

Diastereoselective addition of sugar radicals to camphorsultam glyoxylic oxime ether: a route toward C-glycosylthreonine and allothreonine†

Nicolas Bragnier, Regis Guillot and Marie-Christine Scherrmann*

Received 26th May 2009, Accepted 20th July 2009

First published as an Advance Article on the web 30th July 2009

DOI: 10.1039/b910050d

C-glucosyl, mannosyl and galactosyl 2-iodopropane, readily obtained from the corresponding C-glycosyl ketones, were coupled with (+)- or (–)-camphorsultam glyoxylic oxime ether with diastereoselectivity ranging from 70:30 to 80:20. C-glucosyl allothreonine was obtained by cleavage of the camphorsultam moiety.

Since the introduction of camphorsultam as a chiral auxiliary by Oppolzer and coworkers,¹ many papers have outlined the potential of this moiety in asymmetric induction, in particular for radical additions.^{2,3} Naito and co-workers have extensively studied the radical addition to Oppolzer's camphorsultam derivatives of glyoxylic oxime (+)-**1** (Fig. 1).³ High yields and diastereocontrol were obtained in the stannyl radical-mediated reaction of various alkyl radicals allowing the preparation of enantiomerically enriched α -amino acids.

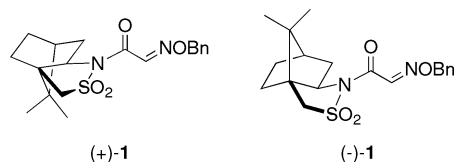
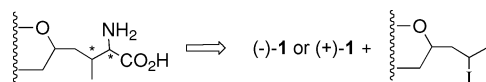


Fig. 1

Recently, our group developed a very efficient one-step synthesis of β -D-C-glycosyl ketones from unprotected sugars.⁴ We decided to investigate the use of C-glycosyl iodopropane, readily obtained from the above ketones, in the carbon radical addition to glyoxylic oxime ether (+)-**1**^{3b} and (–)-**1**⁵ in order to provide an access to C-glycosyl threonine and allothreonine (Scheme 1). The latter compounds belong to the family of unnatural amino acids in which the glycyl moiety is connected directly or through a carbon tether to the anomeric carbon of the sugar by a carbon–carbon bond. Since natural O- and N-glycoproteins play key roles in a large number of biological processes,⁶ they constitute very interesting



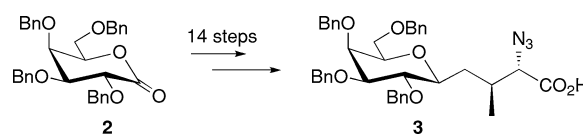
Scheme 1

Université de Paris-Sud 11, Institut de Chimie Moléculaire et des Matériaux d'Orsay, Bâtiment 410, 91405, Orsay, France. E-mail: mcscherr@icmo.u-psud.fr; Fax: +33(0)169154679; Tel: +33(0)169157256

† Electronic supplementary information (ESI) available: Experimental procedures and analytical data for all new compounds. CCDC reference numbers 731615–731618. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b910050d

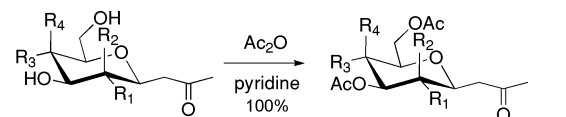
building blocks for the synthesis of artificial, hydrolytically stable C-glycosylated proteins.

Although many efforts have been done to prepare C-glycosyl amino acids, the studies have focussed on cases where the amino acid moiety contains only one stereogenic center, the most common being alanine, serine, and asparagine.⁷ The only example of a C-glycoside analogue of a β -D-galactosylthreonine has been reported by the group of Kihlberg.⁸ The benzylated 2-azido-3-methyl acid derivative **3**, precursor of the corresponding α -amino acid, was prepared in 14 steps from D-galactonolactone **2** (Scheme 2).⁹ Therefore, a general method toward the construction of C-glycosyl amino acids containing two stereocenters onto the amino acid moiety, *i.e.* featuring a glycosyl-threonine skeleton, should be of great interest.



Scheme 2

The ketones **4–6** were prepared from unprotected sugars and pentanedione in water by means of a very convenient method developed in our group.⁴ They were treated with acetic anhydride and pyridine to afford quantitatively the acetylated *gluco*- **7**,¹⁰ *manno*- **8**¹¹ and *galacto*-ketone **9**^{4c} that were allowed to react with NaBH₄ (MeOH, –10 °C) to give the alcohols **10–12** in quantitative yield as diastereoisomeric mixtures (Scheme 3).



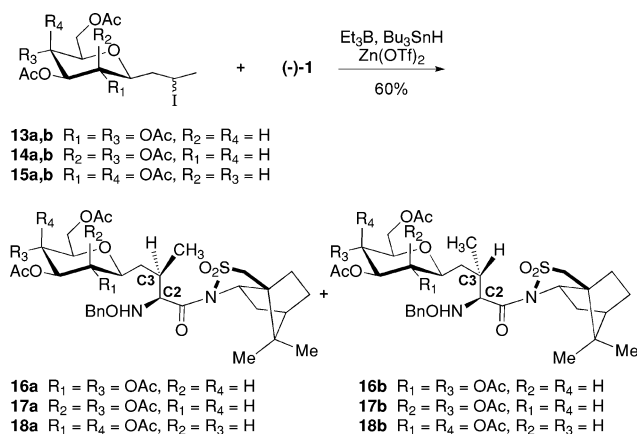
4 R₁ = R₃ = OH, R₂ = R₄ = H
5 R₂ = R₃ = OH, R₁ = R₄ = H
6 R₁ = R₄ = OH, R₂ = R₃ = H
7 R₁ = R₃ = OAc, R₂ = R₄ = H
8 R₂ = R₃ = OAc, R₁ = R₄ = H
9 R₁ = R₄ = OAc, R₂ = R₃ = H

10a,b R₁ = R₃ = OAc, R₂ = R₄ = H (dr = 2:1)
11a,b R₂ = R₃ = OAc, R₁ = R₄ = H (dr = 1:1)
12a,b R₁ = R₄ = OAc, R₂ = R₃ = H (dr = 2:1)

Scheme 3 Gluco series: **4**, **7**, **10**. Manno series: **5**, **8**, **11a,b**. Galacto series: **6**, **9**, **12a,b**.

The transformation of the alcohols **10–12** into the iodo derivatives **13–15** was initially accomplished in one step using

iodine, triphenylphosphine and imidazole in toluene. In this case, although the conversion was total (TLC analysis), the isolated yield was only 80% due to the difficult purification. Thus, this transformation was carried out *via* a two-step procedure involving tosylation (tosyl chloride, pyridine) followed by a nucleophilic substitution with NaI in acetone affording the iodinated compounds in quantitative yields. *Gluco* and *galacto* derivatives **13a**, **13b** and **15a**, **15b** (Scheme 4) were obtained as 2:1 diastereoisomeric mixtures whereas the *manno* isomers **14a** and **14b** were obtained in nearly equimolar amount. Pure samples for all diastereomeric iodide derivatives **13–15** were obtained by preparative HPLC and fully characterized (see ESI).†



Scheme 4 *Gluco* series: **13**, **16**. *Manno* series: **14**, **17**. *Galacto* series: **15**, **18**.

The Oppolzer's camphorsultam derivatives of glyoxilic oxime ether (–)-**1** and (+)-**1** were readily prepared as described^{3b} and used in the carbon radical addition under the experimental conditions described by Naito and coworkers.³ First we examined the stereochemical outcome of the reaction involving (–)-camphorsultam as a chiral auxiliary. The reactions between (–)-**1** and iodo **13–15** were run in CH_2Cl_2 at -78°C using Bu_3SnH , Et_3B and $\text{Zn}(\text{OTf})_2$ as a Lewis acid (Scheme 4). As expected, the radical addition took place regioselectively at the iminocarbon to give in all cases only 2 diastereoisomers in 60% isolated yield for all the sugar derivatives. It appears that the stereochemical outcome did not depend on the configuration of the starting iodide since the reaction of (–)-**1** with diastereomeric pure **13a** gave the same 4:1 mixture of adducts **16a,b**. The selectivity of the radical coupling was determined by ^1H NMR analysis by integration of the NH signal that always resonated at lower field for the major diastereoisomer (Table 1). *Gluco* and *galacto*

Table 1 Results of the radical coupling with (–)-**1**

Substrate	Products	Yield	δ_{NH} (ppm, CDCl_3)		dr (a/b)	C2-C3 configurations	
			a	b		a	b
13a,b	16a,b	60%	6.38	6.18	80:20	<i>S-R</i> ^a	<i>S-S</i> ^b
14a,b	17a,b	60%	6.37	6.15	85:15	<i>S-R</i> ^a	<i>S-S</i> ^b
15a,b	18a,b	60%	6.40	6.18	80:20	<i>S-R</i> ^a	<i>S-S</i> ^b

The major diastereomers were noted as **XXa** and the minor ones as **XXb**.^a Assigned by X-ray analysis. ^b Tentatively assigned configuration.

compounds **16** and **18** were obtained as 80:20 diastereoisomeric mixtures, whereas a 85:15 selectivity was observed with the *manno*-configured sugar. The diastereoisomers were separated by HPLC or crystallisation. NMR studies were unsuccessful in ascertaining the stereochemistry of the newly formed stereocenters, however, suitable crystals for X-ray measurements were obtained for the major *gluco* isomer **16a** ‡ (Fig. 2) and the major *manno* isomer **17a** § (Fig. 3). As expected from previous work employing this chiral auxiliary,^{5,12} the *S* configuration was observed at the amino acid carbon (C2) whereas the stereocenter deriving from the sugar moiety (C3) was *R*. As the selectivity obtained with the Oppolzer's camphorsultam derivatives are always very high in these experimental conditions,³ we assumed that the minor isomers were (*S,S*) configured.¹³

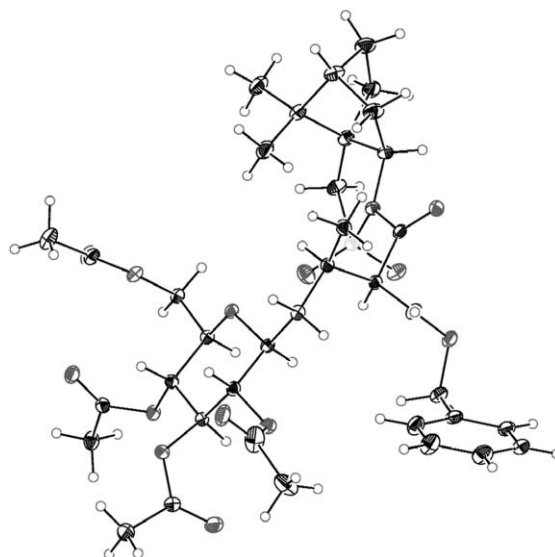


Fig. 2 ORTEP drawing of **16a**. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

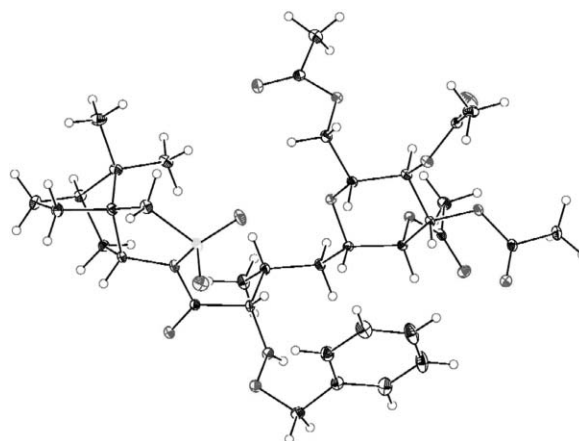


Fig. 3 ORTEP drawing of **17a**. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

Despite our efforts, we were not able to obtain from the *galacto* compound **18a** suitable crystals for the X-ray diffraction studies. However, by similarity with the cases of the *gluco* and *manno*

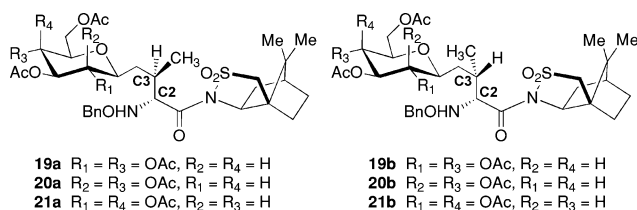
Table 2 Results of the radical coupling with (+)-1

Substrate	Products	Yield	δ_{NH} (ppm, CDCl_3)		dr (a/b)	C2-C3 configurations	
			a	b		a	b
13a,b	19a,b	60%	5.96	6.24	75:25	<i>R-R</i> ^a	<i>R-S</i> ^b
14a,b	20a,b	60%	5.98	6.23	75:25	<i>R-R</i> ^b	<i>R-S</i> ^b
15a,b	21a,b	60%	5.95	6.23	67:33	<i>R-R</i> ^b	<i>R-S</i> ^b

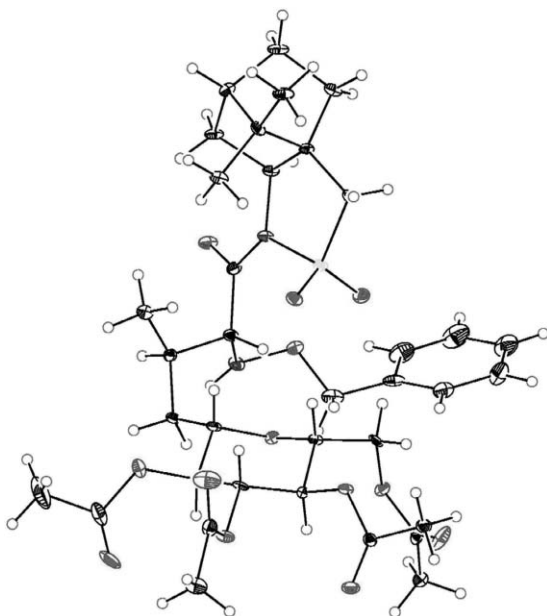
The major diastereomers were noted as **XXa** and the minor ones as **XXb**.^a Assigned by X-ray analysis. ^b Tentatively assigned configuration.

derivatives, the (*S,R*) configuration was tentatively attributed to the major diastereoisomer **18a** and the (*S,S*) configuration to **18b**.

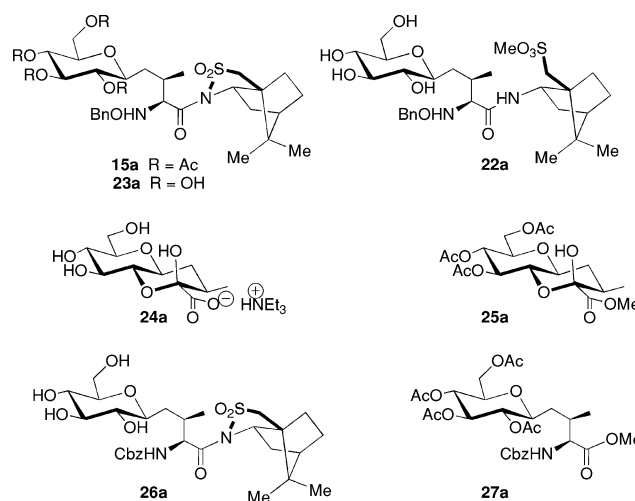
When the above coupling experiments were repeated using the (+)-camphorsultam derivative (+)-1, the corresponding products **19–21** were isolated in 60% yield (Fig. 4, Table 2).

**Fig. 4** Gluco series: **19**. Manno series: **20**. Galacto series: **21**.

Also in this case the selectivity was determined by integration of the NH signal in their ^1H NMR spectra, the major isomer showing always a signal at higher field, contrary to what was observed using the *S* auxiliary (Table 2). In this series, the X-ray structure obtained from the *gluco* major isomer **19a** ¶ allowed us to establish that the configuration at the amino-acid carbon C2 was *R* as expected by the use of (+)-camphorsultam oxime ether (+)-1, and the configuration at C3 was *R* (Fig. 5).

**Fig. 5** ORTEP drawing of **19a**. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

We decided to check the viability of this approach for the preparation of *C*-glycosyl amino acids by deprotecting **16a**. Removal of the camphorsultam moiety was first tried using conventional methods.^{1a} Unfortunately, the hydrolysis of **16a** with lithium hydroxide in aqueous THF gave a complex mixture of products. Attempts to use other bases such as lithium hydroperoxide or tetrabutylammonium hydrogen peroxide, which proved to be effective in difficult cases,¹⁴ also failed. On the other hand, the use of sodium methoxide in methanol gave quantitatively **22a** arising from the N-S bond cleavage as already observed during base-assisted hydrolysis of sterically hindered camphorsultam derivatives.^{14,15} Removal of the acetates was thus carried out in acidic conditions (HCl in MeOH) affording **23a** in quantitative yield. A very mild method, based on formaldehyde catalysis,¹⁶ has been described for the hydrolysis of amides derived from amino-acids, but when applied to **23a**, this method led to the formation of **24a** (Fig. 6). The structure of this unexpected product was ascertained by the X-ray analysis of its peracetylated methyl ester derivative **25a** ¶ (Fig. 7) obtained in 75% yield (3 steps).¹⁷

**Fig. 6**

We thus turn to the cleavage of the N–O bond of **22a** employing $\text{Mo}(\text{CO})_6$, and the resulting amine was protected as NCbz derivative **26a** by standard methods.³ This compound was subjected to basic hydrolysis under optimized reaction conditions, *i.e.* tetrabutylammonium hydrogen peroxide in aqueous THF. Although the N–S bond cleavage could not be totally suppressed (NMR analysis of the crude mixture), we were able to isolate pure *C*-glucosyl allothreonine **27a** in 40% yield (3 steps).

In order to check that no epimerisation occurred during the hydrolysis steps, we prepared all four diastereoisomers **27a,b,c,d** by reacting **13a** with glyoxalic oxime ether **28** (Scheme 5). The equimolar mixture of the four diastereoisomers **29a,b,c,d** obtained in 74% yield was then subjected to reductive cleavage of the N–O bond followed by the *N*-Cbz protection of the amine (Scheme 5).

The NMR spectra of this mixture showed 4 distinguishable signals for the NH proton (^1H NMR) as well as different signals for most of the carbon atoms of the diastereoisomers (^{13}C NMR). No traces of the signals attributed to **27b,c,d** were observed in the spectra of **27a**, proving without ambiguity that the removal of the sultam auxiliary occurred without any loss of stereochemical purity.

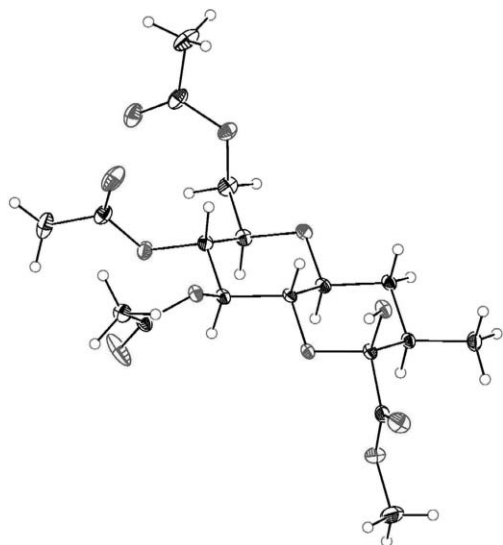
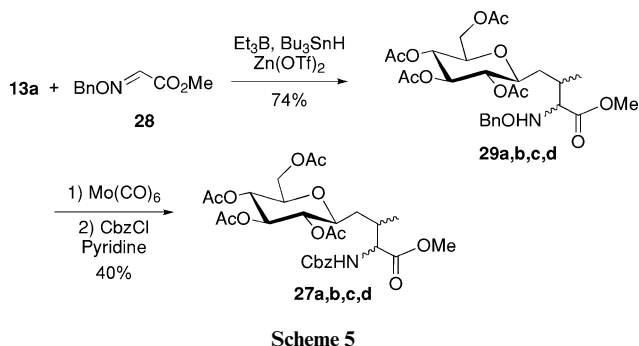


Fig. 7 ORTEP drawing of **25a**. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.



Acknowledgements

N. B. thanks the Ministère de l'Éducation Nationale, de l'Enseignement Supérieur et de la Recherche for a research fellowship. This work was supported by the Université Paris-Sud 11 and the CNRS. We thank J.-P. Baltaze for some help in NMR measurements.

Notes and references

‡ Crystal data for compound **16a**. $C_{36}H_{50}N_2O_{13}S$, $M = 750.85$, orthorhombic, $a = 12.629(5)$, $b = 14.954(5)$, $c = 20.739(5)$ Å, $U = 3917(2)$ Å³, $T = 100(1)$ K, space group $P2_12_12_1$ (no. 19), $Z = 4$, 35511 reflections measured, 11061 independent reflections ($R_{int} = 0.0592$) which were used in all calculations. The final $R(F_2)$ was 0.0687 (all data), Flack parameter = 0.01(5).
§ Crystal data for compound **17a**. $C_{36}H_{50}N_2O_{13}S$, $M = 750.85$, monoclinic, $a = 8.9756(5)$, $b = 17.3489(10)$, $c = 12.2509(7)$ Å, $\beta = 94.036(2)^\circ$, $U = 1902.94(19)$ Å³, $T = 100(1)$ K, space group $P2_1$ (no. 4), $Z = 2$, 10784 reflections measured, 7481 independent reflections ($R_{int} = 0.0204$) which were used in all calculations. The final $R(F_2)$ was 0.0386 (all data), Flack parameter = 0.04(5).

¶ Crystal data for compound **19a**. $C_{37}H_{52}Cl_2N_2O_{13}S$, $M = 835.78$, orthorhombic, $a = 7.4542(15)$, $b = 23.187(5)$, $c = 23.706(5)$ Å, $U = 4097.2(14)$ Å³, $T = 100(1)$ K, space group $P2_12_12_1$ (no. 19), $Z = 4$, 22600 reflections measured, 7989 independent reflections ($R_{int} = 0.0437$) which were used in all calculations. The final $R(F_2)$ was 0.0927 (all data), Flack parameter = 0.11(13).

|| Crystal data for compound **25a**. $C_{18}H_{26}O_{11}$, $M = 418.39$, orthorhombic, $a = 9.9034(12)$, $b = 10.2924(13)$, $c = 20.413(2)$ Å, $U = 2080.7(4)$ Å³, $T =$

100(1) K, space group $P2_12_12_1$ (no. 19), $Z = 4$, 22090 reflections measured, 9135 independent reflections ($R_{int} = 0.0239$) which were used in all calculations. The final $R(F_2)$ was 0.0737 (all data), Flack parameter = 0.3(2).

- (a) W. Oppolzer, C. Chapuis and G. Bernardinelli, *Helv. Chim. Acta*, 1984, **67**, 1397–1401; (b) W. Oppolzer, *Pure Appl. Chem.*, 1988, **60**, 39–48.
- (a) D. P. Curran, W. Shen, J. Zhang and T. A. Heffner, *J. Am. Chem. Soc.*, 1990, **112**, 6738–6740; (b) P. A. Zoretic, X. Y. Weng, C. K. Biggers, M. S. Biggers, M. L. Caspar and D. G. Davis, *Tetrahedron Lett.*, 1992, **33**, 2637–2640; (c) B. H. Kim and D. P. Curran, *Tetrahedron*, 1993, **49**, 293–318; (d) E. Baciocchi, E. Muraglia and C. Villani, *Synlett*, 1994, 821–822; (e) D. P. Curran, S. J. Geib and C.-H. Lin, *Tetrahedron: Asymmetry*, 1994, **5**, 199–202; (f) D. P. Curran, W. Shen, J. Zhang, S. J. Geib and C.-H. Lin, *Heterocycles*, 1994, **37**, 1773–1788.
- (a) H. Miyabe, C. Ushiro and T. Naito, *Chem. Commun.*, 1997, 1789–1790; (b) H. Miyabe, C. Ushiro, M. Ueda, K. Yamakawa and T. Naito, *J. Org. Chem.*, 2000, **65**, 176–185; (c) H. Miyabe, C. Konishi and T. Naito, *Org. Lett.*, 2000, **2**, 1443–1445; (d) M. Ueda, H. Miyabe, A. Nishimura, H. Sugino and T. Naito, *Tetrahedron: Asymmetry*, 2003, **14**, 2857–2859; (e) H. Miyabe, M. Ueda and T. Naito, *Synlett*, 2004, **7**, 1140–1157; (f) M. Ueda, H. Miyabe, H. Sugino and T. Naito, *Org. Biomol. Chem.*, 2005, **3**, 1124–1128; (g) T. Naito, *Chem. Pharm. Bull.*, 2008, **56**, 1367–1383.
- (a) F. Rodrigues, Y. Canac and A. Lubineau, *Chem. Commun.*, 2000, 2049–2050; (b) Y. Hersant, R. Abou-Jneid, Y. Canac, A. Lubineau, M. Philippe, D. Semeria, X. Radisson and M.-C. Scherrmann, *Carbohydr. Res.*, 2004, **339**, 741–745; (c) N. Bragnier and M.-C. Scherrmann, *Synthesis*, 2005, **5**, 814–818.
- S. Hanessian and R. Y. Yang, *Tetrahedron Lett.*, 1996, **37**, 5273–5276.
- (a) D. H. Dube and C. R. Bertozzi, *Nat. Rev. Drug Discovery*, 2005, **4**, 477–488; (b) R. A. Dwek, *Chem. Rev.*, 1996, **96**, 683–730.
- (a) A. Dondoni and A. Marra, *Chem. Rev.*, 2000, **100**, 4395–4421 and references therein; (b) A. Dondoni, P. P. Giovannini and A. Marra, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2380–2388; (c) A. Dondoni, G. Mariotti, A. Marra and A. Massi, *Synthesis*, 2001, **14**, 2129–2137; (d) T. Nishikawa, M. Ishikawa, K. Wada and M. Isobe, *Synlett*, 2001, 945–947; (e) L. Combo, M. di Giacomo and P. Ciceri, *Tetrahedron*, 2002, **58**, 9381–9386; (f) B. Lygo, B. I. Andrews and D. Slack, *Tetrahedron Lett.*, 2003, **44**, 9039–9041.
- T. Gustafsson, M. Saxin and J. Kihlberg, *J. Org. Chem.*, 2003, **68**, 2506–2509.
- (a) Hydroxyethylene isosteres of glycosyl asparagines have been described, however, these compounds are not isosteres of natural *O*- or *N*-glycosyl amino acids. C. M. Huwe, T. J. Woltering, J. Jiricek, G. Weitz-Schmidt and C.-H. Wong, *Bioorg. Med. Chem.*, 1999, **7**, 773–788; (b) B. Westermann, A. Walter, U. Flörke and H.-J. Altenbach, *Org. Lett.*, 2001, **3**, 1375–1378.
- I. Riemann, M. A. Papadopoulos, M. Knorst and W.-D. Fessner, *Aust. J. Chem.*, 2002, **55**, 147–154.
- S. Norsikian, J. Zeitouni, S. Rat, S. Gérard and A. Lubineau, *Carbohydr. Res.*, 2007, **342**, 2716–2728.
- (a) S. Hanessian, N. Bernstein, R.-Y. Yang and R. Maguire, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1437–1442; (b) S. Hanessian, P.-P. Lu, J.-Y. Sancéau, P. Chemla, K. Gohda, R. Fonne-Pfister, L. Prade and S. W. Cowan-Jacob, *Angew. Chem., Int. Ed.*, 1999, **38**, 3160–3162.
- The (*R,S*) configuration for compound **16b** could also be envisaged whereas the (*R,R*) configuration can be excluded since it was found in product **19a** i.e. that obtained from (+)-**1** (X-ray analysis). However, if the (*R,S*) configuration was assumed, it should be concluded that the stereoselectivity at C3 was total. From the results obtained previously (ref. 2, 3, 5, 12) using camphorsultam derivatives, we think it's more reasonable to make the hypothesis that the choice of the camphorsultam auxiliary allowed a total control of the selectivity at C2, whereas the stereocenter arising from the sugar moiety (C3) is mainly *R*.
- T. Hasegawa and H. Yamamoto, *Synlett*, 1998, 882–884.
- A. Khirman, A. K. Margaryan and W. F. Schmidt, *Tetrahedron*, 2003, **59**, 5475–5480.
- R. Pascal, M. Laspéras, J. Taillades and A. Commeyras, *New J. Chem.*, 1987, **11**, 235–244.
- A proposed mechanism involves the formation of a carbinolamine whose cyclisation gave an oxazolidin-5-one. Hydrolysis of this intermediate should afford the amino acid (ref. 15). Participation of the hydroxyl at C2 of the glucose moiety and elimination of *O*-benzyl *N*-methyl hydroxylamine gave rise to **23a**.