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*Aust. J. Chem.* **2004**, *57*, 25–28

# An Alternative Synthesis of Some Carbohydrate α-Amino Acids

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Several carbohydrate ketones have been converted into their trichloromethyl-branched tertiary alcohols. A subsequent treatment of these alcohols under Corey–Link conditions (base, sodium azide, methanol) has given rise to α-azido esters, transformable into azido acids, amino esters, and amino acids. An amino ester and an azido acid have been coupled to form a dipeptide.

Manuscript received: 27 August 2003.
Final version: 28 October 2003.

The Corey–Link reaction provides a ready access to α-azido esters, which are direct precursors of α-amino acids (Scheme 1).[1–3] We were interested in applying such a sequence to some carbohydrate substrates, in the hope of synthesizing some carbohydrate α-amino acids, rare examples within a general class of carbohydrate containing both amine and carboxylic acid functional groups.[4,5]

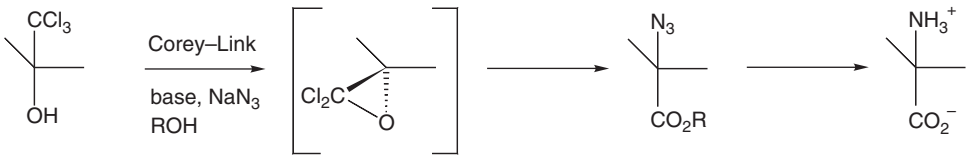
The Strecker synthesis converts the aldehyde **1** into the amino nitrile **2** (Scheme 2);[6] a similar procedure applied to the ketone **3** gives only the cyanohydrin **4**—titanium(IV) isopropoxide must be employed to ensure intermediate imine formation and, subsequently, the addition of trimethylsilyl cyanide provides the amino nitrile **5**.[7] Although **2** is formed as a mixture of diastereoisomers, the amino nitrile **5** confers the (*R*)-configuration on the α-carbon of the derived amino acid **6**.

The dual appeal of the Corey–Link reaction was that it would not only offer some new chemistry as applied to carbohydrates but also probably provide amino acids with the opposite configuration at the α-carbon (to the normal Strecker product), namely of (*S*)-configuration in **7** (Scheme 3).

In our initial investigation, the ketone **3**[8] (Scheme 3) was converted into the alcohol **8** [the use of lithium bis(trimethylsilyl)amide was essential to achieve a good yield[3]], with the configuration of the newly formed stereogenic centre established by a single-crystal X-ray structure determination. The subsequent Corey–Link reaction provided the azido ester **9** and this could be converted into the amino ester **10**, the azido acid **11**, and the α-amino acid **7**. The configuration of **11**, and hence **9**, **10**, and **7** by deduction, was again determined from a single-crystal X-ray structure determination. It is noteworthy that the stereoselectivity of the initial nucleophilic addition to **3** (to form **8**) is guided by its well-established stereochemical bias, and that the subsequent Corey–Link reaction proceeded with inversion of configuration at C3 (Scheme 1).

With such an excellent result in hand for the ketone **3**, we expanded our horizons to the even more stereochemically biased ketone **12**, easily obtained from the alcohol **13**[9] (Scheme 4). The addition of chloroform to **12** gave the alcohol **14** and the subsequent Corey–Link reaction gave the azido ester **15**. Further transformations of **15** then provided **16**–**18**, with the stereochemistry determined by X-ray analysis for **14** and **17**.

For pyranose examples, we prepared the alcohols **19**, **20** (utilizing an improved procedure recently described[10]), and **21**[11] (Scheme 5). These three alcohols were easily converted into their corresponding ketones, and then subsequently into the alcohols **22**–**24**. The Corey–Link reaction on the alcohols **22** and **23** provided the azido esters **25** and **26**, respectively, and the subsequent general transformations on **25** and **26** provided the suites of compounds **27**–**29** and **30**–**32**, respectively. X-ray analysis of **22** and **26** confirmed the configuration of the new stereogenic centre in these two compounds, and strongly supports the assignments of **23**, **25**, **27**–**29**, and **30**–**32**.




**Scheme 1.** Overview of the Corey–Link reaction.

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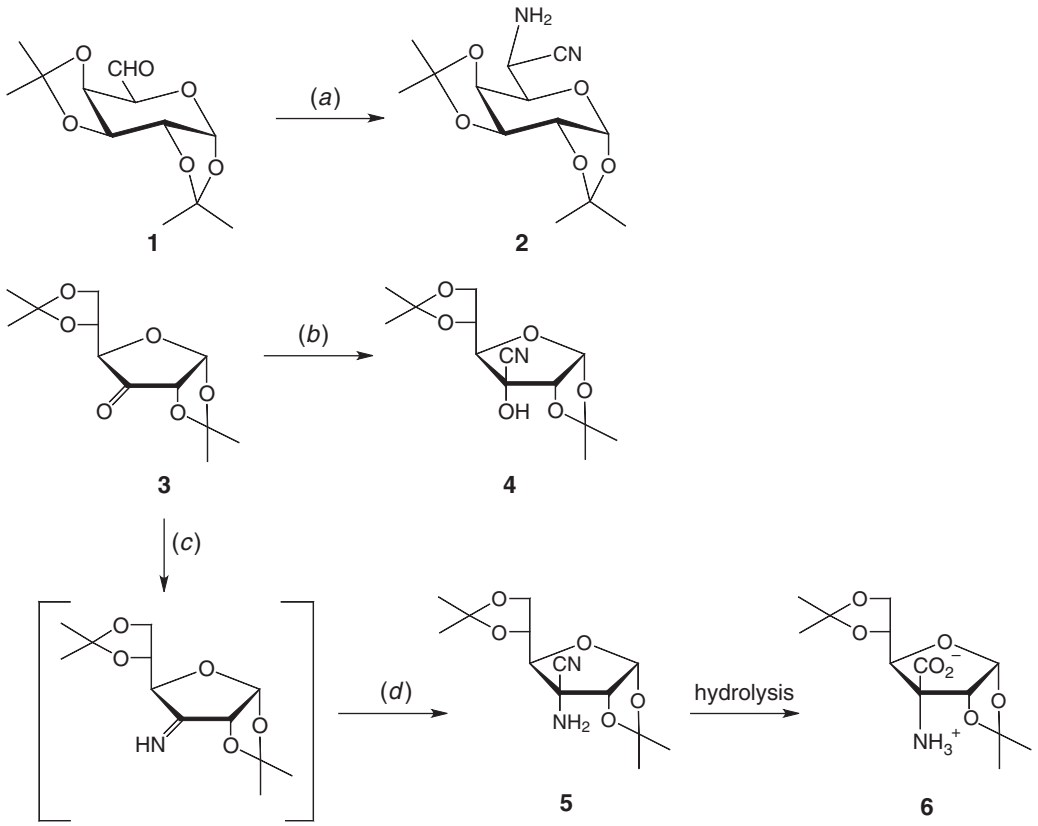
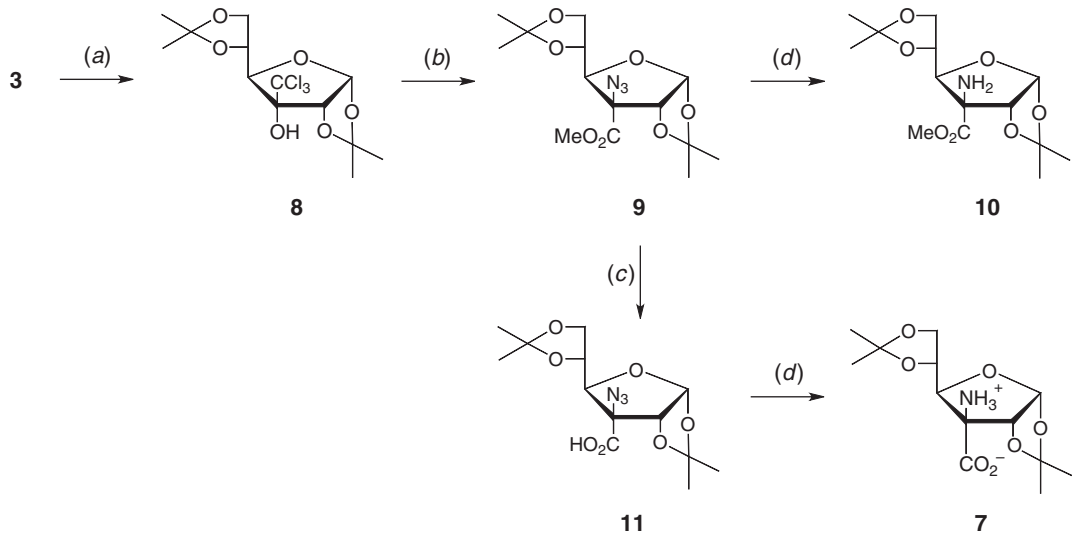



**Scheme 2.** (*a*) KCN, $NH_3$, THF, $H_2O$. (*b*) KCN, $(NH_4)_2CO_3$, MeOH, $H_2O$. (*c*) $Ti(OPr^i)_4$, $NH_3$, MeOH. (*d*) $Me_3SiCN$.



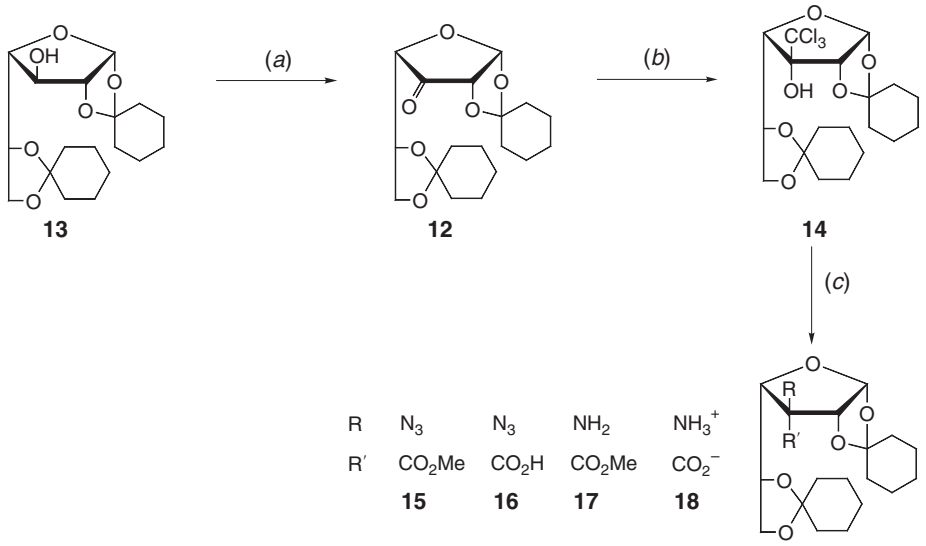

**Scheme 3.** (*a*) $CHCl_3$, $(Me_3Si)_2NLi$, THF. (*b*) DBU, $NaN_3$, [18]crown-6, MeOH. (*c*) KOH, MeOH. (*d*) $H_2$, Pd/C, MeOH.

The configuration of C4 in the alcohol **24** is not confirmed, but suggested. Somewhat perplexingly, treatment of **24** under Corey–Link conditions gave no recognizable carbohydrate product—only amounts of benzyl alcohol were isolated! Further investigation is obviously warranted.

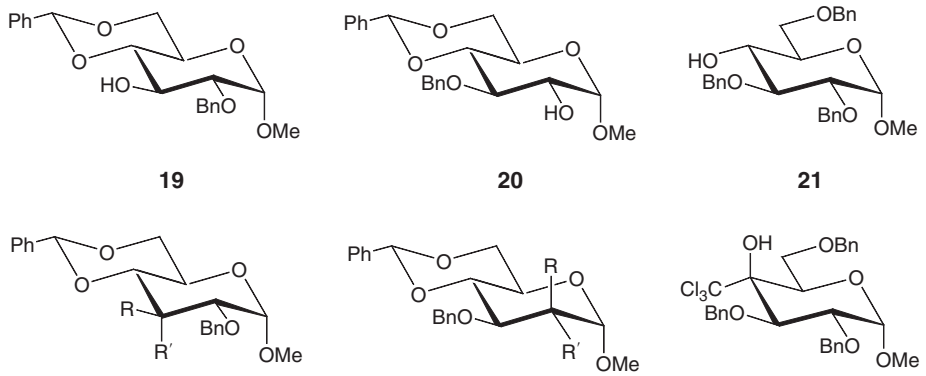
Finally, we report a very preliminary result in our plans for these carbohydrate amino acids. Treatment of the amine **10** and the acid **11** in pyridine with 4-toluenesulfonyl chloride[12] gave the dipeptide **33** in excellent yield (Scheme 6). This result bodes well for the synthesis of oligomers, in both acyclic and cyclic forms.

## Experimental

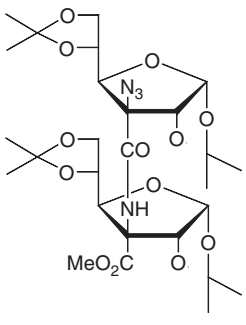
General experimental procedures have been given previously.[13] Typical procedures are described below for the series beginning with the ketone **3**.




**Scheme 4.** (*a*) Pyridinium dichromate, $Ac_2O$, $CH_2Cl_2$. (*b*) $CHCl_3$, $(Me_3Si)_2NLi$, THF. (*c*) Corey–Link sequence (Scheme 3).




**Scheme 5.** Compounds **19**–**32**.



**33**

**Scheme 6.** Compound **33**.

*1,2:5,6-Di*-O-*isopropylidene-3*-C-*trichloromethyl-α-D-allose* ***8***

Lithium bis(trimethylsilyl)amide (LiHMDS; 1.0 M) in tetrahydrofuran (THF; 20 mL, 20 mmol) was added dropwise to the ketone **3** (3.7 g, 14 mmol) and $CHCl_3$ (7.0 mL, 85 mmol) in THF (80 mL) at −78°C. The resulting solution was stirred at −78°C (1 h) before being diluted with saturated $NaHCO_3$ solution. Usual workup ($CH_2Cl_2$) followed by flash chromatography (EtOAc/petrol, 1 : 4) afforded the *alcohol* **8** as prisms (4.4 g, 83%), mp 137–139°C ($Et_2O$), $[\alpha]_D$+34.7° (Found: C 41.0, H 5.0. $C_{13}H_{19}Cl_3O_6$ requires C 41.3, H 5.1%). $\delta_H$ (300 MHz) 1.36, 1.43, 1.45, 1.63 (12H, s × 4, $CH_3$), 3.85 (s, OH), 3.90 (dd, $J_{6,6}$ 8.6, $J_{5,6}$ 7.0, H6), 4.13 (d, $J_{4,5}$ 8.3, H4), 4.14 (dd, $J_{5,6}$ 5.8, H6), 4.78 (m, H5), 4.79, 5.90 (ABq, $J_{1,2}$ 4.4, H1, H2). $\delta_C$ (75.5 MHz) 25.5, 26.4, 26.6, 26.9 (4C, $CH_3$), 67.9 (C6), 71.9, 82.0, 85.0 (C2, C4, C5), 87.6 (C3), 100.9 ($CCl_3$), 104.0 (C1), 109.9, 113.3 (2C, $C(CH_3)_2$). HR-MS *m*/*z* (FAB) 377.0307; $[M+H]^{+\bullet}$ requires 377.0325.

*(3*S*)-3*-C-*Azido-3-deoxy-1,2:5,6-di*-O-*isopropylidene-3*-C-*methoxycarbonyl-α-D-ribo-hexose* ***9***

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU; 5.7 mL, 38 mmol) was added to the alcohol **8** (2.9 g, 7.7 mmol), $NaN_3$ (1.5 g, 23 mmol) and [18]crown-6 (12 mg, 0.04 mmol) in MeOH (60 mL). The resulting solution was stirred at 50°C (1 h) before being diluted with saturated $NH_4Cl$

solution. Usual workup (EtOAc) gave a yellow residue that was subjected to flash chromatography (EtOAc/petrol, 1 : 4) to furnish the azide **9** as a colourless oil (2.4 g, 91%), $[\alpha]_D$ +80.7°, $\nu_{max}$ (film)/cm$^{-1}$ 2120 ($N_3$), 1740 (C=O). $\delta_H$ (300 MHz) 1.32, 1.38, 1.53 (12H, s × 3, $CH_3$), 3.82 (s, $OCH_3$), 4.02 (dd, $J_{6,6}$ 8.8, $J_{5,6}$ 4.4, H6), 4.10 (dd, $J_{5,6}$ 4.2, H6), 4.20 (m, H5), 4.62 (d, $J_{4,5}$ 7.3, H4), 4.64, 5.98 (ABq, $J_{1,2}$ 3.6, H1, H2). $\delta_C$ (75.5 MHz) 24.9, 26.1, 26.4, 26.8 (4C, $CH_3$), 52.9 ($OCH_3$), 66.9 (C6), 73.1, 81.3, 85.1 (C2, C4, C5), 74.4 (C3), 105.0 (C1), 109.6, 113.5 (2C, $C(CH_3)_2$), 166.7 ($CO_2CH_3$). HR-MS $m/z$ (FAB) 344.1478; $[M+H]^{+\bullet}$ requires 344.1458.

*(3*S*)-3-*C*-Amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-methoxycarbonyl-α-*D*-ribo-hexose **10***

10% Pd/C (54 mg) was added to the azide **9** (540 mg) in MeOH (10 mL) and the mixture stirred under a hydrogen atmosphere at room temperature (16 h). Removal of the solvent gave a black residue that was subjected to flash chromatography ($Et_3N$/EtOAc/petrol, 1 : 8 : 12) to yield the amine **10** as a colourless gum (490 mg, 98%), $[\alpha]_D$ +3.8°, $\nu_{max}$ (film)/cm$^{-1}$ 1740 (C=O). $\delta_H$ (300 MHz) 1.23, 1.24, 1.31, 1.42 (12H, s × 4, $CH_3$), 1.82 (bs, $NH_2$), 3.70 (s, $OCH_3$), 3.92 (m, H6), 4.05–4.13 (2H, m, H5, H6), 4.23, 5.90 (ABq, $J_{1,2}$ 3.8, H1, H2), 4.62 (d, $J_{4,5}$ 8.3, H4). $\delta_C$ (75.5 MHz) 24.9, 25.9, 26.6, 26.7 (4C, $CH_3$), 52.1 ($OCH_3$), 67.8 (C6), 68.0 (C3), 73.2, 81.8, 88.4 (C2, C4, C5), 105.5 (C1), 109.5, 112.7 (2C, $C(CH_3)_2$), 171.9 ($CO_2CH_3$). HR-MS $m/z$ (FAB) 318.1551; $[M+H]^{+\bullet}$ requires 318.1553.

*(3*S*)-3-*C*-Azido-3-deoxy-3-*C*-hydroxycarbonyl-1,2:5,6-di-*O*-isopropylidene-α-*D*-ribo-hexose **11***

KOH (400 mg, 7.1 mmol) in MeOH (20 mL) was added to the azide **9** (1.0 g, 2.9 mmol) and the solution stirred at 25°C (1 h). Water was added, followed by evaporation of the MeOH and addition of 1 M HCl until pH 4. Usual workup (EtOAc) afforded the *acid* **11** as prisms (896 mg, 92%), mp 128–130°C ($Et_2O$), $[\alpha]_D$ +86.9°, $\nu_{max}$ (KBr)/cm$^{-1}$ 2120 ($N_3$), 1730 (C=O) (Found: C 47.5, H 5.9, N 12.4. $C_{13}H_{19}N_3O_7$ requires C 47.4, H 5.8, N 12.8%). $\delta_H$ (300 MHz) 1.32, 1.33, 1.39, 1.53 (12 H, s × 4, $CH_3$), 4.03 (dd, $J_{6,6}$ 8.9, $J_{5,6}$ 4.5, H6), 4.12 (dd, $J_{5,6}$ 6.2, H6), 4.24 (m, H5), 4.60 (d, $J_{4,5}$ 7.5, H4), 4.68, 5.95 (ABq, $J_{1,2}$ 3.7, H1, H2), 9.14 (bs, OH). $\delta_C$ (75.5 MHz) 24.9, 25.8, 26.4, 26.7 (4C, $CH_3$), 66.8 (C6), 73.0, 81.2, 85.0 (C2, C4, C5), 74.2 (C3), 105.0 (C1), 109.9, 113.7 (2C, $C(CH_3)_2$), 170.8 ($CO_2H$). HR-MS $m/z$ (FAB) 330.1306; $[M+H]^{+\bullet}$ requires 330.1301.

*(3*S*)-3-*C*-Amino-3-deoxy-3-*C*-hydroxycarbonyl-1,2:5,6-di-*O*-isopropylidene-α-*D*-ribo-hexose, zwitterion **7***

10% Pd/C (10 mg) was added to the acid **11** (100 mg) in MeOH (15 mL) and the mixture stirred under a hydrogen atmosphere at room temperature (16 h). Filtration through Celite, evaporation of the filtrate, and flash chromatography (EtOAc/MeOH, 1 : 1) of the residue yielded the *amino acid* **7** as needles (89 mg, 97%), mp 140–142°C (dec.) (EtOAc/pentane), $[\alpha]_D$ +71.5°. $\delta_H$ (300 MHz, $CD_3OD$) 1.28, 1.30, 1.40, 1.52 (12H, s × 4, $CH_3$), 3.97 (dd, $J_{6,6}$ 8.3, $J_{5,6}$ 5.8, H6), 4.10 (dd, $J_{5,6}$ 6.4, H6), 4.22 (ddd, $J_{4,5}$ 6.0, H5), 4.45, 5.90 (ABq, $J_{1,2}$ 3.8, H1, H2), 4.81 (d, H4). $\delta_C$ (75.5 MHz, $CD_3OD$) 25.5, 26.5, 27.0, 27.2 (4C, $CH_3$), 67.9 (C3), 70.2 (C6), 75.2, 82.7, 88.3 (C2, C4, C5), 106.1 (C1), 110.6, 113.8 (2C, $C(CH_3)_2$), 173.2 ($CO_2H$). HR-MS $m/z$ (FAB) 304.1412; $[M+H]^{+\bullet}$ requires 304.1396.

*(3*S*)-3-*C*-Azido-3-deoxy-3-*C*-hydroxycarbonyl-1,2:5,6-di-*O*-isopropylidene-α-*D*-ribo-hexose **11**, Amide with (3*S*)-3-*C*-Amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-methoxycarbonyl-α-*D*-ribo-hexose **10** (33)*

Tosyl chloride (116 mg, 0.60 mmol) was added to the acid **11** (100 mg, 0.30 mmol) and the amine **10** (96 mg, 0.30 mmol) in pyridine (2 mL) at 0°C. The resulting solution was stirred at 25°C (12 h) before being diluted with saturated $NaHCO_3$ solution. Usual workup ($CH_2Cl_2$) followed by flash chromatography (EtOAc/petrol, 2 : 3) furnished the dipeptide **33** as cubes (147 mg, 77%), mp 183–185°C (EtOAc/pentane), $[\alpha]_D$ +65.1°, $\nu_{max}$ (KBr)/cm$^{-1}$ 3270 (NH), 2120 ($N_3$), 1740 (OC=O), 1680 (NHC=O). $\delta_H$ (300 MHz) 1.23, 1.27, 1.29, 1.33, 1.34, 1.42, 1.48, 1.53 (24H, s × 8, $CH_3$), 3.77 (s, $OCH_3$), 3.95 (dd, $J_{6,6}$ 8.9, $J_{5,6}$ 6.2, H6),[14] 4.03–4.37 (6H, m, H4–H6, H5′, H6′), 4.76, 5.81 (ABq, $J_{1,2}$ 3.5, H1, H2), 4.82 (d, $J_{4',5'}$ 8.6, H4′), 5.27, 6.23 (ABq, $J_{1',2'}$ 4.0, H1′, H2′), 8.02 (bs, NH). $\delta_C$ (75.5 MHz) 25.2–26.6 (8C, $CH_3$), 52.7 ($OCH_3$), 67.2, 67.8 (C6, C6′), 71.5, 73.8, 80.6, 83.1, 84.9, 86.0 (C2, C2′, C4, C4′, C5, C5′), 72.5, 75.4 (C3, C3′), 103.5, 106.9 (C1, C1′), 109.3, 110.8, 112.0, 113.3 (4C, $C(CH_3)_2$), 164.2, 168.0 (2C, C=O). HR-MS $m/z$ (FAB) 629.2694; $[M+H]^{+\bullet}$ requires 629.2670.

## Acknowledgements

We thank Professor Allan H. White and Dr Brian W. Skelton for the X-ray investigations, and the University of Western Australia for financial assistance.

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[14] It was not possible to assign unambiguously any of the ring hydrogen atoms to the amine or the acid portion of the molecule.