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Tetrahedron Letters 44 (2003) 7649–7653

TETRAHEDRON LETTERS

Stereoselective synthesis of the α-glucosidase inhibitor nectrisine

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Received 19 June 2003; revised 30 July 2003; accepted 8 August 2003

Abstract—The α-glucosidase inhibitor nectrisine was synthesised in 12 steps (31% overall yield) starting from D-serine. The three contiguous stereocentres of this iminosugar were introduced via a highly diastereoselective boron mediated glycolate aldol reaction.

1. Introduction

Oligosaccharides have been shown to play important roles in a large number of biological recognition events that range from cell–cell communication, fertilization, and cell differentiation, to pathological processes including cancer metastasis, and inflammation.[1] Imino-analogues of sugars (also known as azasugars) are known to behave as glycosidase[2] or glycosyltransferase[3] inhibitors by acting as transition state mimics, where the flattened pyrrolidine ring and protonated nitrogen mimic the distorted structure of the glycosyl cation intermediate.[4] Hence, this class of sugar mimetics offers therapeutic potential in areas such as inflammatory diseases, lysosomal storage disorders, and cancer.[5] Two such iminosugars are the pyrrolidine 1,4-dideoxyimino-D-arabinitol (DAB-1) **1**[6] and the polyhydroxylated dihydropyrrole nectrisine (FR 900483) **2**[7] (Fig. 1). These compounds are extremely potent α-glucosidase inhibitors [IC_{50} 1.8×10^{-7} and 4.8×10^{-8} M, respectively (yeast α-glucosidase)],[8] and the synthesis of nectrisine **2** and related unsaturated analogues has attracted the attention of a number of groups.[9] We recently reported an extremely efficient synthesis of DAB-1 (**1**) from serine-derived aldehyde **3**.[10] In this paper, we further demonstrate the utility of aldehyde **3** by disclosing our synthesis of the related iminosugar nectrisine **2**.

2. Results and discussion

A number of serine derived aldehydes can be found in the literature.[11] Unfortunately, many of these demonstrate a propensity to undergo racemisation and/or exhibit poor diastereoselectivity under nucleophilic addition.[12] However, the addition of nucleophiles to *N*,*N*-dibenzyl protected amino aldehydes has been shown to take place with high diastereoselectivity under both chelation and non-chelation controlled conditions making aldehyde **3** an attractive building block.[13] The key step in our synthetic strategy was the construction of the diol motif in **4** which we envisaged could be achieved via either dihydroxylation of a γ-amino-α,β-unsaturated ester, or a boron-mediated asymmetric aldol condensation. Protecting group 'tuning' of the dihydroxylation reaction of γ-amino-α,β-unsaturated ester derivatives has been reported for a range of less complex amino acid derivatives,[14] and the dihydroxylation reaction of a number of carbamate and oxazoline protected serine derivatives has also been reported.[15]

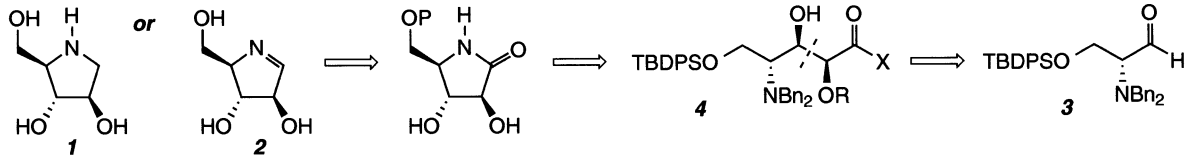

Figure 1. Retrosynthetic analysis of the polyhydroxylated plant alkaloids DAB-1 (**1**) and nectrisine **2**.

Keywords: iminosugars; glycolate aldol; glycosidase inhibitors.
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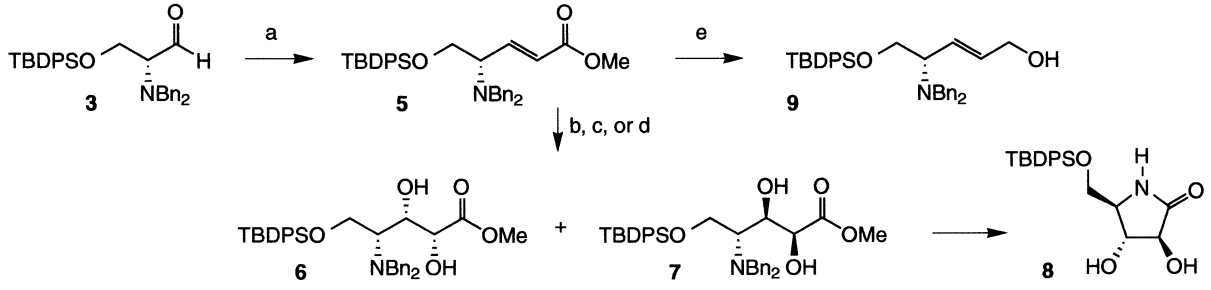
doi:10.1016/j.tetlet.2003.08.030

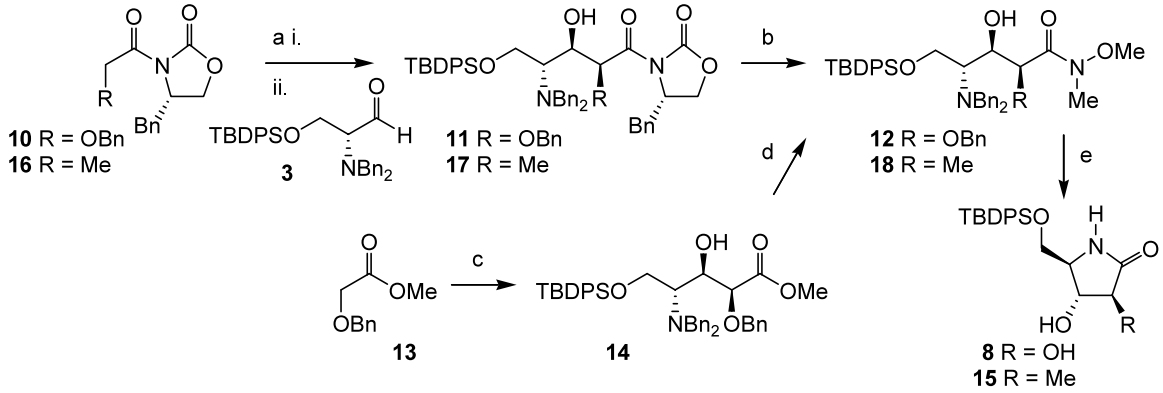
The dihydroxylation reaction of γ-amino-α,β-unsaturated ester derivatives has recently been used in the synthesis of several natural product targets including deoxyaminohexoses,[16a] polyhydroxylated indolizidine plant alkaloids,[16b,c] and α,β-dihydroxy-γ-aminoacids[16d] including hydroxystatine isosteres,[16e] and the AI-77's.[16f] On the other hand, the glycolate aldol reaction has recently been shown to represent a viable alternative to the dihydroxylation reaction, offering both *syn* and *anti* diastereocontrol.[17]

The synthesis of aldehyde **3** was achieved in five steps from D-serine with 88% overall yield and >98% ee, using our previously reported procedure.[10,18] This aldehyde was found to be stable to racemisation on storage at 4°C for up to 48 h. Aldehyde **3** was converted to the α,β-unsaturated ester **5** in excellent yield (95%) under Horner–Wadsworth–Emmons conditions using the mild base $Ba(OH)_2$ (Scheme 1).[19] Osmium tetroxide catalysed dihydroxylation resulted in a moderate yield (59%) of diols **6** and **7** in a 65:35 diastereomeric ratio, favouring the undesired all-*syn* diol **6**.[20,21] The use of AD-mix-α resulted in a very sluggish reaction and only a modest improvement in yield (65% based on unrecovered starting material) and no apparent increase in diastereoselectivity. However, the diastereoselectivity could be overturned in favour of the desired *syn* diol **7** by use of AD-mix-β, but again the reaction rate was very slow (7 days) and the diastereoselectivity modest (32:68, **6**:**7**). Separation of the desired *syn* diastereomer **7**, conversion to the corresponding Weinreb amide and removal of the *N*-benzyl protecting groups using Pearlman's catalyst resulted in conversion in situ to the previously reported lactam **8**.[10] In an attempt to improve the alkene reactivity towards dihydroxylation, ester **5** was reduced to alcohol **9**. This allylic alcohol was found to undergo dihydroxylation more readily than its ester counterpart (75% yield, 60 h), but similarly disappointing levels of diastereoselectivity (~3:1) were observed, deterring further investigation of this route.

We have previously shown that reaction of aldehyde **3** with Evan's chiral glycolate equivalent **10**[22] affords the desired *syn* aldol adduct (Felkin–Anh product) **11** in excellent yield as a single diastereomer (Scheme 2).[10] Aldol adduct **11** may be converted to pyrrolidinone **8** via Weinreb amide **12** in 71% over the two steps.[10] This combination of Evans oxazolidinone and α-chiral aldehyde was shown to represent a 'matched' stereo-inductive pairing,[23] by the stereochemical outcome of the reaction of methyl benzyloxyacetic acid **13**[24] with aldehyde **3** which also provided a single diastereomeric aldol adduct **14**[25] in good yield (75%). The identity of



Scheme 1. *Reagents and conditions*: (a) $(MeO)_2POCH_2CO_2Me$, $Ba(OH)_2$ (activated), THF:H_2O (40:1), rt, 1 h; **3**, THF, rt, 18 h (95%); (b) OsO_4 (18 mol%), NMO, acetone:H_2O (8:1), rt, 5 h (59%, 65:35 ratio **6**:**7**); (c) AD-mix-α, $MeSO_2NH_2$, acetone:H_2O (3:1), rt, 7 d (65%, 66:34 ratio **6**:**7**); (d) AD-mix-β, $MeSO_2NH_2$, acetone:H_2O (3:1), rt, 7 d (68%, 32:68 ratio **6**:**7**); (e) $LiAlH_4$, Et_2O, −78°C, 45 min (85%).

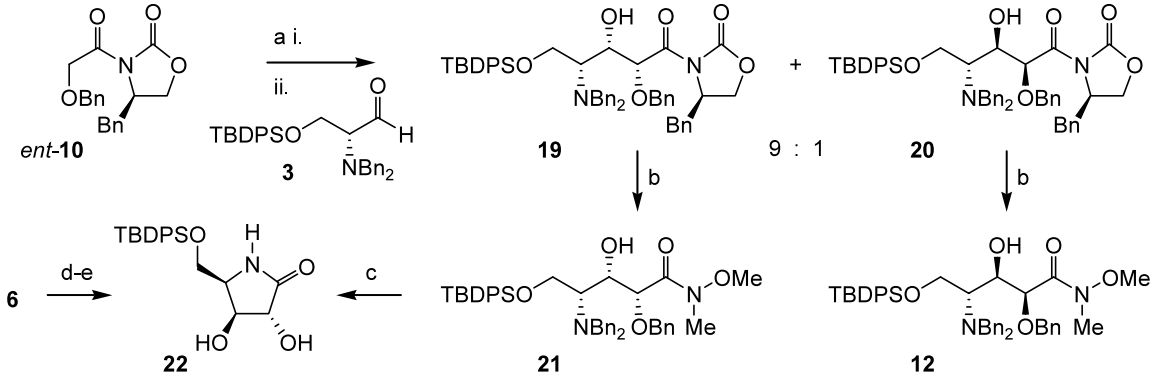


Scheme 2. *Reagents and conditions*: (a) i. Et_3N, *n*-Bu_2BOTf, CH_2Cl_2, −78°C to 0°C, 3 h; ii. **3**, −78°C to 0°C, 2.5 h (82% for **11**, 87% for **17**); (b) (MeO)NHMe·HCl, Me_3Al, THF, −30°C; **11** or **17**, 0°C, 2.5 h (100% for **12**, 90% for **18**); (c) i. $^iPr_2NEt$, *n*-Bu_2BOTf, Et_2O, −78°C, 1.5 h; ii. **3**, −78°C to 0°C, 2 h (75%); (d) (MeO)NHMe·HCl, Me_3Al, THF, −30°C; **14**, −30°C to rt, 18 h (91%); (e) $Pd(OH)_2$, H_2, MeOH, rt, 72 h (71% for **8**, 65% for **15**).

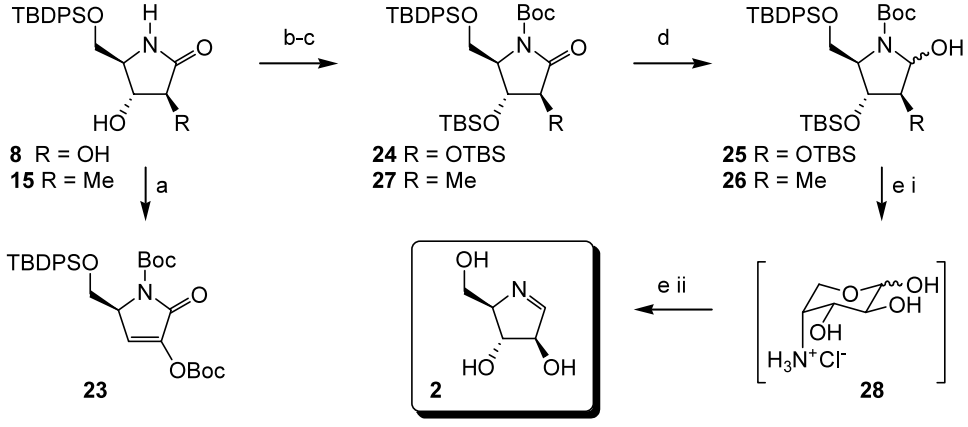
14 was confirmed by its one-step conversion to the previously reported Weinreb amide **12**. The same reaction sequence has also allowed the synthesis of the methyl pyrrolidinone analogue (R = Me, **15**)[26] via reaction of acylated Evans auxiliary **16** to give a single diastereomer of aldol adduct **17**, conversion of this adduct to Weinreb amide **18** and subsequent deprotection and cyclisation (51% for three steps from **16** to **15**).

Aldol addition of the enolate of the enantiomeric glycolate equivalent (*ent*-**10**) to aldehyde **3** resulted in the formation of a separable 9:1 diastereomeric mixture of *syn* aldol adducts **19** and **20** (Scheme 3).[27] Thus whilst the Felkin–Anh selectivity of aldehyde **3** is sufficiently high to provide a single diastereomeric adduct in the 'matched' case, or in the absence of a chiral auxiliary, the directing power of aldehyde **3** can easily be overcome under 'mis-matched' conditions. This would allow the generation of a range of aldol stereoisomers with high diastereoselectivities, simply by judicious choice of chiral auxiliary and chirality of aldehyde **3** (derivable from L- or D-serine). Aldol adducts **19** and **20** were converted to Weinreb amides **21** and **12**, respectively, on treatment with *N*,*O*-dimethylhydroxylamine·HCl and $AlMe_3$. All-*syn* amide **21** was converted to the diastereomeric pyrrolidinone **22** in good yield (69%). This material was found to be identical to that generated by the two-step conversion of all-*syn* diol **6** to **22**.[28]

A number of different routes to the synthesis of nectrisine **2** from either the Weinreb amide **12**, or pyrrolidinone **8**, were pursued, but we found that partial reduction of the pyrrolidinone followed by dehydration proved the most fruitful (Scheme 4). Direct reduction of **8** with DIBAL-H or Super Hydride® gave no reaction. We therefore surmised that introduction of an electron withdrawing protecting group on the nitrogen atom, as has been used in the reduction of other lactams,[9c,29] might improve the yield of the desired pyrrolidinol. Initial attempts to effect a global Boc protection resulted only in the isolation of a compound which was tentatively assigned as dihydropyrrol-2-one **23**. Thus prior protection of the diol was required, followed by *N*-Boc activation to give **24**.[30] As predicted, the increased carbonyl electrophilicity resulting from *N*-Boc protection facilitated the smooth reduction of the lactam with Super Hydride® even at −78°C to give **25**. This strategy was similarly successful for the synthesis



Scheme 3. *Reagents and conditions*: (a) i. Et_3N, *n*-Bu_2BOTf, CH_2Cl_2, −78°C to 0°C, 3 h; ii. **3**, −78°C to 0°C, 2.5 h (79%, 9:1 ratio **19**:**20**); (b) (MeO)NHMe·HCl, Me_3Al, THF, −30°C; **19** or **20**, −30°C to 0°C, 24 h (94% for **21**, 93% for **12**); (c) $Pd(OH)_2$, H_2, MeOH, rt, 72 h (69%); (d) (MeO)NHMe·HCl, Me_3Al, THF, −30°C; **6**, −30°C to rt, 24 h (93%); (e) $Pd(OH)_2$, H_2, MeOH, rt, 24 h (85%).



Scheme 4. *Reagents and conditions*: (a) Boc_2O, Et_3N, DMAP (cat.), CH_2Cl_2, rt, 30 min (86%); (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 3 h (85% for R = OTBS, 94% for R = Me); (c) Boc_2O, Et_3N, DMAP (cat.), CH_2Cl_2, rt, 1.5 h (96% for **24**, 97% for **27**); (d) $LiEt_3BH$, THF, −78°C, 15 min (96% for **25**, 93% for **26**); (e) i. 6N HCl (aq.), THF, 50°C, 2 h; ii. Dowex 1X2 (HO^-), H_2O (80%).

of the methyl analogue **26** via Boc-activated pyrrolidinone **27** (85% yield over three steps from **15**). Heating amino alcohol **25** with 6N HCl at 50°C for 2 h led to the clean removal of all of the protecting groups and the formation of an intermediate aminosugar **28**.[9c] Neutralisation and purification by ion-exchange chromatography [Dowex 1X2 (HO^-)] provided nectrisine **2** in excellent yield.[31]

In conclusion, we have synthesized nectrisine **2** in 12 steps from D-serine with an overall yield of 32%. The key carbon–carbon bond forming reaction, a glycolate aldol condensation, was shown to take place with excellent diastereoselectivity. Furthermore, the aldol based approach offers a flexible strategy for the synthesis of a range of stereoisomers and other analogues of this iminosugar.

Acknowledgements

The authors gratefully acknowledge the EPSRC (GR/96309957 to CHM) for funding this work.

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20. Compound **6** was unambiguously determined as the all-*syn* product by single crystal X-ray diffraction.
21. All new compounds gave spectroscopic data in agreement with their assigned structures: **6**; mp 112–113°C; $[\alpha]_D$ −32.9 (*c* 1.4, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3530, 1747; δ_H (250 MHz, $CDCl_3$) 7.73–7.17 (20H, m), 4.30 (1H, br s), 3.97–3.87 (4H, m), 3.94 (2H, d, $J=13.0$), 3.78 (3H, s), 3.53 (2H, d, $J=13.0$), 3.13 (1H, ddd∼dt, $J=8.2$, 4.0), 2.85 (1H, br s), 1.11 (9H, s); δ_C (50.3 MHz, $CDCl_3$) 173.3, 138.5 (2C), 135.6 (2C), 135.6 (2C), 132.5 (2C), 130.0, 129.9, 129.0 (4C), 128.4 (4C), 127.8 (4C), 127.3 (2C), 70.5, 68.2, 59.5, 59.0, 54.4 (2C), 52.2, 26.7 (3C), 18.9. **7**; $[\alpha]_D$ −30.6 (*c* 1.15, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3482, 1738; δ_H (250 MHz, $CDCl_3$) 7.74–7.20 (20H, m), 4.66 (1H, br s), 4.12–4.07 (4H, m), 4.06 (2H, d, $J=13.4$), 3.77 (3H, s), 3.53 (2H, d, $J=13.4$), 3.04 (1H, dt, $J=9.4$, 5.7), 2.75 (1H, br s), 1.08 (9H, s); δ_C (50 MHz, $CDCl_3$) 174.3,

139.3 (2C), 135.6 (2C), 135.5 (2C), 132.6, 132.5, 129.9 (2C), 128.9 (4C), 128.2 (4C), 127.8 (4C), 127.0 (2C), 72.4, 70.5, 61.5, 58.7, 54.9 (2C), 52.3, 26.7 (3C), 18.9.

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25. **14**; $[\alpha]_D$ −32.2 (*c* 1.94, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3546, 1751, 1601, 1588, 1494; δ_H (250 MHz, $CDCl_3$) 7.82–7.15 (25H, m), 4.40 (1H, d, $J=10.2$), 4.38 (1H, d, $J=1.4$), 4.18 (1H, dd, $J=10.7$, 5.6), 4.17–4.10 (1H, m), 4.09 (1H, dd, $J=10.7$, 5.6), 3.91 (2H, d, $J=13.5$), 3.77 (3H, s), 3.62 (2H, d, $J=13.5$), 3.52 (1H, d, $J=10.2$), 3.18 (1H, dt, $J=9.1$, 5.6), 2.70 (1H, br d, $J=9.2$), 1.12 (9H, s); δ_C (62.9 MHz, $CDCl_3$) 172.3, 140.0 (2C), 137.4, 135.6 (2C), 135.5 (2C), 133.1, 132.9, 129.7, 129.6, 129.2 (4C), 128.2 (4C), 127.9 (4C), 127.6 (4C), 127.5, 126.9 (2C), 77.3, 72.8, 72.1, 61.2, 59.1, 54.8 (2C), 51.8, 26.7 (3C), 18.9.
26. **15**; $[\alpha]_D$ −6.4 (*c* 0.95, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3385, 3272, 1696; δ_H (250 MHz, $CDCl_3$) 7.66–7.25 (10H, m), 5.86 (1H, br s), 3.80 (1H, dd, $J=10.2$, 4.5), 3.72 (1H, m), 3.63 (1H, dd, $J=10.2$, 6.6), 3.52 (1H, dt, $J=6.6$, 4.5), 2.82 (1H, br s), 2.38 (1H, dq ~ qn, $J=7.2$), 1.18 (3H, d, $J=7.2$), 1.05 (9H, s); δ_C (62.9 MHz, $CDCl_3$) 176.6, 135.4 (4C), 132.6, 129.9 (2C), 127.8 (4C), 76.9, 65.1, 61.2 (2C), 44.9, 16.7 (3C), 19.0, 13.0.
27. **19**; $[\alpha]_D$ −29.2 (*c* 0.9, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3331, 1773, 1708; δ_H (360 MHz, $CDCl_3$) 7.81–7.77 (4H, m), 7.53–7.22 (24H, m), 7.09–7.06 (2H, m), 5.22 (1H, d, $J=2.4$), 4.56–4.52 (1H, m), 4.52 (1H, d, $J=11.5$), 4.50 (1H, ddt, $J=9.8$, 6.2, 3.1), 4.27 (1H, d, $J=11.5$), 4.15–4.11 (1H, m), 4.13 (1H, dd, $J=11.3$, 4.4) 4.04 (1H, dd, $J=11.3$, 8.0), 3.93 (2H, d, $J=13.1$), 3.86–3.81 (3H, m), 3.56 (1H, td, 8.0, 4.4), 3.30 (1H, dd, $J=13.3$, 3.1), 2.72 (1H, dd, $J=13.3$, 9.8), 1.94 (9H, s); δ_C (90.6 MHz, $CDCl_3$) 170.7, 153.7, 139.5 (2C), 137.7, 136.2 (4C), 135.8, 133.6, 130.3, 130.2, 129.9 (2C), 129.7 (3C), 129.4 (2C), 129.0, 128.9 (3C), 128.8, 128.7, 128.6 (2C), 128.2 (4C), 128.1 (2C), 127.9, 127.8, 127.6 (2C), 77.8, 72.8, 68.2, 67.2, 62.3, 60.3, 56.2, 54.7 (2C), 38.2, 27.6 (3C), 19.6. **20**; $[\alpha]_D$ −33.6 (*c* 1.00, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3451, 1779, 1705; δ_H (360 MHz, $CDCl_3$) 7.77–7.75 (4H, m), 7.51–7.37 (10H, m), 7.35–7.19 (16H, m), 5.46 (1H, d, $J=1.7$), 4.70 (1H, ddt, $J=9.2$, 5.2, 3.2), 4.38 (1H, br d, $J=7.7$), 4.26 (1H, d, $J=10.7$), 4.22–4.11 (4H, m), 3.99 (1H, d, $J=10.7$), 3.98 (2H, d, $J=13.7$), 3.67 (2H, d, $J=13.7$), 3.41 (1H, dt, $J=7.7$, 5.3), 3.30 (1H, dd, $J=13.6$, 3.2), 2.74 (1H, dd, $J=13.6$, 9.2), 1.10 (9H, s); δ_C (50.3 MHz, $CDCl_3$) 171.7, 153.1, 140.0 (2C), 137.4, 135.7 (2C), 135.6 (2C), 135.0, 133.1, 133.0, 129.7 (2C), 129.3 (2C), 129.1 (4C), 128.8 (2C), 128.1 (2C), 128.0 (4C), 127.9 (2C), 127.7 (4C), 127.5, 127.2, 126.7 (2C), 78.3, 72.2, 72.0, 66.7, 61.5, 59.7, 54.7 (3C), 37.7, 26.7 (3C), 18.9.
28. **22**; $[\alpha]_D$ +40.2 (*c* 1.25, $CHCl_3$); ν_{max} 3305, 1689; δ_H (250 MHz, $CDCl_3$) 7.67–7.59 (4H, m), 7.41–7.30 (6H, m), 6.52 (1H, br s), 5.00 (1H, br s), 4.42 (1H, br d, $J=2.7$), 4.12–3.98 (1H, br m), 3.83 (1H, dd, $J=10.8$, 5.2), 3.76–3.61 (2H, m), 1.00 (9H, s); δ_C (62.9 MHz, $CDCl_3$) 175.4, 135.5 (2C), 135.4 (2C), 132.6, 132.4, 129.8, 129.8, 127.8 (4C), 74.9 (2C), 62.6, 55.5, 26.7 (3C), 18.9.
29. For recent examples of the use of this strategy see: (a) Zhang, J.; Xiong, C.; Wang, W.; Ying, J.; Hruby, V. J. *Org. Lett.* **2002**, *4*, 4029–4032; (b) Mulzer, J.; Schülzchen, F.; Bats, J.-W. *Tetrahedron* **2000**, *56*, 4289–4298; (c) Oba, M.; Miyakawa, A.; Nishiyama, K. *J. Org. Chem.* **1999**, *46*, 9275–9278; (d) Langlois, N. *Tetrahedron: Asymmetry* **1998**, *9*, 1333–1336.
30. **24**; $[\alpha]_D$ −33.1 (*c* 0.75, $CHCl_3$); ν_{max} (neat)/cm^{-1} 1794, 1761, 1719; δ_H (250 MHz, $CDCl_3$) 7.66–7.58 (4H, m), 7.45–7.30 (6H, m), 4.31 (1H, t, $J=1.5$), 4.13–3.96 (2H, m), 3.88–3.74 (2H, m), 1.38 (9H, s), 1.05 (9H, s), 0.88 (9H, s), 0.86 (9H, s), 0.15 (3H, s), 0.13 (3H, s), 0.12 (3H, s), 0.10 (3H, s); δ_C (62.9 MHz, $CDCl_3$) 172.0, 149.7, 135.4 (4C), 133.0, 132.9, 129.7 (2C), 127.7 (4C), 82.9, 78.8, 72.0, 66.7, 62.6, 27.8 (3C), 26.7 (3C), 25.7 (3C), 25.6 (3C), 19.1, 18.0, 17.8, −4.5, −4.6 (2C), −5.2. **27**; $[\alpha]_D$ −30.0 (*c* 0.2, $CHCl_3$); ν_{max} (neat)/cm^{-1} 1791, 1754, 1715; δ_H (250 MHz, $CDCl_3$) 7.63–7.56 (4H, m), 7.45–7.33 (6H, m), 4.14 (1H, dd, $J=3.7$, 2.4), 3.90–3.85 (2H, m), 3.73 (1H, m), 2.48 (1H, dq, $J=7.7$, 3.7), 1.43 (9H, s), 1.24 (3H, d, $J=7.7$), 1.04 (9H, s), 0.85 (9H, s), 0.06 (3H, s), 0.00 (3H, s); δ_C (50.3 MHz, $CDCl_3$) 175.5, 149.8, 135.5 (4C), 132.8, 132.5, 129.8 (2C), 127.7 (4C), 82.8, 72.7, 66.8, 62.0, 47.8, 27.8 (3C), 26.8 (3C), 25.5 (3C), 19.1, 17.7, 14.5, −4.5, −4.7.
31. Nectrisine **2**; $[\alpha]_D$ +21.0 (*c* 0.4, H_2O) [lit.[9c] $[\alpha]_D$ +21.8 (*c* 0.6, H_2O)]; δ_H (600 MHz, D_2O) 7.72 (1H, d, $J=2.4$), 4.75 (1H, dt, $J=5.2$, 1.0), 4.11 (1H, t, $J=5.3$), 3.91 (1H, dd, $J=11.5$, 3.9), 3.88 (1H, ddddd, $J=5.3$, 4.2, 3.9, 2.3, 1.2), 3.79 (1H, dd, $J=11.5$, 4.2); δ_C (62.9 MHz, D_2O) 170.5, 83.4, 78.2, 76.8, 61.2; *m/z* (FAB) 131 ($[M]^+$, 38%), 91 (100); HRMS (FAB) ($C_5H_9NO_3$ requires 131.0582, found 131.0582).