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Synthesis of enantiopure *C*-glycosides and pseudo *C*-glycosides: Lewis-acid mediated heterolysis of methyl acetals

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Abstract

Lewis-acid mediated heterolysis of substituted methoxy acetals derived from anomeric [3.3.1] oxabicyclic lactones leads to enantiopure deoxy *C*-glycosides in excellent chemical yield. An alternative route to *C*-glycosidic esters involves simple one-step opening of [3.3.1] oxabicyclic lactones with in situ esterification.

Keywords: *C*-glycosides; asymmetric synthesis; glycoheptopyranuronic acids; natural product synthesis.

The synthesis of *C*-glycosides has been a continuing challenge during the last decades. The massive work on carbohydrates and carbohydrate mimics reflects unabated interest in this area of natural product chemistry.[1] Several techniques to generate *C*-glycosidic structures have been developed. Most of these are substitutions of common leaving groups as in anomeric acetates, halides,[2a] sulfones[2b] and trichloroacetimidates.[2c] Depending on reaction conditions, the new carbon–carbon bond has been formed by nucleophilic,[3] electrophilic and radical attack.[4] A well established route in carbohydrate chemistry is the Lewis-acid mediated *C*-glycosidation of anomeric methyl acetals.[5] This method has already been applied by us in natural product synthesis for the preparation of the C3–C13 segment of the phorboxazoles A and B.[6]

We herein report the broad application of trimethylsilyl triflate mediated cleavage of monocyclic anomeric methyl acetals for the synthesis of deoxy and pseudo *C*-glycosides in solvent acetonitrile. Moreover, we have developed a simple one-step procedure for obtaining the *C*-glycosidic esters from [3.3.1] oxabicyclic lactones.

As we have shown, these anomeric [3.3.1] oxabicyclic lactones are easily prepared from 8-oxabicyclo-[3.2.1]oct-6-en-3-ones.[3,7] The anomeric methyl acetals **1–5**, which can be regarded as glycoheptopyranuronic acid methyl esters (Scheme 1), are readily accessible in high yield via acid catalyzed methanolysis (Scheme 2).[8] Further transformations provide functionalized acetals **6** and **7**.[6,9] Treatment with trimethyl-

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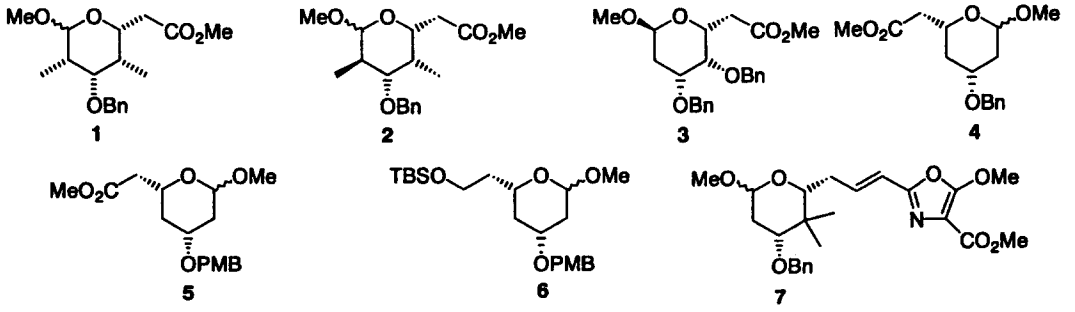
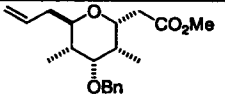
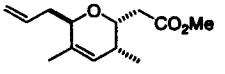
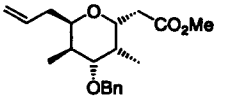
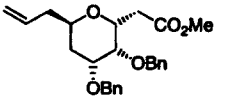
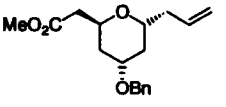
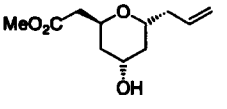
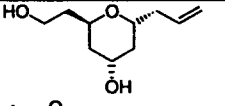
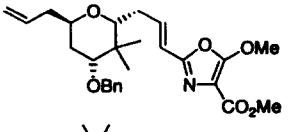
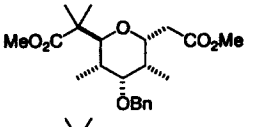
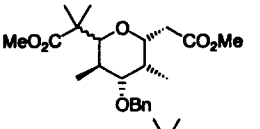
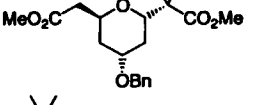
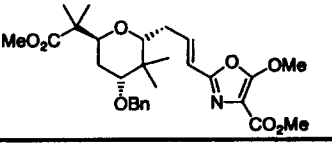
silyl triflate at low temperature and addition of silylated nucleophile furnishes a series of *C*-glycosides. The results are summarized in Table 1.

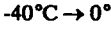


Scheme 1.

Trimethylsilyl triflate in acetonitrile as solvent and allylsilane as nucleophile (conditions **A**) furnished the expected 1,5-*trans* configurated *C*-glycosides **1a**, **2a**, **3a** and **4a** (Table 1, entries a, c, d, e).[10] More complex acetals gave also good yields (Table 1, entries h, l).

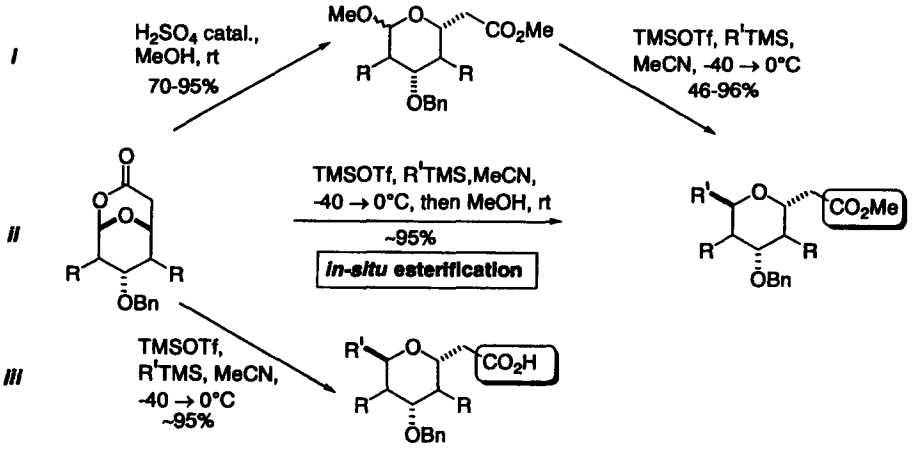
Table 1
Lewis acid mediated heterolysis of methyl acetals

	Acetal	Conditions	Product	Yield [%] α:β
a)	1	A		**1a** 71
b)	1	A'		**1d** 66
c)	2	A		**2a** 83
d)	3	A		**3a** 95
e)	4	A		**4a** 83
f)	5	A		**5a** 85
g)	6	A		**6a** 80
h)	7	A		**7a** 73
i)	1	B		**1b** 96
j)	2	B		**2b** 46 **1:1.3**
k)	4	B		**4b** 94
l)	7	B		**7b** 78

Conditions: A:  , 1 eq. TMSOTf, MeCN, -40°C → 0°C; A':  , 1 eq. TMSOTf, DCM, -40°C;

B: , 1 eq. TMSOTf, MeCN, -40°C

TMSOTf in dichloromethane led to elimination (Table 1, entry b).[11] Simultaneous deprotection occurred without loss of chemodifferentiation when acid labile protecting groups were used (Table 1, entries f, g). As chemical yields and selectivities are still very good this is a useful feature when further functionalization is necessary.[6] For the sterically more demanding silyl ketene acetal (conditions **B**) good selectivities were obtained in the case of methyl acetal **1**, **4** and **7** (Table 1, entries i, k, l). Stereoselectivity decreased only when using methyl acetal **2**. The neighbouring axial methyl group disfavours attack of the nucleophile from the top so that the 1,2-*trans* configuration becomes more favourable giving a nearly 1:1 mixture of epimers (Table 1, entry j).



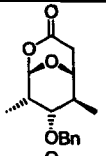
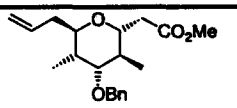
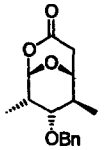
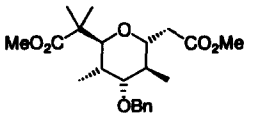
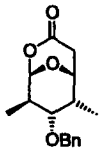
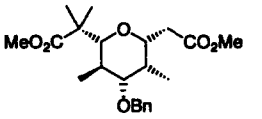
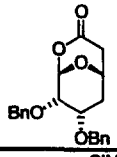
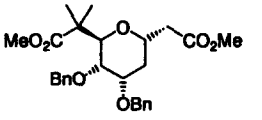
Scheme 2.

Unlike *C*-glycosidic acids the corresponding *C*-glycosidic esters resulting from the methyl acetal cleavage ***i*** are much easier to isolate and functionalize (Scheme 2). While all reactions listed in Table 1 gave good yield and stereoselectivity they did not reach the results of the anomeric lactone opening method ***iii*** described by us recently.[3] The newly developed one-step procedure ***ii*** (Scheme 2) combines both advantages of excellent yield and convenient isolation (Table 2).

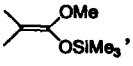
Treatment of lactones **8** and **9** with equimolar amounts of trimethylsilyl triflate and either allylsilane or silyl ketene acetal followed by addition of excess methanol furnished the esterified *C*-glycosides, after complete conversion of starting material, in excellent yield and with still better selectivity (Table 2, entry c). Even lactone **10** which resists acid catalyzed methanolysis was transformed into the *C*-glycoside **10b** (Table 2, entry d). The in situ esterification with methanol probably occurs on a trimethylsilyl ester intermediate.

In conclusion we have prepared a series of 1,5-*trans*-*C*-glycoheptopyranuronic acid esters selectively and easily in high yield from monocyclic anomeric methyl acetals and also from anomeric [3.3.1] oxabicyclic lactones. The methoxide group as a supposedly poor leaving group serves well in polar acetonitrile as solvent and trimethylsilyl triflate as Lewis acid, giving favourable results concerning yield and stereoselectivity. A further development involves addition of a nucleophile with subsequent in situ esterification. This one-step procedure significantly improves yield, 1,5-*trans* selectivity and handling. We think that our de novo approach to a variety of *C*-glycosides[3,6] has enormous potential and contributes to the field of carbohydrate chemistry.

Table 2
One-step lactone opening procedure with in situ esterification

Entry	Lactone		Conditions	Product		Yield[%]
a)		8	A		1a	97
b)		8	B		1b	97
c)		9	B		2b	95 α:β= 1:10
d)		10	B		10b	95 α:β= 11.5:1

Conditions: A:  , 1 eq. TMSOTf, MeCN, -40°C → 0°C, then excess MeOH, rt

B:  , 1 eq. TMSOTf, MeCN, -40°C → 0°C, then excess MeOH, rt

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3. We ourselves have investigated a new method to single-isomer deoxygenated and alkylated *C*-glycosidic acids starting from anomeric [3.3.1] oxabicyclic lactones: Gaertzen, O.; Misske, A. M.; Wolbers, P.; Hoffmann, H. M. R. *Synlett* **1999**, 1041.
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7. (a) Lampe, T. F. J.; Hoffmann, H. M. R. *J. Chem. Soc., Chem. Comm.* **1996**, 1931; (b) Weiss, J. M.; Hoffmann, H. M. R. *Tetrahedron: Asymmetry* **1997**, *8*, 3913; (c) Misske, A. M.; Hoffmann, H. M. R. *Tetrahedron* **1999**, *55*, 4315.
8. The stereochemical notation follows the convention of H. Maehr. Racemates are drawn with joists, whereas enantiopure compounds are designated with wedges: Maehr, H. *J. Chem. Ed.* **1985**, *62*, 114.
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10. A typical procedure is as follows: To a solution of methyl ester **2** (100 mg, 0.311 mmol) and allyltrimethylsilane (178 mg, 1.55 mmol) in acetonitrile (1 ml) was added dropwise an equimolar amount of trimethylsilyl triflate (69 mg, 0.31 mmol) at –40°C. The solution was allowed to warm to 0°C. After 1 h the mixture was diluted with MTBE and saturated aqueous solutions of $NaHCO_3$ (1 ml) and NH_4Cl (2 ml) were added. The aqueous layer was extracted with MTBE (4×10 ml). The combined organic layers were dried over $MgSO_4$, filtrated, concentrated in vacuo and purified by column chromatography (PE:EtOAc, 5:1) to yield methyl ester **2A** (86 mg, 0.26 mmol, 83%) as a colourless oil. Analytical data for (2*R*,3*R*,4*S*,5*R*,6*R*) methyl (6-allyl-4-benzyloxy-3,5-dimethyltetrahydropyran-2-yl) acetate (**2A**): $[\alpha]_D^{20}$=+130.0 (*c* 0.9, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3068, 2999, 2980, 2938, 1734, 1642, 1603, 1496, 1454, 1438, 1380, 1354, 1332, 1284, 1194, 1176, 1148, 1092, 1066, 1027, 993, 918, 856, 603; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5H), 5.76 (m, 1H), 5.02 (ddd, *J*=17.1, 1.9, 1.3 Hz, 1H), 5.07 (ddd, *J*=10.1, 1.3, 0.9 Hz, 1H), 4.53 (d, *J*=11.8 Hz, 1H), 4.47 (d, *J*=11.8 Hz, 1H), 4.19 (ddd, *J*=10.3, 4.5, 4.3 Hz, 1H), 3.97 (ddd, *J*=9.7, 4.8, 4.5 Hz, 1H), 3.66 (s, 3H), 3.36 (dd, *J*=7.7, 4.5 Hz, 1H), 2.94 (m, 1H), 2.40 (dd, *J*=17.5, 4.8 Hz, 1H), 2.35 (m, 1H), 2.20 (m, 1H), 2.06 (m, 2H), 0.93 (d, *J*=7.0 Hz, 3H), 0.92 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 172.5 (*C*O), 138.7 (Ar*C*), 135.4 (R*C*H=), 128.2 (Ar*C*H), 127.4 (Ar*C*H), 127.3 (Ar*C*H), 116.1 (H_2C=), 78.6 (O*C*HR_2), 70.2 (O*C*H_2Ph), 66.2 (O*C*HR_2), 54.9 (O*C*HR_2), 51.5 (OCH_3), 37.9 (CH_2), 33.7 (CH), 33.3 (CH), 33.2 (CH_2), 12.7 (CH_3), 5.2 (CH_3); MS (80°C): M^+=332 (1.1), 301 (1.2), 292 (6.4), 273 (0.9), 274 (0.93), 259 (1.0), 241 (1.0), 223 (4.6), 199 (5.0), 183 (30.8), 161 (3.2), 151 (3.8), 123 (2.8), 109 (9.43), 91 (100), 81 (2.9), 69 (3.0); HRMS calcd for $C_{20}H_{28}O_4$ (M^+): 332.1988, found: 332.1987.
11. The suggested mechanism includes 1,2-elimination and subsequent substitution of corresponding glycal via S_N2' mechanism. The benzyloxy moiety serves as leaving group: