Pergamon

Tetrahedron Letters, Vol. 37, No. 14, pp. 2479-2482, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00298-5

'β-Acarbose': A Potential Inhibitor of β-D-Glucosidases and β-D-Glucan Hydrolases

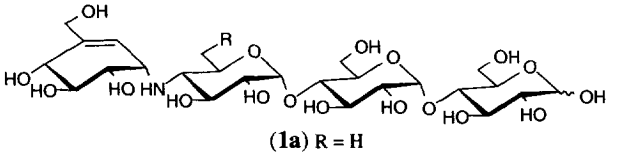
Joseph C McAuliffe,[a] Robert V Stick[a*] and Bruce A Stone[b]

[a] Department of Chemistry
The University of Western Australia
Nedlands, Western Australia 6907

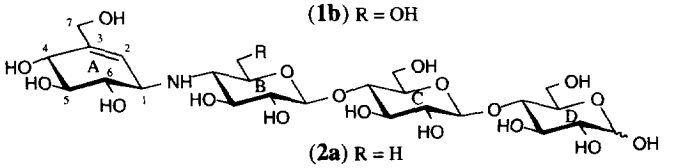
[b] School of Biochemistry
La Trobe University
Bundoora, Victoria, Australia 3083

Abstract: 'β-Adiposin-2', the 6″-hydroxylated derivative of 'β-acarbose', itself a diastereoisomer of the naturally occurring acarbose, has been prepared from a 1-epivalienamine derivative, 1,6:3,4-dianhydro-2-*O*-benzyl-β-D-galactose and benzyl 2,3,6,2′,3′,6′-hexa-*O*-benzyl-β-cellobioside.

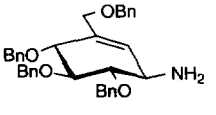
Acarbose (1a), a carba-tetrasaccharide isolated in the late 1970's from culture filtrates of actinomycetes in the Actinoplanaceae family (*Streptomyces*, *Actinoplanes* and *Streptosporangium*),[1,2] is an extraordinarily potent inhibitor of various α-D-glucosidases and α-amylases.[2] This inhibitory activity has been exploited in approaches to the treatment of diabetes, obesity and hyperlipoproteinaemia.[3,4] It occurred to us that a diastereoisomer of acarbose, namely 'β-acarbose' (2a), may have the potential to be an inhibitor of β-D-glucosidases and some β-D-glucan hydrolases and so we set about its synthesis.



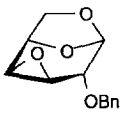
(1a) R = H
(1b) R = OH



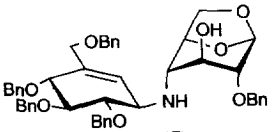
(2a) R = H
(2b) R = OH



(3)



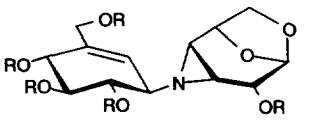
(4)



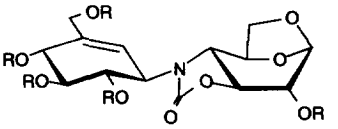
(5)

The carbocyclic portion of β-acarbose is derived from 1-epivalienamine and a derivative of this, namely (3), was prepared from methyl α-D-glucopyranoside in ten steps by some modifications to the excellent procedure described by Panza and co-workers.[5] Condensation of (3) with the easily prepared 1,6:3,4-dianhydro-2-*O*-benzyl-β-D-galactose (4)[6] gave the amino alcohol (5) in 67% yield.

Treatment of the amino alcohol (5) with methanesulfonyl chloride interestingly gave the aziridine (6), a precursor of the putative enzyme inhibitor (7) (Li/NH_3). As an alternative, (5) was converted into the cyclic carbamate (8) in 95% yield by the action of triphosgene. All attempts to convert (8) into a glycosyl donor, *e.g.* $Ac_2O/BF_3{\cdot}Et_2O$, were hampered by the inherent reactivity of the allylic benzyl ethers and, therefore, (8) was converted into the pentaacetate (9) (Li/NH_3 and then Ac_2O/pyridine) in acceptable yield (63%).

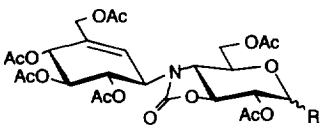


(**6**) R = Bn
(**7**) R = H

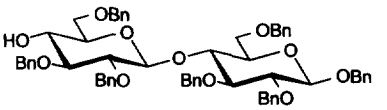


(**8**) R = Bn
(**9**) R = Ac

Treatment of (9) with triethylsilyl triflate and acetic anhydride[7] gave the heptaacetate (10) (91%) which was transformed, *via* the bromide (11) (HBr/HOAc), into the phenyl thioglycoside (12) ($PhSH/Et_3N/CH_2Cl_2$) in an overall yield of 80%. Condensation of (12) with the β-cellobioside (13)[8] in the presence of *N*-iodosuccinimide and triflic acid gave the carba-tetrasaccharide (14) in 50% yield.

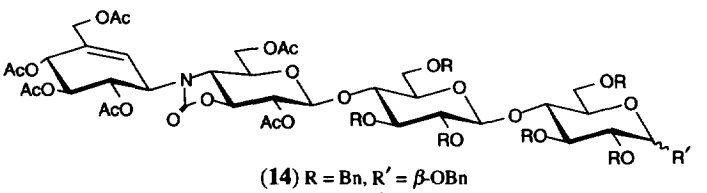


(**10**) R = OAc
(**11**) R = α-Br
(**12**) R = β-SPh

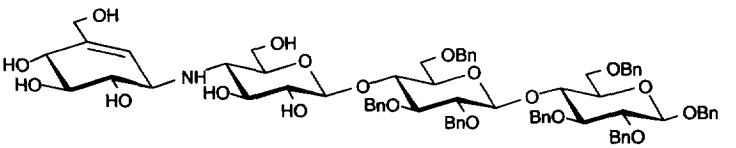


(**13**)

The deprotection of (14) to obtain the final product was not a trivial exercise. Treatment of (14) with lithium in liquid ammonia appeared to give the desired free sugar (15) but the molecule was not stable to the subsequent alkaline conditions necessary to remove the cyclic carbamate. More successfully, treatment of (14) firstly with aqueous sodium hydroxide in pyridine at 100° gave the polyol (16) which was successfully converted (Li/NH_3) into the 6″-hydroxylated derivative (2b) of β-acarbose.[9]



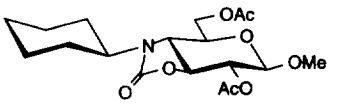
(**14**) R = Bn, R′ = β-OBn
(**15**) R = H, R′ = OH



(**16**)

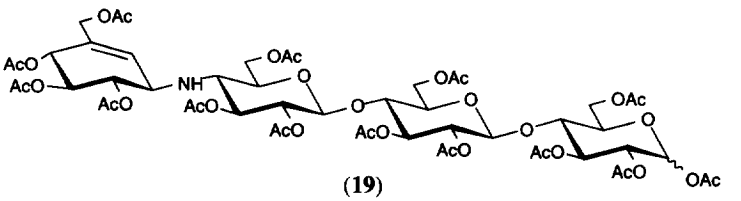
Several points in this work are worthy of comment. Firstly, although structural assignments were made routinely from the various spectroscopic techniques available and corroborated by combustion analyses, single-crystal X-ray structure determinations were performed on the aziridine (17) and the cyclic carbamate (18), employed as models of compounds (6) and (14), respectively. Secondly, this work has not produced β-acarbose (2a) but the 6″-hydroxylated derivative (2b) which is a diastereoisomer of the naturally occurring adiposin-2 (1b).[10] If results of inhibition experiments from derivatives of acarbose are any guide, (2b) should be at least as useful a candidate for enzyme inhibition as (2a).

(17)



(18)

Finally, acetylation of (2b) with acetic anhydride in pyridine gave the *per*-acetate (19) where the amine remained intact – no amide formation was observed. This is in line with similar chemistry associated with acarbose itself.[11]



(19)

We will soon report on the results of the various inhibition experiments utilising (7) and (2b) as well as direct procedures to prepare β-acarbose itself.

Acknowledgments: We thank Dr Matthew Tilbrook for his invaluable collaboration and the Australian Research Council for financial support.

References and Notes

1. Schmidt, D.D.; Frommer, W.; Junge, B.; Müller, L.; Wingender, W.; Truscheit, E.; Schäfer, D. *Naturwissenschaften*, **1977**, *64*, 535.
2. Truscheit, E.; Frommer, W.; Junge, B.; Müller, L.; Schmidt, D.D.; Wingender, W. *Angew. Chem. Int. Ed. Eng.* **1981**, *20*, 744.
3. Puls, W.; Keup, U.; Krause, H.P.; Thomas, G.; Hoffmeister, F. *Naturwissenschaften*, **1977**, *64*, 536.
4. Clissold, S.P.; Edwards, C. *Drugs*, **1988**, *35*, 214.
5. Nicotra, F.; Panza, L.; Ronchetti, F.; Russo, G. *Gazz. Chim. Italiana*, **1989**, *119*, 577.
6. Paulsen, H.; Röben, W. *Liebigs Ann. Chem.* **1985**, 974.

7. Zottola, M.; Venkateswara Rao, B.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1991**, 969.
8. Takeo, K.; Okushio, K.; Fukuyama, K.; Kuge, T. *Carbohydr. Res.* **1983**, *121*, 163.
9. For (2b):

^{1}H n.m.r. (500 MHz, D_2O)[a]

	Ring				
	A	B	C	α-D	β-D
H1	3.24-3.29, m	4.46, d	4.51, d	5.20, d	4.64, d
($J_{1,2}$)		(7.9)	(7.9)	(3.7)	(8.0)
H2	5.77, bs	3.32, dd	3.34, m	3.56, dd	3.26, dd
($J_{2,3}$)	-	(9.2)	(9.1)	(9.8)	(9.2)
H3	-	3.41, t	3.64, m[b]	3.82, dd[b]	3.63, m[b]
($J_{3,4}$)	-	(9.9)			
H4	4.17, m	2.72, t	3.64, m[b]	3.62, m[b]	3.62, m[b]
($J_{4,5}$)	(8.0)	(10.0)			
H5	3.52, dd	3.46, m	3.64, m[b]	3.92, m[b]	3.60, m[b]
($J_{5,6}$)	(10.3)	(2.3)			
H6	3.39, dd	3.82, m	3.81, m[b]	3.85, m[b]	3.78, m[b]
($J_{1,6}$)	(8.9)	4.02, dd	3.96, m	3.85, m[b]	3.93, dd
($J_{6,6}$)	-	(12.2)			
H7	4.07, bd	-	-	-	-
	4.20, bd				
($J_{7,7}$)	(13.5)	-	-	-	-

a) chemical shifts (p.p.m.) relative to sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) *b)* 2-D assignment (COSY)
c) chemical shifts (p.p.m.) relative to 1,4-dioxane (67.4 p.p.m.)

^{13}C n.m.r. (125.8 MHz, D_2O)[c] δ 138.22 ($C3^A$), 125.04 ($C2^A$), 103.40, 103.09 ($C1^B$,1^C), 96.53 (β-$C1^D$), 92.60 (α-$C1^D$), 79.30, 79.24, 79.14 ($C4^C$,α-4^D,β-4^D), 77.85, 77.06, 75.57, 75.27, 75.10, 75.01, 74.86, 74.66, 74.59, 73.69, 72.41, 72.07, 72.00, 70.90 (C4,5,6^A,2,3,5^B,2,3,5^C,α-2,3,5^D,β-2,3,5^D), 62.12, 61.45, 60.74, 60.69, 60.62 ($C7^A$,6^B,6^C,α-6^D,β-6^D), 60.33, 58.41 ($C1^A$,4^B).

FAB-MS (thioglycerol matrix) *m/z* 662.2554 ($C_{25}H_{43}NO_{19}$ requires 662.2507 for M+H).

10. Namiki, S.; Kangouri, K.; Nagate, T.; Hara, H.; Sugita, K.; Ōmura, S. *J. Antibiot.* **1982**, *35*, 1234.
11. Ogawa, S.; Iwasawa, Y.; Toyokuni, T.; Suami, T. *Carbohydr. Res.* **1985**, *141*, 29.

(*Received in UK* 12 *December* 1995; *revised* 12 *February* 1996; *accepted* 16 *February* 1996)