

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 1231

www.rsc.org/obc

PAPER

Rapid and practical synthesis of (–)-1-deoxyaltronojirimycin†

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Received 19th September 2010, Accepted 4th November 2010

DOI: 10.1039/c0ob00747a

Herein a practical and scalable route to 1-deoxyaltronojirimycin is presented. The target is achieved in 9 steps and 43% yield featuring only two chromatographic purifications.

Introduction

The story of the nojirimycins begins with the isolation of nojirimycin (**1**, Fig. 1) in 1966 by Inuoye *et al.* from several strains of *Streptomyces*.¹ This highly polar “heterosugar” was first identified as an antibiotic and later recognized as a glucosidase inhibitor.² In 1976, Bayer chemists discovered that the stable, naturally occurring 1-deoxynojirimycin (**2**, originally synthesized in 1966 by Paulsen *et al.*³) is a potent α -glucosidase inhibitor. Since these seminal discoveries nojirimycins have attracted a great deal of attention both from the academia⁴ as well as the pharma industry. Two derivatives of **2** are currently in the market for the treatment of two different human conditions. The inhibitory power of **2** is being realized in miglitol (Glyset®, **3**), a drug for treating type II diabetes mellitus.⁵ The drug effectively lowers blood sugar levels by inhibiting the break down of dietary sugars. On the other hand, N-butyl-DNJ (Zavesca®, **4**) is being used for the treatment of Gaucher disease, a serious lysosomal storage disorder previously only treatable through enzyme replacement therapy.⁶ Zavesca® inhibits the biosynthesis of glycosphingolipids, thereby decreasing their accumulation in the body. Besides these two targets, inhibition of several other enzymes have been or are being investigated,

including glycosyl transferases,⁷ glycogen phosphorylase,⁸ sugar nucleoside mutase⁹ and metalloproteinases.¹⁰ Zavesca® has also shown some promise as a male contraceptive.¹¹ Iminosugar derivatives have been reported to be active against the *Flaviviridae* viral family,¹² cytotoxic against several cancer cell lines¹³ and to inhibit angiogenesis.¹⁴ Hence the need to be able to produce practical amounts of nojirimycin analogues with varying stereochemical configurations is apparent. Herein we wish to describe a practical route to (–)-1-deoxyaltronojirimycin (**5**); a nojirimycin analogue having altrose stereochemistry.¹⁵ The compound itself shows modest activity towards glycosidases,¹⁶ however it serves as a proof-of-concept towards derivatives having such stereochemistry.

Results and discussion

Due to the high interest the synthetic community has had in these so called azasugars, many imaginative synthetic routes have been devised. Nojirimycins and derivatives thereof have been accessed for example from carbohydrates, amino acids and tartaric acid.¹⁷ Our laboratory has had a long term interest in diastereoselective synthesis of enantiopure (vicinal) amino alcohols from amino acids. Previously we described the diastereoselective synthesis of (–)-1-deoxygalactonojirimycin (DGJ, **6**) using the general strategy outlined in Scheme 1.¹⁸ Disconnection along the C1–N bond gives rise to an open-chain compound **8** with a leaving group at C1. This can be thought to be derived from the differentially protected bis-allylic alcohol **9**. This is in turn accessible from Garner's aldehyde (**10**) and a protected propargyl alcohol **11** via formal reductive coupling.

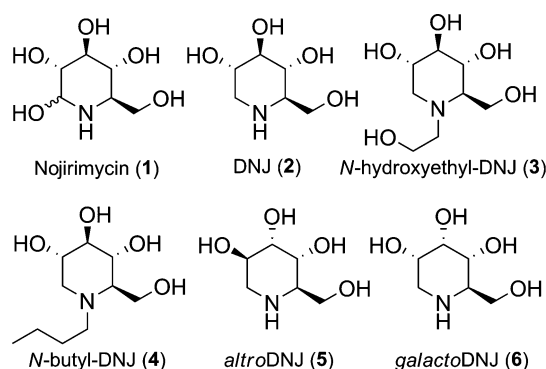
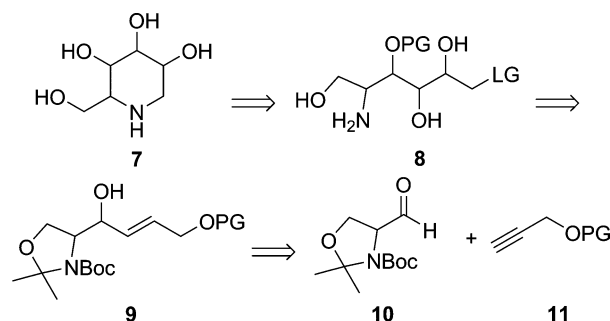


Fig. 1 Nojirimycin and several of its derivatives.

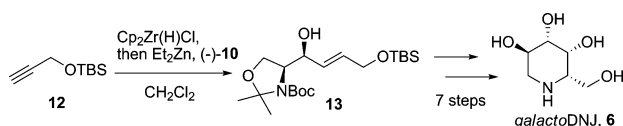
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† Electronic Supplementary Information (ESI) available: Copies of ¹H and ¹³C spectra are included in the ESI. See DOI: 10.1039/c0ob00747a/



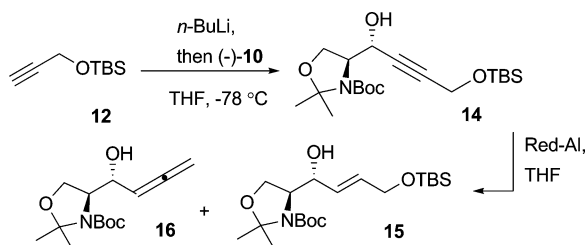
Scheme 1 General retrosynthetic strategy.

allylic alcohols such as **9** through Horner–Wadsworth–Emmons reaction between an amino acid derived β -keto phosphonate and the corresponding aldehyde followed by diastereoselective reduction.¹⁹ However, we noted that the diastereoselectivity of the reduction is highly sensitive to the actual substrate, and more importantly partial racemization of the phosphonate becomes a problem in large scale synthesis. To overcome this problem, we have used a zinc nucleophile generated by hydrozirconation–transmetalation sequence to couple (–)-**10** and **12** with exceptional *syn* (>20 : 1) selectivity (Scheme 2).²⁰ Now we wanted to be able to access the *anti* relationship between the C4 and C5 substituents. This would in turn call for reversal of diastereoselectivity in the coupling step. Despite a promising literature precedent, we were not able to reverse the diastereoselectivity.²¹ Instead, we turned our attention to lithiated nucleophiles, as it is known that their addition to **10** proceeds with *anti* preference.



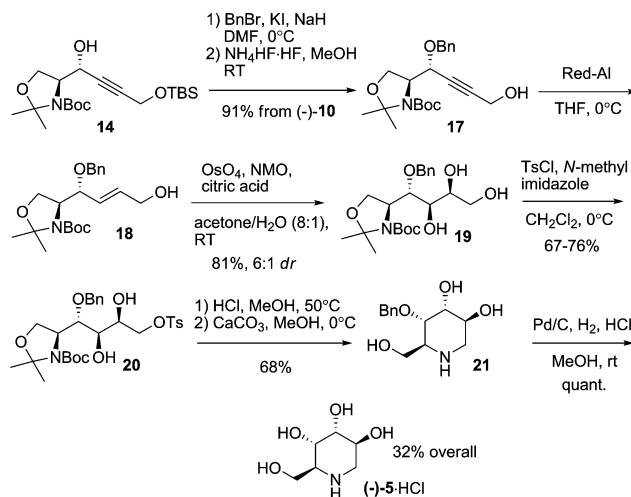
Scheme 2 Key reductive coupling.

The synthesis commenced with the addition of lithiated **12** to the (–)-Garner aldehyde (Scheme 3).²² We found out that if performed in THF, the addition proceeded smoothly and in useful diastereomeric ratio (>15 : 1). No difference in diastereomeric ratio was detected in the presence of HMPA. We then envisioned that reduction of the triple bond with Red-Al would deliver the *anti* congener of **13**. Instead a mixture of **15** and the allene **16** was produced as evidenced by the high carbon shift at $\delta = 207.9$ ppm.²³ Under no conditions could the undesired elimination of TBSO be suppressed.



Scheme 3 Alkynylation of **10** and attempted reduction.

In order to avoid problems in the reduction step, we protected the secondary alcohol of **14** as the benzyl ether²⁴ (Scheme 4) followed by desilylation of the primary alcohol. $\text{NH}_4\text{F}\cdot\text{HF}$ proved to be a far superior desilylation reagent compared to the standard TBAF (tetrabutylammonium fluoride) both in terms of price and practicality, as no hard to remove tetrabutyl ammonium residues are formed in the reaction. In fact, simple silica gel filtration after the desilylation was to provide **17** in more than adequate purity. Treatment of **17** with 2 equivalents of Red-Al produced exclusively the desired *trans*-allylic alcohol **18** in near quantitative yield, again without any need to resort to chromatography. Osmium catalyzed dihydroxylation under modified Upjohn conditions provided the tetraol **19** in 81% yield (6 : 1 *d*-²⁵).²⁶ The diastereomeric mixture proved to be extremely difficult to purify. One of the diastereomers



Scheme 4 First generation approach to (–)-**5**.

is a good ligand for osmium as the black Os(VI) was still present even after three chromatographic runs. Nevertheless, adequate amounts of pure **19** could be produced through this route for further experiments.

Attempted mesylation of the primary alcohol only led to decomposition upon isolation. On the other hand, the tosylate **20** was found to be relatively stable. Our first attempt (TsCl , NEt_3 , CH_2Cl_2) delivered the tosylate in meager 35% yield. In an effort to improve the yield, we tried numerous bases and conditions (Table 1). Increasing the temperature significantly improved the yield (entry 2). Added secondary base (DMAP) did not improve the yield, on the contrary significant decomposition was evident (entry 3). We also attempted to catalyze the reaction with dibutyl tin oxide as reported.²⁷ However, the substrate proved to be reluctant to such catalysis (entries 4 and 5). We then proceeded to test several other bases, of which *N*-methyl imidazole proved to be the best, delivering the desired monotosylate **20** in 67–76% yield. It should be noted, that under no conditions we detected any bistosylated products.

With every functionality in place we were now ready for the ring closure. Removal of the *N,O*-acetal and the BOC-group was accomplished with hydrochloric acid in methanol in quantitative

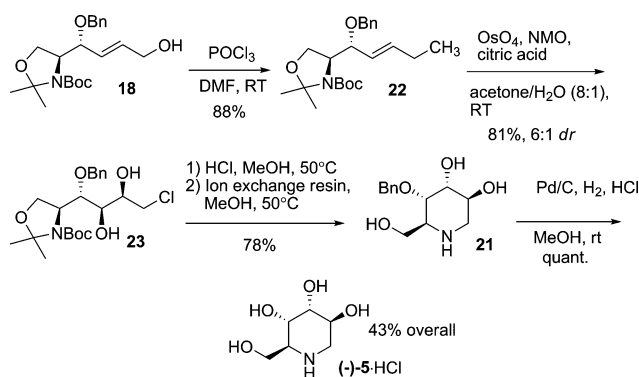
Table 1 Monotosylation of **19**^a

Entry	Base	Additive	T/°C	Yield (%) ^b
1	1.3 eq NEt_3	—	–10–RT	35
2	1.3 eq NEt_3	—	0–RT	58
3	1.3 eq NEt_3	0.1 eq DMAP	RT	n. i. ^c
4	1.0 eq NEt_3	2% Bu_2SnO	0	n. i. ^c
5	1.1 eq NEt_3	5% Bu_2SnO	0	40
6	5.0 eq pyr.	—	0–RT	n. r. ^d
7	2.0 eq DMAP	—	0	45
8	5.0 eq 2,4,6-collidine	0.2 eq DMAP	0	66
9	1.2 eq <i>N</i> -methyl imidazole	—	0	67–76

^a Reaction conditions: A flame-dried flask under argon was loaded with **19** (125 mg, 0.30 mmol, 100 mol%) and 3 mL of CH_2Cl_2 . The flask was cooled down to the appropriate temperature, after which base was added followed by TsCl (63 mg, 0.33 mmol, 105 mol%). Stirred until complete consumption of starting material or for 48 h. ^b Isolated yields after chromatography. ^c Not isolated. ^d No reaction took place.

yield. The cyclization was effected by treating the crude salt with calcium carbonate in methanol, yielding the piperidine **21** in 68% yield after chromatography. If the cyclization was effected using triethyl amine or diisopropylethyl amine the crude reaction mixture was difficult to purify due to the oily amine salts. Hydrogenolysis of the remaining protecting group under acidic conditions delivered **5-HCl** in quantitative yield, thereby completing the synthesis in 32% overall yield over 9 steps.

However, we were not satisfied with the hard-to-purify dihydroxylation product **19**, nor with the low yielding tosylation step. To this end another leaving group was envisioned. Allylic chlorination of **18** delivered the chloride **22** in good yield (88%) with no need for chromatographic purification (Scheme 5). Subsequent dihydroxylation delivered **23** in passable yield (81%) and without erosion of the diastereomeric ratio (6 : 1). Moreover, the diastereomers were now much easier to separate due to lack of the primary hydroxyl group. The dihydroxylation was also attempted using KMnO_4 . Without buffering (CH_2Cl_2 , 1.5 equivalents of KMnO_4) no reaction took place, however when buffered with NaHCO_3 complete decomposition was observed. Deprotection and cyclization worked with similar efficiency compared to the tosylate (78%, 2 steps). After hydrogenolysis of the benzyl protection, (–)-*altro*DNJ hydrochloride (–)-**5** was obtained in improved 43% overall yield. Furthermore one chromatographic purification was omitted.



Scheme 5 Improved endgame.

Conclusions

Herein we have described a method for producing (–)-*altro*DNJ hydrochloride in 9 steps with 43% overall yield. Only two chromatographic purifications in the late stages are required, making the route fast and efficient.

Experimental section

Dichloromethane and tetrahydrofuran were obtained from a solvent drier (MB SPS-800, neutral alumina). Methanol was distilled from $\text{Mg}(\text{OMe})_2$. Dimethyl formamide was distilled from molecular sieves (5 Å) and ninhydrin. Other solvents used in reactions and in chromatography were of p.a. quality. Reagents were obtained from Sigma–Aldrich or from Acros Organics and used as such, unless otherwise stated. TLC monitoring was performed on Merck silica gel 60 F₂₅₄ (230–400 mesh, aluminium) plates. Stains used to visualize the plates were permanganate (3 g

KMnO_4 , 20 g K_2CO_3 , 5 mL 1 M NaOH, diluted to 300 mL with water), vanillin (3 g vanillin, 2.5 mL conc. H_2SO_4 , 1.5 mL acetic acid, 125 mL EtOH) and UV-light ($\lambda = 254$ nm). Flash chromatography was performed on Merck Silica Gel 60 silica. The celite used in filtrations was either Fluka Celite 501 or Sigma–Aldrich Celite 535 Coarse. NMR spectra were recorded on Bruker Avance 400 spectrometer. The spectra were calibrated either to TMS (^1H : δ 0.00 ppm), MeOD (^1H : δ 3.34 ppm, ^{13}C δ : 49.86 ppm), CDCl_3 (^{13}C : δ 77.0 ppm), $\text{Cl}_2\text{CDCDCl}_2$ (^1H : δ 6.00 ppm, ^{13}C δ : 73.8), toluene- d_8 (^1H : δ 2.09 ppm, ^{13}C δ : 20.4) or to D_2O (^1H : δ 4.70 ppm, ^{13}C : δ 49.5 ppm, MeOH as internal standard) depending on the used solvent. Spectra were recorded at 25 °C, unless otherwise stated. Heating of the NMR-samples was performed using a probe heater. IR spectra were recorded on Perkin–Elmer Spectrum One FTIR machine. Optical rotations were measured with Perkin–Elmer 343 polarimeter using sodium lamp and a 10 cm quartz cuvette. HRMS spectra were recorded on Waters Micromass LCT Premier (ESI/TOF) mass spectrometer.

tert-Butyldimethyl(prop-2-ynyloxy)silane (**12**)

To a solution of propargyl alcohol (1.00 g, 17.8 mmol, 100 mol%) in dry dichloromethane (7 mL) under argon was added *tert*-butyldimethylsilyl chloride (2.68 g, 17.8 mmol, 100 mol%) followed by imidazole (2.43 g, 35.7 mmol, 200 mol%). The flask was equipped with a condenser after which the solution was heated to reflux. After 2 h the starting material was consumed by TLC and the flask was allowed to cool to room temperature. The reaction was quenched with 10 mL of ice-cold water. The resulting mixture was filtered through a pad of celite. The filtrate was transferred to a separating funnel and the phases were separated. The aqueous phase was extracted 3 \times 10 mL CH_2Cl_2 . Combined organic phases were washed with brine (25 mL), dried over Na_2SO_4 and the bulk of the solvent was evaporated. Distillation under reduced pressure afforded 2.63 g (98%) of clear colorless liquid. Bp = 52 °C (14 torr);²⁸ R_f 0.68 (1 : 2 EtOAc/Hex, permanganate); ^1H -NMR (CDCl_3) δ ppm 4.31 (d, 2H, $J = 2.4$ Hz), 2.39 (t, 1H, $J = 2.5$ Hz), 0.91 (s, 9H), 0.13 (s, 6H)

(*S*)-*tert*-butyl 4-((*R*)-1-(benzyloxy)-4-hydroxybut-2-yn-1-yl)-2,2-dimethylloxazolidine-3-carboxylate (**17**)

A flame-dried flask under argon was charged with **12** (23.7 g, 138.0 mmol, 130 mol%) and 275 mL of dry THF. The solution was cooled to –78 °C and *n*-BuLi (57.5 mL, 135.0 mmol, 125 mol%, 2.35 M in hexanes) was added over 10 min. The resulting mixture was stirred for an hour. Then **2** (22.7 g, 98.8 mmol, 100 mol%) was added as a THF solution (115 mL + 20 mL for washing, pre-cooled to –78 °C) *via* cannula over 1 h. The resulting solution was stirred for 1 h and then quenched by adding 100 mL of sat. NH_4Cl . The cooling bath was removed and replaced by a warm water bath. After reaching room temperature, the aqueous layer was extracted with EtOAc (2 \times 50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated to yield 42.3 g of crude product as slightly yellow oil. Analytical sample was prepared by flash column chromatography (10% ethyl acetate/hexanes).

R_f 0.56 (2 : 1 Hex/EtOAc); $[\alpha]_D^{20} = -35.0$ (c 2.83, DCM) lit. –35.8 (c 1.1 CDCl_3)¹⁷; HRMS Found 422.2337 Calculated for 422.2339 $\text{C}_{20}\text{H}_{37}\text{NNaO}_5\text{Si}$ [$M + \text{Na}$]; ^1H -NMR (400 MHz, C_6D_6 , 60 °C)

4.64 (br. s, 1 H), 4.21 (d, $J = 2.0$, 2 H), 4.00 (m, 2 H), 3.72 (dd, $J = 8.5$, 7.2, 1 H), 1.69 (s, 3 H), 1.46 (s, 3 H), 1.39 (s, 9 H), 0.94 (s, 9 H), 0.09 (s, 6 H); ^{13}C -NMR 154.1, 94.9, 84.5, 82.5, 81.3, 72.5, 65.0, 64.1, 62.5, 28.3, 25.8, 25.2, 22.9, 18.5, 13.9, -5.2

A flask under argon was charged with the crude product from the previous reaction (42.3 g, assumed circa 98.0 mmol, 100 mol%), and dry DMF (100 mL). The solution was cooled to 0 °C and benzyl bromide (15.4 mL, 130 mmol, 130 mol%) was added together with KI (830 mg, 5 mmol, 5 mol%). Finally sodium hydride (4.8 g, 120 mmol, 120 mol%, 60% dispersion in mineral oil) was added as a single portion. After the gas evolution had stopped the slurry was diluted with 100 mL of dry THF. After 1 h of stirring, the reaction was quenched by adding 60 mL of sat. NaHCO_3 (dropwise at first, until gas no longer forms) and then diluted with 150 mL of water. The mixture was extracted with EtOAc (3 \times 100 mL). The combined organic phases were washed with water (200 mL) and brine, dried over Na_2SO_4 and concentrated. The residue was filtered through a pad of silica gel (eluted with 5% EtOAc/Hexanes) to yield 52.4 g of light yellow oil. Analytical sample was prepared by flash column chromatography (5% Ethyl acetate/hexanes).

R_f 0.66 (30% EtOAc/Hex); $[\alpha]_{\text{D}}^{20} = -76.5$ (c 2.0 DCM); HRMS Found 512.2825 Calculated for 512.2832 ($\text{C}_{27}\text{H}_{43}\text{NNaO}_5\text{Si}$) [$\text{M} + \text{Na}$]; ^1H -NMR (400 MHz, CDCl_3) 7.21–7.39 (m, 5 H), 4.83 (app. t, $J = 11.3$ Hz, 1 H), 4.69–4.74 (m, 0.5 H, rotameric species), 4.51 (dd, $J = 12.1$, 7.2 Hz, 1 H), 4.45–4.48 (m, 0.5 H, rotameric species), 4.37 (d, $J = 13.4$ Hz, 2 H), 4.23–4.29 (m, 1 H), 4.09–4.15 (m, 0.5 H rotameric species), 4.01 (app. t, $J = 8.2$ Hz, 1H), 3.95–3.99 (m, 0.5 H, rotameric species); ^{13}C -NMR: 152.7, 152.0, 138.3, 137.9, 128.9, 128.7, 128.5, 128.3, 128.0, 95.4, 94.8, 81.8, 80.7, 80.3, 71.4, 71.2, 68.3, 67.7, 65.1, 64.7, 61.1, 60.8, 52.2, 28.8, 26.6, 26.3, 26.2, 26.0, 25.6, 24.1, 18.7, -4.6 (c. 2 : 1 mixture of rotamers); IR: $\nu_{\text{max}}/\text{cm}^{-1} = 3351, 1705, 1390, 1366, 1089, 837$ (neat)

The product from the previous reaction (52.8 g, assumed circa 98 mmol, 100 mol%) was dissolved in MeOH (80 mL) under ambient conditions. $\text{NH}_4\text{HF}\cdot\text{HF}$ (11.5 g, 200 mmol, 200 mol%) was added and the resulting mixture was stirred for 18 h. To quench the reaction, 30 g of silica gel was added to the reaction mixture. After 30 min of stirring, the solution was diluted with 350 mL of CH_2Cl_2 , passed through a pad of silica (washed with 10% MeOH– CH_2Cl_2) and concentrated. The crude product was dissolved in 20% EtOAc/Hexanes and filtered through a pad of silica. After concentration 34.0 g (91% over 3 steps) of pale yellow oil was obtained. Analytical sample was obtained by chromatographic purification (20% \rightarrow 30% \rightarrow 50% EtOAc/Hexanes).

R_f 0.47 (1 : 1 EtOAc/Hex); $[\alpha]_{\text{D}}^{20} = -54.9$ (c 1.0 DCM); HRMS Found 398.1953 Calculated for 398.1943 $\text{C}_{21}\text{H}_{29}\text{NNaO}_5$ [$\text{M} + \text{Na}$]; ^1H -NMR (400 MHz, CDCl_3 , 50 °C) 7.21–7.40 (m, 5 H), 4.80 (d, $J = 12.1$ Hz 1 H), 4.52 (d, $J = 12.1$ Hz 1 H), 4.12–4.36 (m, 4 H), 3.93–4.06 (m, 1H), 1.27–1.70 (m, 15 H); ^{13}C -NMR (CDCl_3) 152.5, 151.5, 137.6, 137.3, 128.3, 128.2, 128.0, 127.8, 127.7, 127.6, 94.9, 94.2, 85.7, 85.4, 82.5, 80.4, 79.9, 70.9, 67.9, 97.8, 64.6, 64.4, 60.4, 60.1, 50.7, 28.3, 26.5, 25.5, 24.8, 23.5 (rotamerism); ^1H NMR = (400 MHz, TOLUENE- d_8 , 100 °C) $\delta = 7.28$ –7.20 (m, 2 H), 7.16–7.08 (m, 2 H), 7.08–7.00 (m, 1 H), 4.71 (d, $J = 11.7$ Hz, 1 H), 4.69 (app. d, $J = 12.1$ Hz, 1 H), 4.44 (d, $J = 11.7$ Hz, 1 H), 4.27–4.18 (m, 1 H), 4.09 (d, $J = 2.6$ Hz, 1 H), 3.98–3.90 (m, 2 H), 3.87–3.79 (m, 1 H), 1.71–1.57 (m, 3 H), 1.51–1.44 (m, 3 H), 1.40–1.31 (m, 9 H) IR: $\nu_{\text{max}}/\text{cm}^{-1} = 3436, 2978, 1683, 1392, 1366$ (neat)

(*S*)-*tert*-butyl 4-((*R,E*)-1-(benzyloxy)-4-hydroxybut-2-en-1-yl)-2,2-dimethyloxazolidine-3-carboxylate (18)

A flame-dried flask under argon charged with compound **17** (3.40 g, 9.10 mmol, 100 mol%) and dry THF (45 mL) was placed in an ice/water bath. Then Red-Al was added dropwise (5.55 mL, 18.2 mmol, 65 w-% in tol.). After 15 min of stirring, the reaction was quenched by dropwise addition of MeOH (1 mL, until no further gas evolution occurs). Then 5 g of Rochelle's Salt was added followed by 5 mL of sat. aq. rochelle's salt. After 30 min of stirring the mixture was filtered through a pad of celite (filter cake was washed with 3 \times 30 mL of methylene chloride) and concentrated. The crude residue was dissolved in methylene chloride and filtered through a pad of silica gel (washed with 50% EtOAc/Hexanes). After concentration 3.43 g (99%) of colorless oil was obtained.

R_f 0.35 (1 : 1 EtOAc/Hex) $[\alpha]_{\text{D}}^{20} = -48.2$ (c 2.0 DCM); HRMS Found 400.2118 Calculated for 400.2100 $\text{C}_{21}\text{H}_{31}\text{NNaO}_5$ [$\text{M} + \text{Na}$]; ^1H -NMR (400 MHz, CDCl_3) $\delta = 7.38$ –7.19 (m, 5 H), 5.92–5.77 (m, 1 H), 5.76–5.60 (m, 1 H), 4.60 (d, $J = 11.7$ Hz, 1 H), 4.36 (d, $J = 11.7$ Hz, 1 H), 4.26–3.82 (m, 6 H), 2.46–2.14 (m, 1 H), 1.62–1.33 (m, 15 H); ^{13}C -NMR (CDCl_3 , 50 °C) 152.6, 138.3, 133.1, 129.6, 128.3, 127.7, 127.5, 93.9, 80.0, 70.9, 64.7, 62.5, 60.4, 28.4, 27.1, 24.9, 23.4; IR $\nu_{\text{max}}/\text{cm}^{-1} = 3460, 2979, 1698, 1391, 1366$ (neat)

(*S*)-*tert*-butyl 4-((1*S*,2*R*,3*S*)-1-(benzyloxy)-2,3,4-trihydroxybutyl)-2,2-dimethyloxazolidine-3-carboxylate (19)

To a solution of **18** (2.28 g, 6.06 mmol, 100 mol%) and citric acid (1.40 g, 7.27 mmol, 120 mol%) in acetone/ H_2O (8 : 1, 27 mL) was added OsO_4 (770 μL [4% in H_2O], 0.12 mmol, 2 mol%). To the resulting yellow solution was added *N*-methylmorpholine *N*-oxide (0.98 g, 7.27 mmol, 120 mol%) as a single portion. The light green solution was stirred for 6 h, until complete by TLC (color also changes gradually back to yellow). Acetone was evaporated with rotary evaporator, the aqueous residue was acidified with 1 M HCl (c. 3 mL) and diluted (20 mL H_2O). Extraction (3 \times 20 mL EtOAc), brine wash and drying yielded 2.54 g of dark foamy matter.

Separation of the diastereomeric mixture (c. 6 : 1) is extremely difficult. Repeated chromatographic runs (3–4) on MeOH–DCM or EtOAc–DCM gives the product as white foamy matter.

R_f 0.22 (65% EtOAc/Hex + 1% MeOH); $[\alpha]_{\text{D}}^{20} = -32.6$ (c = 2.0, DCM); HRMS Found 434.2161 Calculated for 434.2155 $\text{C}_{21}\text{H}_{33}\text{NNaO}_7$ [$\text{M} + \text{Na}$]; ^1H -NMR (400 MHz, TCE, 90 °C) $\delta = 7.43$ –7.31 (m, 5 H), 4.80 (d, $J = 11.3$ Hz, 1 H), 4.72 (d, $J = 11.2$ Hz, 1H), 4.30–4.21 (m, 2 H), 4.10–3.99 (m, 2 H), 3.92 (ddd, $J = 9.7$, 5.0, 2.6 Hz, 1 H), (app. t, $J = 5.0$ Hz, 2H), 3.66 (td, $J = 8.6$, 3.0 Hz, 1 H), 3.12 (br. s, 1H), 2.80 (app. d, $J = 4.9$ Hz, 1H), 2.16 (app. t, $J = 5.21$, 1H), 1.63 (s, 3H), 1.58–1.55 (m, 12H); ^{13}C -NMR (100 MHz, TCE, 90 °C) 137.9, 128.3, 127.8, 127.7, 94.0, 80.7, 80.0, 74.7, 72.7, 70.2, 64.8, 63.6, 58.2, 28.4, 26.7; IR $\nu_{\text{max}}/\text{cm}^{-1} = 3420, 1695, 1667, 1395, 1366$ (neat)

(*S*)-*tert*-butyl 4-((1*S*,2*R*,3*S*)-1-(benzyloxy)-2,3-dihydroxy-4-(tosyloxy)butyl)-2,2-dimethyloxazolidine-3-carboxylate (20)

To a stirred solution of **19** (540 mg, 1.33 mmol, 100 mol%) and *p*-toluenesulfonylchloride (280 mg, 1.46 mmol, 110 mol%) in dry CH_2Cl_2 (6 mL) under argon was added *N*-methyl imidazole (250 μL , 2.13 mmol, 150 mol%) at 0 °C. After 4 h of stirring the reaction was quenched with water (10 mL). Aqueous phase

was extracted 3 × 5 mL CH₂Cl₂. Combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated. Chromatographic purification (EtOAc–CH₂Cl₂, 0%–>30%) gave 510 mg of colorless oil. Decomposes if heated!

*R*_f 0.84 (65% EtOAc/Hex + 1% MeOH) [α]_D²⁰ = –20.4 (*c* = 1.0, DCM) HRMS Found 588.2244 Calculated for 588.2243 C₂₈H₃₉NNaO₉S [M + Na]; ¹H-NMR (400 MHz, CDCl₃) δ = 7.67–7.74 (m, 2 H), 7.20–7.31 (m, 7 H), 4.41–4.82 (m, 2 H), 3.84–4.21 (m, 7 H), 3.34 (br. s, 1 H), 2.36 (s, 3 H), 1.33–1.57 (m, 15 H) ¹³C-NMR: We were unable to obtain a clear spectrum due to the extensive rotamerism and heat sensitivity IR ν_{max} /cm^{–1} = 3392, 1661, 1396, 1366, 1176 (neat)

(3*S*,4*R*,5*S*,6*S*)-5-(benzyloxy)-6-(hydroxymethyl)piperidine-3,4-diol (21)

Compound **20** (500 mg, 0.88 mmol, 100-mol%) was dissolved in MeOH (4 mL) and the flask was then cooled to 0 °C. Freshly prepared, saturated HCl(g)/MeOH was added (*c.* 4 mL) and the cooling bath was removed. After 1 h of stirring, starting material was completely consumed. Solvent was evaporated to give 430 mg of crude as white foam.

HRMS Found 426.1651 Calculated for 426.1586 C₂₀H₂₉NO₇S [M + H]; ¹H NMR (400 MHz, MeOD) δ = 7.84–7.79 (m, 2 H), 7.46–7.42 (m, 2 H), 7.42–7.31 (m, 5 H), 4.73 (d, *J* = 11.0 Hz, 1 H), 4.68 (d, *J* = 11.0 Hz, 1 H), 4.15 (dd, *J* = 5.8, 9.8 Hz, 1 H), 4.09 (dd, *J* = 7.0, 9.8 Hz, 1 H), 4.00–3.88 (m, 3 H), 3.82 (dd, *J* = 7.7, 11.6 Hz, 1 H), 3.70 (dd, *J* = 1.5, 8.1 Hz, 1 H), 3.60 (td, *J* = 4.3, 8.0 Hz, 1 H); ¹³C-NMR (100 MHz, MeOD): 147.5, 139.8, 135.1, 132.0, 130.4, 129.9, 129.9, 78.7, 76.0, 73.0, 72.4, 70.0, 60.4, 57.1, 22.4

To an ice-cold solution of the crude from previous reaction (420 mg, 0.85 mmol, 100 mol%) in MeOH (8 mL) was added calcium carbonate (295 mg, 2.13 mmol, 250 mol%) and the resulting mixture was stirred for 3 h at 0 °C. The ice-cold solution was then filtered through a pad of celite (filter cake was washed 2 × 1 mL ice-cold MeOH) and concentrated to yield 550 mg of slightly yellow sticky solid. Chromatographic purification (20% MeOH–CHCl₃ + 1% aq. ammonia (25%)) yielded 204 mg (69%, over 2 steps) of the title compound.

*R*_f 0.24 (20% MeOH–CHCl₃ + 1% aq. ammonia (25%)); [α]_D²⁰ = –43.5 (*c* 2.02 MeOH); HRMS Found 254.1397 Calculated for 254.1406 C₁₃H₂₀NO₄; ¹H NMR (400 MHz, MeOD) δ = 7.43–7.22 (m, 5 H), 4.69 (d, *J* = 11.3 Hz, 1 H), 4.51 (d, *J* = 11.3 Hz, 1 H), 4.12 (t, *J* = 3.5 Hz, 1 H), 3.82–3.71 (m, 3 H), 3.67 (dd, *J* = 2.9, 11.0 Hz, 1 H), 3.05 (dd, *J* = 1.8, 13.9 Hz, 1 H), 2.86 (td, *J* = 3.4, 10.0 Hz, 1 H), 2.71 (ddd, *J* = 0.7, 2.2, 13.9 Hz, 1 H); ¹³C-NMR (100 MHz, METHANOL-*d*₄) 140.8, 130.2, 129.9, 129.5, 76.1, 72.8, 71.8, 69.7, 62.9, 57.2, 47.5; IR ν_{max} /cm^{–1} = 3307, 2925, 2884, 1454, 1074 (neat)

(*S*)-tert-butyl 4-((*R,E*)-1-(benzyloxy)-4-chlorobut-2-en-1-yl)-2,2-dimethyloxazolidine-3-carboxylate (22)

A flame-dried flask was charged with **18** (3.05 g, 8.08 mmol, 100 mol%), dry DMF (60 mL) and then cooled to 0 °C. POCl₃ (1.63 mL, 17.8 mmol, 220 mol%) was added as a single portion. The cooling bath was removed and the solution was stirred for 3 h. The previously colorless solution had taken a bright yellow color. The reaction was quenched by adding sat. NaHCO₃ (25 mL)

dropwise at 0 °C. The mixture was diluted with water 120 mL and extracted 3 × 80 mL of Et₂O. Combined organic phases were dried over Na₂SO₄ and concentrated. The yellow residue was dissolved in 20% EtOAc/hexanes and filtered through a pad of silica gel. After concentration 2.82 g (88%) of slightly yellow oil was obtained.

*R*_f 0.74 (60% Et₂O/Hex); [α]_D²⁰ = –47.5 (*c.* 1.93, DCM); HRMS Found 418.1755 Calculated for 418.1761 C₂₁H₃₀NNaO₄Cl [M + Na]; ¹H-NMR (400 MHz, Tol, 90 °C) δ = 7.24–6.94 (m, 5 H), 5.71–5.57 (m, 2 H), 4.45 (d, *J* = 11.7 Hz, 1 H), 4.26 (d, *J* = 12.1 Hz, 1 H), 4.08 (t, *J* = 6.0 Hz, 1 H), 3.97 (dd, *J* = 2.6, 8.8 Hz, 1 H), 3.87 (t, *J* = 6.0 Hz, 1 H), 3.71–3.68 (m, 2 H), 3.65 (dd, *J* = 6.0, 8.6 Hz, 1 H), 1.56 (s, 3 H), 1.46 (s, 2 H), 1.37 (s, 7 H); ¹³C-NMR (100 MHz, Tol, 90 °C) 152.7, 139.4, 133.8, 130.4, 128.9, 128.4, 94.8, 80.4, 80.0, 72.0, 65.3, 61.5, 44.2, 28.9, 27.6 IR ν_{max} /cm^{–1} = 3436, 1698, 1387 (neat)

(*S*)-tert-butyl 4-((1*S*,2*R*,3*R*)-1-(benzyloxy)-4-chloro-2,3-dihydroxybutyl)-2,2-dimethyloxazolidine-3-carboxylate (23)

To a stirred solution of **2** (2.79 g, 7.39 mmol, 100 mol%) in acetone/H₂O (8:1, 40 mL) was added citric acid (2.49 g, 12.93 mmol, 175 mol%) followed by OsO₄ (0.94 mL, 0.15 mmol, 2 mol%, 4 w-% in H₂O). After the addition of osmium, the solution changed to yellow/green in color. Finally *N*-methyl morpholine *N*-oxide (1.1 g, 8.13 mmol, 110 mol%) was added and the flask was sealed with a cap. After 18 h of stirring the color had changed to bright yellow. To quench the reaction 470 mg of sodium thiosulfate was added. In 5 min black precipitate had formed. Acetone was evaporated under reduced pressure and the residue was dissolved in 35 mL of water. The aqueous mixture was extracted with EtOAc (3 × 25 mL). Combined organic phases were dried over Na₂SO₄ and concentrated to give 2.84 g of foamy glass-like product. Chromatographic purification (30% → 50% → 60% EtOAc/Hex) yielded 2.08 g (65%) of pure **23** and 390 mg of mixed **23** and 2,3-*epi*-**23**. Combined yield 2.47 g (81%), 6:1 *dr* (by NMR).

*R*_f 0.56 (60% EtOAc/Hex); [α]_D²⁰ = –35.1 (*c.* 1.93, DCM); HRMS Found 452.1812 Calculated for 452.1816 C₂₁H₃₂NNaO₆Cl [M + Na]; ¹H-NMR (400 MHz, tetrachloroethane-*d*₂, 60 °C) δ = 7.43–7.31 (m, 5 H), 4.79 (d, *J* = 11.3 Hz, 1 H), 4.65 (d, *J* = 11.3 Hz, 1 H), 4.28–4.21 (m, 2 H), 4.09–3.95 (m, 3 H), 3.69–3.57 (m, 3 H), 1.62 (s, 3 H), 1.57–1.51 (m, 12 H); ¹³C-NMR: (100 MHz, TETRACHLOROETHANE-*d*₂, 60 °C) 137.7, 128.4, 128.8, 127.9, 94.0, 80.8, 78.9, 74.6, 71.7, 70.4, 63.3, 58.2, 46.5, 28.3, 28.2, 26.5; IR ν_{max} /cm^{–1} = 3369, 1659, 1399 (neat)

(3*S*,4*R*,5*S*,6*S*)-5-(benzyloxy)-6-(hydroxymethyl)piperidine-3,4-diol (21) from 23

To a flask charged with **23** (560 mg, 1.3 mmol, 100 mol%) was added ice-cold, freshly prepared HCl(g)/MeOH (10 mL). The solution was stirred at room temperature for 40 min and then heated gently to 50 °C. After further 40 min of stirring the starting material was consumed by TLC, and the previously colorless solution had turned yellow. Solvent was evaporated to yield 430 mg of yellow glass-like gel. The residue was then dissolved in methanol (12 mL) and the ion exchange resin was added (Merck ionenaustaucher II, 500 mg). The mixture was heated to 50 °C and stirred for 16 h. The reaction was not complete by TLC, so 200 mg

more of the resin was added and stirred for further 5 h at reflux. The mixture was filtered through a fritted funnel and concentrated. The crude product was purified by flash chromatography (20% MeOH–CHCl₃ + 1% NH₄OH [25%]) to yield 258 mg of slightly yellow oil (78%) which solidifies into a gummy solid on standing. Spectroscopically identical to one prepared from **20**.

(–)-1-Deoxyaltronojirimycin hydrochloride ((–)-5 HCl)

To a stirred solution of **21** (125 mg, 0.494 mmol, 100 mol%) in MeOH (5 mL) and conc. HCl (100 µL, 1.00 mmol, 200 mol%) was added Pd/C (100 mg, 0.05 mmol, 10 mol%, 5% in Pd). H₂ atmosphere was then introduced and the solution was vigorously stirred for 1 h. The mixture was filtered through a pad of celite and concentrated to yield 106 mg (100%) of the title compound as white foam.

R_f 0.00 (20% MeOH–DCM + 1% NH₄OH [25%]); [α]_D²⁰ = –36.7 (c. 1.00, MeOH; lit. –33.2 (c. 0.5, MeOH),²⁹ 31.0 (c. 2.0, MeOH)³⁰); HRMS Found 164.0923 Calculated for 164.0923 C₆H₁₅NO₄ [M + H]; ¹H-NMR (400 MHz, D₂O) δ = 4.12–4.07 (m, 1 H), 4.00–3.87 (m, 3 H), 3.77 (dd, *J* = 6.8, 12.8 Hz, 1 H), 3.36–3.27 (m, 2 H), 3.17 (dd, *J* = 2.7, 13.5 Hz, 1 H); ¹³C-NMR (100 MHz, D₂O (MeOH iSTD) 69.4, 67.1, 64.6, 59.1, 56.8, 49.9, 44.9

Notes and references

- 1 S. Inouye, T. Tsuruoka and T. Niida, *J. Antibiotics*, 1966, **19**, 288–292.
- 2 T. Niwa, S. Inouye, T. Tsuruoka and T. Niida, *Agrig. Biol. Chem.*, 1970, **34**, 966–967.
- 3 H. Paulsen, *Angew. Chem., Int. Ed. Engl.*, 1966, **5**, 495–511.
- 4 For an excellent introduction to the subject see: A. Stutz, *Iminosugars as glycosidase inhibitors: Nojirimycin and beyond*, Wiley-VCH, New York, 1999; P. Compain and O. R. Martin, *Iminosugars: From synthesis to therapeutic applications*, Wiley-VCH, New York, 2007.
- 5 E. Fattorusso and O. T. Scafati, *Modern Alkaloids*, Wiley-VCH, New York, 2008, 111–133.
- 6 T. Cox, R. Lachmann, C. Hollak, J. Aerts, S. van Weely, M. Hribicek, F. Platt, T. Butters, R. Dwek, C. Moyses, I. Gow, D. Elstein and A. Zimran, *Lancet*, 2000, **355**, 1481–1485.
- 7 P. Compain and O. R. Martin, *Curr. Top. Med. Chem.*, 2003, **3**, 541–560.
- 8 M. Bols, R. Hazelle and I. B. Thomsen, *Chem.–Eur. J.*, 1997, **3**, 940–947; L. Somsak, V. Nagy, Z. Hadady, T. Docsa and P. Gergely, *Curr. Pharm. Des.*, 2003, **9**, 1177–1189.
- 9 R. E. Lee, M. D. Smith, R. J. Nash, R. C. Griffiths, M. McNeil, R. K. Grewal, W. Yau, G. S. Besra, P. J. Brennan and G. W. Fleet, *Tetrahedron Lett.*, 1997, **38**, 6733–6736.
- 10 H. Moriyama, T. Tsukida, Y. Inoue, K. Yokota, K. Yoshino, H. Kondo, N. Miura and S.-I. Nishimura, *J. Med. Chem.*, 2004, **47**, 1930–1938; R.-J. Wang, C.-H. Yang and M.-L. Hu, *J. Agrig. Food Chem.*, 2010, **58**, 8988–8993.
- 11 C. M. Walden, T. D. Butters, R. A. Dwek, Frances M. Platt and A. C. Van Der Spoel, *Hum. Reprod.*, 2006, **21**, 1309–1315.
- 12 J. Chang, L. Wang, D. Ma, X. Qu, H. Guo, X. Xu, P. M. Mason, N. Bourne, R. Moriarty, B. Gu, J.-T. Guo and T. M. Block, *Antimicrob. Agents Chemother.*, 2009, **53**, 1501–1508; A. J. Stevens, M. E. Gahan, S. Mahalingam and P. A. Keller, *J. Med. Chem.*, 2009, **52**, 7911–7926.
- 13 M. Padró, J. A. Castillo, L. Gómez, J. Joglar, P. Clapés and C. de Bolós, *Glycoconjugate J.*, 2010, **27**, 277–285.
- 14 Y. Zhou, Y. Zhao, K. M. O'Boyle and P. V. Murphy, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 954–958.
- 15 For recent publications concerning altroDNJ see: A. M. C. H. van den Nieuwendijk, M. Ruben, S. E. Engelsma, M. D. P. Risseuw, R. J. B. H. N. van den Berg, R. G. Boot, J. M. Aerts, J. Brussee, G. A. van der Marel and H. S. Overkleeft, *Org. Lett.*, 2010, **12**, 3957–3959; S. K. Bagal, S. G. Davies, J. A. Lee, P. M. Roberts, A. J. Russell, P. M. Scott and J. E. Thomson, *Org. Lett.*, 2010, **12**, 136–139; R. Rengasamy, M. J. Curtis-Long, H. W. Ryu, K. Y. Oh and K. H. Park, *Bull. Korean Chem. Soc.*, 2009, **30**, 1531–1534; P. D. Dhavale, S. D. Markad, N. S. Karanjule and J. PrakashaReddy, *J. Org. Chem.*, 2004, **69**, 4760–4766.
- 16 A. Kato, N. Kato, E. Kano, I. Adachi, K. Ikeda, L. Yu, T. Okamoto, Y. Banba, H. Ouchi, H. Takahata and N. Asano, *J. Med. Chem.*, 2005, **48**, 2036–2044.
- 17 For synthetic methods see: M. S. Pearson, M. Mathe-Allainmat, V. Fargeas and J. Lebreton, *Eur. J. Org. Chem.*, 2005, **11**, 2159–2191; K. Afarinkia and A. Bahar, *Tetrahedron: Asymmetry*, 2005, **16**, 1239–1287; and ref. 4.
- 18 O. K. Karjalainen, M. Passiniemi and A. M. P. Koskinen, *Org. Lett.*, 2010, **12**, 1145–1147.
- 19 A. M. P. Koskinen and P. M. Koskinen, *Tetrahedron Lett.*, 1993, **34**, 6765–6768; P. M. Koskinen and A. M. P. Koskinen, *Methods Enzymol.*, 1999, **311**, 458–479.
- 20 P. Wipf and W. Xu, *Tetrahedron Lett.*, 1994, **35**, 5197–5200.
- 21 T. Murakami and K. Furusawa, *Tetrahedron*, 2002, **58**, 9257–9263.
- 22 H. Gruza, K. Kiciak, A. Krasinski and J. Jurczak, *Tetrahedron: Asymmetry*, 1997, **8**, 2627–2631.
- 23 The allene **16** has the following spectroscopic properties: ¹H-NMR (400 MHz, CDCl₃) δ = 5.21 (dd, *J* = 13.0 Hz, 6.6 Hz, 1 H), 4.85 (app. d, *J* = 5.7 Hz, 2 H), 3.80–4.44 (m, 5 H), 1.58 (bs, 3 H), 1.50 (s, 9H); ¹³C-NMR (100 MHz, CDCl₃) 207.9, 153.8, 151.7, 94.3, 92.1, 90.9, 80.9, 80.0, 71.0, 70.3, 64.6, 62.0, 61.2, 28.2, 26.2, 25.7, 24.5, 22.9; HRMS Found 292.1535 Calculated for 292.1525 (C₁₄H₂₃NO₄ + Na).
- 24 S. Czernecki, C. Georgoulis and C. Provelenghiou, *Tetrahedron Lett.*, 1976, **17**, 3535–3536.
- 25 The diastereoselectivity is in full agreement with published data; K. J. Cha, W. G. Christ and Y. Kishi, *Tetrahedron Lett.*, 1983, **37**, 3943–1946.
- 26 V. VanRheenen, R. C. Kelly and D. Y. Cha, *Tetrahedron Lett.*, 1976, **17**, 1973–1976; P. Dupau, R. Eppele, A. A. Thomas, V. V. Fokin and K. B. Sharpless, *Adv. Synth. Catal.*, 2002, **344**, 421–433.
- 27 M. J. Martinelli, R. Vaidyanathan, J. M. Pawlak, N. K. Nayyar, U. P. Dhokte, C. W. Doecke, L. M. H. Zollars, E. D. Moher, V. V. Khau and B. Košmrlj, *J. Am. Chem. Soc.*, 2002, **124**, 3578–3585.
- 28 A. De Mico, R. Margarita, L. Parlantini, A. Vescovi and G. Piancatelli, *J. Org. Chem.*, 1997, **62**, 6974–6977.
- 29 O. V. Singh and H. Han, *Tetrahedron Lett.*, 2003, **44**, 2387–2392.
- 30 P. D. Dhavale, S. D. Markad, N. S. Karanjule and J. PrakashaReddy, *J. Org. Chem.*, 2004, **69**, 4760–4766.