Stereoselective Ring Closure of 6-[[(Methylamino)carbonyl]oxy]-2*H*-pyran-3(6*H*)-ones. Formation of the 5*H*-Pyrano[3,2-*d*]oxazole-2,6-dione Ring System

Minas P. Georgiadis* and Elias A. Couladouros [1]

Agricultural University of Athens, Chemistry Laboratory,
Iera Odos 75, Athens, 11855, Greece
Received February 26, 1990

The stereospecific formation of the 5*H*-pyrano[3,2-*d*]oxazole-2,6-dione ring system from 2,2-disubstituted-6-[[(methylamino)carbonyl]oxy]-2*H*-pyran-3(6*H*)-one *via* an enolization at C-5 is presented. The outcome of the same reaction in the case of 2-monosubstituted 2*H*-pyran-3(6*H*)-ones is also discussed.

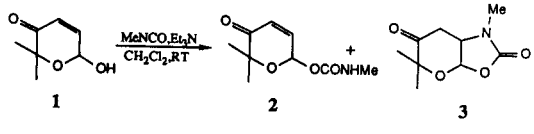
J. Heterocyclic Chem., **27**, 1757 (1990).

Introduction.

The 2*H*-pyran-3(6*H*)-ones of the general formula **1**, are widely used as starting materials for the synthesis of a variety of compounds [2-3] including several sugar and aminosugar derivatives [4]. For example, 1,4-addition of an *N*-nucleophile at the Michael center of **1**, gives efficiently 2-amino-sugar precursors for the synthesis of antibiotics [5], anticoccidials [6], *etc.* Although the conditions of the above addition have been well studied [7], the reported stereoselectivity is usually poor.

No attention has been given, so far, to the 5*H*-pyrano-[3,2-*d*]oxazole-2,6-dione ring system, **3**, (Scheme I) a minor by-product formed during the conversion of the hemiacetal hydroxyl group of **1**, to an aminocarbonyloxy group [3]. The fact that this by-product which is formed in one step from **1**, may be considered as a protected 2-aminosugar precursor, stimulated our interest to improve the yield towards **3** under stereocontrolled conditions.

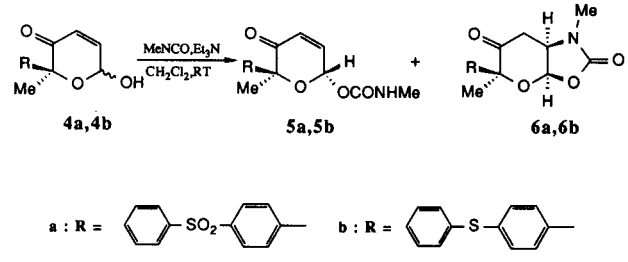
Scheme I



Results and Discussion.

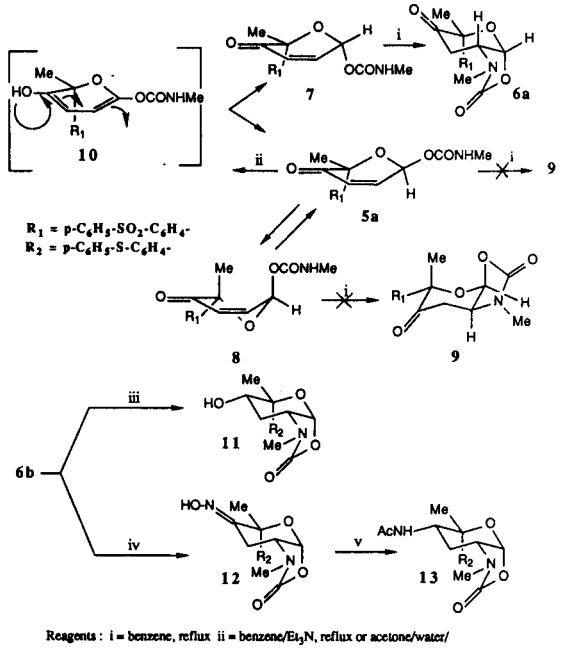
We have observed [3b] that when an anomeric mixture of **4a** (Scheme II), is treated with methyl isocyanate and triethylamine in methylene dichloride at room temperature, only one isomer of carbamate **5a** is formed, together with 1,5-dimethyl-5-[4-(benzenesulfonyl)phenyl]dihydro-[1*H*,7*H*]-5*H*-pyrano[3,2-*d*]oxazole-2,6-dione, **6a**, as a minor by-product. It must be noted that the conformation of **5a** is correlated with the β-anomer of **4a**, while the conformation of the fused system **6a**, is correlated with the α-anomer. In a second run, using **4b** as a starting material, we obtained analogous results.

Scheme II



It is obvious from the above observation that the bicyclic compound **6a** (Scheme III) is formed *via* the intermediate **7**, by an endo-Michael reaction. The axial orientation of the [(methylamino)carbonyl]oxy group favours this intramolecular Michael addition. Since the intermediate **7** is not detectable during the reaction, this transformation should be fast.

Scheme III



On the contrary, the β-anomer **5a** is quite stable even after refluxing in acetone or benzene solution for 48 hours. The position of the nucleophile on **5a** is very far apart from the electrophilic center while on its conformer **8** there is a repulsion between the *syn*-diaxial oriented methyl[(methylamino)carbonyl]oxy groups. Thus, compound **9** is not formed at all.

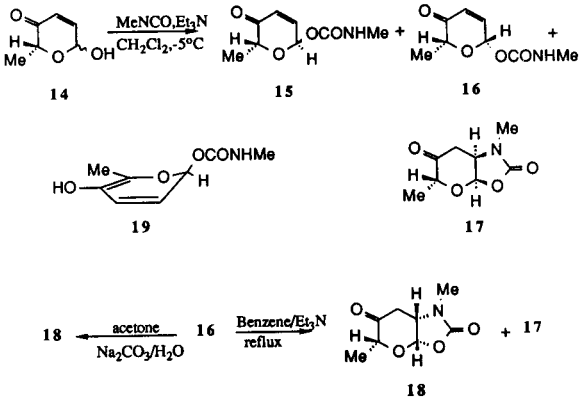
However, when **5a** was treated with triethylamine at elevated temperature it did react yielding **6a** instead of isomer **9**. The formation of **6a** from **5a**, due to an isomerization under basic conditions may be explained *via* an enolization of the unsaturated ketone **5a** to **10**. Intermediate **10**, has an sp^2 hybridization at C-1, thus it may be isomerized again either to the starting compound **5a** or to its reactive isomer **7**, which is subsequently and irreversibly fast converted to the fused system **6a**.

The above transformation is quantitative, thus oxazole **6a** is synthesized from **4a** stereospecifically in two steps with 92% overall yield.

Since the rigid molecules **6a** and **6b** have no flexibility it is easy to convert the carbonyl group on the pyran ring stereospecifically to a hydroxy or an amino functionality. Thus, reduction of **6b** with lithium aluminum hydride gave only one alcohol **11** having the hydroxyl group equatorially oriented, while oximation and catalytic reduction-acetylation yielded **13**, having the acetylamino-group equatorially oriented.

In the case of the more reactive molecule **14**, the outcome of the above mentioned ring closure is not the same. When **14** is treated with methyl isocyanate/triethylamine at −5° (Scheme IV) the main product which is isolated from the reaction mixture is the α-anomer **15** (yield 38%), while the β-anomer **16** is isolated in only 26% yield. A small amount of the expected bicyclic analog **17** is also detected (yield 5.9%). The reaction is carried out at lower temperature than before, because **14** is very sensitive in alkaline media. Thus in this case (contrary to the previous example with the disubstituted substrate) the α-carbamate **15** is relatively stable under these reaction conditions and it is isolated from the reaction mixture. It has also to be noted that the α-anomer predominates in the equilibrium of **14**, because of the anomeric effect.

Scheme IV



Anomer **15**, is efficiently subjected to an intramolecular Michael addition yielding oxazoledione **17**, by refluxing in plain benzene. Additionally, when **15** is treated with sodium bicarbonate in acetone/water solution at room temperature, it is converted to **17** almost quantitatively. So the total yield of the convertion **14**→**17** is 37%.

Surprisingly, when **16** is refluxed in benzene in the presence of triethylamine it gives both isomers of oxazoledione, that is **17** and **18** (ratio 1:4) in contrast to the previous example (**5a**→**6a**). Moreover, reaction of **16** at room temperature with aqueous sodium carbonate in acetone, yields only isomer **18**, (yield 70%).

The above may be explained through an intermediate of structure **19**. The presence of a hydrogen atom at position 2, favors an enolization from this site of the molecule, resulting an intramolecular Michael addition of the pseudo-equatorial substituent. The above enolization of 2*H*-pyran-3(6*H*)-ones under basic conditions has been previously observed [8].

Conclusion.

2,2-Disubstituted 2*H*-pyran-3(6*H*)-ones may yield stereospecifically 5*H*-pyrano[3,2-*d*]oxazole-2,6-diones in high yield. On the other hand, 2-mono-substituted 2*H*-pyran-3(6*H*)-ones yield two isomeric oxazolediones at a ratio 3:2.

We are now investigating the application of these oxazolediones to sugar chemistry.

EXPERIMENTAL

General Methods.

All melting points are in degrees centigrade and were determined in open capillary tubes with a Buchi melting point apparatus and are uncorrected. Analytical thin-layer chromatography (tlc) was performed with 0.2 mm silica gel precoated plastic sheets with fluorescent indicator UV_{254} (Merck). The nmr spectra were recorded on a Varian 60 MHz spectrometer (Model 360EM) or on a Brucker instrument (400 MHz), in the indicated solvents. Chemical shifts are reported in parts per million from tetramethylsilane as an internal reference (δ 0.00). The coupling constants are given in Hertz. Infrared (ir) spectra were recorded on a Perkin-Elmer Model 283B infrared spectrophotometer, from samples prepared in accordance with the potassium bromide disk technique. Elemental Analysis were performed at the University of Thessaloniki.

1,5-Dimethyl-5-[4-(benzenesulfonyl)phenyl]dihydro[1*H*,7*H*]-5*H*-pyrano[3,2-*d*]oxazole-2,6-dione **6a**.

To a solution of **4a** [3b] (3.45 g, 0.01 mole) and methyl isocyanate (2 ml, 0.03 mole) in methylene chloride (50 ml), was added triethylamine (1 ml, 0.01 mole) portionwise. The mixture was stirred for 6 hours at room temperature. Afterwards it was washed with

water to neutrality, dried over magnesium sulfate and evaporated under reduced pressure. Column chromatography on silica gel with ether-ethyl acetate (9:1) as the elution solvent gave two compounds. The fast moving spot (Rf = 0.5, ether) was proved to be compound **5a** (3.44 g, yield 86%, see ref [2b] for characteristics of **5a**) and the lower spot (Rf = 0.1) compound **6a**, 0.4 g, yield 10%. Recrystallization from acetone/hexane gave analytically pure **6a**, mp 173-174°; ir (potassium bromide): ν max (cm^{-1}) 3080, 1585, 1940, 750 [aromatic], 1720 [carbonyl], 1740, 1520, 1250 [-OCON-], 2820 [N-Me], 1180, 1010 [COC], 1300, 1150 [$-SO_2$]; ^1H nmr (deuteriochloroform): 400 MHz δ 7.3 [m, 9H, aromatic], 5.7 [d, $J_{3a,7a}$ = 7.4, 1H, H_{3a}], 4.2 [q, $J_{7a,7}$ = 3.4, 1H, H_{7a}], 2.6 [s, N-Me], 2.6 [dq, AB system, J = 14.1, 2H, $-CH_2-$], 1.6 [s, 3H, angular Me].

Anal. Calcd. for $C_{20}H_{19}NO_6S$: C, 59.83; H, 4.77; N, 3.49. Found: C, 59.82; H, 4.47; N, 3.52.

Conversion of **5a** to **6a**.

To a solution of **5a** (1 g, 2.5 mmoles) in acetone (30 ml), a saturated solution of sodium carbonate (10 ml) was added and the mixture was vigorous stirred for 0.5 hour. After the reaction was over, the mixture was diluted with methylene chloride, washed with water, saturated ammonium chloride, dried over magnesium sulfate, filtrated and concentrated under reduced presure, affording an amorphous pale yellow solid. Crystallization from acetone/hexane gave analytically pure **6**, (0.96 g, yield 96%).

The same compound was obtained when **5** was refluxed in acetone (0.2 *M*) with 1/5 equivalant triethylamine for 2 hours (yield 78%).

6-[[(Methylamino)carbonyl]oxy]-2-methyl-2-[4-(phenylthio)phenyl]-2*H*-pyran-3(6*H*)-one **5b** and 1,5-Dimethyl-5-[4-(phenylthio)phenyl]-dihydro[1*H*,7*H*]-5*H*-pyrano[3,2-*d*]oxazole-2,6-dione **6b**.

Compound **4b** (11 g, 0.035 mole) was treated as described for the synthesis of **6a**, for 2 hours. After the usual workup and column chromatography separation with ether:hexane 6:4, 10.7 g (yield 82%) of analytically pure **5b** and 1.1 g (yield 7.8%) of pure **6b** were obtained.

Compound **6b** was recrystallized from acetone/hexane giving white crystals of mp 111-112°; ir (potassium bromide): ν max (cm^{-1}) 3080, 3060, 1590, 1480, 820, 750 [aromatic], 1738 [OCON], 1720 [carbonyl], 2860 [N-Me], 1190, 1010 [COC], 760 w [C-S]; ^1H nmr (deuteriochloroform): 60 MHz, δ 7.25 [m, 9H, aromatic], 6.1 [d, $J_{H3a-H7a}$ = 7.8, 1H, H_{3a}], 4.3 [quintet, $J_{7a,7}$ = 4, 1H, H_{7a}], 2.8 [octet, J = 16.8, 2H, $-CH_2-$], 2.8 [s, 3H, N-Me], 1.7 [s, 3H, angular Me].

Anal. Calcd. for $C_{20}H_{19}NO_4S$: C, 65.02; H, 5.18; N, 3.79. Found: C, 64.88; H, 5.22; N, 3.61.

Conversion of **5b** to **6b**.

When 4.3 g (0.012 mole) of **5b** was treated with sodium carbonate at 5° for 15 minutes as before, crystllization from acetone/hexane gave 4.1 g of analytically pure **6b** (yield 95%).

1,5-Dimethyl-5-[4-(phenylthio)phenyl]-6-hydroxyperhydropyrano[3,2-*d*]oxazole-2-one **11**.

To a solution of 0.2 g (0.5 mmole) of **6b** in anhydrous tetrahydrofuran (25 ml), lithium aluminum hydride (10 mg, 0.25 mmole) was added in portions. The reaction was stirred for 1 hour, then quenched with a stoichiometric amount of saturated ammonium chloride, filtered and concentrated under reduced pressure to afford a yellowish solid. Recrystallization from acetone/hexane gave analytically pure **11** (0.16 g, yield 82%), mp 200-202°; ir (potassium bromide): ν max (cm^{-1}) 3340 [OH], 1680, 1515, 1260 [-OCON-], 1190, 1015 [COC], 1310, 1160 [$-SO_2-$], 3080, 3060, 1595, 1470, 750 [aromatic], 2840 [N-Me]; ^1H nmr (deuteriochloroform): 60 MHz, δ 7.2 [m, 9H, aromatic], 5.6 [d, $J_{3a,7a}$ = 5.4, 1H, H_{3a}], 3.6 [dd, J = 13, J = 1.6, 1H, H_6], 4.2 [q, $J_{7a,7}$ = 3.8, 1H, H_{7a}], 2.1 [m, 2H, $-CH_2-$], 2.1 [s, 3H, N-Me], 1.5 [s, 3H, angular Me].

Anal. Calcd. for $C_{21}H_{23}NO_4S$: C, 65.43; H, 5.96; N, 3.36. Found: C, 65.38; H, 6.05; N, 3.70.

1,5-Dimethyl-5-[4-(phenylthio)phenyl]perhydropyrano[3,2-*d*]oxazole-2,6-dione-6-oxime **12**.

A solution of **6b** (1.5 g, 4 mmoles) in 35 ml of methanol was combined with a solution of hydroxylamine hydrochloride (1.8 g)/sodium acetate (3 g). The mixture was stirred for 12 hours at 40°. After the reaction was over, most of the methanol was evaporated under vacuum and the mixture cooled down and the product filtered off. Recrystallization from ether/hexane gave 1.36 g (yield 88%) of analytically pure **12**, mp 157-158°; Rf = 0.5, ether; ir (potassium bromide): ν max (cm^{-1}) 3350, 1650, 1270, 940 [=N-OH], 3050, 1580, 1480, 820, 680 [aromatic], 1735, 1300 [OCON], 3005, 2995 [-CH-], 1190, 1015 [COC], 750 w [C-S]; ^1H nmr (deuteriochloroform): 60 MHz, δ 8.1 [s, 1H, N-OH], 7.2 [m, 9H, aromatic], 5.8 [d, $J_{3a,7a}$ = 7.1, 1H, H_{3a}]. 3.9 [m, 1H, H_{7a}], 3.4 [dd, J = 1.3, J = 2.1, 2H, $-CH_2-$], 2.8 [s, 3H, N-Me], 1.6 [s, 3H, angular Me].

Anal. Calcd. for $C_{20}H_{20}N_2O_4S$: C, 62.46; H, 5.24; N, 7.28; S, 8.34. Found: C, 62.07; H, 5.27; N, 7.09; S, 8.66.

6-Acetylamino-1,5-dimethyl-5-[4-(phenylthio)phenyl]perhydropyrano[3,2-*d*]oxazole-2-one **13**.

A mixture of **12** (550 mg, 1.4 mmoles), acetic acid (12 ml), acetic anhydride (40 ml) and 10% Pd/C (80 mg) was stirred under hydrogen (1 atmosphere) for 2 hours. After the reaction was complete (tlc ether:ethyl acetate 1:1), the mixture was filtrated from Celite and azeotroped with toluene to a solid which after recrystallization from acetone gave 490 mg (yield 84%) of analytically pure **13**, mp 160-161°; Rf = 0.15 ether; ir (potassium bromide): ν max (cm^{-1}) 3330 [N-CO], 1645 [NH-CO], 1770 [O-CO-N], 3060, 1580, 1490, 820, 695 [aromatic], 1205, 1015 [COC], 750 w [C-S]; ^1H nmr (deuteriochloroform): 60 MHz, δ 7.1 [m, 9H, aromatic], 5.9 (d, $J_{3a,7a}$ = 7.6, 1H, H_{3a}], 4.1 [m, 1H, H_{7a}], 3.3 [dd, $J_{6,7ax}$ = 14.0, $J_{6,7eq}$ = 2.9, 1H, H_6], 2.8 [s, 3H, N-Me], 2.2 [s, 3H, N-Ac], 2.0 [m, 2H, $-CH_2-$], 1.8 [s, 3H, angular Me].

Anal. Calcd. for $C_{22}H_{24}N_2O_4S$: C, 64.06; H, 5.86; N, 6.79; S, 7.77; Found: C, 65.73; H, 5.25; N, 6.38; S, 7.50.

2-Methyl-6-[[(methylamino)carbonyl]oxy]-2*H*-pyran-3(6*H*)-one *cis* **16** and *trans* **15**.

A solution of **14** (3.5 g, 0.027 mole) in methylene chloride (70 ml), triethylamine (1 ml, 0.01 mole) and methyl isocyanate (2.5 ml, 0.038 mole) was kept at −5° for 20 hours. Evaporation of the solvents at low temperature under vacuum and flash column chromatography with ether:hexane 1:1 as the elution solvent gave three compounds:

The fast moving compound gave after crystallization from ether/hexane, white crystals of compound **16**, Rf = 0.3, ether: hexane 1:1, mp 98-100° dec, 1.35 g, yield 27%; ir (potassium bromide): ν max (cm^{-1}) 3320, 1730, 1550, 1270 [OCONHMe], 1690

[allylic carbonyl], 1240, 1095, 1005 [COC], 2995, 2880 [-CH-]; ^{1}H nmr (deuteriochloroform): 400 MHz, δ 6.86 [dd, $J_{5,4}$ 10.2, $J_{5,6}$ = 3.7, 1H, H_5], 6.46 [d, 1H, H_6], 6.18 [d, $J_{4,6}$ = 0, 1H, H_4], 4.8 [bd, 1H, NH], 4.57 [q, $J_{2\text{-Me}}$ = 6.8, 1H, H_2], 2.86 [d, $J_{\text{NH-Me}}$ = 5.2, 3H, N-Me], 1.41 (d, $J_{2\text{-Me}}$ = 6.8, 3H, Me].

The second moving compound gave after crystallization from ether/hexane, white crystals of compound **15**, mp 66-68°, Rf = 0.22, 1.9 g, yield 38%; ir (potassium bromide): ν max (cm^{-1}) 3360, 1730, 1535, 1255 [OCONHMe], 1700 [allylic carbonyl], 1230, 1105, 1045 [COC], 2995, 2940 [-CH-]; ^{1}H nmr (deuteriochloroform): 400 MHz, δ 6.87 [dd, $J_{5,4}$ = 10.2, $J_{5,6}$ = 2.1, 1H, H_5], 6.53 [m, 1H, H_6], 6.20 [dd, $J_{4,6}$ = 0.9, 1H, H_4], 4.8 [bd, 1H, NH], 4.35 (q, $J_{2\text{-Me}}$ = 6.8, 1H, H_2], 2.86 [d, $J_{\text{NH-Me}}$ = 5.2, 3H, N-Me], 1.48 [d, 3H, Me].

The slower moving compound gave after crystallization from ether/hexane, white crystals of compound **17**, mp 154-156° dec, Rf = 0.07; 0.3 g, yield 5.9%; ir (potassium bromide): ν max (cm^{-1}) 1735, 1520 [OCON], 2840 [N-ME], 1715 [carbonyl], 1190, 1010 [COC], 2970, 2930; ^{1}H nmr (deuteriochloroform): 400 MHz, δ 6.0 [d, $J_{3a,7a}$ = 7.2, 1H, H_{3a}], 4.28 [m, 1H, H_{7a}], 4.18 [q, J = 6.9, 1H, H_5], 2.8 [s, 3H, N-Me], 2.7 [dq, J = 16.4, 2H, -CH_2], 1.37 [d, 3H, angular Me].

Preparation of **18**.

A solution of **16** (0.4 g, 2 mmoles) in acetone (25 ml), water (10 ml) and saturated sodium carbonate solution (2 ml) was stirred for 1 hour (temperature 0°-RT). Usual workup and column chromatography separation gave traces of **17** and 0.28 g (yield 70%) of **18**, which was crystallized from ethyl acetate, mp 157-159° dec; ir (potassium bromide): ν max (cm^{-1}) 1730, 1520 [OCON], 2830 [N-Me], 1720 [carbonyl], 1200, 1100 [COC], 2970, 2940; ^{1}H nmr (deuteriochloroform): 400 MHz, δ 5.9 [d, $J_{3a,7a}$ = 7.1, 1H, H_{3a}], 4.23 [m, 1H, H_{7a}], 4.35 [q, J = 6.8, 1H, H_5), 2.8 [s, 3H, N-Me], 2.9 [dq, J = 16.1, 2H, -CH_2-], 1.35 [d, 3H, angular Me].

Compound **16** afforded after refluxing in acetone (0.2 *M*) with 1/5 of equivalent triethylamine for 2 hours, a mixture of compounds **17** and **18** (ratio 4:1).

Conversion of **15** to **17**.

A solution of **15** (0.4 g, 2 mmoles) in acetone/water was treated as before (see preparation of compound **18**) yielding 0.33 g (yeild 83%) of **17**.

Acknowledgement.

We thank Professor N. Alexandrou of the University of Thessaloniki and his laboratory staff for the elemental analysis and Dr. Rubini of the University of Nancy, France for the ^{1}H nmr (400 MHz) spectra.

REFERENCES AND NOTES

[1a] Taken in part from the Ph.D. Thesis of EAC, Agricultural University of Athens, 1984; [b] Part **IX** in the series Products From Fuzans. For parts **I-VIII** see *Chim. Chron. Int. Ed.*, **17**, 245 (1988).

[2a] N. Holder, *Chem. Rev.*, **82**, 287 (1982); [b] M. P. Georgiadis and E. A. Couladouros, *J. Org. Chem.*, **51**, 2725 (1986); [c] S. Martin, C. Gluchowski, C. Campbell and R. Chapman, *Tetrahedron*, **44**, 3171 (1988) and references therein; [d] P. DeShong, R. Waltermire and H. Ammon, *J. Am. Chem. Soc.*, **110**, 1901 (1988); [e] M. A. Bates, P. G. Sammes and G. A. Thomson, *J. Chem. Soc., Perkin Trans I*, 3037 (1988).

[3a] J. B. Hendrickson and J. S. Farina, *J. Org. Chem.*, **45**, 3359 (1980); [b] M. P. Georgiadis, E. A. Couladouros, M. G. Polissiou, S. Filippakis, D. Mentzafos and A. Tersis, *J. Org. Chem.*, **47**, 3054 (1982).

[4a] A. Zamojski, A. Banaszek and G. Grynkiewicz, *Adv. in Carbohydr. Biochem.*, **40**, 1 (1982); [b] O. Achmatowicz, Jr., P. Bukowski, B. Szechner, Z. Swierzchowska and A. Zamojski, *Tetrahedron*, 1973 (1971); [c] H. Paulsen, H. Tietz, W. Koebernick and V. Sinnwell, *Chem. Ber.*, **113**, 2616 (1980).

[5a] J. Leboul, J. Cleophax, S. D. Gero, A. Rolland and A. Forchioni, *Tetrahedron*, 965 (1977) and references therein; [b] M. P. Georgiadis and E. A. Couladouros, submitted for publication.

[6] M. P. Georgiadis, *J. Med. Chem.*, **19**, 346 (1976).

[7a] T. Sakakibara, T. Kawahara and R. Sudoh, *Carbohydr. Res.*, **58**, 39 (1977); [b] S. David and A. Lubineau, *Nouv. J. Chim.*, **1**, 375 (1977).

[8] H. Paulsen, W. Koebernick and H. Koebernick, *Tetrahedron Letters*, 2297 (1976).