Synthesis of Enantiopure C-Glycosides and Pseudo C-Glycosides. Lewis Acid Mediated Cleavage of [3.3.1] Oxabicyclic Lactones

Oliver Gaertzen, Andrea M. Misske, Peter Wolbers, H. M. R. Hoffmann*

Department of Organic Chemistry, University of Hannover, Schneiderberg 1B, D-30167 Hannover, Germany
Fax (+49) 511-762-3011; E-mail: hoffmann@mbox.oci.uni-hannover.de
Received 12 March 1999

Abstract: Lewis acid mediated cleavage of substituted 2,9-dioxabicyclo[3.3.1]nonan-3-ones affords enantiopure 2,6-*trans*-C-glycosides in excellent yield. Variation of nucleophile, solvent and Lewis acid were investigated.

Key words: C-glycosides, asymmetric synthesis, bicyclic lactones, solvent effect, anomeric activation

C-Glycosides and structurally simplified pseudo C-glycosides have been of major interest in carbohydrate, enzymatic and metabolic chemistry as well as in organic synthesis and natural product synthesis.[1] Along with the discovery and structure elucidation of biologically active natural products (e.g. palytoxin,[2] the phorboxazoles[3]) containing carbon-linked substituted tetrahydropy-rans, the development of methodology for their synthesis has accelerated especially in the last two decades.

A variety of approaches have been described to generate carbon-linked carbohydrate patterns, i.e. *cis*- and *trans*-C-glycosides. Most of these start from anomeric halides, acetates,[4] benzoates, aryl thioethers[5] and also from sulfones.[6] A challenging task is the synthesis of substituted deoxy C-glycosides. Several routes have been reported, including the use of glycals,[7] defunctionalization of sugar derived C-glycosides,[8] intramolecular C-glycosidation[5] and anomeric oxygen-to-carbon rearrangements.[9] All these approaches take advantage of the availability of natural products. This is, of course, also a limiting factor. Stereo- and regioselective defunctionalization and/or alkylation are necessary to prepare deoxy- or alkylated sugar derivatives.

We herein report the *de novo* synthesis of deoxy, dideoxy and alkylated deoxy C-glycosides. Our strategy is based on a ring-opening of oxabicyclic lactones **1** to **8** (Figure 1).

Our lactones can be regarded as tethered anomeric acetates serving as intramolecular leaving groups (Figure 2). Unlike conventional glycosidations where the leaving group is lost, the carboxylate is incorporated convergently into the glycosidic framework with useful chemodifferentiation of the side chains attached to C2 and C6.

Starting from substituted 8-oxabicyclo[3.2.1]oct-6-en-3-ones, which are readily available by our [4+3] cycloaddition methodology, we have prepared a wide variety of [3.3.1] oxabicyclic lactones in five steps in high chemical and optical yield.[3h,10-12] Treatment with trimethylsilyl tri-

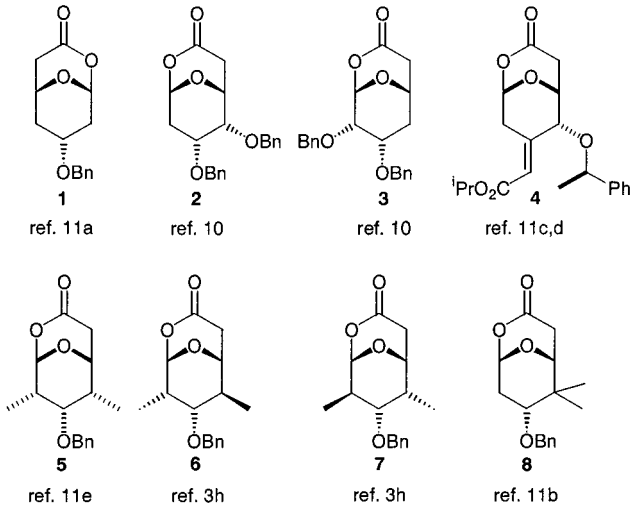


Figure 1

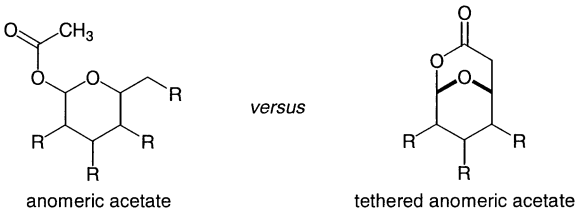
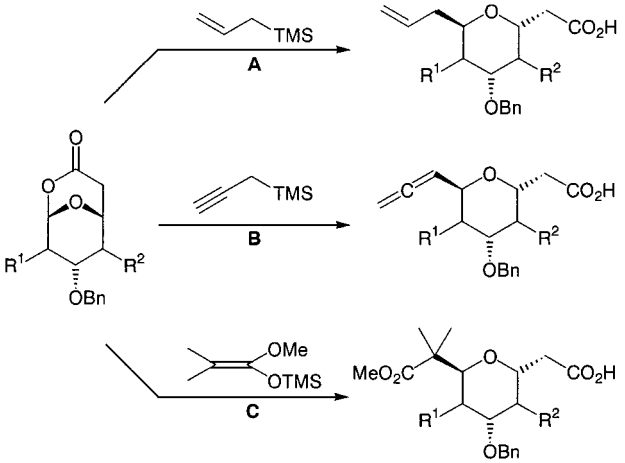
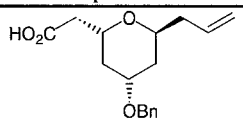
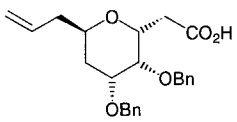
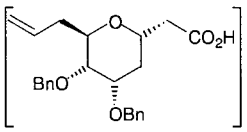
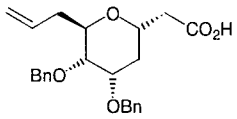
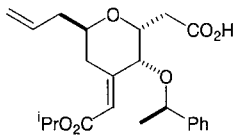
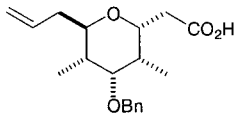
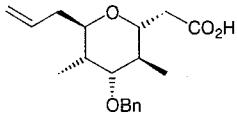
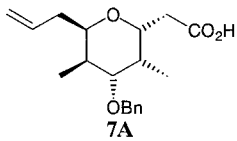
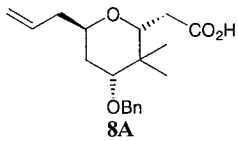
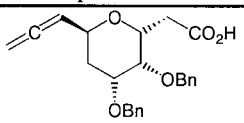
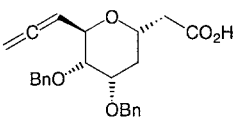
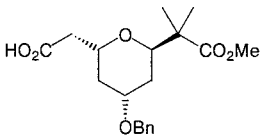
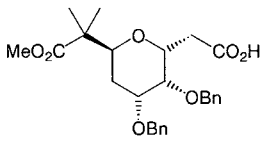
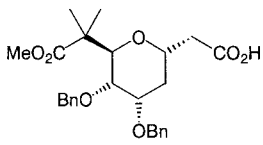
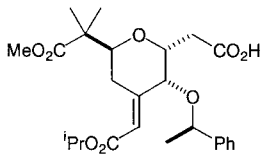
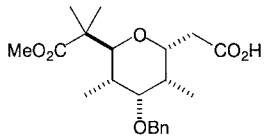
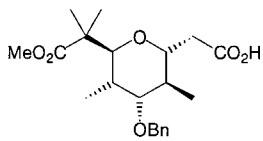
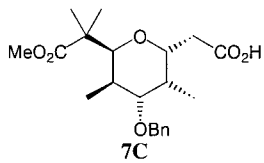


Figure 2



Scheme 1

Table 1 Results of C-glycosidation reactions

entry	lactone	solvent	conditions	product	Yield [%]
a)	**1**	DCM	i)	 **1A**	95
b)	**2**	DCM	i)	 **2A**	95
c)	**3**	DCM	ii)	 **3A**	0
d)	**3**	MeCN	iii)	 **3A**	95
e)	**4**	MeCN	iii)	 **4A**	98
f)	**5**	MeCN	iii)	 **5A**	83
g)	**6**	MeCN	iii)	 **6A**	95
h)	**7**	MeCN	iii)	 **7A**	86
i)	**8**	MeCN	iii)	 **8A**	80
j)	**2**	DCM	i)	 **2B**	95
k)	**3**	MeCN	iii)	 **3B**	95
l)	**1**	DCM	i)	 **1C**	92
m)	**2**	DCM	i)	 **2C**	79
n)	**3**	MeCN	iii)	 **3C**	90
o)	**4**	MeCN	iii)	 **4C**	96 α:β=6:1
p)	**5**	MeCN	iii)	 **5C**	98
q)	**6**	MeCN	iii)	 **6C**	76
r)	**7**	MeCN	iii)	 **7C**	95 α:β=1:4

Conditions: i) 1 eq. TMSOTf, DCM, -78°C (30 min), Nu; → -20°C
ii) 1 eq. TMSOTf, DCM, -78°C (30 min), Nu; → RT
iii) Nu; 1 eq. TMSOTf, MeCN, -40°C → -20°C

flate at low temperatures and addition of the silylated nucleophile furnished the desired C-glycosides (Scheme 1). The results are summarized in Table 1.[13]

Lactones **1** and **2** gave excellent yields of the derived 2,6-*trans*-C-glycosides in dichloromethane under mild conditions and short reaction times (Table 1, entry *a, b, j, l, m*).[14] Lactone **3** could not be transformed into the required

glycosides under these conditions (entry *c*). However, employing acetonitrile as the solvent in case of lactone **3** led to significant improvement (entry *d*). In general, by changing the solvent from dichloromethane to acetonitrile, all reactions gave excellent chemical yields. Nitromethane also served well in some cases, but provided no major advantage over acetonitrile. Other Lewis acids, such as $BF_3{\cdot}Et_2O$ or $ZnCl_2$, were used, but gave mainly elimination products or decomposition under similar conditions. In nearly all cases the 2,6-*trans*-C-glycoside stereochemistry was established exclusively, which is a result of the anomeric effect and shielding by the carboxylate leaving group. Examples are reactions of lactones **3** to **6**. Even lactones unsubstituted in 3-position gave exclusively the 2,6-*trans* product. In contrast, steric hindrance of the *axial* methyl group of lactone **7** furnished a mixture of epimers where 2,6-*cis* configuration is favored when bulky silyl ketene acetal was used (entry *r*). The less hindered allylsilane gave only the 2,6-*trans*-C-glycoside (entry *h*). Considering lactone **4**, the selectivity of silyl ketene acetal addition is reduced, perhaps caused by conformational flexibility of the tetrahydropyran ring due to the exocyclic double bond (entry *o*).

In summary, we have shown that 2,6-*trans*-C-glycosides are easily and selectively prepared in high yield from oxabicyclic lactones. Thanks to Lewis acid the lactone moiety serves as an efficient leaving group and the stereochemistry of nucleophilic attack at the anomeric centre is predetermined. In our opinion the methodology is of high utility for the synthesis of carbon linked pyran rings. The diversity of our anomeric oxabicyclic [3.3.1] lactones provides high flexibility of this synthetic approach. The C-glycosides prepared are useful precursors for the synthesis of a variety of biologically important natural products.[3g]

Acknowledgement

We thank the Fonds der Chemischen Industrie for a PhD fellowship (A. M. M.), the Deutsche Forschungs-gemeinschaft for a PhD fellowship (P. W., Graduiertenkolleg *Chemische und technische Grundlagen der Naturstofftransformation*) and Ulrike Eggert and Marc Schinner for their help and experimental contributions.

References and Notes

(1) Recent reviews on C-glycosides: a) Hosomi, A.; Sakata, Y.; Sakurai, H. *Carbohydr. Res.* **1987**, *171*, 223; b) Jaramillo, C.; Knapp, S. *Synthesis* **1994**, 1; c) Postema, M. H. D. *C-Glycoside Synthesis*, CRC Press Inc., Boca Raton, Fl 1995; Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545; d) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*, Pergamon Press, Tarrytown 1995; e) Bertozzi, C.; Bednarski, M. in *Modern Methods in Carbohydrate Synthesis*, Khan, S. H.; O´Neill, R. A. ed., Harwood Amsterdam 1996, 319.

(2) Discovery and structure elucidation: a) Uemura, M.; Ueda, K.; Hirata, Y.; Naoki, H.; Iwashita, T. *Tetrahedron Lett.* **1981**, *22*, 2781; b) Moore, R. E.; Bartolini, G. *J. Am. Chem. Soc.* **1981**, *103*, 2491; total synthesis: Kishi, Y.; Suh, E. M. *J. Am. Chem. Soc.* **1994**, *116*, 11205, and references cited therein.

(3) a) Discovery and structure elucidation: Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, *117*, 8126; Searle, P. A.; Molinski, T. F.; Brzezinski, L. J.; Leahy, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 9422; Molinski, T. F. *Tetrahedron Lett.* **1996**, *37*, 7879; b) total synthesis: Forsyth, C. J.; Ahmed, F.; Cink, R. D.; Lee, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 5597, and references cited therein; other synthetic efforts: c) Ye, T.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 319; d) Pattenden, G.; Plowright, A. T.; Tornos, J. A.; Ye, T. *Tetrahedron Lett.* **1998**, *39*, 6099; e) Paterson, I.; Arnott, E. A. *Tetrahedron Lett.* **1998**, *39*, 7185; f) Williams, D. R.; Brooks, D. A.; Meyer, K. G.; Clark, M. P. *Tetrahedron Lett.* **1998**, *39*, 7251; g) Wolbers, P.; Hoffmann, H. M. R. *Tetrahedron* **1999**, *55*, 1905; h) Misske, A. M.; Hoffmann, H. M. R. *Tetrahedron* **1999**, *55*, 4315.

(4) a) Hosomi, A.; Sakata, Y.; Sakurai, H. *Tetrahedron Lett.* **1984**, *25*, 2383; b) Jégou, A.; Pacheco, C.; Veyrières, A. *Tetrahedron* **1998**, *54*, 14779.

(5) a) Craig, D.; Munasinghe, V. R. N. *Tetrahedron Lett.* **1992**, *33*, 663; b) Craig, D.; Pennington, M. W.; Warner, P. *Tetrahedron Lett.* **1995**, *36*, 5815.

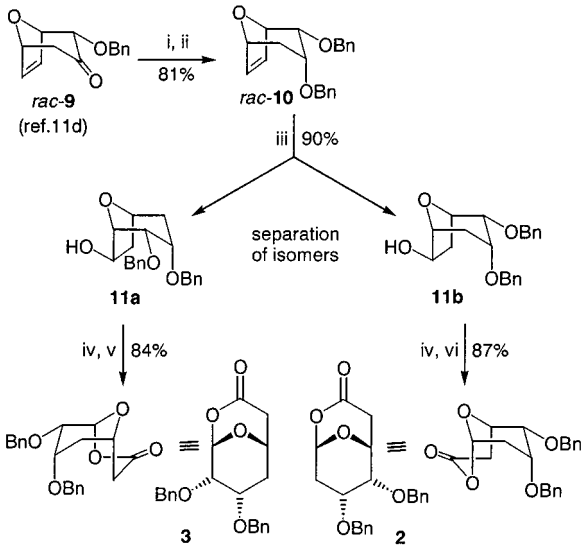
(6) Brown, D. S.; Bruno, M.; Davenport, R. J.; Ley, S. V. *Tetrahedron* **1989**, *45*, 4293.

(7) Fernandez-Megia, E.; Gourlaouen, N.; Ley, S. V.; Rowlands, G. J. *Synlett* **1998**, 991.

(8) a) Minehan, T. G.; Kishi, Y. *Tetrahedron Lett.* **1997**, *38*, 6815; b) Ichikawa, Y.; Isobe, M.; Konobe, M.; Goto, T. *Carbohydr. Res.* **1987**, *171*, 193.

(9) a) Buffet, M. F.; Dixon, D. J.; Ley, S. V.; Tate, E. W. *Synlett* **1998**, 1091; b) Dixon, D. J.; Ley, S. V.; Tate, E. W. *Synlett* **1998**, 1093; c) Dixon, D. J.; Ley, S. V.; Tate, E. W. *J. Chem. Soc. Perkin Trans. I* **1998**, 3125.

(10) Illustrative procedure for the preparation of lactones **2** and **3**:



Conditions: i) L-Selectride®, THF, -78ºC, 2 h; ii) NaH, THF, BnBr, reflux, 16 h; iii) a) (-)-$(Ipc)_2BH$, THF; b) NaOH, H_2O_2; iv) PCC, NaOAc, 4Å molecular sieves, DCM, rt, 1 h; v) *m*-CPBA, F_3CCO_2H, DCM, rt, 15 h; vi) *m*-CPBA, $NaHCO_3$, DCM, rt, 15 h.
For preparation of lactones **1**, **4**-**8** see refs. 3h and 11.

(11) a) Lampe, T. F. J.; Hoffmann, H. M. R. *J. Chem. Soc. Chem. Commun.* **1996**, 1931; b) Weiss, J. M.; Hoffmann, H. M. R. *Tetrahedron: Asymmetry* **1997**, *8*, 3913; c) Stark, C. B. W.; Eggert, U.; Hoffmann, H. M. R. *Angew. Chem.* **1998**, *110*, 1337; *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1266; d) Schinner, M.; PhD thesis, Universität Hannover 1999; see also: Wittenberg, J.; Beil, W.; Hoffmann, H. M. R.

Tetrahedron Lett. **1998**, *39*, 8259 and references cited therein; e) Misske, A. M.; unpublished results.

(12) Ashcroft, M. R.; Hoffmann, H. M. R. *Org. Synth. Coll. Vol. 6*, 512 (**1988**).

(13) A typical procedure is as follows: To a stirred solution of lactone **3** (115 mg, 0.324 mmol) in acetonitrile (3.3 ml) at -40 °C allyltrimethylsilane (0.216 ml, 1.35 mmol) was added, followed by dropwise addition of trimethylsilyl triflate (0.061 ml, 0.36 mmol). The reaction mixture was allowed to warm to -20 °C. After 1h the mixture was diluted with MTBE, followed by addition of saturated aqueous $NaHCO_3$ (1 ml) and saturated aqueous NH_4Cl (1 ml). The aqueous layer was extracted with MTBE (3×10 ml) and the combined organic layer was dried over $MgSO_4$. The crude product was further purified by short column chromatography to yield the C-glycosidic acid **3A** (122 mg, 0.308 mmol, 95%).

(14) Selected spectroscopic data for (*2S,4S,5S,6R*)-(6-allyl-4,5-bisbenzyloxytetrahydropyran-2-yl) acetic acid **3A**: ^{1}H NMR (500 MHz, $CDCl_3$, TMS): 7.33 (m, 10 H, Ph); 5.74 (dddd, 1 H, J=15.0, 7.1, 6.8, 0.3 Hz, =CH-); 5.03 (m, 2 H, H_2C=); 4.69, 4.57 (2×d, 2 H, ^{2}J=11.9 Hz, $PhCH_2$-O); 4.65 (dd, 2 H, ^{2}J=12.2 Hz, $PhCH_2$-O); 4.36 (ddd, 1 H, J=4.3, 4.6, 9.3 Hz, -CHOR); 4.02 (dddd, 1 H, J=3.1, 3.5, 7.5, 14.3 Hz, allyl-CHOR); 3.88 (ddd, 1 H, J=2.8, 3.3, 6.6 Hz, -C*H*OCH_2Ph); 3.67 (dd, 1 H, J=3.0, 4.3 Hz, -C*H*OCH_2Ph); 3.06 (dd, 1 H, J=9.3, 16.1 Hz, -C*H*$_2$-CO_2H); 2.80 (dd, 1 H, J=4.4, 16.1 Hz, -C*H*$_2$-CO_2H); 2.30+2.15 (dm, 2 H, =CH-C*H*$_2$-CHO-); 2.03 (ddd, 1 H, J=3.4, 6.6, 13.5 Hz, -CH_2); 1.50 (ddd, 1 H, J=3.0, 7.9, 13.5 Hz, -CH_2); ^{13}C NMR (125 MHz, $CDCl_3$):177.4 (-CO_2H), 138.5, 138.1 (Ph); 134.45 (=CH-), 128.3, 128.0, 127.7, 127.6, 127.4, 127.3 (Ph); 116.9 (CH_2=); 75.2, 73.3 (-*C*HOCH_2Ph); 73.0, 71.9 (Ph-CH_2); 71.5 (-CHOR); 70.4 (allyl-CHOR); 38.2 (=CH-*C*H_2-CHO); 34.6 (-*C*H_2CO_2H); 26.9 (-CH_2); IR ($CHCl_3$, rt): ν = 3680, 3512, 3168, 3068, 1744, 1708, 1640, 1600, 1496, 1364, 1264, 1232, 1076 cm^{-1}; MS (110 °C); m/z (%): M^+ = 396 (1.9); 395 (3.5); 305 (25.1); 247 (17.1); 181 (100); 139 (38.6); 107 (30.4); HRMS: calcd. 396.1916, found 396.1937; $[\alpha]_D^{22}$+20.9°, c = 1.1, $CHCl_3$. The *trans* geometry of **3A** was confirmed by 500 MHz NOESY experiments.

Article Identifier:
1437-2096,E;1999,0,07,1041,1044,ftx,en;G09699ST.pdf