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Concise and highly selective asymmetric synthesis of acosamine from sorbic acid

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Dedicated to Professor Harry H. Wasserman on the occasion of his 90th birthday

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ABSTRACT

Diastereoselective conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to *tert*-butyl sorbate and subsequent chemo- and diastereoselective ammonium-directed olefinic oxidation of the resultant conjugate addition product {*tert*-butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-ene} have been used as the key steps in a concise and highly selective asymmetric synthesis of the 2,3,6-trideoxy-3-aminohexose L-acosamine. This sequence of two chemical operations allows rapid assembly of the molecular architecture and facilitates the de novo asymmetric synthesis of methyl *N*,*O*-diacetyl-α-L-acosaminide in only 7 steps from commercially available sorbic acid in 15% overall yield.

1. Introduction

Compounds incorporating the amino sugar scaffold are prevalent in nature and play important biological roles: for example, they are present in skeletal tissues[1] and biopolymers such as body movement lubricants,[2] and are also involved in chemical signalling.[3] The 2,3,6-trideoxy-3-aminohexose family of amino sugars comprises daunosamine **1**,[4] 3-*epi*-daunosamine **2**,[5] ristosamine **3**[6] and acosamine **4**.[7] One of the most important roles of these compounds is their occurrence as the glycosidic fragment of a variety of naturally occurring and synthetic antibiotics.[8] For instance, naturally occurring daunorubicin **5**[9] and doxorubicin **6**[10] contain an L-daunosamine residue and are approved as anti-cancer agents[11] whilst the synthetic analogue epirubicin **7** (containing an L-acosamine residue) is marketed by Pfizer as Pharmorubicin® as a treatment for breast cancer[12] (Fig. 1).

Owing to their biological significance, the members of this family of amino sugars are popular synthetic targets and a variety of approaches reliant on manipulation of carbohydrate[13] and non-carbohydrate[14] chiral pool starting materials, as well as asymmetric syntheses,[15] have been reported.[16] In this Letter we report an efficient and highly selective asymmetric synthesis of methyl *N*,*O*-diacetyl-α-L-acosaminide in 7 steps from sorbic acid, employing the conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide[17] to *tert*-butyl sorbate and the chemo- and diastereoselective ammonium-directed olefinic oxidation[18] of the resultant conjugate addition product {*tert*-butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-ene} as the key steps to introduce the stereochemistry.[19]

2. Results and discussion

Sorbic acid **8** was converted to the corresponding methyl and *tert*-butyl esters **9** and **10** under standard conditions (MeOH/H^+ and isobutylene/H^+, respectively).[20] Conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **11** (99% ee)[21] to both **9** (R = Me) and **10** (R = ^{t}Bu) proceeded to give the corresponding known β-amino esters **12**[19] and **13**[22] as single diastereoisomers (>99:1 dr), which were isolated in 77 and 92% yield, respectively[23] (Scheme 1).

We have previously reported a method to effect the chemo- and diastereoselective olefinic oxidation of a range of conformationally constrained cycloalkenyl amines reliant on protection of the nitrogen atom against oxidation by in situ conversion to the corresponding ammonium ion[24] and have recently applied this methodology to the asymmetric synthesis of the imino sugars (+)-1-deoxynojirimycin and (+)-1-deoxyaltronojirimycin.[25] We envisaged that application of this protocol to the conformationally labile acyclic alkenyl amines **12** and **13** would enable diastereoselective oxidation of the olefin. Attempted oxidation of **12** with

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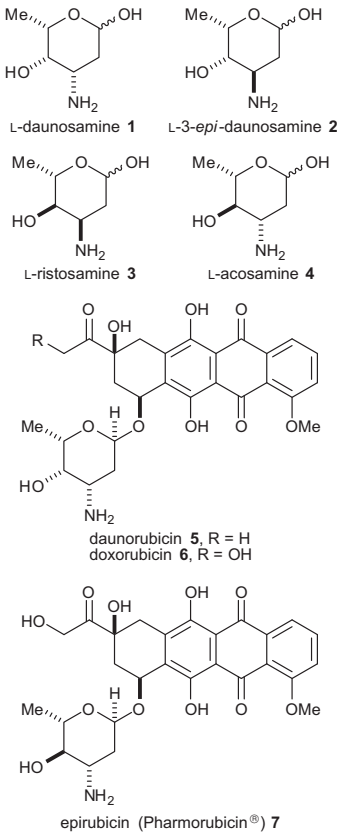
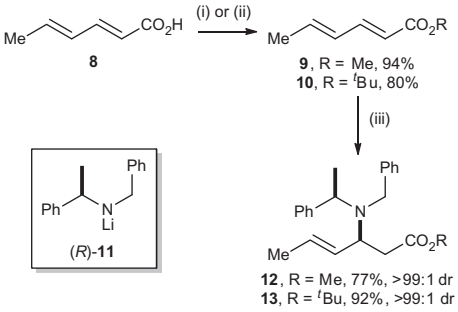
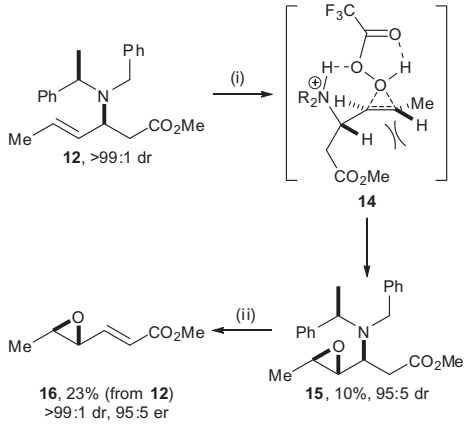


Figure 1. Structures of L-daunosamine **1**, L-3-*epi*-daunosamine **2**, L-ristosamine **3**, L-acosamine **4**, daunorubicin **5**, doxorubicin **6** and epirubicin **7**.



Scheme 1. Reagents and conditions: (i) $SOCl_2$, MeOH, −10 °C to rt, 2 h; (ii) isobutylene, H_2SO_4 (concd aq), CH_2Cl_2, 0 °C to rt, 48 h; (iii) lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **11**, THF, −78 °C, 2 h.

m-CPBA in the presence of Cl_3CCO_2H under our literature conditions[24a] returned only starting material, although use of the more reactive peracid F_3CCO_3H[26] in the presence of F_3CCO_2H resulted in complete conversion to epoxide **15** in 95:5 dr, and with quantitative mass return. Unfortunately, epoxide **15** proved somewhat unstable towards chromatographic purification and was isolated in only 10% yield and 95:5 dr (a number of unidentifiable products of decomposition were also isolated). The absolute configurations of the C(4)- and C(5)-stereocentres within **15** were determined by correlation to the known epoxide (*R*,*R*)-**16**:[27] treatment of **15** with *m*-CPBA in $CHCl_3$ promoted N-oxide formation and subsequent regioselective Cope elimination to give **16**, which was isolated in 23% yield (2 steps from **12**), >99:1 dr and 95:5 er[28] {$[\alpha]_D^{25}$ +9.0 (*c* 0.4 in $CHCl_3$); lit.[27] for >99:1 er $[\alpha]_D^{26}$ +10.2 (*c* 0.4 in $CHCl_3$)}. The stereochemical outcome of the epoxidation of β-amino ester

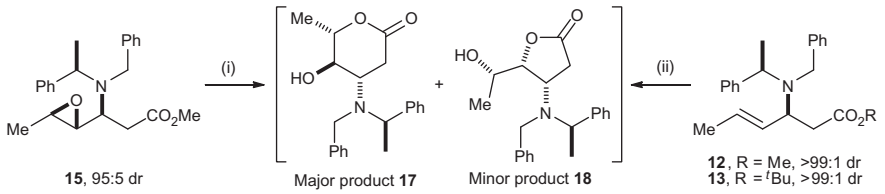


Scheme 2. Reagents and conditions: (i) F_3CCO_2H, F_3CCO_3H, CH_2Cl_2, rt, 16 h; (ii) *m*-CPBA, $CHCl_3$, 0 °C, 30 min.

12 is, therefore, consistent with an ammonium-directed epoxidation step proceeding via transition state model **14** in which 1,3-allylic strain is minimised (Scheme 2). The very high diastereoselectivity of this reaction is remarkable, and is consistent with our previous observations concerning the diastereoselective synthesis of carbonates from tertiary allylic amines with a stereocentre α to the amino functionality: significant levels of diastereoselectivity are imparted in ammonium-directed reactions of these substrates even in the absence of significant levels of 1,3-allylic strain.[29]

Treatment of epoxide **15** with aqueous HBF_4 in CH_2Cl_2 gave complete conversion to a mixture of products containing six-membered ring lactone **17** (major product) and five-membered ring lactone **18** (minor product) as the principal components, along with several unidentifiable impurities (Scheme 3). Unfortunately, neither chromatography nor recrystallisation enabled separation of these impurities on a preparative scale, although recrystallisation of an aliquot gave fine crystals of six-membered ring lactone **17**. Single crystal X-ray diffraction allowed unambiguous assignment of the relative configuration within **17**, with the absolute (4*S*,5*R*,6*S*,α*R*)-configuration being assigned from the known configuration of the (*R*)-α-methylbenzyl stereocentre (Fig. 2).[30] Five-membered ring lactone **18** was assigned as the minor product on the basis of ^{1}H NMR chemical shift and ^{1}H–^{1}H NMR COSY analyses, whilst the absolute (4*S*,5*R*,1′*S*,α*R*)-configuration was assigned by analogy to that unambiguously established for **17**, and by single crystal X-ray analysis of a derivative (vide infra). The observation of six-membered ring lactone **17** as the major product from this reaction is consistent with a mechanism involving regioselective ring opening of the epoxide at C(5) in an S_N2-type fashion by H_2O[31] followed by lactonisation under the acidic reaction conditions. The direct formation of lactones **17** and **18** from β-amino esters **12** and **13** was, therefore, investigated: in each case, treatment with *m*-CPBA (4 equiv) in the presence of aqueous HBF_4[25] gave six-membered ring lactone **17** as the major product along with five-membered ring lactone **18** as the minor product. Substantial peak overlap in the ^{1}H NMR spectra (as well as the presence of unidentifiable impurities) precluded an accurate determination of the ratio of six-membered ring lactone **17** to five-membered ring lactone **18** within these product mixtures, although in each case it was estimated as ~3:1 (Scheme 3).

Hydrogenolysis of a mixture of six-membered ring lactone **17** and five-membered ring lactone **18** in the presence of Boc_2O in EtOAc gave a 70:30 mixture of the six- and five-membered ring *N*-Boc protected lactones **19** and **20**, which were separated via flash column chromatography to give **19** and **20** in 25 and 8% overall yield (respectively) in 2 steps from *N*-benzyl-*N*-α-methylbenzyl



Scheme 3. Reagents and conditions: (i) HBF_4 (40% w/w in H_2O), CH_2Cl_2, rt, 48 h; (ii) HBF_4 (40% w/w in H_2O), *m*-CPBA (4 equiv), CH_2Cl_2, rt, 48 h.

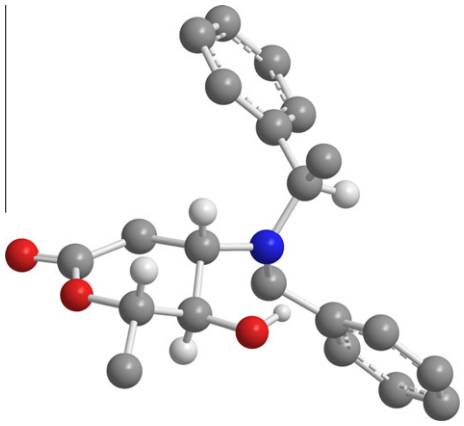


Figure 2. Chem 3D representation of the single crystal X-ray structure of **17** (some H atoms omitted for clarity).

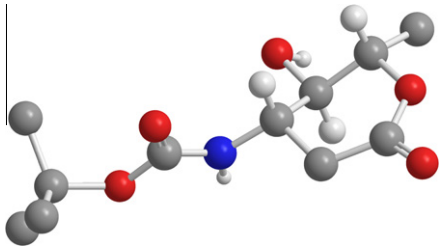


Figure 3. Chem 3D representation of the single crystal X-ray structure of **19** (some H atoms omitted for clarity).

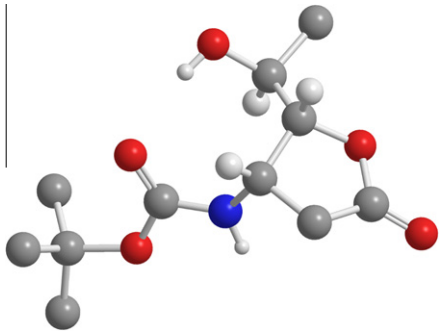
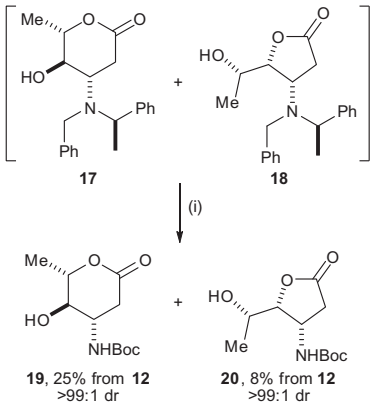


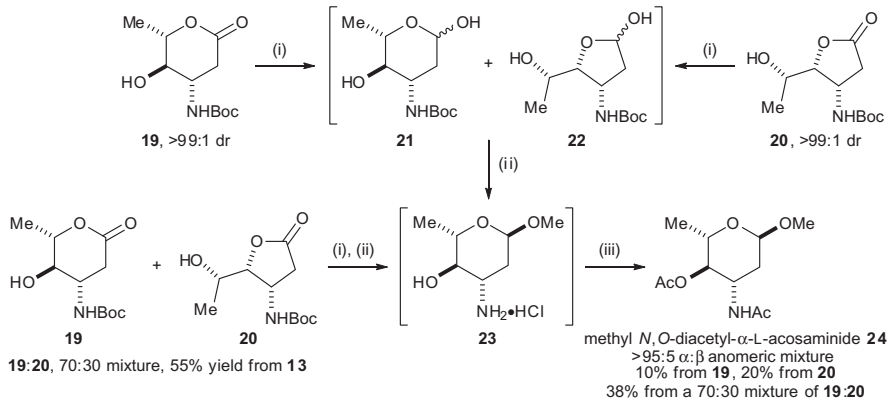
Figure 4. Chem 3D representation of the single crystal X-ray structure of **20** (some H atoms omitted for clarity).

protected β-amino ester **12**. The relative configurations within six-membered ring lactone **19** and five-membered ring lactone **20** were unambiguously assigned by single crystal X-ray diffraction (Figs. 3 and 4),[32,33] with the absolute configuration assigned in each case from the known absolute configuration at C(4) [formed upon conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **11**] and by reference to the known absolute configuration within the *N*-benzyl-*N*-α-methylbenzyl protected six-membered ring lactone **17**. The observation that a mixture of *N*-benzyl-*N*-α-methylbenzyl protected lactones **17** and **18** is converted into a mixture of *N*-Boc protected lactones **19** and **20** supports the structural and stereochemical assignments made for *N*-benzyl-*N*-α-methylbenzyl protected five-membered ring lactone **18** (Scheme 4).



Scheme 4. Reagents and conditions: (i) H_2 (5 atm), $Pd(OH)_2/C$ (50% w/w substrate), EtOAc, rt, 48 h.

Treatment of six-membered ring lactone **19** with DIBAL-H resulted in a mixture of the six- and five-membered ring lactols **21** and **22** (as mixtures of anomers), which were immediately treated with HCl in MeOH followed by peracetylation and recrystallisation to give methyl *N*,*O*-diacetyl-α-L-acosaminide **24** (>95:5 α/β anomeric mixture) in 10% isolated yield (3 steps). An analogous sequence of reactions was applied to five-membered ring lactone **20** to deliver methyl *N*,*O*-diacetyl-α-L-acosaminide **24** (>95:5 α/β anomeric mixture) in 20% isolated yield (3 steps). Alternatively, hydrogenolysis of a mixture of *N*-benzyl-*N*-α-methylbenzyl protected six- and five-membered ring lactones **17** and **18** followed by purification of the crude reaction mixture by filtration through a short plug of silica gel gave a 70:30 mixture of *N*-Boc protected 6- and 5-membered ring lactones **19** and **20** (in 55% yield from β-amino ester **13**), which was reduced upon treatment with DIBAL-H, followed by sequential treatment with HCl in MeOH, peracetylation and recrystallisation to give methyl *N*,*O*-diacetyl-α-L-acosaminide **24** (>95:5 α/β anomeric mixture) in 38% yield (3 steps). This corresponds to an overall yield of 15% in 7 steps from sorbic acid **8** (Scheme 5). The relative configuration within **24** was unambiguously established by single crystal X-ray diffraction (Fig. 5)[34,35] whilst the absolute configuration was inferred from the sign of the specific rotation {$[\alpha]_D^{25}$ −116 (*c* 0.5 in MeOH); $[\alpha]_D^{25}$ −177 (*c* 1.0 in MeOH); lit.[7a] for sample of methyl *N*,*O*-diacetyl-L-acosaminide isolated from natural source[36] $[\alpha]_D^{20}$ −84 (*c* 0.5 in MeOH); lit.[7c] for sample of methyl *N*,*O*-diacetyl-α-D-acosaminide isolated from natural source $[\alpha]_D^{20}$ +204 (*c* 0.3 in MeOH); lit.[7c] for sample of methyl *N*,*O*-diacetyl-β-D-acosaminide isolated from natural source $[\alpha]_D^{20}$ +39 (*c* 0.3 in MeOH); lit.[15b] for 80:20 α/β anomeric mixture of methyl *N*,*O*-diacetyl-D-acosaminide $[\alpha]_D^{23}$ +87.5 (*c* 0.5 in MeOH)}.[37]



Scheme 5. Reagents and conditions: (i) DIBAL-H, CH_2Cl_2, −78 °C, 30 min; (ii) MeOH, HCl (concn aq), rt, 16 h; (iii) Ac_2O, pyridine, DMAP, rt, 30 min.

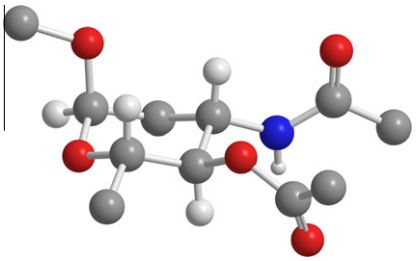


Figure 5. Chem 3D representation of the single crystal X-ray structure of **24** (some H atoms omitted for clarity).

3. Conclusion

In conclusion, the diastereoselective conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to *tert*-butyl sorbate and subsequent chemo- and diastereoselective ammonium-directed olefinic oxidation of the resultant conjugate addition product {*tert*-butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hex-4-ene} have been used as the key steps in a concise and highly selective asymmetric synthesis of the 2,3,6-trideoxy-3-aminohexose L-acosamine. This sequence of two chemical operations allows rapid assembly of the molecular architecture and facilitates the synthesis of methyl *N*,*O*-diacetyl-α-L-acosaminide in only 7 steps from commercially available sorbic acid in 15% overall yield. The further application of this ammonium-directed oxidation protocol towards the synthesis of other amino sugars is currently underway in our laboratory.

Acknowledgements

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29. Davies, S. G.; Fletcher, A. M.; Kurosawa, W.; Lee, J. A.; Poce, G.; Roberts, P. M.; Thomson, J. E.; Williamson, D. M. *J. Org. Chem.* submitted for publication.
30. *X-ray crystal structure determination for* **17**: Data were collected using an Enraf-Nonius k-CCD diffractometer with graphite monochromated Mo Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[38]
X-ray crystal structure data for **17** [$C_{21}H_{25}NO_3$]: M = 339.43, monoclinic, space group $P2_1$, a = 10.5740(4) Å, b = 7.1467(3) Å, c = 12.3396(6) Å, β = 99.4375(18)°, V = 919.87(7) Å^3, Z = 2, μ = 0.081 mm^{-1}, colourless block, crystal dimensions = 0.12 × 0.20 × 0.23 mm^3. A total of 2211 unique reflections were measured for $5 < \theta < 27$ and 1868 reflections were used in the refinement. The final parameters were wR_2 = 0.115 and R_1 = 0.054 [$I > -3.0\sigma(I)$]. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 794238. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
31. For a discussion concerning the regioselectivity of ring opening of epoxides derived from allylic amines under acidic conditions, see: Refs. [24a,b], and references cited therein.
32. *X-ray crystal structure determination for* **19**: Data were collected using an Enraf-Nonius k-CCD diffractometer with graphite monochromated Mo Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[38]
X-ray crystal structure data for **19** [$C_{11}H_{19}NO_5$]: M = 245.28, monoclinic, space group $P2_1$, a = 5.5861(3) Å, b = 10.0003(5) Å, c = 11.8509(6) Å, β = 94.139(2)°, V = 660.30(6) Å^3, Z = 2, μ = 0.097 mm^{-1}, colourless plate, crystal dimensions = 0.05 × 0.22 × 0.25 mm^3. A total of 1581 unique reflections were measured for $5 < \theta < 27$ and 1581 reflections were used in the refinement. The final parameters were wR_2 = 0.099 and R_1 = 0.067 [$I > -3.0\theta(I)$]. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 794239. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
33. *X-ray crystal structure determination for* **20**: Data were collected using an Enraf-Nonius k-CCD diffractometer with graphite monochromated Mo Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[38]
X-ray crystal structure data for **20** [$C_{11}H_{19}NO_5$]: M = 245.28, monoclinic, space group $P2_1$, a = 6.1570(7) Å, b = 9.6600(11) Å, c = 11.1643(14) Å, β = 105.274(5)°, V = 640.56(13) Å^3, Z = 2, μ = 0.100 mm^{-1}, colourless plate, crystal dimensions = 0.04 × 0.14 × 0.16 mm^3. A total of 1511 unique reflections were measured for $5 < \theta < 27$ and 1511 reflections were used in the refinement. The final parameters were wR_2 = 0.118 and R_1 = 0.054 [$I > -3.0\sigma(I)$]. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 794240. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
34. The single crystal X-ray structure of methyl *N*,*O*-diacetyl-α-L-acosaminide **24** has previously been reported; see: Henkel, S.; Menzel, A.; Jäger, V. Z. *Kristallogr. New Cryst. Struct.* **1998**, *213*, 795.
35. *X-ray crystal structure determination for* **24**: Data were collected using an Enraf-Nonius k-CCD diffractometer with graphite monochromated Mo Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[38]
X-ray crystal structure data for **24** [$C_{11}H_{19}NO_5$]: M = 245.28, orthorhombic, space group $P2_12_12_1$, a = 5.0041(2) Å, b = 12.5783(5) Å, c = 20.7349(9) Å, V = 1305.12(9) Å^3, Z = 4, μ = 0.098 mm^{-1}, colourless plate, crystal dimensions = 0.07 × 0.09 × 0.25 mm^3. A total of 1753 unique reflections were measured for $5 < \theta < 27$ and 1287 reflections were used in the refinement. The final parameters were wR_2 = 0.084 and R_1 = 0.053 [$I > -3.0\sigma(I)$]. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 794241. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
36. No anomeric ratio was reported.
37. Data for methyl *N*,*O*-diacetyl-α-L-acosaminide **24** (>95:5 α/β anomeric mixture): mp 157–159 °C; $[\alpha]_D^{25}$ −116 (*c* 0.5 in MeOH); $[\alpha]_D^{25}$ −177 (*c* 1.0 in MeOH); ν_{max} (KBr) 3305 (N–H), 2973, 2916, 2857, 2833 (C–H), 1740 (C=O); δ_H (400 MHz, $CDCl_3$) 1.17 (3H, d, *J* 6.3, C(6)H_3), 1.59 (1H, app dt, *J* 12.5, 3.3, C(2)H_A), 1.90 (3H, s, CO*Me*), 2.07 (3H, s, CO*Me*), 2.21 (1H, dd, *J* 12.5, 4.4, C(2)H_B), 3.33 (3H, s, O*Me*), 3.89 (1H, dq, *J* 8.8, 6.3, C(5)*H*), 4.35–4.50 (2H, m, C(3)*H*, C(4)*H*), 4.70 (1H, d, *J* 3.3, C(1)*H*), 5.65 (1H, br d, *J* 7.3, N*H*); δ_C (100 MHz, $CDCl_3$) 17.7, 20.9, 23.3, 36.4, 46.9, 54.6, 65.6, 75.8, 97.5, 169.8, 171.8; *m*/*z* (ESI$^+$) 268 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{11}H_{19}NNaO_5^+$ ([M+Na]$^+$) requires 268.1155; found 268.1162. Data for β-anomer: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.20 (3H, d, *J* 6.1, C(6)H_3), 3.45 (3H, s, O*Me*); δ_C (100 MHz, $CDCl_3$) [selected peaks] 49.3, 56.6, 70.8.
38. Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. CRYSTALS, 2010, Issue 14, Chemical Crystallography Laboratory, University of Oxford, UK.