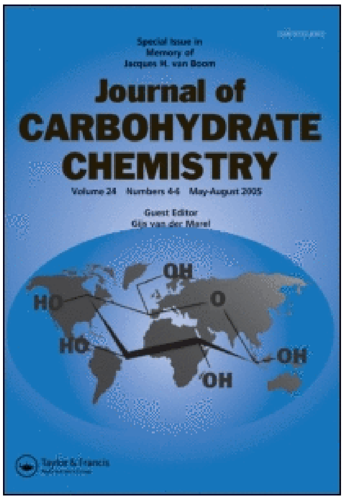

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SYNTHESIS OF CARBOHYDRATE DERIVED α-METHYLENE-γ-LACTONES BY DIASTEREOSELECTIVE, LOW TEMPERATURE REFORMATSKY-TYPE REACTIONS

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ABSTRACT

Hexopyranoside- and hexofuranose uloses with either ethyl 2-(bromomethyl)acrylate in the presence of laminar Zn/Ag-graphite or ethyl 2-(trimethylsilylmethyl)acrylate/tetra-n-butylammonium fluoride undergo stereoselective branching, mainly with formation of spiro α-methylene-γ-lactones.

Introduction

A considerable number of natural products are α-methylene-γ-lactone ring containing di- or tricyclic sesquiterpenes, almost exclusively originating from the large family of compositae.[1] The unusual variety of their biological activities[1] not only led to a wealth of α-methylene-γ-lactone syntheses,[1,2] but also prompted numerous investigations aimed at structures less toxic than those occurring in nature.

The method of choice for the single-step formation of α-methylene-γ-lactone rings consists in Reformatsky-type reactions of carbonyl compounds with esters of 2-(bromomethyl)-2-enoic acids,[3] or with ethyl trimethylsilyl-2-(bromomethyl) acrylates.[4] With reagents of this kind, cyclanones generally yield spiro-bicyclo-α-methylene-γ-lactones.[4,6]

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Results and Discussion

Inasmuch as there are no reports on α-methylene-γ-lactone spiroannelations of carbohydrate derived ketones, and in view of our results recently obtained from branching reactions of such educts with ethyl bromoacetate/Zn[10] as well as ethyl trimethylsilylacetate/tetra-n-butylammonium fluoride (ETSA/TBAF),[7] an investigation of similiar reactions using ethyl 2-bromomethyl)acrylate (5)[3] and ethyl 2-(trimethylsilylmethyl)acrylate (6)[4], respectively, was called for.

When methyl 4,6-O-benzylidene-3-deoxy-α-D-erythro-2-hexulopyranoside (2)[5] was subjected to a reaction with 5 in the presence of zinc under the usual conditions,[6] a separable mixture of the diastereoisomers (2a) and (2b) (2a:2b = 54:10) totaling 64 % was obtained. From treatment of 2 with 6/TBAF, 2a was formed exclusively (60 %), although at greatly reduced rate. These results are quite in agreement with the lower degree of stereoselectivity we observed with zinc- as compared to tetra-n-butylammonium ethyl acetate enolate,[7] which is obviously more nucleophilic than the ethyl methacrylate, originating from 6 with TBAF.

In search of improvements of Reformatsky-type reactions[8,9,13,14] to meet, inter alia, our requirements for stereoselectivity, we recently found laminar zinc/silver-graphite[15] even superior to either laminar zinc-graphite[9] or Rieke-zinc.[8] While both of the latter reacted rapidly at or above 0°C with 5 in the presence of 2 with good to excellent yields, the products were found to be mixtures of diastereoisomers in each case. Lowering the temperature, particularly in reactions employing Rieke-zinc, resulted only in a dramatic decrease in yields.[8]

Diastereoselective conversions in all cases and in excellent yields were finally accomplished when compounds 1-4[5,18,19] were subjected to 5 at -78°C in the presence of laminar Zn/Ag-graphite,[15] readily formed from C_8K and $ZnCl_2$/AgOAc (0.1 molar ratio) in refluxing tetrahydrofuran. While from educts 2-4 spiro α-methylene-γ-lactones could be obtained, compound 1 by this procedure only yielded the homo-aldol product (1a). Its resistance to lactonization may be envisaged to be connected with the highly rigid conformation of 4,6-O-benzylidene-hexopyranosides, branched at C-3.[10] The stereochemistry of 1a-3a, and hence that of 1b and 2b at their respective sites of branching, was found to be identical to Reformatsky products previously described.[7,10,15,17] In addition, the equatorial branching in 2a also follows from the deshielding effect of the axially oriented -O-C(=O)-R substituent on the protons at C-3 (due to their closer vicinity to the lactone carbonyl moiety) as well as the shielding of C-2 by the same substituent (C-2 in 2a δ = 80.39, C-2 in 2b δ = 82.21) - all being in best accordance with the rules given by Gajewski and Rücker.[21] The exo-configuration in 4a not only corresponds to the steric arrangement in 3a but is also in accordance with the stereochemistry of nucleophilic reactions of bicyclic educts.

Experimental

In a typical experiment 1.55 g of graphite and 0.66 g of clean potassium were stirred at 150°C under argon as described by Umani-Ronchi.[9] To the resulting bronze-coloured C_8K,[20] suspended in 15 ml of anhyd tetrahydrofuran, 1 g of anhyd $ZnCl_2$ and 0.1 g of AgOAc were added in portions at room temperature with vigorous stirring causing the solvent to reflux. Refluxing was continued for an additional 30 min., the suspension was cooled to -78°C and a solution of 2 mmol of the corresponding ulose (1, 2, 3, or 4) and 0.5 g of 5 in 5 ml of anhyd tetrahydrofuran was slowly added. After 5 min of stirring at that temperature the mixture was filtered, diluted with 50 ml of ether, extracted twice with water (20 ml each), and the organic layer was dried over Na_2SO_4. Evaporation and column chromatography of the residues afforded the products (1a-4a) (cf tables, method D). ^{1}H-NMR ($CDCl_3$; tetramethylsilane as internal standard, Varian XL-200):

1a: 7.59-7.30 (m,5H,aromat.), 6.32 (bs,1H, H-olef.), 5.74 (bs, 1H, H-olef.'), 5.56 (s,1H,CH-benzylidene), 4.79 (d,1H,H-1,$^3J(1,2)$= 3.9 Hz, $^3J(1,2')$= 0), 4.32 (dd,1H,H-5, $^3J(4,5)$= 4.9, $^3J(5,6)$=$^3J(5,6')$=9.8 Hz), 4.24-4.08 (m,1H,H-4), 4.09 and 4.0 (q,2H,CH_2-ester,rotamers), 3.77 and 3.54 (virt.t and virt. d, 2H, H-6 and H-6'), 3.48 (bs,1H,OH), 3.39 (s,3H,OMe), 2.91 and 2.51 (AB,2H,H-3',H-3", $^2J(3',3")$=13.5 Hz), 2.01 and 1.87 (dAB,2H,H-2,H-2', $^2J(2,2')$= 15.0), 1.21 (t,3H,Me-ester,^3J=6.9)

2a: 7.57-7.36 (m,5H,aromat.), 6.35 (vt,A-part of an AMXY, 1H,H-olef., ^4J(H-olef,H-2')= 2.5, ^4J(H-olef.,H-2")=2.9), 5.70 (virt.t, M-part of AMXY,1H, H-olef.',^4J(H-olef.',H-2')= 2.5, ^4J(H-olef.',H-2")= 2.9), 5.54 (s,1H, CH-benzylidene), 4.35 (s,1H,H-1), 4.30 (dd,1H,H-5,$^3J(4,5)$=4.3, $^3J(5,6)$=$^3J(5,6')$= 9.6),3.99-3.73(m,2H,H-6,H-6'), 3.70-3.52 (m,1H, H-4), 3.51 (s,3H,OMe), 2.57 and 2.14 (dAB,2H,H-3,H-3',$^2J(3,3')$=12.0, $^3J(3,4)$=12.0,

Table 1

reaction conditions and yields

educt	conditions [a]	method[b]	products/yield (%)
1	66°/ 200 min.	A	1a (59%), 1b (< 5%)[d]
1	25°/ 90 min.	B[c]	1a (86%), 1b (< 6%)[d]
1	0°/ 10 min.	C	1a (93%), 1b (< 3%)[d]
1	-78°/ 10 min.	D	1a (95%), ---
1	25°/ 60 h	E	1a (65%), ---
2	66°/ 200 min.	A	2a (54%), 2b (10%)
2	0°/ 10 min.	C	2a (84%), 2b (12%)
2	-78°/ 10 min.	D	2a (92%), ---
2	25°/ 60 h	E	2a (60%), ---
3	-78°/ 10 min.	D	3a (92%), ---
4	-78°/ 10 min.	D	4a (96%), ---

[a] temperature and reaction time

[b] A: according to ref.6; B: according to ref.8; C: according to ref.9; D: cf. experimental; E: according to ref.7 using 6/TBAF

[c] this result is noteworthy, inasmuch as C. Benezra et al. (ref. 11) under such conditions experienced decomposition of the reagent

[d] ^{1}H-spectroscopic data give good evidence for 1b to be the other diastereoisomer (cf. fig.)

Table 2

physical properties and elemental analysis

Nr.	mp(°C)	$[\alpha]_D^{20}$	(c)[g]	R_F	IR (C=O)[d]	IR (C=C)[e]	Anal, Calcd for		C	H	Found C	Found H
1a	oil	63.18	(1.5)	0.39[a]	1715[f]	1631	$C_{20}H_{26}O_7$	(378.43)	63.48	6.93	63.53	7.02
2a	156-157	35.25	(0.4)	0.28[b]	1759	1650	$C_{18}H_{20}O_6$	(332.36)	65.05	6.07	65.82	6.15
2b	173-174	55.07	(0.7)	0.34[b]	1760	1652	$C_{18}H_{20}O_6$	(332.36)	65.05	6.07	65.78	6.11
3a	119-121	72.90	(0.5)	0.26[a]	1776	1668	$C_{13}H_{16}O_6$	(268.27)	58.20	6.01	58.81	6.08
4a	107-108	35.03	(0.8)	0.48[c]	1769	1660	$C_{16}H_{22}O_7$	(326.35)	58.89	6.79	59.31	6.82

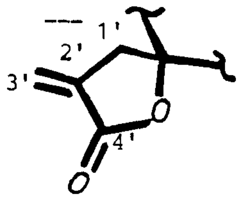
---

[a] on precoated Merck silica gel sheets (Nr. 5554), toluene/ethyl acetate = 3/1
[b] toluene/ethyl acetate = 4/1
[c] toluene/ethyl acetate = 1/1
[d] Beckmann IR 33-instrument, film on NaCl, strong absorption; in cm^{-1}
[e] weak absorption
[f] additional: 3580-3480, broad, OH-absorption
[g] in $CHCl_3$

Table 3

^{13}C-NMR-spectroscopic data (δ in ppm, in $CDCl_3$, tetramethylsilane as internal standard; Bruker WH-90, 22.63 MHz)

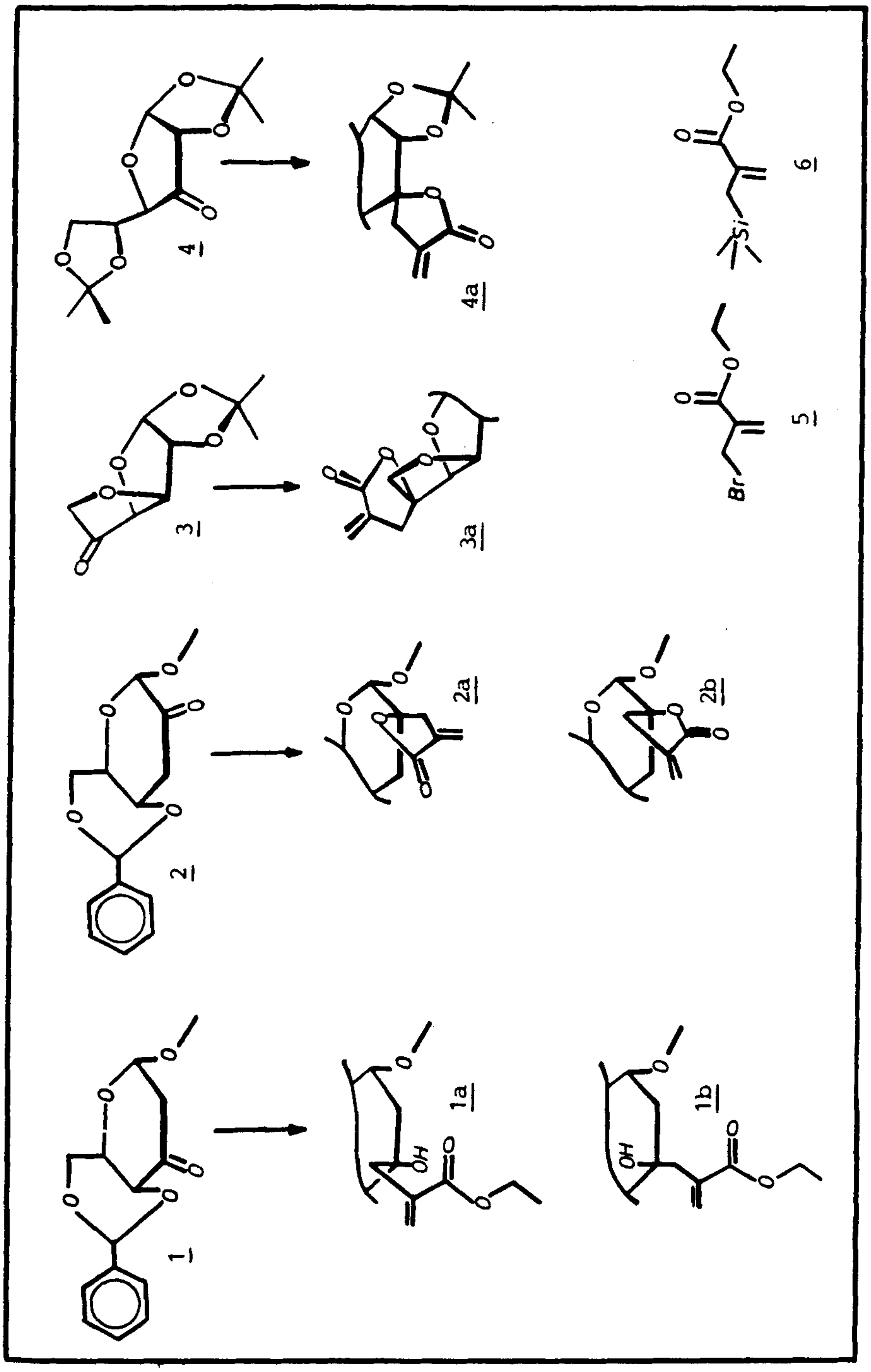
Carbon	**1a**	**2a**	**2b**	**3a**	**4a**
C-1	98.86	100.81	100.81	107.63	103.08
C-2	39.10$^+$	80.39	82.21	86.44$^+$	77.86$^+$
C-3	70.18	35.72	36.50	85.27$^+$	85.20
C-4	81.87	75.65	74.41	85.14$^+$	84.68$^+$
C-5	60.82	63.81	64.59	85.53	73.56$^+$
C-6	69.34	69.34	69.34	73.43	68.10
C-1'	39.49$^+$	37.67	36.50	35.20	31.24
C-2'	136.85	133.38	133.71	132.86	133.45
C-3'	(128.18)§	123.82	123.82	123.89	122.00
C-4'	167.78	168.75	170.00	168.43	168.36
OMe	55.36	55.62	55.42	---	---
C*	101.78	102.17	102.17	113.16	110.04/114.07
Me*	---	---	---	27.53/26.88	25.06/26.30 26.30/26.75
aromatic*	126.29 128.19 128.96 137.67	126.36 128.57 129.42 137.28	126.36 128.57 129.35 137.61	---	---
Me-ester	14.01	---	---	---	---
CH_2-ester	59.52				



§ hidden behind aromatic signals
* of isopropylidene and benzylidene, respectively
\+ our 200 MHz-2-D-NMR-facilities did not allow unequivocal distinction between those carbon atoms marked by +, which possibly may be interchanged.

$^3J(3',4)$= 4.1), 2.46 and 2.62 (vt AB as XY-part of AMXY,2H,H-2',H-2", $^2J(H-2',H-2")$= 17.5 Hz).

2b: 7.56-7.33 (m,5H,aromat.), 6.31 (vt, A part of AMXY, 1H,H-olef., ^4J(H-olef.,H-2')=2.7, ^4J(H-olef.,H-2")=2.5), 5.72 (vt, M part of AMXY, 1H, H-olef.', ^4J(H-olef.',H-2')=2.7, ^4J(H-olef.',H-2")= 2.5), 5.60(s,1H, CH-benzylidene), 4.65 (s,1H, H-1), 4.33 (virt.q,1H,H-5,$^3J(4,5)$=10.5, $^3J(5,6)$=16),4.09(virt.dq,1H,H-4), 3.88 (m,2H,H-6,H-6'), 3.45 (s,3H,OMe), 2.72 and 3.06 (dAB, XY-part of AMXY,2H,H-2',H-2",$^2J(2',2")$=17.5), 2.16 (d,2H,H-3,H-3', $^3J(3,4)$= 8.0,$^3J(3',4)$=0.


1
1a
1b
2
2a
2b
3
3a
4
4a
5
6
OH
Br
Si

3a: 6.35 (virt.t,A-part of AMXY,1H,H-olef.,^4J(H-olef.,5')=^4J(H-olef.,5")= 2.8), 6.06 (d,1H,H-1,^3J(1,2)=3.8), 5.79 (virt.t,M-part of AMXY,1H,H-olef.', ^4J(H-olef',5')=^4J(H-olef.',5")= 2.7, 4.70 (d,1H,H-2),4.65(s,2H,H-3,H-4), 3.71 and 4.02 (AB,2H,H-6,H-6',^2J(6,6')=9.4), 2.91 and 2.96 (virt.t, XY-part cf AMXY,2H,H-5,H-5', ^2J(5,5')=17.0), 1.5 (s,3H,Me-isoprop.,endo), 1.37 (s,3H,Me-isopr.,exo).

4a: 6.26 (virt.t, A part of AMXY,1H,H-olef.,^4J(H-olef,3')=^4J(H-olef.,3")= 2.9), 5.76 (d,1H,H-1,^3J(1,2)=3.6), 5.68 (virt.t,M part of AMXY,1H,H-olef.', ^4J(H-olef.',3')=^4J(H-olef,3")= 2.9), 4.38 (d,1H,H-2), 4.20-3.94 (m,4H, H-4,H-5,H-6,H-6'), 2.65 and 3.24 (virt. AB as XY part of AMXY,2H,H-3',H-3", ^2J(H-3',H-3")=17.3), 1.63, 1.40, 1.36 and 1.25 (each s,3H,Me-isoprop.).

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REFERENCES

1) H. M. R. Hoffmann, and J. Rabe, Angew. Chem., 97, 96 (1985).
2) P. A. Grieco, Synthesis, 1975, 67.
3) K. Ramarajan, K. Ramalingam, D. J. O'Donnell, and K. D. Berlin, Organic Synthesis, 61, 56 (1983).
4) B. M. Trost, and D. T. M. Chan, J. Amer. Chem. Soc., 105, 2326 (1983); A. Hosomi, H. Hashimoto, and H. Sakurai, Tetrahedron Lett., 1980, 951; R. Henning, and H. M. R. Hoffmann, Tetrahedron Lett., 1982, 2305; A. Haider, Synthesis, 1985, 271
5) H. Paulsen, and D. Stoye, Angew. Chem., 80, 120 (1968).
6) E. Öhler, K. Reininger, and U. Schmidt, Angew. Chem., 82, 480 (1970).
7) R. Csuk, A. Fürstner, and H. Weidmann, J. Carbohydr. Chem., in press.
8) R. D. Rieke, Topics Curr. Chem., 59, 1 (1975); R. D. Rieke, Acc. Chem. Res., 10, 301 (1978); R. D. Rieke, and S. J. Uhm, Synthesis, 1975, 452; R. D. Rieke, S. J. Uhm, and P. M. Hudnall, J. Chem. Soc., Chem. Comm., 1973, 269.
9) G. P. Boldrini, D. Savoia, E. Tagliavini, C. Trombini, and A. Umani-Ronchi, J. Org. Chem., 48, 4108 (1983).
10) R. Csuk, A. Fürstner, and H. Weidmann, J. Carbohydr. Chem., in press.
11) H. Mattes, and C. Benezra, Tetrahedron Lett., 1985, 5697.
12) D. J. O'Donnell, K. Ramalingam, S. E. Ealick, D. van der Helm, and K. D. Berlin, J. Org. Chem., 43, 4259 (1978).
13) K. Nützel in "Houben-Weyl", Vol. XIII2a; E. Müller, Ed.; Thieme Verlag, Stuttgart, 1973.

14) R. T. Arnold, and S. T. Kulenovics, Synth. Comm., 7, 223 (1977); M. W. Rathke, and A. Lindert, J. Org. Chem., 35, 3966 (1970); K. Maruoka, S. Hashimoto, Y. Kitagawa, H. Yamamoto, and H. Nozaki, Bull. Chem. Soc. Jpn., 53, 3301 (1980).

15) R. Csuk, A. Fürstner, and H. Weidmann, J. Chem. Soc., Chem. Comm., in press.

16) N. S. Pantaleo, N. Satyamurthy, K. Ramarajan, D. J. O'Donnell, K. D. Berlin, and D. van der Helm, J. Org. Chem., 46, 4284 (1981); W. Gajewski, and G. Rücker, Arch. Pharm., 316, 256 (1983).

17) S. Brandänge, O. Dahlman, and L. Mörch, J. Amer. Chem. Soc., 103, 4452 (1981).

18) A. P. Rauter, and H. Weidmann, Liebigs Ann. Chem., 1982, 2231.

19) S. Czernecki, C. Georgoulis, C. L. Stevens, and K. Vijayakumaran, Tetrahedron Lett., 1985, 1699.

20) A careful preparation of C_8K is a prerequisite for successful reactions.

21) in agreement to previous results (cf. ref. 16b) C-1' is found to be at higher field for a equatorially branched O-C(=O)-R group than for its axially oriented counterpart.