ELSEVIER

Carbohydrate Research 268 (1995) 301–305

CARBOHYDRATE
RESEARCH

Note

# Synthesis of sugar pyrrolidine derivatives from methyl 4,6-*O*-benzylidene-2-deoxy-2-dimethylamino-α-D-altropyranoside *N*-oxide

J. Chastanet [a], G. Roussi [a], G. Negrón [b,*]

[a] *Institut de Chimie des Substances Naturelles, C.N.R.S., 91198, Gif-sur-Yvette, France*
[b] *Area de Química, Universidad Autónoma Metropolitana-Azcapotzalco, Av. San Pablo No. 180, C.P. 02200, México D.F., México*

Received 4 February 1994; accepted in revised form 23 September 1994

*Keywords:* Pyrrolidine derivatives; Methyl 4,6-*O*-benzylidene-2-deoxy-2-dimethylamin-α-D-altropyranoside *N*-oxide

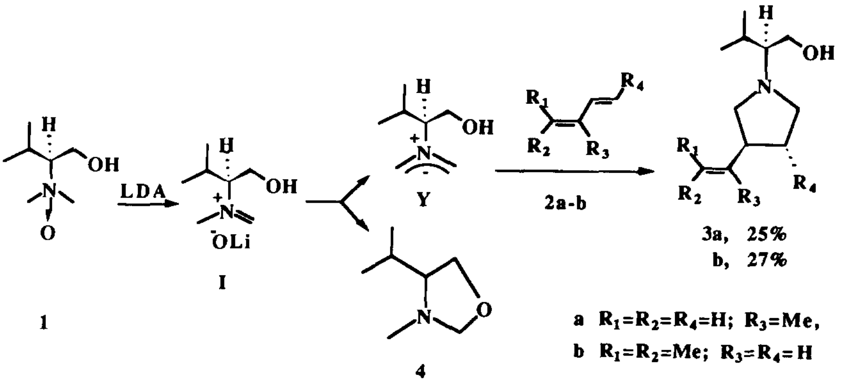
The preparation of pyrrolidines had received extensive attention in recent years, partly due to the important biological activities exhibited by several polysubstituted derivatives [1], among which α-kainic acid exhibits potent neurotransmitting activity in the central nervous system [2]. 1,3-Dipolar cycloaddition of azomethine ylides to olefins represents a powerful route to various substituted pyrrolidines [3]. However, little is known about nonactivated dienes as dipolarophiles, except the preliminary results obtained from our studies on highly reactive non-stabilized ylide Y generated from trimethylamine *N*-oxide [4a] and methylvalinol-*N*-oxide **1** [4b]. In this case, the cycloaddition on dienes **2a–b** gave poor yields of pyrrolidines **3**, due to the concomitant formation of oxazolidine **4** resulting from the intramolecular trapping of the iminium salt intermediate I by lithium alkoxide [5].

As an extension of these preliminary investigations, we studied the reaction of conjugated dienes **2a–d** with ylides generated from amino sugar-*N*-oxide **5** [6] in order to determine whether carbohydrate pyrrolidines **6** could be prepared in this fashion. To prevent the formation of oxazolidine, the hydroxy and *N*-oxide groups possess *trans* diaxial geometry in the starting *N*-oxide [6].

---

[*] Corresponding author.

*SSDI* 0008-6215(94)00331-9



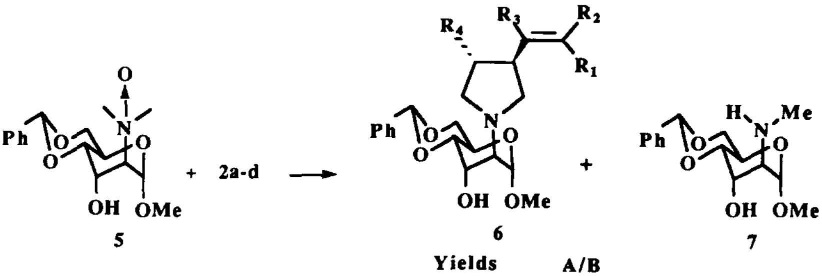
a $R_1=R_2=R_4=H$; $R_3=Me$,
b $R_1=R_2=Me$; $R_3=R_4=H$

Scheme 1.

## 1. Results and Discussion

When amino sugar-*N*-oxide **5**, prepared by oxidation of the corresponding tertiary amine [6], was treated with LDA at 0°C in the presence of dienes **2a–d**, monopyrrolidines **6a–d** were obtained in fair yield (50%). These products resulted from a regiospecific cycloaddition of the ylide Y with the non-disubstituted double bond of the diene. Various amounts of demethylated amine **7** were also formed as previously obtained when using stilbene as dipolarophile [6].

Pyrrolidines **6** were obtained as a mixture of diastereomers, and the unexpectedly low stereoselectivity A : B of the reaction with compounds **2a–c** could be due to the lack of steric hindrance in transition state $TS_1$ and $TS_2$ as indicated by the increased diastereoselectivity with diphenylbutadiene **2d** which led to a 70:30 mixture of diastereomeric pyrrolidines **6d**.



| | | Yields | A/B | |
|---|---|---|---|---|
| a $R_1=R_2=R_4=H$; $R_3=Me$ | 6a | 53% | 60/40 | 16% |
| b $R_1=R_2=Me$; $R_3=R_4=H$ | b | 34% | 55/45 | 30% |
| c $R_1=R_2=H$; $R_3=R_4=Me$ | c | 51% | 60/40 | 30% |
| d $R_1=R_3=H$; $R_2=R_4=Ph$ | d | 53% | 70/30 | 26% |

Scheme 2.

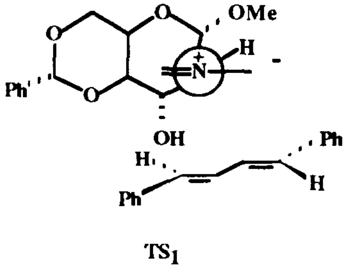
## 2. Experimental

*General methods.*—$^1$H NMR and $^{13}$C NMR spectra were recorded in $CDCl_3$ on a Bruker WP 200-54 NMR spectrometer (200 MHz); chemical shifts relative to tetramethylsilane are given in $\delta$. Mass spectra (ms) were obtained on an AEIMS-50 spectrometer, and CIMS and FAB were recorded on an AEI-MS-9 spectrometer. The reactions were monitored by thin–layer chromatography (TLC) and $^1$H NMR. Purifications were achieved by column chromatography, preparative thin–layer chromatography (TLC), and high pressure liquid chromatography (HPLC) on a Novapak C-18 column (3.5 × 150 mm, 70:30:0.1 $MeOH–H_2O–NEt_3$).

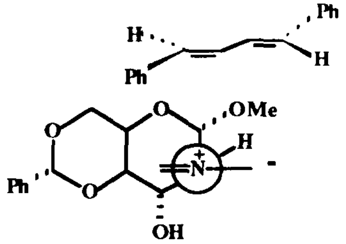
*General procedure.*—Amine *N*-oxide **5** (1 mmol) was dried immediately before use by heating under vacuum at 30°C for 3 h in a three–necked flask equipped with a rubber septum. Diene **2** in anhyd THF was then added via a syringe, and the suspension was cooled to 0°C before LDA (10-equiv) was introduced. The reaction was monitored by TLC. The separation by chromatography (column or ccm) of the various pairs of diastereomers could not be realized. The $^{13}$C NMR spectra provided $\delta$ values of the major compound formed, but differentiation of the characteristic protons was not possible in the $^1$H NMR spectra. The diastereomeric ratios A:B were determined by HPLC.

*Methyl 4,6-*O*-benzylidene-2-deoxy-2-(3-isoprenyl-pyrrolidinyl)-α-*D*-altropyranoside* (**6a**) *and methyl 4,6-*O*-benzylidene-2-deoxy-2-methylamino-α-*D*-altropyranoside* (**7**).—*N*-Oxide **5** [6] (325 mg, 1 mmol) and 2-methyl-1,3-butadiene (**2a**; 74.8 mg, 1.1 mmol) were treated with LDA (10 mmol) at 0°C for 3 h. The reaction yielded, after usual workup and chromatography on alumina (8:2 heptane-EtOAc), **6a** (200 mg, 0.53 mmol, 53%) as a mixture of diastereomers A:B in a 60:40 ratio as deduced from HPLC analysis, and **7** (48 mg, 0.16 mmol, 16%) [6].

Compound **6a** was recovered as an oil; $^1$H NMR: $\delta$ 1.73–1.97 (m, 2 H, H-4′), 1.80 (s, 3 H, Me), 2.48–2.68 (m, 1 H, H-3′), 2.68–3.24 (m, 4 H, H-2′,5′), 3.48–4.63 (m, 6 H, H-2,3,4,5,6), 3.63 (s, 3 H, OMe), 4.87–5.05 (bs, 2 H, $CH_2=$), 5.07–5.14 (d, 1 H, *J* 7 Hz, H-1), 5.92 (s, 1 H, H-7), 7.63–8.09 (m, 5 H, aromatic); $^{13}$C NMR $\delta$ 20.1 Me, 30.1 C-4′, 45.5 C-3′, 53.5 C-2, 56.6, OMe, 57.7 C-5′, 59.7 C-5, 68.8–69.0 C-2 and C-3, 70.4



TS$_1$



TS$_2$

C-6, 77.8 C-4, 101.3 C-1, 103.4 C-7, 110.8 $CH_2$=, 127.5, 129.3, 130.1 aromatic carbons, 138.5 quarternary vinylic carbon, 147.7 quaternary aromatic carbon.
ms m/z 375, 360, 344, 264, 154, 150, 124; HRMS: calcd for $C_{21}H_{29}NO_5$: 375.2045; found, 375.2033.

*Methyl 4,6-*O*-benzylidene-2-deoxy-2-(3-isobutenyl-pyrrolidinyl)-α-*D*-altropyranoside* (**6b**) *and methyl-4,6-*O*-benzylidene-2-deoxy-2-methylamino-α-*D*-altropyranoside* (**7**).—*N*-Oxide **5** (150 mg, 0.46 mmol) and 4-methyl-1,3-pentadiene **2b** (46 mg, 0.56 mmol) were treated with LDA for 2 h at 0°C. The reaction yielded, after usual workup and chromatography on alumina (80 : 20 heptane–EtOAc), **6b** (61 mg, 0.15 mmol, 34%) as a mixture of diastereomers in a 55 : 45 ratio as determined by hplc analysis, and **7** (40 mg, 0.14 mmol, 30%) [6].

Compound **6b** was an oil; $^1$H NMR: δ 1.48–1.58 (m, 1 H, H-4′), 1.63 (s, 3 H, Me), 1.67 (s, 3 H, Me), 1.93–2.16 (m, 1 H, H-3′), 2.17–2.39 (m, 1 H, H-4′), 2.56–3.16 (m, 4 H, H-2′,5), 3.43 (s, 3 H, OMe), 3.86–4.43 (m, 6 H, H-2,3,4,5,6), 4.67–4.99 (d, *J* 14 Hz, 1 H, H-1), 5.06 (bs, 1 H, vinylic proton), 5.63 (s, 1 H, H-7), 7.23–7.66 (m, 5 H, aromatic protons); $^{13}$C NMR δ 18.1 Me, 25.7 C-4′, 25.7 Me, 36.4 C-3′, 52.5 C-2′, 55.6 OMe, 58.7 C-5, 58.9 C-5′, 67.6–67.7 C-2,3, 69.2 C-6, 76.5 C-4, 100.1 C-1, 102.3 C-7, 126.2 $CH=CMe_2$, 127–129 aromatic carbons, 132.0 $=CMe_2$, 137.6 quaternary aromatic carbon; HRMS, calcd for $C_{22}H_{31}NO_5$: 389.2202; found, 389.2196.

*Methyl 4,6-*O*-benzylidene-2-deoxy-2-(*trans*-3-methyl-4-isoprenyl-pyrrolidinyl)-α-*D*-altropyranoside* (**6c**) *and methyl 4,6-*O*-benzylidene-2-deoxy-2-methylamino-α-*D*-altropyranoside* (**7**).—*N*-Oxide **5** (325 mg, 1 mmol) and *trans*-2-methyl-1,3-pentadiene **2c** (123 mg, 1.5 mmol) were treated with LDA (10 mmol) at 0°C for 2 h. The reaction yielded, after usual work up and chromatography on alumina (80 : 20 heptane–EtOAc), **6c** (200 mg, 0.51 mmol, 51%) as a mixture of diastereomers in a 60 : 40 ratio as deduced from HPLC analysis, and **7** (82 mg, 0.29 mmol, 30%) [6].

Compound **6c** was an oil; $^1$H NMR: δ 0.95–1.07 (d, *J* 13 Hz, 3 H, Me), 1.59–1.66 (m, 1 H, H-4′), 1.75 (s, 3 H, $-CH_3$), 1.99–2.23 (m, 1 H, H-3′), 2.35–3.13 (m, 4 H, H-2′,5′), 3.43 (s, 3 H, OMe), 3.60–4.39 (m, 6 H, H-2,3,4,5,6), 4.69–4.93 (m, 1 H, H-1), 4.79 (s, 1 H, H-1), 5.67 (s, 1 H, H-7), 7.29–7.63 (m, 5 H, aromatic); $^{13}$C NMR: δ 18.4 Me, 20.3 –Me, 37.0 C-3′,4′, 53.8 C-2′, 56.0 OMe, 57.7 C-5, 59.1 C-5′, 60.7; 65.1, 67.9, 69.7, 77.1, 100.7 C-1, 102.8 C-7, 111.5 $CH_2$=, 121.3, 126.8, 128.7, 129.5, 138.0 quaternary vinylic carbon; 145.7 quaternary aromatic carbon; FABMS: *m/z* 390, 389, 388, 358, 332; 196, 180; HRMS, calcd for $C_{22}H_{31}NO_5$: 389.2202; found: 389.2185.

*Methyl 4,6-*O*-benzylidene-2-deoxy-2-(*trans*-3-phenyl-4-phenylethenyl-pyrrolidinyl)-α-*D*-altropyranoside* (**6d**) *and methyl 4,6-*O*-benzylidene-2-deoxy-2-methylamino-α-*D*-altropyranoside* (**7**).—*N*-Oxide **5** [6] (325 mg, 1 mmol) and *trans*-1,4-diphenyl-1,3-butadiene **2d** (226 mg, 2.1 mmol) were treated with LDA (10 mmol) at 0°C for 2 h. The reaction yielded, after usual work up and chromatography on alumina (80 : 20 heptane–EtOAc), **6d** (274 mg, 0.53 mmol, 53%) as a mixture of diastereomers in a 70 : 30 ratio as deduced from HPLC analysis, and **7** (78 mg, 0.26 mmol, 26%) [6].

Compound **6d** was an oil, $^1$H NMR δ 2.64–3.29 (m, 5 H, H-2′,3′,5′), 3.39–3.5 6 (m, 1 H, H-4′), 3.44 (s, 3 H, OMe), 3.83–4.46 (m, 6 H, H-2,3,4,5,6), 4.94 (s, 1 H, H-1), 5.69 (s, 1 H, H-7), 6.16–6.39 (m, 2 H, vinylic), 7.03–7.76 (m, 15 H, aromatic); FABMS: *m/z* 513, 498, 291; HRMS, calcd for $C_{32}H_{35}NO_5$: 513.2514; found: 513.2506.

## References

[1] (a) R.C. Brown and A.H. Ingall, in G. Pattenden (Ed.), *General and Synthetic Methods,* Chemical Society, London, 1981, Vol. 5, pp. 336–344, and earlier volumes of this series; (b) A.R. Pinder, in M.F. Grundon (Ed.), *The Alkaloids,* Chemical Society, London, 1982, Vol. 12, pp. 29–35, and earlier volumes of this series; (c) W. Oppolzer and V. Snieckus, *Angew. Chem., Int. Ed. Engl.,* 17 (1978) 476–486.

[2] K. Hashimoto and H. Shirahama, *Tetrahedron Lett.,* 32 (1991) 2625–2628, and references therein.

[3] (a) R. Huisgen, in A. Padwa (Ed.), *1,3-Dipolar Cycloaddition. Introduction, Survey and Mechanism in 1,3-Dipolar Cycloaddition Chemistry,* Wiley, New York, 1986, pp 1–163; (b) E. Vedejs, in D.P. Curran (Ed.), *Advances in Cycloaddition,* Vol. 33, JAI Press, Greenwich, 1988, p 33; (c) O. Tsuge and S. Kanemasa, *Adv. Heterocycl. Chem.,* 45 (1989) 231–349.

[4] (a) R. Beugelmans, L. Benadjila-Iguertsira, J. Chastanet, G. Negron, and G. Roussi, *Can. J. Chem.* 63 (1985) 725–734; (b) G. Negron, G. Roussi, and J. Zhang, *Heterocycles,* 34 (1992) 293–301.

[5] G. Roussi and J. Zhang, *Tetrahedron Lett.,* 32 (1991) 1443–1446.

[6] J. Chastanet, H. Fathallah, G. Negron, and G. Roussi, *Heterocycles,* 34 (1992) 1565–1572.

[7] G. Roussi and J. Zhang, *Tetrahedron,* 47 (1991) 5161–5172.