Chemistry, Polish Academy of Sciences, 01224 Warsaw, Poland

Received December 16, 1986 - Final Form May 8, 1987

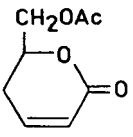
ABSTRACT

Saturated lactone 8, easily available by 1,3-dipolar cycloaddition of nitrone 4 to unsaturated lactone 7 was transformed into the β-lactam 22 having a polyol side chain at the C-3 position of the azetidinone ring. The same sequence of reactions, when applied to 9 and 10 failed to give the respective β-lactams owing to the removal of the nitrogen atoms from those molecules.

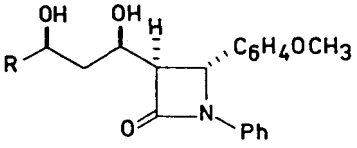
INTRODUCTION

Recently we have reported on a transformation of the racemic α,β-unsaturated δ-lactone 1 into β-lactams 2 and 3 having a polyol side chain.[1] The synthesis, based on the Tufariello[2] approach to β-lactams, consisted of 1,3-dipolar cycloaddition of a nitrone 4 to 1 followed by hydrogenolysis of the resulting isoxazolidine to the β-amino acid stage and subsequent cyclization to the azetidinone ring.

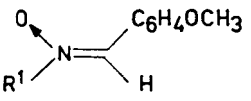
In this paper attention is directed to the threo lactone 7 derived from D-galactose as a source of enantiomerically pure β-lactams. Nitrones 4 - 6 were selected since they provide cycloadducts with a p-methoxybenzyl group which can be utilized further.[3] On the other hand the p-methoxybenzyl position is more resistant to hydrogenolysis which is necessary for spliting of the isoxazolidine N-O bond.[4]



1



2: R=H
3: R=CH_2OH



4: R^1=Ph
5: R^1=Me
6: R^1=Bn

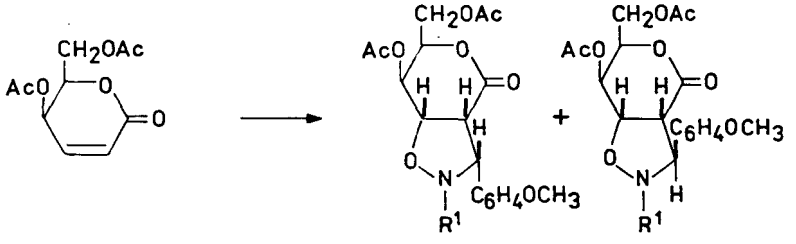
RESULTS AND DISCUSSION

Cycloaddition of nitrones 4 - 6 to lactone 7 proceeded stereoselectively affording anti - exo adducts 8 - 10 as the predominating products (Scheme 1). The configuration of the adducts 9, 10, 12, and 13 were assigned by analogy with data found previously for 8 and 11.[5] It is worth noting that in the ^1H NMR spectra of compounds 9 and 10, the isoxazolidine protons H-3, H-3a, and H-7a are displayed as broad signals. This is caused by the slow pyramidal inversion process at the isoxazolidine nitrogen atom,[6] and two N-configurational isomers are involved in the equilibrium. In contrast to 9 and 10, adducts 12 and 13 probably exist as single isomers. In the N-phenyl compounds 8 and 11 the nitrogen atom is in the plane of the phenyl ring due to coupling of the lone electron pair with the aromatic π electron system.

For further investigations we chose the isomers 8 - 10 which are the dominating products of cycloadditions. The transformation of cycloadducts into β-lactams was attempted in two stages (Scheme 2) owing to the sensitivity of the intermediates to undesirable lactonization. The first stage consisted of the deacetylation of compounds 8 - 10, neutralization to the respective free acids 14 - 16, and periodate oxidation leading to mixtures of hemiacetals 17 - 19. The structures of compounds 17 - 19 were assigned straightforwardly on the basis of MS and ^1H NMR data. Compounds 18 and 19 exhibited line broadening in ^1H NMR spectra taken at room temperature, which was probably caused, as with 9 and 10, by the slow inversion process at the nitrogen atom.

The next stage of the synthesis, involving reduction of the hemiacetal group to the hydroxy acid, silylation, hydrogenolysis of the isoxazolidine ring, and cyclization to the β-lactam was successfully accomplished for the hemiacetal 17 only. The same sequence of reactions, when applied to 18 and 19, failed to give the respective β-lactams owing to

Scheme 1



7	R^1=Ph	8	11
	R^1=Me	9	12
	R^1=Bn	10	13

deamination of these molecules. The β-lactam 22 was obtained from 17 in 60% overall yield.

It is worth mentioning that hydrogenolysis of the adduct 8 in acetic acid led to deamination of the substrate affording 23 as the only product.

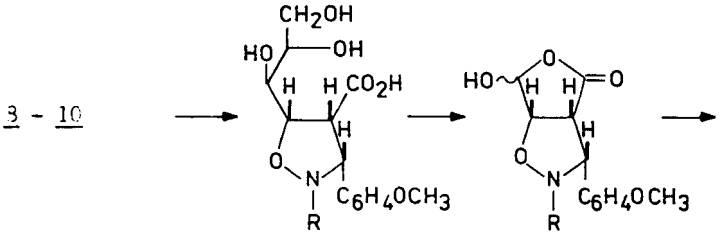
We have shown that opticaly pure α,β-unsaturated sugar lactones can be used for the construction of the β-lactam skeleton via the nitrone cycloaddition approach. However, substitution at the nitrogen atom seems to be crucial for the successful hydrogenolysis of the isoxazolidine five membered ring bearing an aryl group at the C-3 carbon atom; N-alkyl or N-benzyl substituents promote further hydrogenolysis leading to deamination of the substrate.

EXPERIMENTAL

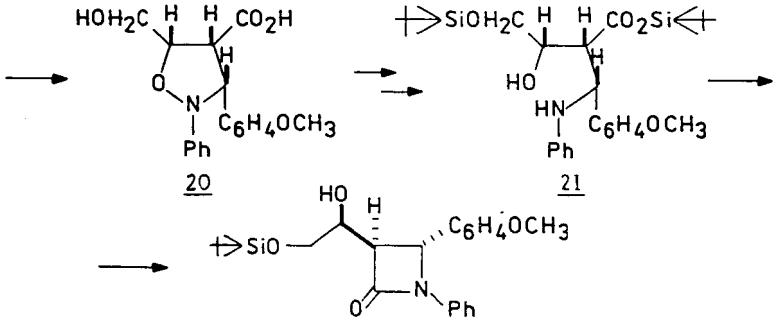
General procedures. ^{1}H NMR spectra were recorded for solutions in $CDCl_3$ on a Bruker - 300 spectrometer (δ scale, TMS=0 ppm). IR spectra were recorded on a Unicam SP-200 spectrophotometer. Optical rotations were measured on a Perkin-Elmer 141 spectropolarimeter. Mass spectra were recorded with Finigan Mat 8200 mass spectrometer. TLC was performed with silica gel Merck (230-400 mesh). Melting points are uncorrected.

Nitrones 5 and 6 were prepared using anisaldehyde and N-methyl or N-benzylhydroxylamine respectively according to the procedure described

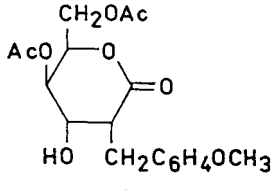
Scheme 2



R =Ph	14	17
R =Me	15	18
R =Bn	16	19



22



23

earlier.[7] Cycloadducts 8 and 11 were obtained from lactone 1[8] and nitrones 4 - 6 according to the procedure described previously.[5]

General method of cycloaddition. A solution (10-20%) of equimolar amounts of the nitrone 5 or 6 and the lactone 7 in toluene was refluxed under nitrogen for 8 h. The progress of the reaction was monitored by TLC. The crude post-reaction mixtures were concentrated and separated into respective diastereomeric adducts on a silica gel column.

(3R,3aR,6R,7S,7aS) and (3S,3aR,6R,7S,7aS)-7-Acetoxy-6-acetoxymethyl--3-p-methoxyphenyl-2-methyl-4-oxo-tetrahydropyrano[3,4-d]isoxazolidine (9 and 12). Diastereomers 9 and 12 were obtained from 7 and 5 in 90% yield in the ratio of 15:1 respectively:

9; mp 122-124 °C; $(\alpha)_D$ +10.0 ° (c 1, CH_2Cl_2); IR (CH_2Cl_2) 1750 cm^{-1}; ^1H NMR ($CDCl_3$) 2.11, 2.12 (2s, 6H, 2OAc), 2.59 (bs, 3H, NCH_3), 3.45 (bs, 1H, w/2 = 22 Hz, H-3), 3.55 (t, 1H, $J_{3,3a}$ =8.9, $J_{3a,7a}$ = 7.9 Hz, H-3a), 3.81 (s, 3H, OCH_3), 4.27 (m, 2H, CH_2OAc), 4.49 (dd, 1H, $J_{7a,7}$ = 2.8 Hz, H-7a), 5.07 (dt, 1H, $J_{6,7}$ = 1.3, $\Sigma J_{6,CH_2}$ = 12.8 Hz, H-6), 5.20 (dd, 1H, H-7), 6.90, 7.28 (2m, 4H, aromatic); MS m/z: M^+, 393.1423 (393.1423 for $C_{19}H_{23}NO_8$).

12; colorless syrup; $(\alpha)_D$ +182.7 ° (c 1, CH_2Cl_2); IR (CH_2Cl_2) 1750 cm^{-1}; ^1H NMR ($CDCl_3$) 2.10, 2.11 (2s, 6H, 2OAc), 2.60 (s, 3H, NCH_3), 3.78 (t, 1H, $J_{3,3a}$ = 8.8, $J_{3a,7a}$ = 8.4 Hz, H-3a), 3.79 (s, 3H, OCH_3), 3.97 (d, 1H, H-3), 4.22 (m, 2H, CH_2OAc), 4.53 (dd, 1H, $J_{7,7a}$ = 2.9 Hz, H-7a), 5.23 (dd, 1H, $J_{6,7}$ = 1.3 Hz, H-7), 5.35 (dt, 1H, $\Sigma J_{6,CH_2}$ = 13.0 Hz, H-6). MS m/z: M^+ 393.

(3R,3aR,6R,7S,7aS) and (3S,3aR,6R,7S,7aS)-7-Acetoxy-6-acetoxymethyl--2-benzyl-3-p-methoxyphenyl-4-oxo-tetrahydropyrano[3,4-d]isoxazolidine (10 and 13). Diastereomers 10 and 13 were obtained from 7 and 6 in 80% yield in the ratio of 6:1 respectively.

10; colorless syrup: $(\alpha)_D$-18.2 ° (c 1, CH_2Cl_2); IR (CH_2Cl_2) 1755 cm^{-1}; ^1H NMR ($CDCl_3$) 2.10, 2.12 (2s, 6H, 2OAc), 3.54 (t, 1H, $J_{3,3a}$ = 9.3, $J_{3a,7a}$ = 8.0 Hz, H-3a), 3.68, 4.04 (2d, 2H, NCH_2Ph), 3.72 (bs, 1H, w/2 = 22 Hz, H-3), 3.82 (s, 3H, OCH_3), 4.23 (m, 2H, CH_2OAc), 4.48 (dd, 1H, $J_{7,7a}$ = 2.5 Hz, H-7a), 4.93 (dt, 1H, $J_{6,7}$ = 1.1, $\Sigma J_{6,CH_2}$ = 12.5 Hz, H-6), 5.19 (dd, 1H, H-7), 6.9-7.4 (m, 9H, aromatic); MS m/z: M^+, 469.1737 (469.1737 for $C_{25}H_{27}NO_8$).

13; colorless syrup: $(\alpha)_D$ +160.3 ° (c 1, CH_2Cl_2); IR (CH_2Cl_2) 1750 cm^{-1}; ^1H NMR ($CDCl_3$) 2.09, 2.10 (2s, 6H, 2OAc), 3.81 (s, 3H, OCH_3), 3.82 (t, 1H, $J_{3,3a}$ = 8.5, $J_{3a,7a}$ = 8.5 Hz, H-3a), 3.68, 4.08 (2d, 2H, CH_2Ph), 4.18 (dd, 1H, $J_{6,A}$ = 6.6, $J_{A,B}$ = 11.7 Hz, CH_AH_BOAc), 4.23 (d, 1H, H-3),

4.24 (dd, 1H, $J_{6,B}$ = 6.6 Hz, $CH_A\underline{H}_BOAc$), 4.54 (dd, 1H, $J_{7,7a}$ = 3.0 Hz, H-7a), 5.18 (dd, 1H, $J_{6,7}$ = 1.2 Hz, H-7), 5.32 (dt, 1H, H-6), 6.9-7.4 (m, 9H, aromatic); MS m/z: M^+, 469.1737 (469.1737 for $C_{25}H_{27}NO_8$).

(3R,3aR,6aS)-6-Hydroxy-3-p-methoxyphenyl-2-phenyl-4-oxo-terahydro-furano[3,4-d]isoxazolidine (17). To a freshly prepared solution of sodium methoxide (32 mg Na in 2 mL of methanol) 8 (0.15 g, 0.3 mmol) was added and the mixture was stirred at room temperature for 15 min. Subsequently the solution was acidified with 1N HCl to pH = 4, methanol was evaporated, and the residue was extracted with dichloromethane. The extract was dried and concentrated to dryness. the crude 14 (0.1 g), mp 150-155 °C was used for the next step without purification. The acid 14 (0.1 g) was dissolved in methanol (5 mL) and treated with sodium metaperiodate (0.106 mg, 0.5 mmol) in water (2 mL) at room temperature for 24 h. The precipitate of sodium iodate was filtered off, methanol was evaporated and the remaining solution was extracted with dichloromethane. The extract was dried and concentrated. The oily residue was purified on a silica gel column to give 17 (0.054 g; 50% overall yield) as a mixture of both hemiacetals in about a 1:1 ratio: colorless syrup; IR (nujol) 3260, 1785 cm^{-1}; ^1H NMR ($CDCl_3$), signals due to the first anomer 3.78 (t, 1H, $J_{3,3a}$ = 9.3, $J_{3a,6a}$ = 8.7 Hz, H-3a), 4.50 (d, 1H, H-3), 5.15 (dd, 1H, $J_{6,6a}$ = 4.6 Hz, H-6a), 5.96 (d, 1H, H-6); signals due to the second anomer 3.87 (dd, 1H, $J_{3,3a}$ = 8.9, $J_{3a,6a}$ = 7.8 Hz, H-3a), 4.74 (d, 1H, H-3), 4.89 (dd, 1H, $J_{6,6a}$ = 1.5 Hz, H-6a), 6.00 (d, 1H, H-6); MS m/z: M^+ 327.

(3R,3aR,6aS)-6-Hydroxy-3-p-methoxyphenyl-2-methyl-4-oxo-tetrahydro-furano[3,4-d]isoxazolidine (18). Compound 18 was obtained from 9 according to the procedure described for 17: colorless oil; IR ($CDCl_3$) 3350, 1785 cm^{-1}; ^1H NMR ($CDCl_3$) 2.45, 2.58 (2bs, 3H, NCH_3 of both hemiacetals), 3.5-4.0 (m, 2H, H-3,3a of both isomers), 3.82 (s, 3H, OCH_3), 4.72 (bd, H-6a of major isomer), 5.00 (bs, H-6a of minor isomer), 5.81 (bs, H-6 of major isomer), 5.88 (bs, H-6 of minor isomer), 6.8-7.4 (m, 9H, aromatic); MS m/z: M^+ 265.

(3R,3aR,6aS)-6-Hydroxy-3-p-methoxyphenyl-2-benzyl-4-oxo-tetrahydro-furano[3,4-d]isoxazolidine (19). Compound 19 was obtained from 10 according to the procedure described for 17: colorless oil; IR (CH_2Cl_2) 3570, 3470, 1780 cm^{-1}; ^1H NMR ($CDCl_3$) 3.2-4.2 (m, 4H, H-3a,6a, N-benzyl of both isomers), 3.80, 3.82 (2s, 3H, OCH_3 of both isomers), 4.69 (d, 1H, $J_{3,3a}$ = 6.3 Hz, H-3), 5.73 (bs, 0.5H, H-6 of the first isomer), 5.79 (d, 0.5 H, $J_{6,6a}$ = 4.9 Hz, H-6 of the second isomer), 6.8-7.6 (m, 9H, aromatic); MS m/z: M^+ 341.

(3R,4R)-3-[(1'S)-1'-Hydroxy-2'-tert-butyldimethylsilyloxyethyl]-4--p-methoxyphenyl-1-phenylazetidinone-2 (22). Compound 17 (0.065 g, 0.2 mmol) and sodium cyanoborohydride (12.5 g) were dissolved in 2 mL of methanol. A trace of methyl orange was added and 2N HCl - methanol was added dropwise with stirring in order to maintain the red color, and after ca 15 min the red color disappeared very slowly. Stirring was continued for an additional 45 min and then the methanol was evaporated in vacuo. The residue was taken up in 3 mL of water and extracted with ether. The extract was dried and concentrated. The oily residue was dissolved in DMF (0.5 mL), treated with tert-butyldimethylsilyl chloride (75 mg) and imidazole (34 mg), and left overnight at room temperature. Water (2 mL) was added to the mixture and the solution was extracted with ether. The extract was dried, evaporated, and passed through silica gel using ethyl ether as an eluent to afford 21 as a colorless syrup (35 mg, 30%) which was taken directly to the next step. Compound 21 (0.12 g) in methanol (20 mL) was shaken at room temperature in the presence of 10% Pd/C under hydrogen (2 atm) for 2 h. The catalyst was filtered off and the methanol was evaporated. The residue was dissolved in dichloromethane (15 mL) and treated with 2-chloro-1-methylpyridinium iodide (85 mg) and triethylamine (66 mg).[9] The mixture was stirred at room temperature for 0.5 h and left overnight. The solvent was evaporated and the crude oil was purified on a silica gel column to give 22 (55 mg, 60%): colorless syrup; $[\alpha]_D$ +36.5 ° (c 1, CH_2Cl_2); IR (CH_2Cl_2) 3400, 1840 cm^{-1}; ^1H NMR ($CDCl_3$) 0.08, 0.09 (2s, 6H, $Si(CH_3)_2$), 0.92 (s, 9H, t-Bu), 3.65 (dd, 1H, $J_{2'a,2'b}$ = 11.9, $J_{1',2'a}$ = 3.4 Hz, H-2'a), 3.80 (s, 3H, OCH_3), 3.84 (dd, 1H, $J_{1',2'b}$ = 3.9 Hz, H-2'b), 3.98 (dd, 1H, $J_{1',3}$ = 4.2, $J_{3,4}$ = 7.1 Hz, H-3), 4.47 (q, 1H, H-1'), 4.76 (d, 1H, H-4); MS m/z: M^+ 427.2179 (427.2179 for $C_{24}H_{33}NO_4Si$).

4,6-Di-O-acetyl-2-deoxy-2-(p-methoxybenzyl)-D-gulo-aldono-1,5-lactone (23). A mixture of compound 8 (0.5 g, 1.1 mmol) in acetic acid (50 mL) was hydrogenated in the presence of 10% Pd/C at 3 atm for 3 h. The catalyst was filtered off, the filtrate was concentrated under reduced pressure to dryness, and purified on a silica gel column to give 23 (0.36 g, 90%): colorless syrup; $[\alpha]_D$ -54.6 ° (c 1, Ch_2Cl_2); IR (film) 3460, 1740, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) 2.06, 2.08 (2s, 6H, 2OAc), 2.79 (ddd, 1H, $J_{2,A}$ = 4.6, $J_{2,B}$ = 7.1, $J_{2,3}$ = 8.1 Hz, H-2), 3.04 (dd, 1H, $J_{A,B}$ = 14.2 Hz, CH_AH_BPh), 3.14 (dd, 1H, CH_AH_BPh), 3.72 (dd, 1H, $J_{3,4}$ = 1.9 Hz, H-3), 3.77 (s, 3H, OCH_3), 4.25 (d, 2H, CH_2OAc), 4.78 (dt, 1H, $J_{4,5}$ = 1.8, $\Sigma J_{5,CH_2}$ = 14.0 Hz, H-5), 4.90 (t, 1H, H-4), 6.82, 7.23 (2m, 4H, aromatic); MS m/z: M^+ 366.1315 (366.1315 for $C_{18}H_{22}O_8$).

ACKNOWLEDGMENTS

The authors wish to thank Dr. Igor Tvaroška, Institute of Chemistry, Slovak Academy of Sciences, CS-842 38 Bratislava, for the recording of the ^{1}H NMR spectra. This work was supported by grant No. CPBP-01.13.2.15. from the Polish Academy of Sciences.

REFERENCES

1. I. Panfil, M. Chmielewski, and C. Belzecki, Heterocycles, 24, 1609 (1986).

2. J. J. Tufariello, G. E. Lee, P. A. Senaratne, and M. Al-Nuri, Tetrahedron Letters, 4359 (1979).

3. D. A. Evans and E. B. Sjogren, Tetrahedron Letters, 26, 3787 (1985).

4. D. R. Buckle, J. Chem. Soc. Perkin I, 627 (1982); Y. Oikawa, T. Tanaka, K. Horita, T. Yoshioka, and O. Yonemitsu, Tetrahedron Letters, 25, 5393 (1984); Y. Oikawa, T. Tanaka, K. Horita, and O. Yonemitsu, Tetrahedron Letters, 25, 5397 (1984).

5. I. Panfil and M. Chmielewski, Tetrahedron, 41, 4713 (1985).

6. R. Gree, F. Tonnard, and R. Carrie, Tetrahedron, 32, 675 (1976).

7. J. Hamer and A. Macaluso, Chem. Rev., 64, 473 (1964).

8. J. Mieczkowski, J. Jurczak, M. Chmielewski, and A. Zamojski, Carbohydr. Res., 56, 180 (1977); M. Chmielewski, J. Jurczak, and S. Maciejewski, Carbohydr. Res., to be published (1987).

9. H. Huang, N. Iwasawa, and T. Mukaiyama, Chem. Letters, 1465 (1984).