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Intramolecular guanidine epoxide ring opening reactions

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Abstract—The synthesis of a range of cyclic guanidines via intramolecular ring opening of epoxides or iodocyclisation is reported. A preliminary investigation of the glycosidase inhibitory activity of these substances is also discussed. © 2003 Published by Elsevier Science Ltd.

As part of a project directed towards the synthesis of the marine natural products ptilomycalin A and the batzelladines we have reported the addition reaction of guanidine to bis-α,β-unsaturated ketones **1**. The intermediates in this process can be directly converted, by stereoselective reduction, to tricyclic structures **2** found in the batzelladine alkaloids or alternately, by deprotection and spirocyclisation of pendent hydroxyl groups, to the pentacyclic guanidine **3** structurally similar to ptilomycalin A[1] (Scheme 1). We were interested in extending this methodology and as part of a project directed towards the synthesis of the marine hepatotoxin cylindrospermopsin **4**[2] (Fig. 1) we wished to investigate the reaction of guanidine with epoxides.

Surprisingly, few examples of epoxide ring opening processes utilising guanidines[3] have been reported. The first of these was the reaction of *cis*-benzene trioxide **5** with guanidine leading to the two isomeric diols **6a** and **6b**.[4] Le Merrer et al. then reported[5] the reaction of carbohydrate derived epoxides, for example **7**, with guanidine leading to the 9-membered cyclic guanidine **8** and also the formation of the furan **10**, initiated by ring opening of the epoxide **9** with guanidine. More recently Taylor and co-workers reported that the cyclic guanidine **11** readily reacts with epoxides to give ring opened products, for example **12** (Scheme 2).[6]

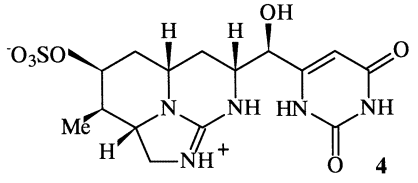
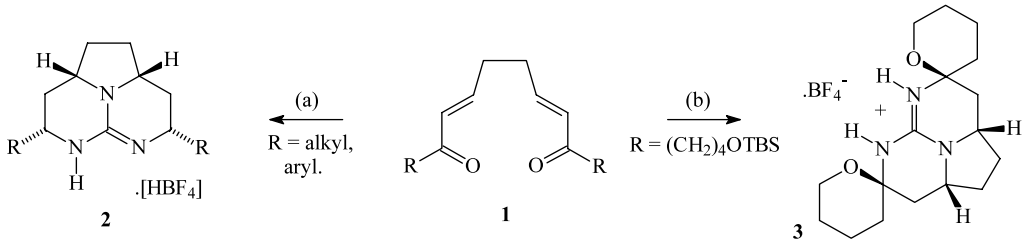


Figure 1.



Scheme 1. *Reagents and conditions*: (a) (i) guanidine, DMF, 0°C, 5 h, (ii) 3:1:3 DMF, H_2O, MeOH, then $NaBH_4$, 16 h, (iii) HCl (aq.), (iv) $NaBF_4$ (satd aq.); (b) (i) guanidine, DMF, 3 h, (ii) MeOH, HCl, 0°C–rt, 24 h, (iii) $NaBF_4$ (satd aq.).

Keywords: guanidines; epoxides; iodocyclisations; β-galactosidase inhibition.
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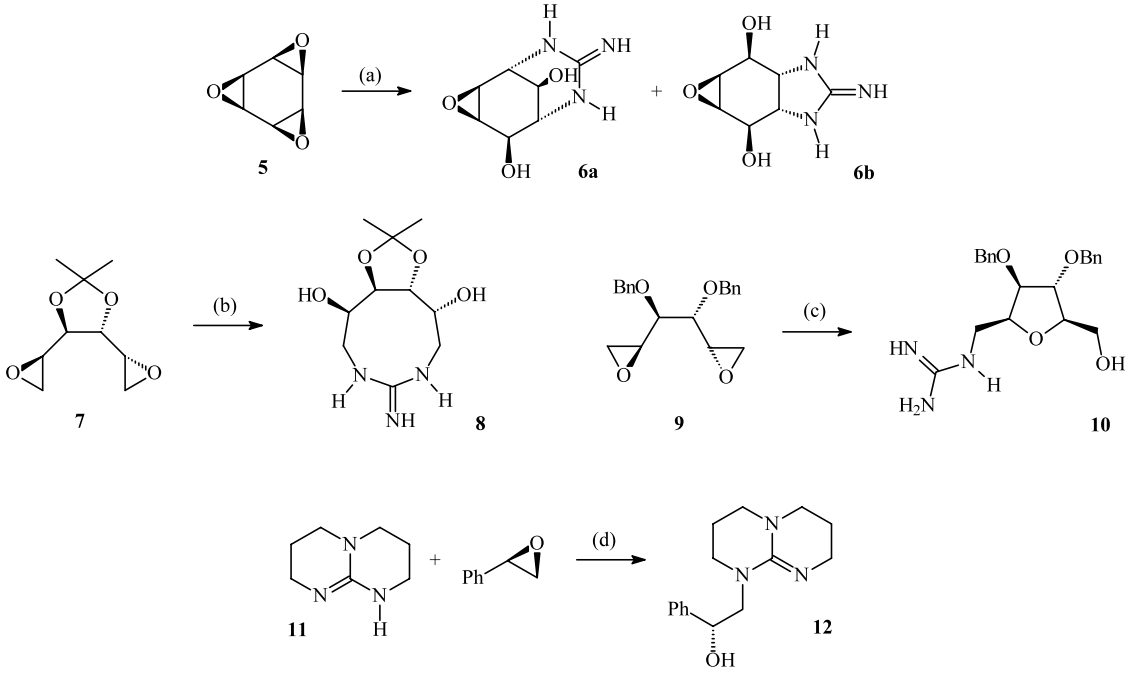


Scheme 2. *Reagents and conditions*: (a) guanidine, *t*-BuOH, Δ, 4 h; (b) guanidine, EtOH, Δ, 1 h; (c) guanidine, *t*-BuOH, 60°C, 130 h; (d) EtOH, Δ.

We were interested in the intramolecular ring opening of epoxides which would lead to the formation of 5- and 6-membered guanidine heterocycles, with the ultimate aim of applying this methodology to the synthesis of the tricyclic ring system found in cylindrospermopsin. We initially used the simple epoxides **13**–**16**[7] and treated them with guanidine in *t*-BuOH at room temperature for 24 h to effect *N*-alkylation of guanidine (which was presumed to be faster than the epoxide ring opening process). At this point potassium *t*-butoxide was added to regenerate the free guanidine from its salt, following which the reaction was heated at 60°C for a further 24–48 h to effect cyclisation. The results of these experiments are given in Table 1.

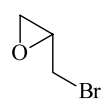
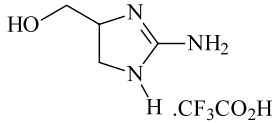
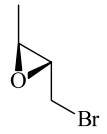
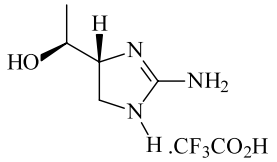
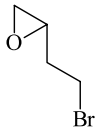
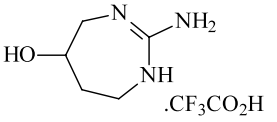
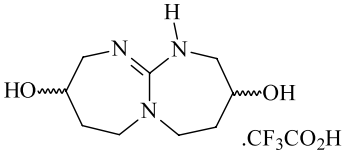
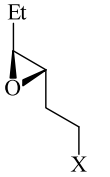
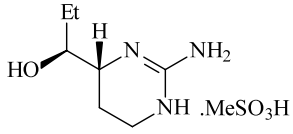
The reaction of epibromohydrin **13** under these conditions, led to the formation of the heterocycle **17**[8] in modest yield together with what appeared to be a trace amount of material arising for the reaction of guanidine with two equivalents of **13**. In addition to this a considerable amount of what appeared to be a polymeric guanidine containing material was also formed. We attempted to increase the amount of the double addition product formed by varying the stoichiometry of the reaction (conditions **B** and **C**), however this led only to the formation of further polymeric material. Only the 5-*exo* product was isolated from these reactions and no evidence for the formation of a 6-*endo* product was found. The reaction of epoxide **14** under identical conditions was then investigated and it was found to give essentially the same result. Typical yields of 30% were obtained and the 5-*exo* product **18** was the major product, together with trace amounts of a double addition product which was inseparable from the considerable quantity of polymeric material formed. In both these reactions, purification of the product proved problematic and repeated chromatographic separation was necessary.

On reaction of epoxide **15** under these conditions a different outcome was observed, in that the 7-*endo* product **19** was formed in high yield, together with the double addition product identified as **20**. Analysis of the NMR spectrum of the crude product indicated a 70:30 ratio of **19** to **20**, from which **19** could be isolated typically in 40–50% yield. Very little polymeric material was found indicating that the primary epoxide position is very susceptible to intramolecular ring opening. We were able to increase the relative amount of **20** formed, by varying the stoichiometry of the reaction. Where 2 equiv. of the epoxide **15** were used (conditions **B**) the two products, **19** and **20**, were isolated in a 35:65 ratio. This could be increased to some extent if 3 equiv. were employed (conditions **C**); however, considerable decomposition and lower overall yields were observed in these reactions.

Finally we investigated the substrates **16** (X = Hal) and were disappointed to find that the major products formed in these reactions were alkenes produced by dehydrohalogenation of the starting materials, probably arising from a base catalysed process. We attempted to prevent this elimination by using the mesylate **16** (X = OMs) and found that this underwent cyclisation to give the 6-*exo* product **21** in 58% yield together with some alkene and very little double addition product or polymeric material.

Our overall conclusions from these reactions are that in the case of substrates **13** and **14** the 5-*exo* cyclisation is

Table 1.

Epoxide	Conditions[(i)]	Products	
		Cyclic guanidine	Double addition product[(ii)]
			Trace
13	**A**	**17** (33%)	
			Trace
14	**A**	**18** (30%)	
			
15	**A**		**19 : 20**; 70 : 30 (**19**; 43%)
	B		**19 : 20**; 35 : 65
	C		**19 : 20**; 25 : 75
			Trace
16	**A**	**21** (58%)	

(i) Conditions

A. (a) Guanidine hydrochloride, 1 equiv *t*-BuOK, *t*-BuOH, then epoxide **13-16** 16 h, RT. (b) 1 equiv *t*-BuOK, 60°C, 24 h. (c) CF_3CO_2H, MeOH.

B. (a) Guanidine hydrochloride, 1 equiv *t*-BuOK, *t*-BuOH, then epoxide **15** 16 h, RT. (b) 1 equiv *t*-BuOK, 2 h. (c) epoxide **15**, 22 h. (d) 1 equiv *t*-BuOK, 60°C, 24 h. (e) CF_3CO_2H, MeOH.

C. (a) Guanidine hydrochloride, 1 equiv *t*-BuOK, *t*-BuOH, then epoxide **15** 16 h, RT. (b) 1 equiv *t*-BuOK, 2 h. (c) epoxide **15**, 22 h. (d) 1 equiv *t*-BuOK, 2 h. (e) epoxide **15**, 22 h. (f) 1 equiv *t*-BuOK, 60°C, 24 h. (g) CF_3CO_2H, MeOH.

(ii) MS analysis gave evidence for the formation of double addition product, except for **20** which was isolated.

preferred over the 6-*endo* process, however the process is complicated by the formation of high molecular weight polymeric by-products. The situation is more complex for substrates **15** and **16** where the 7-*endo* product is favoured for substrate **15**, but the 6-*exo* is preferred in the case of **16**. One possible explanation for this difference is that the 7-*endo* cyclisation to give **19** is a sterically more favourable ring opening at a primary position and is thus preferred over the 6-*exo* cyclisation.

With these heterocyclic products in hand we hoped to prepare derivatives of them in order that we might investigate further synthetic modifications. We attempted to bis-Boc protect the guanidine function found in substrate **17** (Boc_2O, NaOH (aq.), rt, 24 h) and were disappointed to find that the product obtained was an inseparable mixture of several *mono*- and bis-protected guanidines. We also attempted to silyl protect the hydroxyl function of the monocyclic products **17**–**19** and **21** and found that although we could prepare the corresponding silyl derivatives **22**–**25** the yields were low and the products somewhat prone to hydrolysis (Scheme 3). The reason for this instability has not been investigated, however the presence of the internal guanidinum species acting as a proton source might be a contributing factor and Elliot and Long have reported[9] that in a compound structurally similar to **22**, a desilylation occurs as a result of anchimeric assistance by the guanidine.

The failure to discriminate effectively between the functional groups in these heterocycles and the other complications associated with polymer formation, together with the associated purification problems are obvious drawbacks of this methodology. Despite this, the work does demonstrate a predictable mode of cyclisation for ω-halo-epoxides.

We wished to improve upon this initial work and to direct it more towards a synthesis of cylindrospermopsin and as the most predictable ring-opening mode is the 5-*exo* cyclisation of substrates **13** and **14**, we studied these reactions further. We investigated an in situ method for the formation of an intermediate similar to those proposed for the preparation of **17** and **18**. We thus took the known *N*-allyl-bis-Boc-guanidine[10] **26** and treated it with dimethyl dioxirane (DMDO) under neutral conditions and on monitoring the reaction by ^{1}H NMR it was apparent that after 24 h ca. 80% of the substrate had been converted into the epoxide **27**. On continued stirring this intermediate was consumed to give, on work up, a 62% yield of the cyclic product **28**,[8] the structure of which was confirmed by X-ray analysis (Fig. 2)[11] and by conversion to the previously prepared compound **17** by treatment with CF_3CO_2H. We also investigated the iodocyclisation of the guanidine **26** and found that this was also an effective reaction leading to the cyclic guanidine **29**[8] in 85% yield. Again the structure was confirmed by X-ray crystallography (Fig. 3)[11] (Scheme 4).

The synthesis of these two compounds in high yield should enable us to prepare a range of related heterocycles and also enable us to study a unique biomimetic[2b] approach to cylindrospermopsin. In addition heterocy-

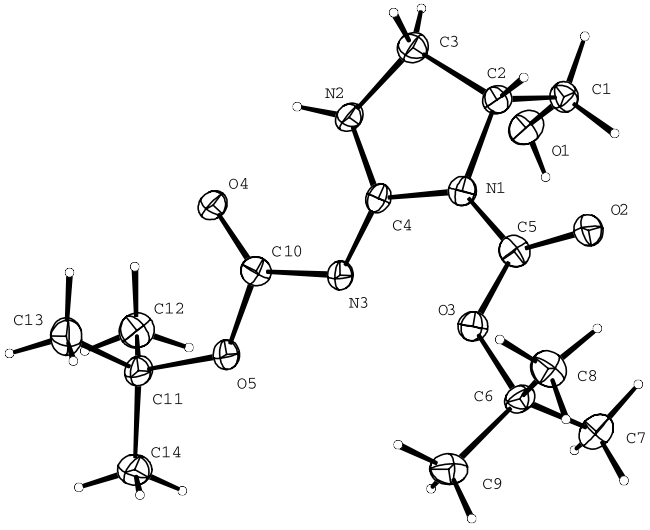


Figure 2.

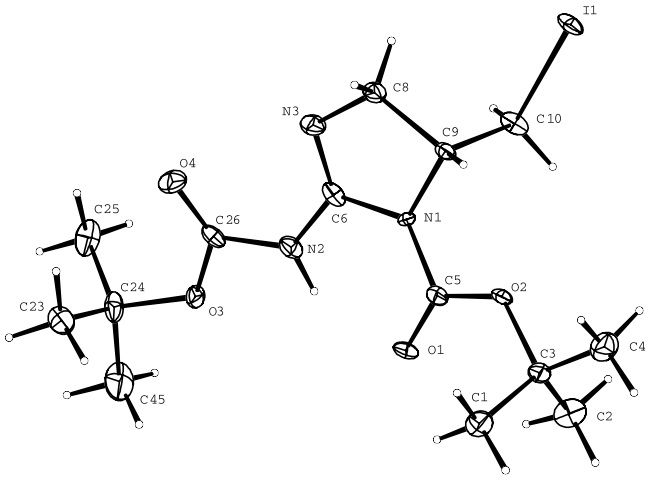
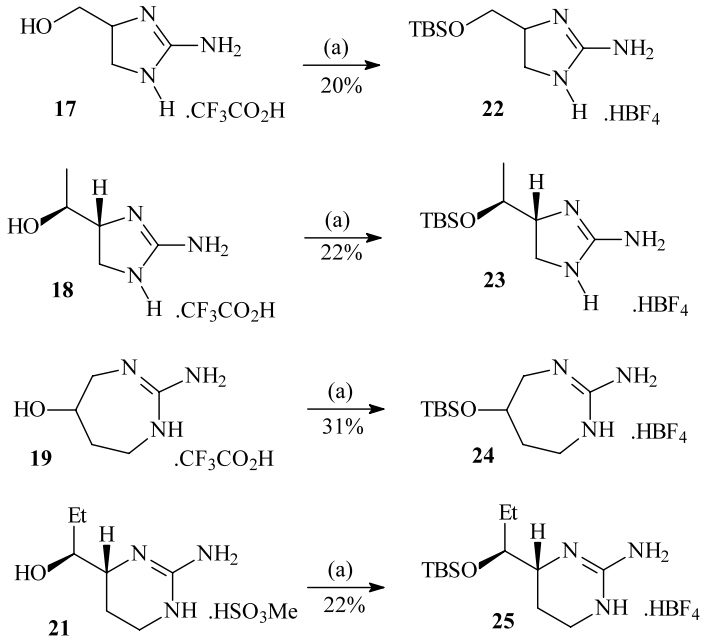
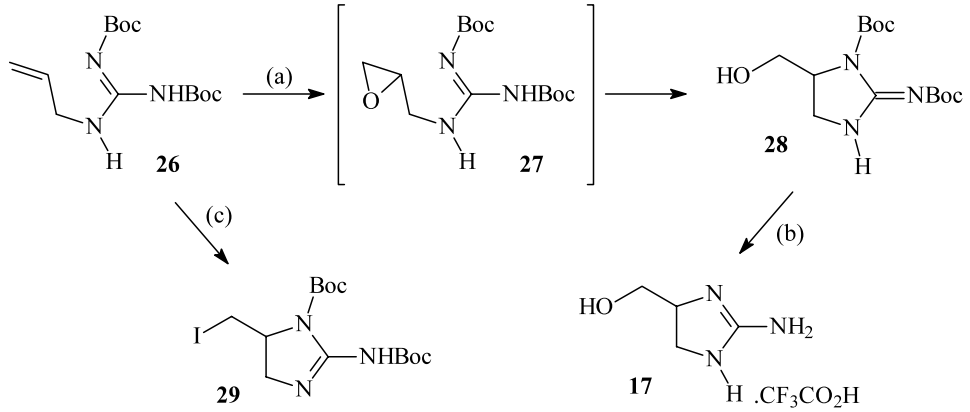


Figure 3.



Scheme 3. *Reagents and conditions*: (a) (i) 3 equiv. TBSCl, imid., DMF, 16–24 h, (ii) $NaBF_4$ (satd aq.).



Scheme 4. *Reagents and conditions*: (a) 1.5 equiv. DMDO, acetone 0°C–rt, 48 h; (b) CF_3COOH, 1 h; (c) 4 equiv. I_2, 4 equiv. K_2CO_3, MeCN, 48 h.

cles of this type are of general interest, as related compounds such as 1-deoxynojirimycin[12] and certain amidines[13] and guanidines[14] are known to disrupt biosynthesis of *N*-linked glycoproteins and glycolipids and are very effective glycosidase inhibitors.

We have performed a range of glycosidase assays[15] on compounds **17**–**19** and **21**–**25**, and in general these compounds appeared to be relatively weak but specific inhibitors of β-galactosidase (Bovine liver) with compound **25** being the most inhibitory ($IC_{50}=5.6$ μg ml^{-1}, Ki = 18 μM) and **23** ($IC_{50}=31$ μg ml^{-1}) and **19** ($IC_{50}=$ 49 μg ml^{-1}) having less activity. There was an interesting stimulation of β-galactosidase from *E. coli* by **19** (approximately threefold increase at 0.6 mM) and less by **25** (twofold at 0.4 mM). Removal of the trifluoroacetate from **19** by anion exchange removed the stimulation but not the inhibition whilst the trifluoroacetate anion had no effect. Similarly, changing the counterion of **25** to chloride removed the stimulation whilst not changing the inhibition. Whilst the level of inhibitory and stimulatory activity is still fairly low, the specificity for β-galactosidase is of interest and we are directing our synthetic efforts towards related compounds.

Acknowledgements

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7. Epibromohydrin **13** was purchased from Sigma–Aldrich; epoxides **14** and **15** were prepared by epoxidation of the corresponding bromides (*m*CPBA, 0°C–rt, CH_2Cl_2, 16 h; for **14**, 80%, for **15**, 92%). Mesylated epoxide **16** was prepared in two steps from *E*-1-hydroxyhex-3-ene [(i) *m*CPBA, 0°C–rt, CH_2Cl_2, 16 h; 72%; (ii) $MeSO_2Cl$, Et_3N, 0°C–rt, CH_2Cl_2, 16 h; 73%].
8. **Selected spectroscopic data**. Compound **17**; oil, δ_H (CD_3OD) 3.73, (1H, dd, $J=6.1$, 12.1 CH*H*), 3.77 (1H, dd, $J=5.2$, 10.1 Hz, CH*H*), 3.84 (1H, dd, $J=4.2$, 12.1

Hz, CH*H*), 3.93 (1H, dd, $J=10.1$, 10.1 Hz, CH*H*), 4.30 (1H, m, CH*H*). FTIR ν_{max} 3352, 1550. MS (CI): m/z 116 (40%, $[M+H]^+$) HRMS (CI): $C_4H_{10}N_3O$ ($[M+H]^+$) requires 116.0824, found 116.0825. Compound **28**; mp 130°C. δ_H ($CDCl_3$) 1.49 (9H, s, *t*-Bu), 1.54 (9H, s, *t*-Bu), 3.72, (1H, dd, $J=3.5$, 11.5 Hz, CH*H*), 3.78–3.83 (2H, m, 2×CH*H*), 3.85 (1H, dd, $J=9.1$, 12.5 Hz, CH*H*), 4.2 (2H, br s, NH, OH), 4.25 (1H, m, CH). FTIR: ν_{max} 3346, 2983, 2975, 1753, 1743, 1602. MS (CI): m/z 316 (100%, $[M+H]^+$) HRMS (CI): $C_{14}H_{26}N_3O$ ($[M+H]^+$) requires 316.1872, found 316.1868. Compound **29**; mp 60°C. δ_H ($CDCl_3$) 1.50 (9H, s, *t*-Bu), 1.56 (9H, s, *t*-Bu), 3.29 (1H, t, $J=9.2$ Hz, CH*H*), 3.39 (1H, dd, $J=2.7$, 9.7, Hz, CH*H*), 3.63 (1H, dd, $J=3.7$, 13.4 Hz, CH*H*), 3.97 (1H, dd, $J=9.5$, 13.4 Hz, CH*H*), 4.22 (1H, br m, CH), 9.2 (1H, br s, NH). FTIR: ν_{max} 3316, 2981, 2934, 1758, 1706, 1530. MS (CI): m/z 426 (30%, $[M+H]^+$). HRMS (CI): $C_{14}H_{25}N_3O_4I$ ($[M+H]^+$) requires 426.0890, found 426.0886.

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11. Cell dimensions and intensity data for **28** and **29** were recorded using a Bruker Nonius KappaCCD area detector diffractometer mounted at the window of a molybdenum rotating anode following standard procedures. Crystal data for **28** (CCDC number = 190508). Colourless block, $C_{14}H_{24}N_3O_5$, Mr = 314.36, $T=293(2)$ K, monoclinic, space group $P2_1/c$, $a=19.380(2)$, $b=13.2761(11)$, $c=13.0097(11)$ Å, $\beta=91.600(3)$, $V=3346.0(5)$ Å^3, $\rho_{calcd}=1.248$ g cm^{-3}, $\mu=0.095$ mm^{-1}, $Z=8$, reflections collected: 15984, independent reflections: 5259 ($R_{int}=0.1193$), final R indices [$I>2I$]: $R_1=0.0849$, $wR_2=0.2158$, R indices (all data): $R_1=0.1774$. $wR_2=0.2612$. Crystal data for **29** (CCDC no. 190507). Colourless plates, $C_{14}H_{24}N_3O_4I$, Mr = 425.26, $T=120(2)$ K, monoclinic, space group $P2_1/n$, $a=8.2871(3)$, $b=9.5256(3)$, $c=22.8746(6)$ Å, $\beta=92.77(1)$, $V=1803.61(10)$ Å^3, $\rho_{calcd}=1.566$ g cm^{-3}, $\mu=1.795$ mm^{-1}, $Z=4$, reflections collected: 11437, independent reflections: 11441 ($R_{int}=0.000$), final R indices [$I>2I$]: $R_1=0.0765$, $wR_2=0.1879$, R indices (all data): $R_1=0.1289$. $wR_2=0.2234$.
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15. The Sigma enzymes used were: β-galactosidase (bovine liver), α-glucosidase (Bakers yeast), α-mannosidase (Jack bean), β-glucosidase (almond), α-L-fucosidase (human placenta), *N*-acetyl-β-glucosaminidase (bovine kidney), Naringinase (*Penicillium decumbens*) and α-galactosidase (green coffee beans). The substrates were 5 mM *p*-nitrophenylglycopyranosides and enzymes 1 unit/ml. The method was as described previously.[16]
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