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Iodine-mediated ring-closing iodoamination with concomitant N-debenzylation for the asymmetric synthesis of polyhydroxylated pyrrolidines

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This paper is dedicated to Professor George Fleet, on the occasion of his 65th birthday

ABSTRACT

Treatment of a range of homochiral unsaturated β-amino esters (containing a *cis*-dioxolane unit) with iodine promotes a novel ring-closing alkene iodoamination reaction which proceeds with concomitant N-debenzylation, providing a simple and stereoselective route to iodomethyl pyrrolidines. Functional group interconversion of the resulting iodomethyl pyrrolidines upon treatment with AgOAc proceeds via the corresponding aziridinium ion, with subsequent deprotection giving access to polyhydroxylated pyrrolidines.

1. Introduction

Polyhydroxylated nitrogen-containing heterocycles have received enormous attention as glycosidase inhibitors.[1] These multifunctional compounds bear a structural resemblance to carbohydrates, and can be divided into a range of families, including the polyhydroxylated pyrrolidines such as **1**, piperidines such as 1-deoxynojirimycin **2**, indolizidines such as castanospermine **3** and pyrrolizidines such as alexine **4** (Fig. 1). As a result of their diverse biological activities and their potent glycosidase inhibitory effects, a range of methodologies for their synthesis have been developed, including manipulation of carbohydrates,[2] synthesis from α-amino acids[3] and asymmetric synthesis.[4]

The conjugate addition of homochiral lithium amides to α,β-unsaturated esters and amides has been widely used in this and in other laboratories for the asymmetric synthesis of β-amino acid derivatives.[5] We recently demonstrated the doubly diastereoselective conjugate addition of homochiral lithium amides to homochiral α,β-unsaturated esters containing *cis*- and *trans*-dioxolane units for the asymmetric synthesis of polyoxygenated β-amino esters,[6] and delineate herein the utility of the β-amino ester products from this protocol for the asymmetric synthesis of polyhydroxylated pyrrolidines. It was envisaged that the β-amino ester products of conjugate addition **5** would act as suitable precursors for a novel, stereoselective iodine-mediated ring-closing alkene iodoamination[7] with concomitant N-debenzylation protocol that would allow access to iodomethyl pyrrolidines **6**. Functional group manipulation and deprotection were anticipated to facilitate the asymmetric synthesis of polyhydroxylated pyrrolidines **7** (Fig. 2). We report herein our full investigations within this area, part of which has been communicated previously.[8]

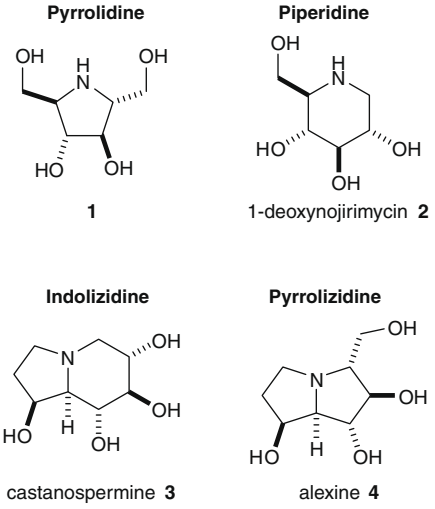

Figure 1. Representative polyhydroxylated nitrogen-containing heterocycles **1**–**4**.

2. Results and discussion

2.1. Development of a ring-closing iodoamination reaction

Initial studies of the proposed ring-closing iodoamination reaction focused upon the cyclisation of homochiral β-amino ester **8**.[6]

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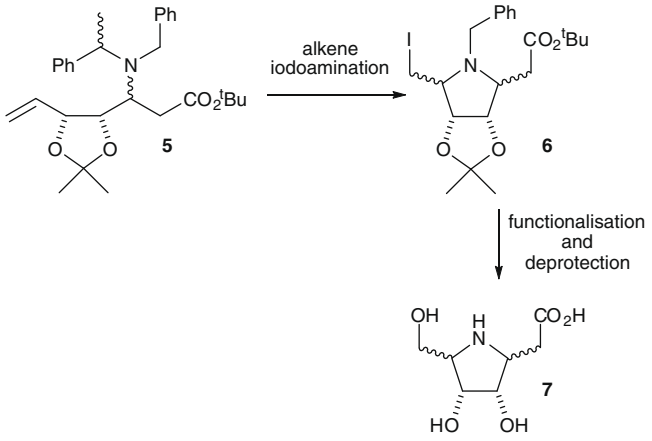
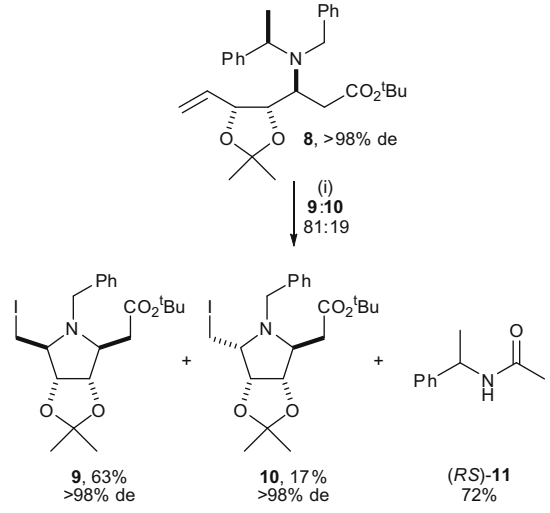


Figure 2. Proposed synthetic route to polyhydroxylated pyrrolidines **7**.

Treatment of **8** with iodine (1 equiv) and $NaHCO_3$ in MeCN gave 64% conversion to an 81:19:1 mixture of *N*-benzyl iodomethyl pyrrolidines **9** and **10**, respectively (along with racemic α-methylbenzyl acetamide **11**), in which ring closure to the pyrrolidine and chemoselective removal of the α-methylbenzyl group had been effected in a single reaction step. Use of 3 equiv of iodine proved optimal, giving quantitative conversion to an 81:19 mixture of *N*-benzyl iodomethyl pyrrolidines **9**:**10**. Chromatography allowed separation, giving the major 2,5-*cis*-diastereoisomer **9** in 63% yield, and the minor 2,5-*trans*-diastereoisomer **10** in 17% yield, in >98% de in both cases, and essentially racemic α-methylbenzyl acetamide **11** {$[\alpha]_D^{25} = -3.8$ (*c* 0.7 in $CHCl_3$); lit.[9] for (*R*)-**11** $[\alpha]_D^{19} = +129.5$ (*c* 1.0 in $CHCl_3$)} in 72% yield (Scheme 1).

The relative configuration within the major diastereoisomeric iodomethyl pyrrolidine **9** could not be identified unambiguously using ^1H NMR spectroscopic analysis; it was subsequently determined by single-crystal X-ray analysis of a derivative (vide infra).[10] However, consistent with the observations of Yoshida et al. in related systems,[11] the ^{13}C NMR chemical shift of the iodomethyl carbon of the pyrrolidines described herein is diagnostic of their relative configuration. When the iodomethyl group and the neighbouring acetonide group have a *cis*-relationship, the ^{13}C NMR signal corresponding to the iodomethyl carbon appears between 1.9 and 3.2 ppm, while for those in which the two groups have a *trans*-relationship the signal appears between 10.1 and 11.4 ppm, irrespective of their configuration at C(5). For example, the ^{13}C NMR signal corresponding to the iodomethyl carbon of the minor diastereoisomer **10** (*cis*-relationship between iodomethyl group and the neighbouring acetonide group) appears at 2.4 ppm, while the corresponding ^{13}C NMR signal of the major diastereoisomer **9** (*trans*-relationship between iodomethyl group and the neighbouring acetonide group) appears at 11.4 ppm (Fig. 3).



Scheme 1. Reagents and conditions: (i) I_2 (3 equiv), $NaHCO_3$, MeCN, −20 °C, 2 h, then rt, 20 h.

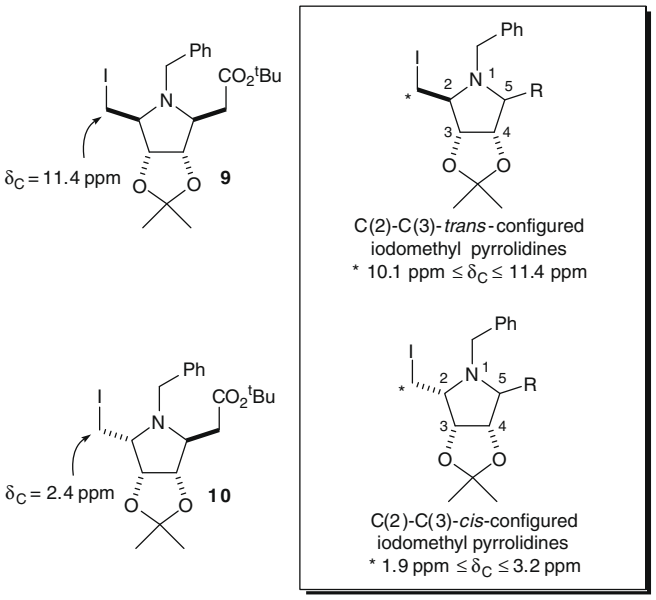


Figure 3. Diagnostic ^{13}C NMR chemical shifts for 2-iodomethyl-3,4-*O*-isopropylidene-pyrrolidines.

This iodoamination protocol shows remarkable chemoselectivity, with the selective removal of the *N*-α-methylbenzyl group in the presence of the *N*-benzyl group being entirely complementary to the previously reported chemoselective N-debenzylations under oxidative[12] or hydrogenative[13] conditions that have been developed within this laboratory. The isolation of essentially racemic α-methylbenzyl acetamide **11** from this reaction protocol is consistent with a mechanism involving initial formation of iodonium ion **12** followed by intramolecular trapping by the tertiary amine to give quaternary ammonium species **13**. The preponderance of the 5-*exo* cyclisation pathway leading to the corresponding pyrrolidine products rather than a 6-*endo* cyclisation pathway leading to the corresponding piperidine products is to be expected on stereoelectronic grounds.[14] Preferential S_N1 loss of the *N*-α-methylbenzyl-protecting group from **13** gives iodomethyl pyrrolidines **9** and **10**. Trapping of the α-methylbenzyl cation **14** by MeCN and interception by water in a Ritter reaction lead to (*RS*)-α-methylbenzyl acetamide **11** (Fig. 4).

Assuming that there is a geometrical requirement for the nitrogen atom to attack *anti* to the iodonium ion (i.e., in an S_N2-type process), the stereoselective formation of iodomethyl pyrrolidine **9** from this reaction protocol may be due to either (i) stereoselective, irreversible formation of one diastereoisomer of iodonium ion **12** followed by ring closure and N-debenzylation; or (ii) reversible formation of iodonium **12** followed by preferential cyclisation of one of the diastereoisomers of **12** to the corresponding diastereoisomer of the ammonium ion **13** and subsequent N-debenzylation. In order to probe this hypothesis, the effect of changing the reaction solvent to one of lower polarity was investigated. Reaction in PhMe, THF or $CHCl_3$ gave >90% conversion to iodomethyl pyrrolidines **9** and **10**, but proceeded with a noticeable decrease in stereoselectivity as compared to the reaction in MeCN

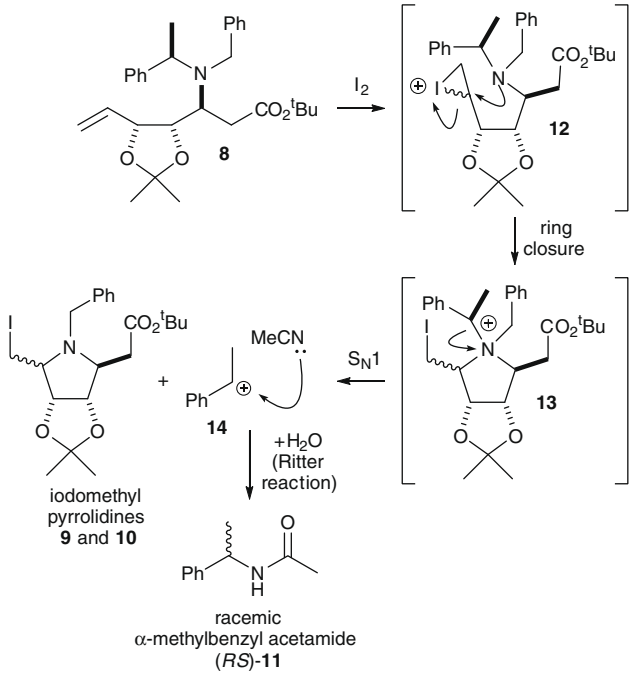
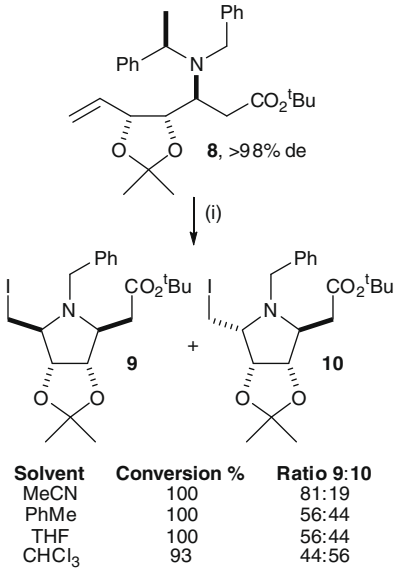


Figure 4. Proposed mechanism of iodoamination of **8** with concomitant, chemoselective N-debenzylation.



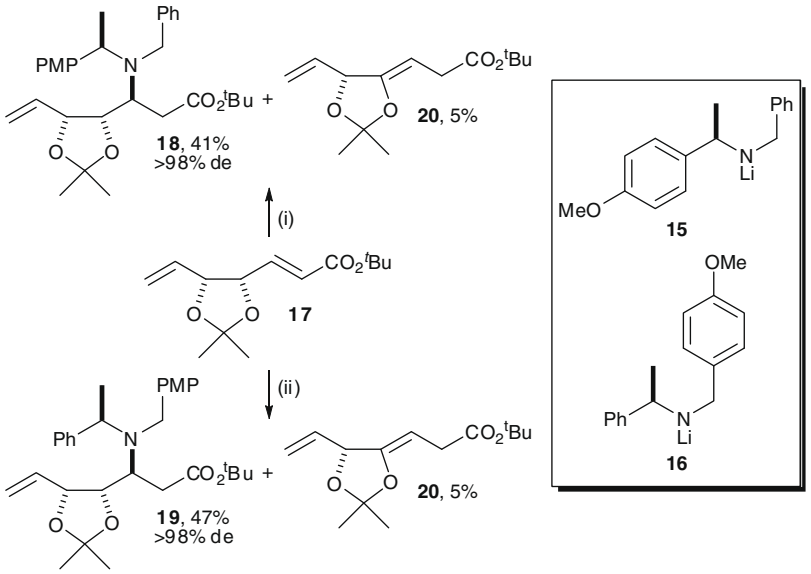
Scheme 2. Reagents and conditions: (i) I_2 (3 equiv), $NaHCO_3$, solvent, −20 °C, 2 h, then rt, 20 h.

(Scheme 2). These results are consistent with a rapid equilibration of the two diastereoisomeric iodonium ions **12** in the polar solvent MeCN, followed by rate determining cyclisation of one of the diastereoisomeric iodonium ions **12** to the corresponding ammonium ion **13**, and subsequent N-debenzylation.

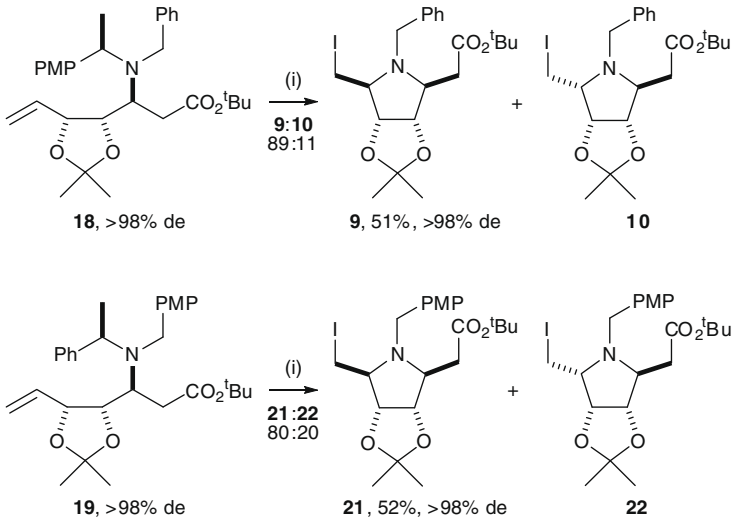
With an efficient procedure for ring-closing iodoamination and concomitant N-debenzylation of β-amino ester **8** established, subsequent studies focused on probing the substrate scope of this reaction, in order to gain further mechanistic insights and to generate a range of iodomethyl pyrrolidines for subsequent elaboration into the corresponding polyhydroxylated derivatives.

2.2. Substrate scope of the ring-closing iodoamination reaction

Analogues of β-amino ester **8** containing substituted *N*-benzyl-protecting groups with electron-donating groups on the arene ring were prepared in order to probe their effect upon the stereo- and chemoselectivity of the iodoamination/N-debenzylation protocol. Doubly diastereoselective 'matched'[6,15] conjugate addition of homochiral lithium (*R*)-*N*-benzyl-*N*-(α-methyl-4-methoxybenzyl)amide **15** and lithium (*R*)-*N*-(4-methoxybenzyl)-*N*-(α-methylbenzyl)amide **16** to homochiral α,β-unsaturated ester **17**[6] both proceeded with high stereoselectivity (>98% de and 92% de, respectively) to furnish the corresponding β-amino esters **18** and **19**, which were isolated as single diastereoisomers (>98% de), in 41% and 47% yields after purification. The product of γ-deprotonation **20** was also isolated in 5% yield in each case[6] (Scheme 3).



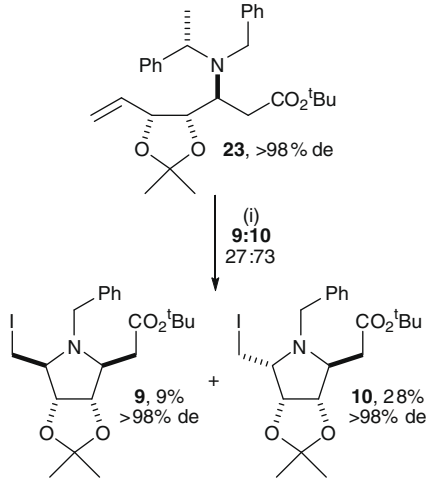
Scheme 3. Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-(α-methyl-4-methoxybenzyl)amide **15**, THF, −78 °C, 2 h; (ii) lithium (*R*)-*N*-(4-methoxybenzyl)-*N*-(α-methylbenzyl)amide **16**, THF, −78 °C, 2 h [PMP = 4-methoxyphenyl].



Scheme 4. Reagents and conditions: (i) I_2 (3 equiv), $NaHCO_3$, MeCN, −20 °C, 2 h, then rt, 20 h.

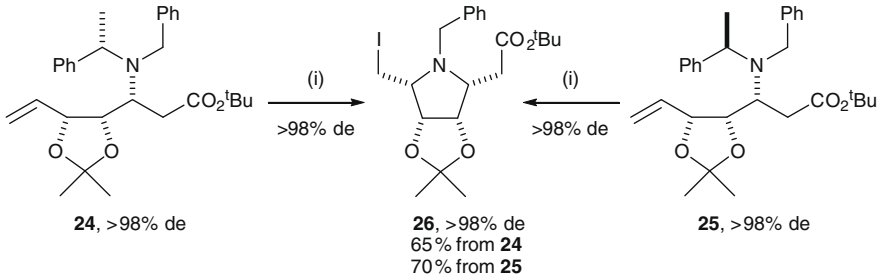
Treatment of β-amino esters **18** and **19** with iodine in MeCN promoted iodoamination and concomitant N-debenzylation in both cases, giving an 89:11 and 80:20 mixture of iodomethyl pyrrolidine diastereoisomers **9**:**10** and **21**:**22**, respectively (>90% crude yield in both cases), with chromatographic purification giving the major diastereoisomers **9** and **21** in 51% and 52% yields, and >98% de in both cases (Scheme 4). The relative configuration within **21** was inferred by a combination of ^{1}H NMR NOE and ^{13}C NMR chemical shift analyses. These results suggest that the incorporation of electron donor groups has a slight impact on the stereoselectivity of the reaction, but has no effect upon the chemoselectivity of the N-debenzylation protocol, with S_N1 loss of the more bulky α-methylbenzyl substituent (vs the benzyl substituent) from the sterically congested nitrogen atom being preferred in both cases.

The iodine-promoted cyclisation of all diastereoisomers of β-amino ester **5** resulting from variation of the C(3) and *N*-α-methylbenzyl stereocentres was next investigated in order to determine the effect of the configuration of these stereocentres upon the stereoselectivity of the iodoamination reaction. Treatment of β-amino ester (3*S*,α*S*)-**23**,[6] with iodine in MeCN proceeded to give a 27:73 mixture of iodomethyl pyrrolidines **9** and **10**, respectively, along with racemic α-methylbenzyl acetamide **11**. While the same three products are obtained as for the cyclisation of β-amino ester (3*S*,α*R*)-**8**, in this case the 2,5-*trans* iodomethyl pyrrolidine **10** was the major diastereoisomer. This suggests that with a (3*S*)-configuration within the β-amino ester framework, the configuration of the α-methylbenzyl stereocentre has a major impact on the stereoselectivity of the ring-closing reaction. Chromatography allowed the isolation of **9** in 9% yield, **10** in 28% yield, and (*RS*)-α-methylbenzyl acetamide **11** in 59% yield (Scheme 5).



Scheme 5. Reagents and conditions: (i) I_2 (3 equiv), $NaHCO_3$, MeCN, −20 °C, 2 h, then rt, 20 h.

Treatment of the (3*R*)-configured β-amino esters (3*R*,α*S*)-**24**[6] or (3*R*,α*R*)-**25**[6] with iodine in MeCN furnished a single diastereoisomeric iodomethyl pyrrolidine 2,5-*cis*-**26** (and (*RS*)-α-methylbenzyl acetamide **11**) in both cases. The results from cyclisation of **24** and **25** indicate that the configuration of the α-methylbenzyl stereocentre has no effect on the stereoselectivity of the iodocyclisation reaction, and are in direct contrast to the results obtained from cyclisation of the (3*S*)-configured β-amino esters **8** and **23** (vide supra). Iodomethyl pyrrolidine **26** was isolated in 65% yield from **24** and in 70% yield from **25** after chromatography (Scheme 6). The configuration within **26** was assigned by a combination of ^{1}H



Scheme 6. Reagents and conditions: (i) I_2 (3 equiv), $NaHCO_3$, MeCN, −20 °C, 2 h, then rt, 20 h.

NMR NOE and ^{13}C NMR chemical shift analyses, with δ_C 1.9 ppm for the iodomethyl carbon consistent with this group lying on the same face of the pyrrolidine ring as the acetonide group.

The formation of iodomethyl pyrrolidine **26** as a single diastereoisomer from the cyclisation of either β-amino ester **24** or **25** may be rationalised by the reaction occurring through the favoured 'chair-boat'[16] transition state **27**. In this low-energy conformation the ester, iodonium ion and *N*-α-methylbenzyl groups are all able to occupy pseudoequatorial positions around the forming pyrrolidine ring. Steric interactions with the α-methylbenzyl group are presumably unimportant contributors to the overall energy of the transition states for cyclisation of **24** and **25**, since the configuration of the *N*-α-methylbenzyl group exerts no influence on the outcome of the cyclisation. This is consistent with the formation of iodomethyl pyrrolidine **26** with high stereoselectivity from both epimeric β-amino esters **24** and **25** (Fig. 5). However, with a configurational change at C(3), the all-equatorial disposition of the α-methylbenzyl, ester and iodonium ion groups is no longer possible. Several alternative, higher energy transition states may therefore be available, the relative energies of which may depend upon minimisation of steric interactions with the α-methylbenzyl group, enabling the configuration of the α-methylbenzyl stereocentre to exert an influence on the stereochemical course of the reaction. Thus, cyclisation of β-amino esters (3*S*,α*R*)-**8** and (3*S*,α*S*)-**23** give opposite outcomes, producing 2,5-*cis*-**9** and 2,5-*trans*-**10** as the major diastereoisomers, respectively.

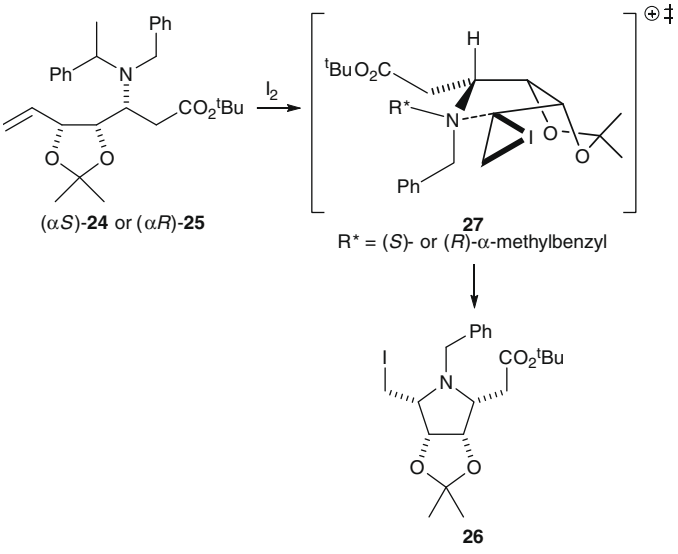
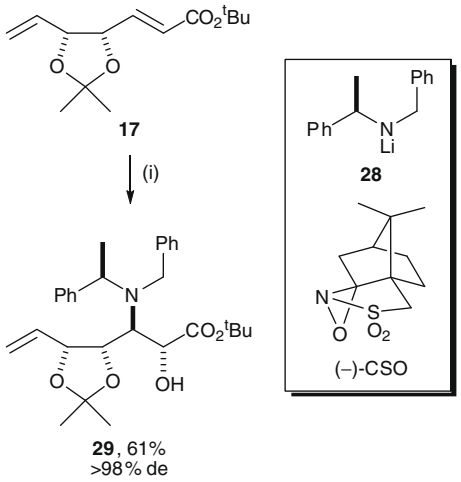


Figure 5. Postulated transition state **27** for the ring-closing iodoamination with concomitant N-debenzylation of β-amino esters **24** and **25** to iodomethyl pyrrolidine **26**.

The effect of incorporation of an α-hydroxyl substituent within the β-amino ester scaffold upon the stereoselectivity of the iodoamination and N-debenzylation protocol was next investigated. *anti*-α-Hydroxy-β-amino ester **29** was prepared by the conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **28** to α,β-unsaturated ester **17**, followed by oxidation of the resultant β-amino enolate with (−)-camphorsulfonyloxaziridine [(−)-CSO],[17] giving **29** in >98% de and in 61% isolated yield and >98% de after column chromatography (Scheme 7). The relative configuration within *anti*-α-hydroxy-β-amino ester **29** was established unambiguously by single-crystal X-ray analysis. The absolute (2*R*,3*S*,4*S*,5*R*,α*R*)-configuration within **29** was assigned from the known configurations of the *N*-α-methylbenzyl and 4,5-*O*-isopropylidene stereocentres (Fig. 6). The stereochemical outcome of this aminohydroxylation reaction is consistent with the established *anti*-selectivity of the conjugate addition/enolate oxidation protocol.[17]



Scheme 7. Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **28**, THF, −78 °C, 2 h, then (−)-CSO, THF, −78 °C to rt, 12 h.

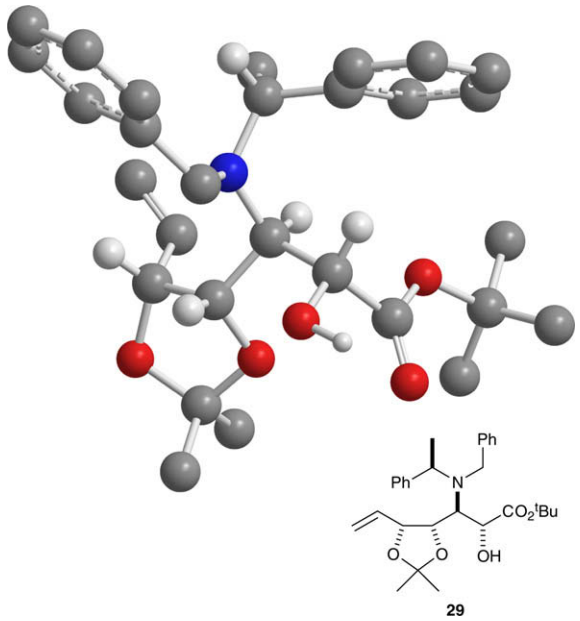
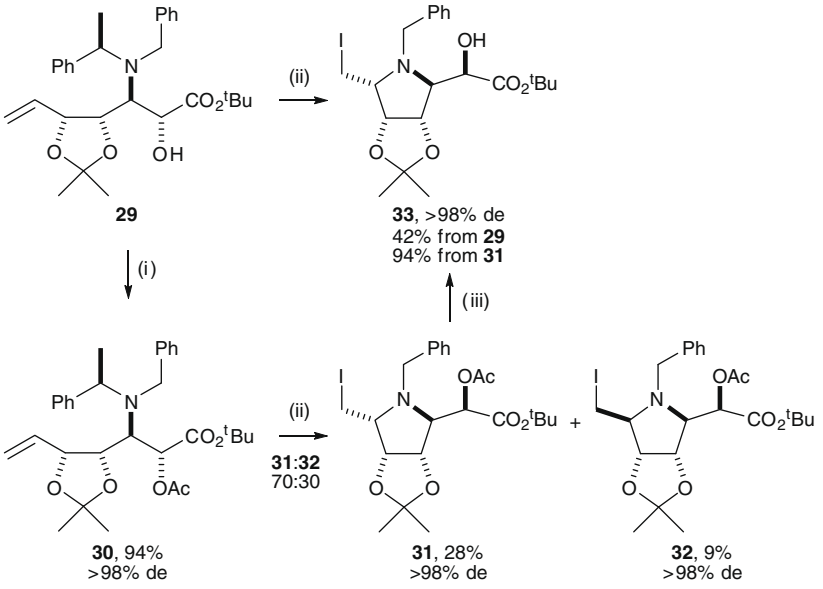


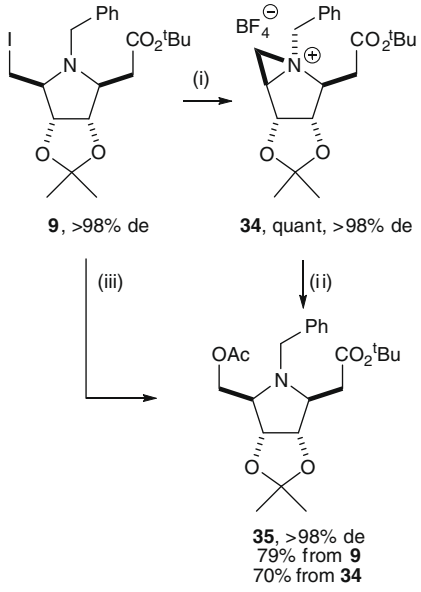
Figure 6. Chem 3D representation of the X-ray crystal structure of **29** (some H atoms omitted for clarity).

Treatment of *anti*-α-hydroxy-β-amino ester **29** with iodine in MeCN promoted iodoamination and concomitant N-debenzylation, furnishing 2,5-*trans*-iodomethyl pyrrolidine **33** as a single diastereoisomer in 42% isolated yield. The configuration within **33** was assigned by a combination of ^{1}H NMR NOE and ^{13}C NMR chemical shift analyses, with the chemical shift of δ_C 3.2 ppm for the iodomethyl carbon being consistent with this group lying on the same face of the pyrrolidine ring as the acetonide group. This result demonstrates that the incorporation of the α-hydroxyl functionality has a marked effect upon the product distribution of the reaction: iodoamination of the parent β-amino ester **8** gives preferentially



Scheme 8. Reagents and conditions: (i) Ac_2O, DMAP, pyridine, DCM, rt; (ii) I_2, $NaHCO_3$, MeCN, −20 °C, 2 h, then rt, 20 h; (iii) K_2CO_3, MeOH, rt.

2,5-*cis*-iodomethyl pyrrolidine **9** with modest selectivity (81:19), whereas iodoamination of α-hydroxy-substituted β-amino ester **29** gives 2,5-*trans*-iodomethyl pyrrolidine **33** exclusively. Although the reasons for this change in stereoselectivity are unclear, it is possible that the presence of the α-oxygen atom may alter the preferred conformation of the molecule in the transition state leading to cyclisation, possibly through formation of a hydrogen bond.[18] In order to investigate this hypothesis, *anti*-α-hydroxy-β-amino ester **29** was treated with Ac_2O, DMAP and pyridine to give α-acetoxy-β-amino ester **30** in 94% yield. Treatment of α-acetoxy-β-amino ester **30** with iodine in MeCN proceeded to give a 70:30 mixture of iodomethyl pyrrolidines 2,5-*trans*-**31** and 2,5-*cis*-**32**, suggesting that the inability of the α-acetoxy group to act as a hydrogen bond donor within **30** may have a deleterious effect on the diastereoselectivity of the cyclisation reaction when compared to the parent α-hydroxyl system **29**. Chromatographic purification of the crude reaction mixture gave the major 2,5-*trans*-diastereoisomer **31** in 28% yield, and the minor 2,5-*cis*-diastereoisomer **32** in 9% yield, as single diastereoisomers (>98% de) in each case, along with (*RS*)-α-methylbenzyl acetamide **11** in 52% yield. The configuration of the major diastereoisomeric iodomethyl pyrrolidine **31** was proven by chemical correlation, with deprotection of **31** with K_2CO_3 in MeOH furnishing **33** in 94% yield (Scheme 8).



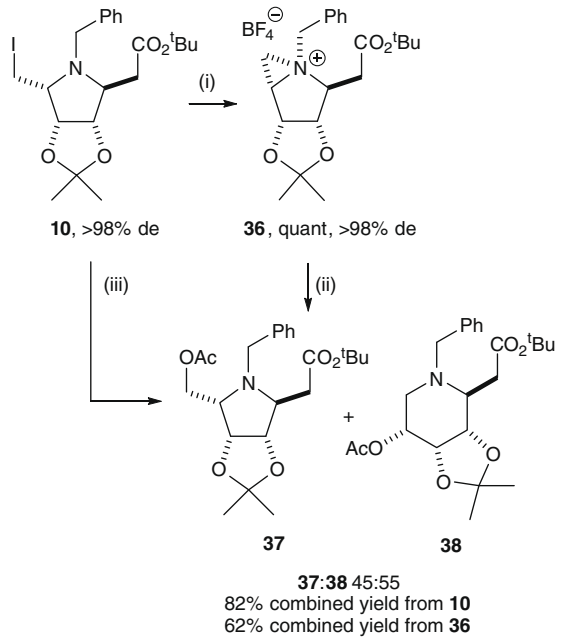
Scheme 9. Reagents and conditions: (i) $AgBF_4$, DCM, rt; (ii) NaOAc, PhMe, rt; (iii) AgOAc, PhMe, rt.

2.3. Asymmetric synthesis of polyhydroxylated pyrrolidines

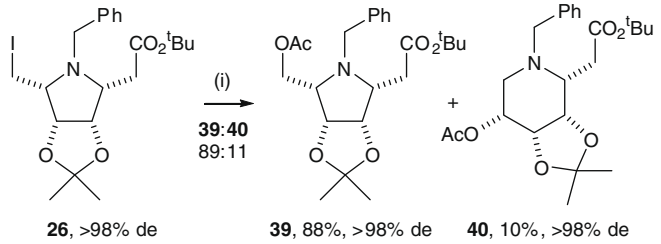
Elaboration of iodomethyl pyrrolidine scaffolds **9**, **10** and **26** to polyhydroxylated pyrrolidines, via functional group manipulation and deprotection, was next investigated. It was envisaged that replacement of the iodide for a hydroxyl functionality could be achieved via the intermediacy of the corresponding aziridinium ion.[19] Iodomethyl pyrrolidine **9** (>98% de) was treated with $AgBF_4$, giving the isolable aziridinium **34** in quantitative yield. Subsequent ring opening of **34** upon treatment with NaOAc in toluene proceeded with complete regioselectivity to give pyrrolidine acetate **35** as a single diastereoisomer in 70% yield. The possibility of achieving this transformation in one pot was next examined by treatment of **9** with AgOAc in toluene, which gave the corresponding pyrrolidine acetate **35** as a single diastereoisomer in 79% yield after purification (Scheme 9).

Treatment of the diastereoisomeric iodomethyl pyrrolidine **10** with $AgBF_4$ gave aziridinium **36** in quantitative yield, which upon treatment with NaOAc in toluene gave a 45:55 mixture of the inseparable pyrrolidine and piperidine acetates **37** and **38**, respectively, in 62% isolated yield, indicating that the ring opening of aziridine **36** does not proceed in a regioselective manner. This transformation could also be achieved in one pot upon treatment of iodomethyl pyrrolidine **10** with AgOAc, which gave an inseparable 45:55 mixture of the pyrrolidine and piperidine acetates **37** and **38**, respectively, in 82% combined yield (Scheme 10).

AgOAc-promoted iodide displacement of iodomethyl pyrrolidine **26** also furnished a mixture of the corresponding pyrrolidine and piperidine products **39** and **40** as an 89:11 mixture, respectively, with chromatographic purification furnishing pyrrolidine acetate **39** in 88% yield and piperidine acetate **40** in 10% yield



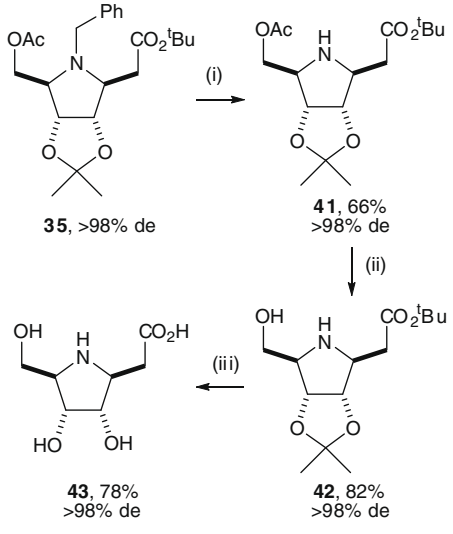
Scheme 10. Reagents and conditions: (i) $AgBF_4$, DCM, rt; (ii) NaOAc, PhMe, rt; (iii) AgOAc, PhMe, rt.



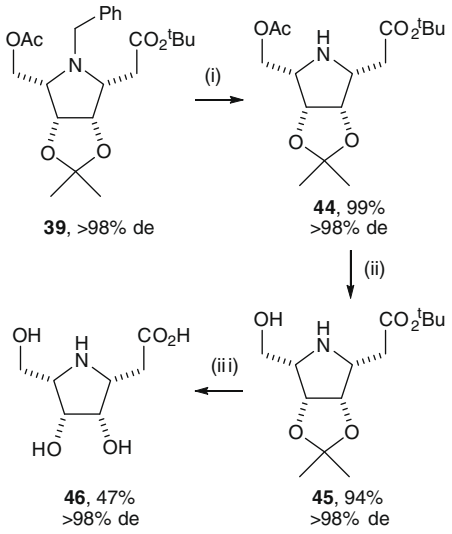
Scheme 11. Reagents and conditions: (i) AgOAc, PhMe, rt.

(Scheme 11). This product distribution is consistent with an aziridinium ion intermediate being involved in this reaction.

With homogenous pyrrolidine acetates **35** and **39** in hand, deprotection to the corresponding polyhydroxylated pyrrolidines was investigated. N-Debenzylation of **35** followed by methanolysis of the acetate gave pyrrolidine **42** in good yield and as a single diastereoisomer. The relative configuration within **42** was established unambiguously by single-crystal X-ray analysis, with the absolute (2*R*,3*R*,4*S*,5*S*)-configuration being assigned from the known stereocentres of the 3,4-*O*-isopropylidene moiety, derived from D-ribose.[10] This analysis also allowed the assigned relative configuration within iodomethyl pyrroldine **9** to be unambiguously confirmed. Subsequent acidic hydrolysis of **42** followed by ion-exchange chromatography gave the β-amino acid derived, polyhydroxylated pyrroldine **43** in 78% yield as a single diastereoisomer (Scheme 12). Similarly, N-debenzylation of **39** followed by methanolysis gave **45** in excellent yield and as a single diastereoisomer, with subsequent acidic hydrolysis and ion-exchange chromatography giving polyhydroxylated pyrrolidine **46** in 47% yield as a single diastereoisomer (Scheme 13).



Scheme 12. Reagents and conditions: (i) $Pd(OH)_2/C$, H_2 (1 atm), MeOH; (ii) K_2CO_3, MeOH; (iii) TFA, then Dowex 50WX8-200.



Scheme 13. Reagents and conditions: (i) $Pd(OH)_2/C$, H_2 (1 atm), MeOH; (ii) K_2CO_3, MeOH; (iii) TFA, then Dowex 50WX8-200.

3. Conclusion

In conclusion, treatment of a range of homochiral, unsaturated β-amino esters (containing a *cis*-dioxolane unit) with iodine promotes a novel ring-closing iodoamination with N-debenzylation reaction that provides a simple and stereoselective route to iodomethyl pyrrolidines. The stereoselectivity of this iodoamination protocol is dependent upon both the absolute configuration of the *N*-α-methylbenzyl-protecting group and upon the configuration at C(3) within the β-amino ester substructure. Functional group interconversion of the resulting iodomethyl pyrrolidines with AgOAc proceeds via the corresponding aziridinium ion, with subsequent deprotection giving access to β-amino acid-derived polyhydroxylated pyrrolidines.

4. Experimental

4.1. General experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[20] Water was purified by an Elix® UV-10 system.

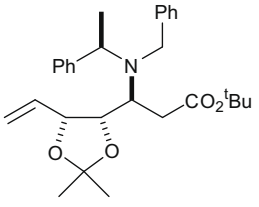
All other solvents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq $KMnO_4$ or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

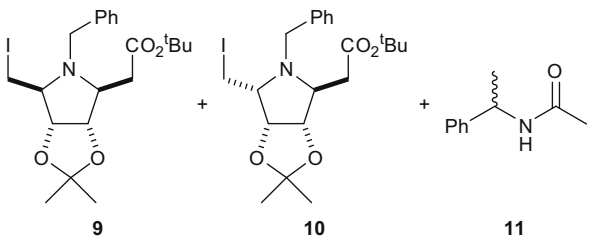
Elemental analyses were recorded by the microanalysis service of the Inorganic Chemistry Laboratory, University of Oxford, UK. Melting points were recorded on a Gallenkamp Hot Stage apparatus and were uncorrected. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates (film) or a KBr disc (KBr), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. Low-resolution mass spectra were recorded on either a VG MassLab 20–250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass.

4.2. General procedure for iodocyclisation of tertiary amines

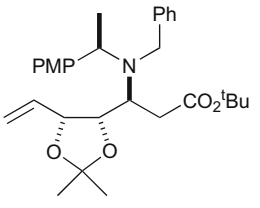
$NaHCO_3$ (3.0 equiv) and I_2 (3.0 equiv) were added sequentially to a stirred solution of the requisite tertiary amine (1.0 equiv) in MeCN at −20 °C. After stirring for 2 h, the reaction mixture was allowed to warm to rt over 20 h. The reaction mixture was diluted with Et_2O, washed sequentially with satd aq $Na_2S_2O_3$ and water, dried and concentrated in vacuo.

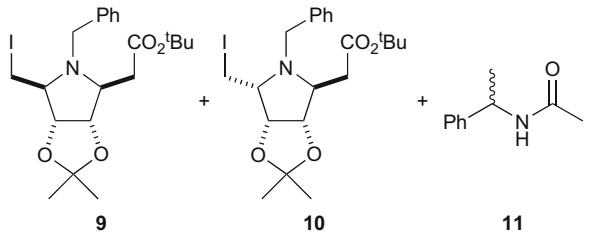
4.2.1. (2*S*,3*R*,4*S*,5*S*)- and (2*R*,3*R*,4*S*,5*S*)-*N*(1)-Benzyl-2-iodomethyl-3,4-*O*-isopropylidene-5-(*tert*-butoxycarbonylmethyl)pyrrolidine (2*S*,3*R*,4*S*,5*S*)-9 and (2*R*,3*R*,4*S*,5*S*)-10



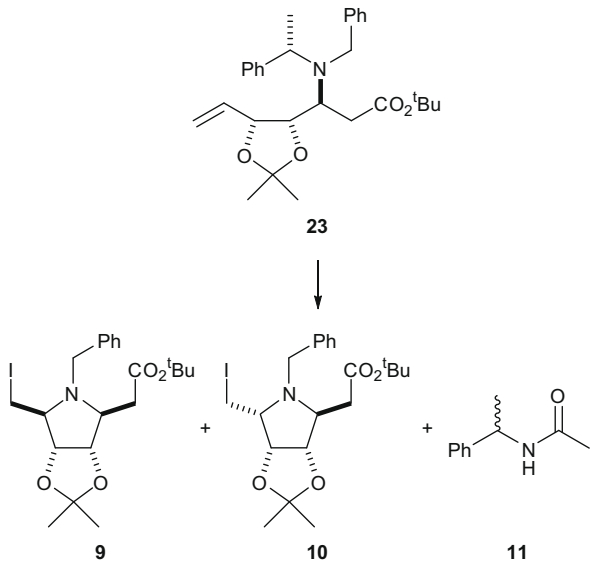


From **8***:* Following the *General Procedure*, $NaHCO_3$ (108 mg, 1.29 mmol), I_2 (328 mg, 1.29 mmol) and **8** (200 mg, 0.430 mmol) in MeCN (20 mL) gave a mixture containing **9**, **10** and **11** (the ratio of **9**:**10** was 81:19). Purification via flash column chromatography (eluent pentane/Et_2O, 11:1) gave **10** as a colourless oil (36 mg, 17%, >98% de); R_f 0.4 (pentane/Et_2O, 9:1); $[\alpha]_D^{25} = +52.8$ (*c* 0.9 in $CHCl_3$); ν_{max} (film) 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 1.37 (3H, s, *Me*CMe), 1.42 (9H, s, C*Me*$_3$), 1.57 (3H, s, MeC*Me*), 2.09 (1H, dd, *J* 14.6, 9.9, C*H*$_A$H$_B$CO$_2$^{t}Bu), 2.43 (1H, dd, *J* 14.6, 3.8, CH$_A$*H*$_B$CO$_2$^{t}Bu), 3.10–3.16 (3H, m, C(2)*H*, C*H*$_2$I), 3.62 (1H, app dd, *J* 9.9, 4.1, C(5)*H*), 3.70 (1H, d, *J* 14.6, NC*H*$_A$), 3.84 (1H, d, *J* 14.6, NC*H*$_B$), 4.56 (1H, app d, *J* 6.3, C(3)*H*), 4.77 (1H, dd, *J* 6.3, 3.0, C(4)*H*), 7.24–7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 2.4 (*C*H$_2$I), 25.3, 26.4 (C*Me*$_2$), 28.1 (C*Me*$_3$), 31.5 (*C*H$_2$CO$_2$^{t}Bu), 51.3 (NCH$_2$), 64.1 (*C*(5)), 66.9 (*C*(2)), 80.6 (*C*(3)), 81.0 (*C*Me$_3$), 81.7 (*C*(4)), 111.6 (*C*Me$_2$), 127.0 (*p-Ph*), 128.1, 128.4 (*o-*, *m-Ph*), 139.1 (*i-Ph*), 171.1 (*C*O$_2$^{t}Bu); *m/z* (APCI$^+$) 488 ([M+H]$^+$, 100%), 432 (59); HRMS (ESI$^+$) $C_{21}H_{31}INO_4^+$ ([M+H]$^+$) requires 488.1292; found 488.1293. Further elution gave **9** as a colourless oil (133 mg, 63%, >98% de); R_f 0.37 (pentane/Et_2O, 9:1); $[\alpha]_D^{24} = +2.1$ (*c* 0.8 in $CHCl_3$); ν_{max} (film) 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, s, *Me*CMe), 1.45 (9H, s, C*Me*$_3$), 1.48 (3H, s, MeC*Me*), 2.32 (1H, dd, *J* 14.7, 7.9, C*H*$_A$H$_B$CO$_2$^{t}Bu), 2.46 (1H, dd, *J* 14.7, 4.6, CH$_A$*H*$_B$CO$_2$^{t}Bu), 2.86–2.93 (2H, m, C(2)*H*, CH$_A$H$_B$I), 3.10 (1H, dd, *J* 9.7, 2.2, CH$_A$*H*$_B$I), 3.33–3.38 (1H, m, C(5)*H*), 3.84 (2H, ABq, *J* 14.2, NC*H*$_2$), 4.39 (1H, dd, *J* 6.2, 3.1, C(3)*H*), 4.55 (1H, dd, *J* 6.2, 3.9, C(4)*H*), 7.25–7.32 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.4 (*C*H$_2$I), 25.3, 28.1 (C*Me*$_2$), 28.6 (C*Me*$_3$), 40.3 (*C*H$_2$CO$_2$^{t}Bu), 57.5 (NCH$_2$), 67.5 (*C*(5)), 69.5 (*C*(2)), 81.2 (*C*Me$_3$), 83.5 (*C*(4)), 85.0 (*C*(3)), 113.0 (*C*Me$_2$), 127.8 (*p-Ph*), 128.8, 129.3 (*o-*, *m-Ph*), 138.7 (*i-Ph*), 171.3 (*C*O$_2$^{t}Bu); *m/z* (APCI$^+$) 488 ([M+H]$^+$, 100%), 432 (92); HRMS (ESI$^+$) $C_{21}H_{31}INO_4^+$ ([M+H]$^+$) requires 488.1292; found 488.1297. Further elution (eluent pentane/Et_2O, 1:6) gave **11** as a white solid (51 mg, 72%); R_f 0.21 (pentane/Et_2O, 1:6); mp 82–83 °C (pentane/Et_2O); $[\alpha]_D^{25} = -3.8$ (*c* 0.7 in $CHCl_3$); {lit.[9] for (*R*)-**11** $[\alpha]_D^{19} = +129.5$ (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.48 (3H, d, *J* 7.1, C(α)*Me*), 1.97 (3H, s, CO*Me*), 5.08–5.16 (1H, m, C(α)*H*), 5.98 (1H, br s, N*H*), 7.24–7.36 (5H, m, *Ph*).



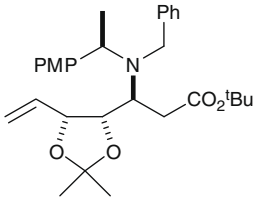


From **18***:* Following the *General Procedure*, $NaHCO_3$ (81 mg, 0.96 mmol), I_2 (243 mg, 0.96 mmol) and **18** (158 mg, 0.32 mmol) in MeCN (15 mL) gave a mixture containing **9**, **10** and **11** (the ratio of **9**:**10** was 89:11). Purification via flash column chromatography (eluent pentane/Et_2O, 20:1) gave **9** as a colourless oil (79 mg, 51%, >98% de).



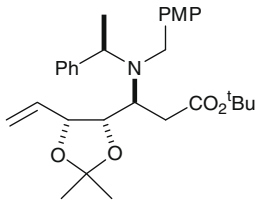
From **23***:* Following the *General Procedure*, $NaHCO_3$ (26 mg, 0.30 mmol), I_2 (77 mg, 0.30 mmol) and **23** (47 mg, 0.10 mmol) in MeCN (5 mL) gave a mixture containing **9**, **10** and **11** (the ratio of **9**:**10** was 27:73). Purification via flash column chromatography (eluent pentane/Et_2O, 12:1) gave **10** as a colourless oil (14 mg, 28%, >98% de). Further elution gave **9** as a colourless oil (5 mg, 9%, >98% de). Further elution (eluent pentane/Et_2O, 1:6) gave **11** as a white solid (10 mg, 59%).

4.2.2. *tert*-Butyl (3*S*,4*S*,5*R*,α*R*)-3-[*N*-benzyl-*N*-(α-methyl-4′-methoxybenzyl)amino]-4,5-*O*-isopropylidene-hepta-6-enoate 18



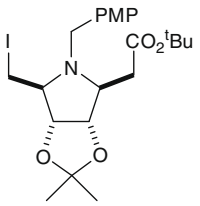
BuLi (2.5 M in hexanes, 0.49 mL, 1.22 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methyl-4-methoxybenzyl)amine (304 mg, 1.26 mmol) in THF (5 mL) at −78 °C, and the resulting solution was stirred for 30 min. A solution of **17** (200 mg, 0.79 mmol) in THF (5 mL) at −78 °C was added dropwise via cannula. The reaction mixture was stirred for 2 h before addition of satd aq NH_4Cl (10 mL). The reaction mixture was warmed to rt and concentrated in vacuo. The residue was dissolved in DCM (10 mL) and washed sequentially with 10% aq citric acid (10 mL), satd aq $NaHCO_3$ (10 mL) and brine (10 mL), dried and concentrated in vacuo. Purification via flash column chromatography (eluent pentane/Et_2O, 15:1) gave **20** as a colourless oil (10 mg, 5%, >98% de);[6] R_f 0.26 (pentane/Et_2O, 20:1); $[\alpha]_D^{24} = -35.8$ (*c* 1.15 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.43 (3H, s, C*Me*$_A$Me$_B$), 1.45 (9H, s, C*Me*$_3$), 1.52 (3H, s, CMe$_A$*Me*$_B$), 2.98–3.12 (2H, m, C(2)H_2), 4.32 (1H, app td, *J* 7.0, 1.8, C(3)*H*), 4.94–4.97 (1H, m, C(5)*H*), 5.29 (1H, dd, *J* 10.1, 0.4, C(7)H_A), 5.38 (1H, app d, *J* 17.0, C(7)H_B), 5.74–5.83 (1H, m, C(6)*H*). Further elution gave **18** as a colourless oil (159 mg, 41%, >98% de); R_f 0.11 (pentane/Et_2O, 10:1); $[\alpha]_D^{25} = +12.1$ (*c* 0.9 in $CHCl_3$); ν_{max} (film) 1729 (C=O); 1610 (C=C); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, s, *Me*CMe), 1.35 (3H, d, *J* 7.0, C(α)*Me*), 1.42 (3H, s, MeC*Me*), 1.46 (9H, s, C*Me*$_3$), 2.15–2.25 (2H, m, C(2)H_2), 3.69–3.77 (2H, m, NCH_2), 3.77–3.82 (1H, m, C(3)*H*), 3.80 (3H, s, O*Me*), 3.89 (1H, q, *J* 7.0, C(α)*H*), 4.20 (1H, app t, *J* 6.2, C(4)*H*), 4.58–4.62 (1H, m, C(5)*H*), 5.29–5.32 (1H, m, C(7)H_A), 5.36–5.41 (1H, m, C(7)H_B), 5.94–6.01 (1H, m, C(6)*H*), 6.81–6.85 (2H, m, C(3′)*H*, C(5′)*H*), 7.21–7.34 (7H, m, C(2′)*H*, C(6′)*H*, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.1 (C(α)*Me*), 25.1, 27.6 (C*Me*$_2$), 28.1 (C*Me*$_3$), 36.0 (*C*(2)), 50.1 (NCH_2), 54.1 (*C*(3)), 55.2 (O*Me*), 58.3 (*C*(α)), 78.9 (*C*(4)), 79.7 (*C*(5)), 80.0 (*C*Me$_3$), 107.9 (*C*Me$_2$), 113.3 (*C*(3′), *C*(5′)), 119.0 (*C*(7)), 126.6 (*p-Ph*), 128.1, 128.2, 129.2 (*C*(2′), *C*(6′), *o-*, *m-Ph*), 134.7 (*C*(6)), 134.8 (*i-Ph*), 141.4 (*C*(1′)), 158.6 (*C*(4′)), 171.5 (*C*(1)); *m/z* (APCI$^+$) 496 ([M+H]$^+$, 21%), 362 (100), 306 (57); HRMS (ESI$^+$) $C_{30}H_{42}NO_5^+$ ([M+H]$^+$) requires 496.3057; found 496.3057.

4.2.3. *tert*-Butyl (3*S*,4*S*,5*R*,α*R*)-3-[*N*-(4′-methoxybenzyl)-*N*-(α-methylbenzyl)amino]-4,5-*O*-isopropylidene-hept-6-enoate 19



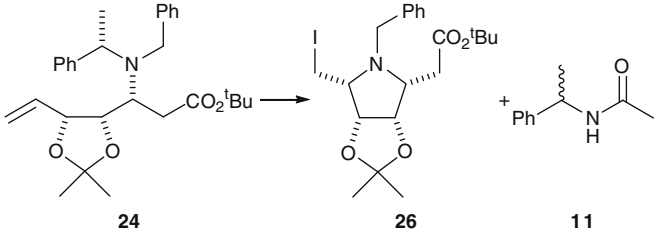
BuLi (1.6 M in hexanes, 0.76 mL, 1.22 mmol) was added dropwise to a stirred solution of (*R*)-*N*-(4′-methoxybenzyl)-*N*-(α-methylbenzyl)amine (304 mg, 1.26 mmol) in THF (4 mL) at −78 °C, and the resulting solution was stirred for 30 min. A solution of **17** (200 mg, 0.79 mmol) in THF (4 mL) at −78 °C was added dropwise via cannula. The reaction mixture was stirred for 2 h before addition of satd aq NH_4Cl (10 mL). The reaction mixture was warmed to rt and concentrated in vacuo. The residue was dissolved in DCM (10 mL) and washed sequentially with 10% aq citric acid (10 mL), satd aq $NaHCO_3$ (10 mL) and brine (10 mL), dried and concentrated in vacuo. Purification via flash column chromatography (eluent pentane/Et_2O, 15:1) gave **20** as a colourless oil (11 mg, 5%, >98% de).[6] Further elution gave **19** as a colourless oil (184 mg, 47%, >98% de); R_f 0.15 (pentane/Et_2O, 10:1); $[\alpha]_D^{25} = +11.4$ (*c* 1.25 in $CHCl_3$); ν_{max} (film) 1729 (C=O), 1612 (C=C); δ_H (400 MHz, $CDCl_3$) 1.30 (3H, s, *Me*CMe), 1.37 (3H, d, *J* 7.1, C(α)*Me*), 1.42 (3H, s, MeC*Me*), 1.49 (9H, s, C*Me*$_3$), 2.18 (2H, app dd, *J* 6.1, *J* 2.1 C(2)H_2), 3.68 (2H, ABq, J_{AB} 15.1, NCH_2), 3.76–3.79 (1H, m, C(3)*H*), 3.81 (3H, s, O*Me*), 3.93 (1H, q, *J* 7.1, C(α)*H*), 4.21 (1H, app t, *J* 6.3, C(4)*H*), 4.60 (1H, app t, *J* 6.6, C(5)*H*), 5.29–5.41 (2H, m, C(7)H_2), 5.93–6.01 (1H, m, C(6)*H*), 6.85–6.87 (2H, m, C(3′)*H*, C(5′)*H*), 7.22–7.34 (7H, m, C(2′)*H*, C(6′)*H*, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.7 (C(α)*Me*), 25.4, 27.5 (C*Me*$_2$), 27.9 (C*Me*$_3$), 36.0 (*C*(2)), 49.5 (NCH_2), 54.0 (C(3)), 55.2 (*C*(α)), 58.6 (O*Me*), 78.8 (*C*(4)), 79.6 (*C*(5)), 80.8 (*C*Me$_3$), 107.9 (*C*Me$_2$), 113.5 (*C*(3′), *C*(5′)), 118.7 (*C*(7)), 127.0 (*p-Ph*), 128.0, 128.2, 129.3 (*C*(2′), *C*(6′), *o-*, *m-Ph*), 133.2 (*i-Ph*), 134.7 (*C*(6)), 142.8 (*C*(1′)), 158.4 (*C*(4′)), 171.5 (*C*(1)); *m/z* (APCI$^+$) 496 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{42}NO_5^+$ ([M+H]$^+$) requires 496.3057; found 496.3066.

4.2.4. (2*S*,3*R*,4*S*,5*S*)-*N*(1)-(4′-Methoxybenzyl)-2-iodomethyl-3,4-*O*-isopropylidene-5-(*tert*-butoxycarbonylmethyl)pyrrolidine 21

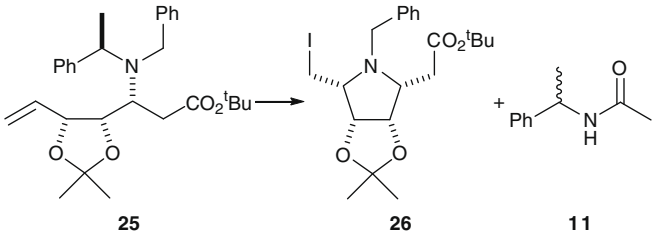


Following the *General Procedure*, $NaHCO_3$ (457 mg, 5.45 mmol), I_2 (1.38 g, 5.45 mmol) and **19** (900 mg, 1.82 mmol) in MeCN (75 mL) gave an 80:20 mixture of **21**:**22**. Purification via flash column chromatography (eluent pentane/Et_2O, 15:1) gave **21** as a colourless oil (486 mg, 52%, >98% de); R_f 0.09 (pentane/Et_2O, 15:1); $[\alpha]_D^{25} = -2.9$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1727 (C=O), 1612 (C=C); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, s, *Me*CMe), 1.45 (9H, s, C*Me*$_3$), 1.47 (3H, s, MeC*Me*), 2.32 (1H, dd, *J* 14.7, 7.9, C*H*$_A$H$_B$CO$_2$^{t}Bu), 2.45 (1H, dd, *J* 14.7, 4.5, CH$_A$*H*$_B$CO$_2$^{t}Bu), 2.81–2.84 (1H, m, C(2)*H*), 2.90 (1H, dd, *J* 10.2, 7.5, C*H*$_A$H$_B$I), 3.09 (1H, dd, *J* 10.2, 2.6, CH$_A$*H*$_B$I), 3.30–3.34 (1H, m, C(5)*H*), 3.73 (1H, d, *J* 14.2, NC*H*$_A$), 3.80 (1H, d, *J* 14.2, NC*H*$_B$), 3.81 (3H, s, O*Me*), 4.37 (1H, dd, *J* 6.0, 3.3, C(3)*H*), 4.53 (1H, dd, *J* 6.0, 4.2, C(4)*H*), 6.83–6.86 (2H, m, C(3′)*H*, C(5′)*H*), 7.20–7.24 (2H, m, C(2′)*H*, C(6′)*H*); δ_C (100 MHz, $CDCl_3$) 11.0 (*C*H$_2$I), 25.6, 27.6 (C*Me*$_2$), 28.1 (C*Me*$_3$), 39.8 (*C*H$_2$CO$_2$^{t}Bu), 55.2 (O*Me*), 56.2 (NCH$_2$), 66.7 (*C*(5)), 68.7 (*C*(2)), 80.7 (*C*Me$_3$), 83.0 (*C*(4)), 84.5 (*C*(3)), 112.5 (*C*Me$_2$), 113.7 (*C*(3′), *C*(5′)), 130.0 (*C*(2′), *C*(6′)), 130.1 (*C*(1′)), 158.9 (*C*(4′)), 170.6 (*C*O$_2$^{t}Bu); *m/z* (APCI$^+$) 518 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{33}INO_5^+$ ([M+H]$^+$) requires 518.1398; found 518.1403.

4.2.5. (2*R*,3*R*,4*S*,5*R*)-*N*(1)-Benzyl-2-iodomethyl-3,4-*O*-isopropylidene-5-(*tert*-butoxycarbonylmethyl)pyrrolidine 26

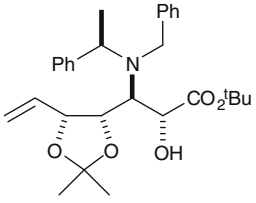


From **24***:* Following the *General Procedure*, $NaHCO_3$ (243 mg, 2.89 mmol), I_2 (734 mg, 2.89 mmol) and **24** (448 mg, 0.96 mmol) in MeCN (40 mL) gave a mixture containing **11** and **26** only. Purification via flash column chromatography (eluent pentane/Et_2O, 20:1) gave **26** as a colourless oil (305 mg, 65%, >98% de); R_f 0.26 (pentane/Et_2O, 10:1); $[\alpha]_D^{25} = +4.5$ (*c* 0.4 in $CHCl_3$); ν_{max} (film) 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 1.36 (3H, s, *Me*CMe), 1.43 (9H, s, C*Me*$_3$), 1.53 (3H, s, MeC*Me*), 2.40 (1H, dd, *J* 16.6, 4.2, C*H*$_A$H$_B$CO$_2$^{t}Bu), 2.70 (1H, dd, *J* 16.6, 9.3, CH$_A$*H*$_B$CO$_2$^{t}Bu), 2.75–2.79 (1H, m, C(2)*H*), 2.89–2.93 (1H, m, C(5)*H*), 3.02 (1H, dd, *J* 9.1, 3.6, C*H*$_A$H$_B$I), 3.16 (1H, dd, *J* 11.0, 9.1, CH$_A$*H*$_B$I), 3.62 (1H, d, *J* 16.0, NC*H*$_A$), 3.78 (1H, d, *J* 16.0, NC*H*$_B$), 4.65–4.72 (2H, m, C(3)*H*, C(4)*H*), 6.83–6.86 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 1.9 (*C*H$_2$I), 25.6, 26.2 (C*Me*$_2$), 28.1 (C*Me*$_3$), 34.5 (*C*H$_2$CO$_2$^{t}Bu), 55.0 (NCH$_2$), 65.0 (*C*(5)), 70.4 (*C*(2)), 78.4, 79.3 (*C*(3), *C*(4)), 80.7 (*C*Me$_3$), 111.2 (*C*Me$_2$), 127.1 (*p*-*Ph*), 128.0, 128.4 (*o*-, *m*-*Ph*), 135.8 (*i*-*Ph*), 171.3 (*C*O$_2$^{t}Bu); *m/z* (APCI$^+$) 488 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{31}INO_4$ ([M+H]$^+$) requires 488.1292; found 488.1277. Further elution (eluent pentane/Et_2O, 1:6) gave **11** as a white solid (35 mg, 22%).



From **25***:* Following the *General Procedure*, $NaHCO_3$ (22 mg, 0.26 mmol), I_2 (66 mg, 0.26 mmol) and **25** (40 mg, 0.09 mmol) in MeCN (4 mL) gave a mixture containing **11** and **26** only. Purification via flash column chromatography (eluent pentane/Et_2O, 20:1) gave **26** as a colourless oil (29 mg, 70%, >98% de). Further elution (eluent pentane/Et_2O, 1:6) gave **11** as a white solid (5 mg, 36%).

4.2.6. *tert*-Butyl (2*R*,3*S*,4*S*,5*R*,α*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5-*O*-isopropylidene-hept-6-enoate 29



BuLi (2.5 M in hexanes, 9.2 mL, 23.0 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (4.98 g, 23.6 mmol) in THF (30 mL) at −78 °C. After 30 min, a solution of **17** (3.0 g, 11.8 mmol) in THF (30 mL) was added via cannula. After stirring for 2 h, the reaction mixture was quenched with (−)-CSO (5.27 g, 23.0 mmol), followed after 12 h by satd aq NH_4Cl (10 mL). The mixture was extracted with Et_2O (3 × 50 mL), and the combined organic extracts were concentrated in vacuo. The residue was dissolved in DCM (50 mL) and washed sequentially with 10% aq citric acid (50 mL) and satd aq $NaHCO_3$ (50 mL), dried and concentrated in vacuo. The residue was dissolved in Et_2O (50 mL), the insoluble CSO residues were filtered off, and the filter cake was washed with Et_2O (2 × 20 mL). The filtrate was concentrated in vacuo and the process was repeated. Purification via flash column chromatography (eluent pentane/Et_2O, 20:1) gave **29** as a colourless oil (3.44 g, 61%, >98% de); R_f 0.23 (pentane/Et_2O, 8:1); mp 79–81 °C (pentane/Et_2O); $[\alpha]_D^{24} = +20.7$ (*c* 0.8 in $CHCl_3$); ν_{max} (film) 3502 (br, O−H), 1731 (C=O); δ_H (400 MHz, $CDCl_3$) 1.26 (3H, s, *Me*CMe), 1.36–1.38 (6H, m, MeC*Me*, C(α)*Me*), 1.54 (9H, s, C*Me*$_3$), 3.01 (1H, d, *J* 7.2, O*H*), 3.77 (1H, d, *J* 16.2, NC*H*$_A$), 3.83 (1H, app d, *J* 7.2, C(2)*H*), 3.88 (1H, app d, *J* 9.9, C(3)*H*), 3.93 (1H, q, *J* 7.1, C(α)*H*), 4.40 (1H, dd, *J* 9.8, *J* 5.4, C(4)*H*), 4.84 (1H, d, *J* 16.2, NC*H*$_B$), 4.60–4.63 (1H, m, C(5)*H*), 5.28 (1H, dd, *J* 10.3, 0.8, C(7)*H*$_A$), 5.41–5.45 (1H, m, C(7)*H*$_B$), 5.86–5.94 (1H, m, C(6)*H*), 7.25–7.42 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.4 (C(α)*Me*), 25.5 (*Me*CMe), 28.1 (C*Me*$_3$), 28.2 (MeC*Me*), 50.9 (NCH$_2$), 57.3 (*C*(3)), 58.8 (*C*(α)), 71.0 (*C*(2)), 75.6 (*C*(4)), 79.1 (*C*(5)), 82.0

(*C*Me$_3$), 107.6 (*C*Me$_2$), 118.9 (*C*(7)), 126.6, 127.4 (*p-Ph*), 127.7, 128.1, 128.4, 128.7 (*o-*, *m-Ph*), 135.0 (*C*(6)), 141.2, 141.7 (*i-Ph*), 172.9 (*C*(1)); *m/z* (APCI$^+$) 482 ([M+H]$^+$, 88%), 426 (47), 105 (100); HRMS (ESI$^+$) $C_{29}H_{40}NO_5^+$ ([M+H]$^+$) requires 482.2901; found 482.2919.

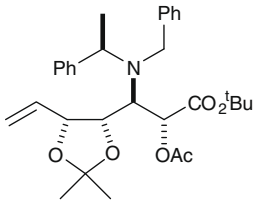
4.2.7. X-ray crystal structure determination for 29

Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite-monochromated Mo Kα radiation using standard procedures at 190 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.[21]

X-ray crystal structure data for **29** [$C_{29}H_{39}NO_5$]: M = 481.63, orthorhombic, space group $P2_12_12_1$, a = 11.6031(2) Å, b = 12.8707(2) Å, c = 18.6428(3) Å, V = 2784.1 Å^3, Z = 4, μ = 0.078 mm^{-1}, colourless plate, crystal dimensions = 0.4 × 0.6 × 0.8 mm^3. A total of 3554 unique reflections were measured for $5 < \theta < 27$, and 2797 reflections were used in the refinement. The final parameters were wR_2 = 0.041 and R_1 = 0.038 [$I > 3\sigma(I)$].

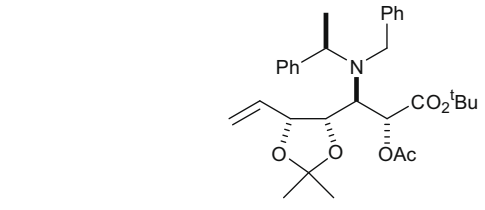
Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 693429. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223–336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.2.8. *tert*-Butyl (2*R*,3*R*,4*S*,5*R*,α*R*)-2-acetoxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5-*O*-isopropylidene-hepta-6-enoate 30

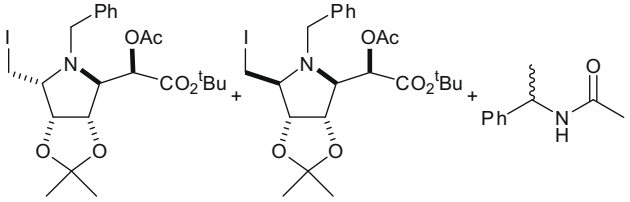


Pyridine (0.05 mL, 0.62 mmol), DMAP (cat.) and Ac_2O (0.2 mL, 2.10 mmol) were added sequentially to a stirred solution of **29** (200 mg, 0.42 mmol) in DCM (4 mL). The resultant solution was stirred for 15 h, diluted with Et_2O (4 mL), washed sequentially with 10% aq $CuSO_4$ (2 × 10 mL) and brine (2 × 10 mL), dried and concentrated in vacuo. Purification via flash column chromatography (eluent pentane/Et_2O, 5:1) gave **30** as a white solid (309 mg, 94%, >98% de); R_f 0.15 (pentane/Et_2O, 5:1); $C_{31}H_{41}NO_6$ requires C, 71.1; H, 7.9; N, 2.7. Found: C, 70.9; H, 8.0; N, 2.7; mp 93–95 °C (pentane/Et_2O); $[\alpha]_D^{27} = +37.9$ (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 1761 (C=O), 1748 (C=O), 1601 (C=C); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, s, *Me*CMe), 1.34 (3H, d, *J* 6.9, C(α)*Me*), 1.38 (3H, s, MeC*Me*), 1.46 (9H, s, C*Me*$_3$), 2.09 (3H, s, CO*Me*), 3.63 (1H, d, *J* 15.7, NC*H*$_A$), 3.93 (1H, q, *J* 6.9, C(α)*H*), 3.98 (1H, app d, *J* 9.4, C(3)*H*), 4.15 (1H, d, *J* 15.7, NC*H*$_B$), 4.43 (1H, dd, *J* 9.8, 5.4, C(4)*H*), 4.57–4.61 (1H, m, C(5)*H*), 5.15 (1H, app s, C(2)*H*), 5.23–5.26 (1H, m, C(7)*H*$_A$), 5.43 (1H, app d, *J* 17.1, C(7)*H*$_B$), 5.87–5.95 (1H, m, C(6)*H*), 7.26–7.37 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.3 (C(α)*Me*), 21.0 (CO*Me*), 25.3 (*Me*CMe), 28.0 (C*Me*$_3$), 28.2 (MeC*Me*), 50.5 (NCH$_2$), 56.4 (*C*(3)), 59.8 (*C*(α)), 71.0 (*C*(2)), 75.4 (*C*(4)), 79.0 (*C*(5)), 81.6 (*C*Me$_3$), 107.7 (*C*Me$_2$), 119.1 (*C*(7)), 126.8, 127.6 (*p-Ph*), 127.5, 128.2, 128.4, 128.5 (*o-*, *m-Ph*), 134.9 (*C*(6)), 141.2, 141.3 (*i-Ph*), 167.2, 169.8 (*C*(1), *C*OMe); *m/z* (ESI$^+$) 546 ([M+Na]$^+$, 53%), 524 (100).

4.2.9. *tert*-Butyl (2*R*,2′*R*,3′*R*,4′*S*,5′*R*)- and (2*R*,2′*S*,3′*R*,4′*S*,5′*R*)-2-acetoxy-2-(*N*(1′)-benzyl-2′-iodomethyl-3′,4′-*O*-isopropylidene-pyrrolidin-5′-yl)acetate (2*R*,2′*R*,3′*R*,4′*S*,5′*R*)-31 and (2*R*,2′*S*,3′*R*,4′*S*,5′*R*)-32



30



31 32 11

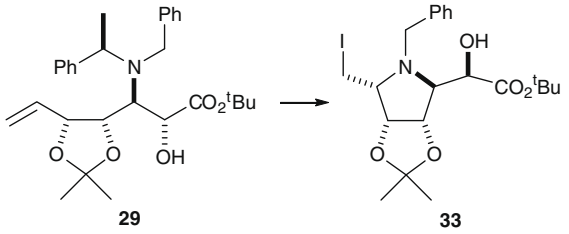
Following the *General Procedure*, $NaHCO_3$ (94 mg, 1.12 mmol), I_2 (284 mg, 1.12 mmol) and **30** (195 mg, 0.37 mmol) in MeCN (20 mL) gave a mixture containing **11**, **31** and **32** (the ratio of **31**:**32** was 70:30). Purification via exhaustive flash column chromatography (eluent pentane/Et_2O, 8:1) gave **31** as a white solid (57 mg, 28%, >98% de), **32** as a colourless oil (19 mg, 9%, >98% de) and **11** as a white solid (32 mg, 52%).

Data for **31**: R_f 0.28 (pentane/Et_2O, 6:1); mp 82–84 °C (pentane/Et_2O); $[\alpha]_D^{24} = +66.6$ (*c* 0.9 in $CHCl_3$); ν_{max} (KBr) 1748 (C=O), 1738 (C=O); δ_H (400 MHz, $CDCl_3$) 1.35 (12H, s, C*Me*$_3$, *Me*CMe), 1.55 (3H, s, MeC*Me*), 2.18 (3H, s, CO*Me*), 3.16–3.18 (2H, m, C*H*$_2$I), 3.43–3.48 (1H, m, C(2)*H*), 3.60–3.64 (2H, m, C(5)*H*, NC*H*$_A$), 3.97 (1H, d, *J* 14.8, NC*H*$_B$), 4.66 (1H, app d, *J* 6.1, C(4)*H*), 4.84 (1H, app t, *J* 5.7, C(3)*H*), 5.26 (1H, d, *J* 1.8, C*H*CO$_2$^{t}Bu), 7.23–7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 2.8 (*C*H$_2$I), 21.2 (CO*Me*), 25.2, 26.4 (C*Me*$_2$), 27.8 (C*Me*$_3$), 51.0 (NCH$_2$), 66.4 (*C*(5)), 68.6 (*C*(2)), 70.1 (*C*HCO$_2$^{t}Bu), 78.8 (*C*(4)), 81.0 (*C*Me$_3$), 82.9 (*C*(3)), 111.5 (*C*Me$_2$), 127.2 (*p-Ph*), 128.0, 128.5 (*o-*, *m-Ph*), 138.2 (*i-Ph*), 167.5, 169.5 (*C*OMe, *C*O$_2$^{t}Bu); *m/z* (ESI$^+$) 546 (100%, [M+H]$^+$); HRMS (ESI$^+$) $C_{23}H_{33}INO_6^+$ ([M+H]$^+$) requires 546.1347; found 546.1356.

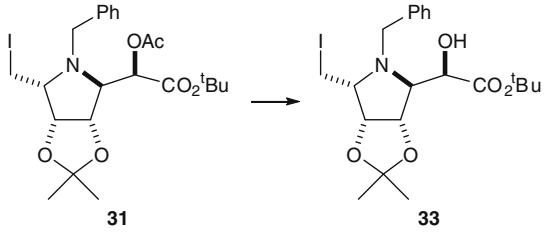
Data for **32**: R_f 0.12 (pentane/Et_2O, 6:1); $[\alpha]_D^{21} = -10.4$ (*c* 0.65 in $CHCl_3$); ν_{max} (film) 1746 (C=O); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, s, *Me*CMe), 1.42 (3H, s, MeC*Me*), 1.47 (9H, s, C*Me*$_3$), 2.18 (3H, s, CO*Me*), 2.91–2.96 (2H, m, C(2)*H*, C*H*$_A$H$_B$I), 3.07–3.12 (1H, m, CH$_A$*H*$_B$I), 3.51 (1H, dd, *J* 3.8, 2.3, C(5)*H*), 3.88 (2H, ABq, *J* 14.1, NC*H*$_2$), 4.36 (1H, dd, *J* 6.0, 2.6, C(3)*H*), 4.68 (1H, dd, *J* 6.0, 3.8, C(4)*H*), 4.98 (1H, d, *J* 2.3, C*H*CO$_2$^{t}Bu), 7.27–7.35 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 10.1 (*C*H$_2$I), 21.0 (CO*Me*), 25.6, 27.6 (C*Me*$_2$), 28.0 (C*Me*$_3$), 56.5 (NCH$_2$), 68.2 (*C*(2)), 69.8 (*C*(5)), 71.4 (*C*HCO$_2$^{t}Bu), 78.9 (*C*Me$_3$), 82.7 (*C*(4)), 84.3 (*C*(3)), 112.5 (*C*Me$_2$), 127.9 (*p-Ph*), 128.4, 129.1 (*o-*, *m-Ph*), 137.0 (*i-Ph*), 167.1, 170.0 (*C*OMe, *C*O$_2$^{t}Bu); *m/z* (ESI$^+$) 546 ([M+H]$^+$, 100%,), 450 (75), 418

(65); HRMS (ESI$^+$) $C_{23}H_{33}INO_6^+$ ([M+H]$^+$) requires 546.1347; found 546.1342.

4.2.10. *tert*-Butyl (2*R*,2′*R*,3′*R*,4′*S*,5′*S*)-2-hydroxy-2-(*N*(1′)-benzyl-2′-iodomethyl-3′,4′-*O*-isopropylidene-pyrrolidin-5′-yl)acetate 33

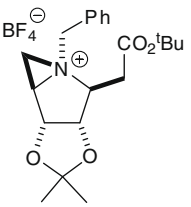


From **29**: Following the *General Procedure*, $NaHCO_3$ (103 mg, 1.23 mmol), I_2 (312 mg, 1.23 mmol) and **29** (200 mg, 0.41 mmol) in MeCN (20 mL) gave **33** in >98% de. Purification via flash column chromatography (eluent pentane/Et_2O, 12:1) gave **33** as a colourless oil (88 mg, 42%, >98% de); R_f 0.17 (pentane/Et_2O, 8:1); $[\alpha]_D^{22} = +66.8$ (*c* 1.2 in $CHCl_3$); ν_{max} (film) 3482 (O–H), 1723 (C=O); δ_H (500 MHz, $CDCl_3$) 1.39 (3H, s, *Me*CMe), 1.44 (9H, s, C*Me*$_3$), 1.60 (3H, s, MeC*Me*), 2.97 (1H, d, *J* 3.0, O*H*), 3.18–3.20 (2H, m, C*H*$_2$I), 3.59 (1H, app s, C(5)*H*), 3.76–3.80 (1H, m, C(2)*H*), 3.89 (1H, d, *J* 14.8, NC*H*$_A$), 4.07 (1H, d, *J* 14.8, NC*H*$_B$), 4.42 (1H, d, *J* 6.1, C(4)*H*), 4.40–4.47 (1H, m, C*H*CO$_2$^{t}Bu), 4.82 (1H, app t, *J* 5.6, C(3)*H*), 7.19–7.39 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 3.2 (*C*H$_2$I), 25.2, 26.5 (C*Me*$_2$), 27.8 (C*Me*$_3$), 51.3 (NCH$_2$), 68.2 (*C*(2)), 68.4 (*C*HCO$_2$^{t}Bu), 69.0 (*C*(5)), 79.0 (*C*(4)), 81.2 (*C*(3)), 83.5 (*C*Me$_3$), 111.1 (*C*Me$_2$), 127.0 (*p-Ph*), 127.8, 128.4 (*o-*, *m-Ph*), 139.2 (*i-Ph*), 173.4 (*C*O$_2$^{t}Bu); *m/z* (APCI$^+$) 504 ([M+H]$^+$, 35%), 448 (100); HRMS (ESI$^+$) $C_{21}H_{31}INO_5^+$ ([M+H]$^+$) requires 504.1241; found 504.1256.



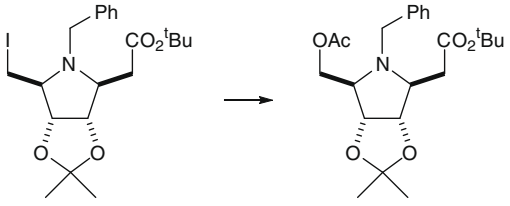
From **31**: K_2CO_3 (7.6 mg, 0.055 mmol) was added to a stirred solution of **31** (30.0 mg, 0.055 mmol) in MeOH (2 mL). After stirring for 2 h, satd aq NH_4Cl (5 mL) was added, and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried and concentrated in vacuo. Purification via flash column chromatography (eluent pentane/Et_2O, 12:1) gave **33** as a colourless oil (26 mg, 94%, >98% de).

4.2.11. (1*S*,2*S*,3*S*,4*R*,5*R*)-*N*(1)-Benzyl-2-(*tert*-butoxycarbonylmethyl)-3,4-*O*-isopropylidene-1-azoniabicyclo[3.1.0]hexane tetrafluoroborate 34

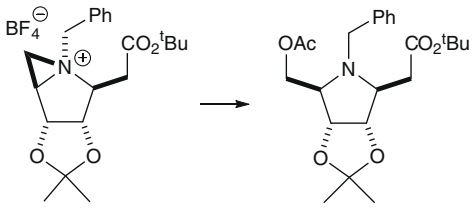


$AgBF_4$ (30 mg, 0.16 mmol) was added to a solution of **9** (63 mg, 0.13 mmol) in DCM (5 mL). The resultant solution was stirred for 2 h, filtered through Celite (eluent DCM) and concentrated in vacuo to give **34** as a colourless oil (59 mg, quant, >98% de); $[\alpha]_D^{26} = -15.1$ (*c* 1.6 in $CHCl_3$); ν_{max} (film) 1731 (C=O), 1634 (C=C); δ_H (400 MHz, $CDCl_3$) 0.97 (3H, s, *Me*CMe), 1.19 (3H, s, MeC*Me*), 1.45 (9H, s, C*Me*$_3$), 2.75 (1H, dd, *J* 16.5, 8.3, C*H*$_A$H$_B$CO$_2$^{t}Bu), 3.04 (1H, dd, *J* 16.5, 5.8, CH$_A$*H*$_B$CO$_2$^{t}Bu), 3.31 (1H, dd, *J* 6.5, 5.1, C(6)*H*$_A$), 3.63 (1H, dd, *J* 8.4, 5.1, C(6)*H*$_B$), 3.98–4.02 (1H, m, C(2)*H*), 4.17 (1H, d, *J* 14.3, NC*H*$_A$H$_B$Ph), 4.32 (1H, app dd, *J* 8.5, 6.9, C(5)*H*), 4.55 (1H, dd, *J* 5.7, 4.4, C(3)*H*), 4.80 (1H, d, *J* 14.3, NCH$_A$*H*$_B$Ph), 5.00 (1H, app d, *J* 5.9, C(4)*H*), 7.46–7.59 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 24.6, 26.4 (C*Me*$_2$), 27.9 (C*Me*$_3$), 34.7 (*C*H$_2$CO$_2$^{t}Bu), 40.1 (*C*(6)), 55.5 (*C*(5)), 60.5 (NCH$_2$Ph), 66.5 (*C*(2)), 78.6 (*C*(4)), 82.8 (*C*Me$_3$), 84.2 (*C*(3)), 114.5 (*C*Me$_2$), 129.0, 129.4, 130.5, 131.6 (*Ph*), 167.9 (*C*O$_2$^{t}Bu); *m/z* (ESI$^+$) 360 ([M–BF$_4$]$^+$, 100%), 304 (56); HRMS (ESI$^+$) $C_{21}H_{30}NO_4^+$ ([M–BF$_4$]$^+$) requires 360.2169; found 360.2175.

4.2.12. (2*R*,3*R*,4*S*,5*S*)-*N*(1)-Benzyl-2-acetoxymethyl-3,4-*O*-isopropylidene-5-(*tert*-butoxycarbonylmethyl)pyrrolidine 35



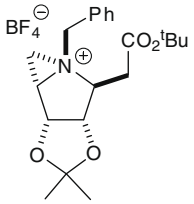
From **9**: AgOAc (154 mg, 0.92 mmol) was added to a stirred solution of **9** (300 mg, 0.62 mmol) in PhMe (25 mL) at rt. After stirring for 2 h, the reaction mixture was filtered through Celite (eluent EtOAc) and concentrated in vacuo to give **35** in >98% de. Purification via flash column chromatography (eluent pentane/Et_2O, 4:1) gave **35** as a colourless oil (203 mg, 79%, >98% de); R_f 0.14 (pentane/Et_2O, 4:1); $[\alpha]_D^{26} = +10.3$ (*c* 0.6 in $CHCl_3$); ν_{max} (film) 1741 (C=O), 1732 (C=O); δ_H (400 MHz, $CDCl_3$) 1.30 (3H, s, *Me*CMe), 1.44 (9H, s, C*Me*$_3$), 1.47 (3H, s, MeC*Me*), 2.01 (3H, s, CO*Me*), 2.28 (1H, dd, *J* 14.7, 8.0, C*H*$_A$H$_B$CO$_2$^{t}Bu), 2.44 (1H, dd, *J* 14.7, 4.4, CH$_A$*H*$_B$CO$_2$^{t}Bu), 3.11–3.15 (1H, m, C(2)*H*), 3.28–3.32 (1H, m, C(5)*H*), 3.86–3.96 (4H, m, C*H*$_2$OAc, NC*H*$_2$), 4.45 (1H, dd, *J* 6.3, 3.4, C(3)*H*), 4.55 (1H, dd, *J* 6.3, 3.6, C(4)*H*), 7.22–7.34 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.8 (CO*Me*), 25.5, 27.6 (C*Me*$_2$), 28.0 (C*Me*$_3$), 39.7 (*C*H$_2$CO$_2$^{t}Bu), 57.5 (NCH$_2$), 64.7 (*C*H$_2$OAc), 66.7 (*C*(5)), 67.6 (*C*(2)), 80.6 (*C*Me$_3$), 81.9 (*C*(3)), 83.7 (*C*(4)), 112.4 (*C*Me$_2$), 127.1 (*p-Ph*), 128.2, 128.7 (*o-*, *m-Ph*), 138.5 (*i-Ph*), 170.5, 170.7 (*C*OMe, *C*O$_2$^{t}Bu); *m/z* (APCI$^+$) 420 ([M+H]$^+$, 82%), 364 (100); HRMS (ESI$^+$) $C_{23}H_{34}NO_6^+$ ([M+H]$^+$) requires 420.2381; found 420.2390.



From **34**: NaOAc (16 mg, 0.2 mmol) was added to a stirred solution of **34** (58 mg, 0.13 mmol) in PhMe (2 mL), and the resultant suspension was stirred for 2 h. The solid residue was filtered off,

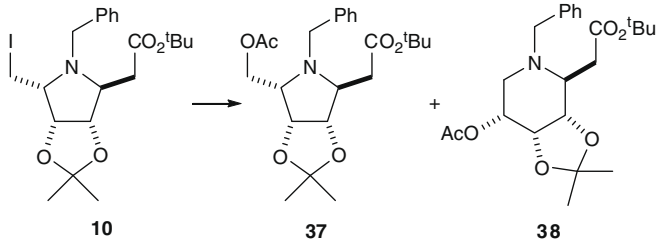
and the filtrate was concentrated in vacuo to give **35** in >98% de. Purification via flash column chromatography (eluent pentane/Et_2O, 4:1) gave **35** as a colourless oil (38 mg, 70%, >98% de).

4.2.13. (1*R*,2*S*,3*S*,4*R*,5*S*)-*N*(1)-Benzyl-2-(*tert*-butoxycarbonylmethyl)-3,4-*O*-isopropylidene-1-azoniabicyclo[3.1.0]hexane tetrafluoroborate 36



$AgBF_4$ (22 mg, 0.11 mmol) was added to a solution of **10** (46 mg, 0.09 mmol) in DCM (5 mL). The resultant solution was stirred for 2 h, filtered through Celite (eluent DCM) and concentrated in vacuo to give **36** as a colourless oil (42 mg, quant, >98% de); $[\alpha]_D^{22} = -8.4$ (*c* 1.4 in $CHCl_3$); ν_{max} (film) 1724 (C=O), 1634 (C=C); δ_H (400 MHz, $CDCl_3$) 1.30 (3H, s, *Me*CMe), 1.47 (3H, s, MeC*Me*), 1.51 (9H, s, CMe_3), 3.05 (1H, dd, *J* 7.9, *J* 4.2, C$H_AH_BCO_2{}^tBu$), 3.11 (1H, dd, *J* 18.6, 3.9, C(6)H_A), 3.20 (1H, dd, *J* 6.5, 4.2, $CH_AH_BCO_2{}^tBu$), 3.39 (1H, dd, *J* 18.6, 6.2, C(6)H_B), 3.74–3.80 (1H, m, C(2)*H*), 4.35 (1H, d, *J* 12.1, NCH_AH_BPh), 4.65 (1H, app t, *J* 4.6, C(5)*H*), 4.84–4.89 (2H, m, C(4)*H*, NCH_AH_BPh), 5.47 (1H, app t, *J* 5.6, C(3)*H*), 7.44–7.50 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 24.1, 25.9 (CMe_2), 27.9 (CMe_3), 35.0 (*C*(6)), 39.9 ($CH_2CO_2{}^tBu$), 53.7 (*C*(2)), 56.8 (NCH_2Ph), 71.0 (*C*(5)), 77.3 (*C*Me$_3$), 83.5 (*C*(3)), 86.4 (*C*(4)), 114.4 (*C*Me$_2$), 127.4, 129.7, 130.8, 131.8 (*Ph*), 169.6 ($CO_2{}^tBu$); *m/z* (ESI^+) 360 ($[M-BF_4]^+$, 100%), 304 (12); HRMS (ESI^+) $C_{21}H_{30}NO_4{}^+$ ($[M-BF_4]^+$) requires 360.2169; found 360.2182.

4.2.14. (2*S*,3*R*,4*S*,5*S*)-*N*(1)-Benzyl-2-acetoxymethyl-3,4-*O*-isopropylidene-5-(*tert*-butoxycarbonylmethyl)pyrrolidine 37 and (2*S*,3*S*,4*R*,5*R*)-*N*(1)-benzyl-2-(*tert*-butoxycarbonylmethyl)-3,4-*O*-isopropylidene-5-acetoxy-piperidine 38

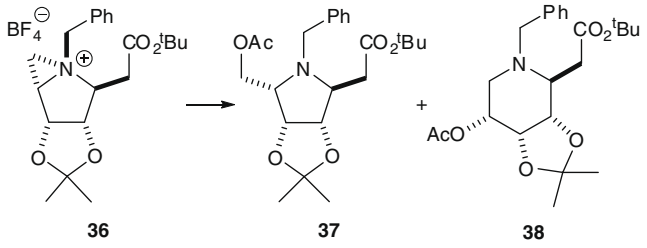


10 **37** **38**

From **10**: AgOAc (21 mg, 0.13 mmol) was added to a stirred solution of **10** (41 mg, 0.08 mmol) in PhMe (5 mL) at rt. After stirring for 2 h, the reaction mixture was filtered through Celite (eluent EtOAc) and concentrated in vacuo to give a 45:55 mixture of **37**:**38**. Purification via flash column chromatography (eluent pentane/Et_2O, 4:1) gave a 45:55 mixture of **37**:**38** as a colourless oil (29 mg, 82%); R_f 0.1 (pentane/Et_2O, 4:1); ν_{max} (film) 1732 (br, C=O); *m/z* ($APCI^+$) 420 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{34}NO_6{}^+$ ($[M+H]^+$) requires 420.2381; found 420.2392.

Data for **37**: δ_H (400 MHz, $CDCl_3$) 1.33 (3H, s, *Me*CMe), 1.40 (9H, s, CMe_3), 1.55 (3H, s, MeC*Me*), 2.03 (3H, s, CO*Me*), 2.01–2.06 (1H, m, C$H_AH_BCO_2{}^tBu$), 2.42–2.48 (1H, m, $CH_AH_BCO_2{}^tBu$), 3.03 (1H, app q, *J* 5.4, C(2)*H*), 3.45–3.51 (1H, m, C(5)*H*), 3.66 (1H, d, *J* 14.3, NCH_AH_BPh), 3.96 (1H, obsc d, NCH_AH_BPh), 4.19 (1H, dd, *J* 11.4, 5.4, CH_AH_BOAc), 4.31 (1H, dd, *J* 11.4, 5.8, CH_AH_BOAc), 4.56 (1H, app d, *J* 6.3, C(4)*H*), 4.72 (1H, dd, *J* 6.2, 5.3, C(3)*H*), 7.20–7.34 (5H, obsc m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.0 (CO*Me*), 25.3, 26.4 (CMe_2), 28.0 (CMe_3), 31.2 ($CH_2CO_2{}^tBu$), 51.2 (NCH_2), 62.7 (*C*(2), *C*(5)), 63.2 (CH_2OAc), 80.0 (*C*Me$_3$), 80.8 (*C*(3)), 82.5 (*C*(4)), 109.9 (*C*Me$_2$), 126.9 (*p-Ph*), 127.8, 128.3 (*o-*, *m-Ph*), 138.7 (*i-Ph*), 170.2, 171.2 (*C*OMe, $CO_2{}^tBu$).

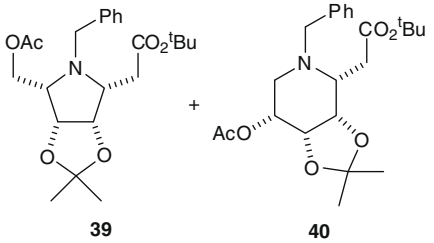
Data for **38**: δ_H (400 MHz, $CDCl_3$) 1.37 (3H, s, *Me*CMe), 1.45 (9H, s, CMe_3), 1.60 (3H, s, MeC*Me*), 2.04 (3H, s, CO*Me*), 2.36–2.44 (2H, m, C(6)H_A, C$H_AH_BCO_2{}^tBu$), 2.65–2.70 (2H, m, C(6)H_B, C$H_AH_BCO_2{}^tBu$), 2.95 (1H, app td, *J* 8.4, 3.8, C(2)*H*), 3.22 (1H, d, *J* 13.0, NCH_A), 3.96 (1H, obsc d, NCH_B), 4.06 (1H, dd, *J* 8.5, 4.6, C(3)*H*), 4.47 (1H, app t, *J* 4.4, C(4)*H*), 5.01–5.06 (1H, m, C(5)*H*), 7.20–7.34 (5H, m, obsc *Ph*); δ_C (100 MHz, $CDCl_3$) 21.1 (CO*Me*), 25.5, 26.4 (CMe_2), 28.0 (CMe_3), 37.2 ($CH_2CO_2{}^tBu$), 49.1 (*C*(6)), 56.4 (NCH_2), 60.6 (*C*(2)), 67.7 (*C*(5)), 72.9 (*C*(4)), 77.3 (*C*(3)), 81.9 (*C*Me$_3$), 111.8 (*C*Me$_2$), 127.1 (*p-Ph*), 128.4, 128.5 (*o-*, *m-Ph*), 138.9 (*i-Ph*), 170.8, 171.3 (*C*OMe, $CO_2{}^tBu$).



36 **37** **38**

From **36**: NaOAc (16 mg, 0.2 mmol) was added to a stirred solution of **36** (42 mg, 0.09 mmol) in PhMe (3 mL), and the resultant suspension was stirred for 2 h. The solid residue was filtered off, and the filtrate was concentrated in vacuo to give a 45:55 mixture of **37**:**38**. Purification via flash column chromatography (eluent pentane/Et_2O, 4:1) gave **a** 45:55 mixture of **37**:**38** as a colourless oil (24 mg, 62%).

4.2.15. (2*S*,3*R*,4*S*,5*R*)-*N*(1)-Benzyl-2-acetoxymethyl-3,4-*O*-isopropylidene-5-(*tert*-butoxycarbonylmethyl)pyrrolidine 39 and (2*R*,3*S*,4*R*,5*R*)-*N*(1)-benzyl-2-(*tert*-butoxycarbonylmethyl)-3,4-*O*-isopropylidene-5-acetoxy-piperidine 40

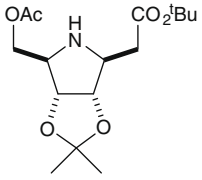


39 **40**

AgOAc (115 mg, 0.69 mmol) was added to a stirred solution of **26** (223 mg, 0.46 mmol) in PhMe (10 mL) at rt. After stirring for 2 h, the reaction mixture was filtered through Celite (eluent EtOAc) and concentrated in vacuo to give an 89:11 mixture of **39**:**40**. Purification via flash column chromatography (eluent pentane/Et_2O, 5:1) gave a **39** as a white solid (169 mg, 88%, >98% de); R_f 0.18 (pentane/Et_2O, 4:1); $C_{23}H_{33}NO_6$ requires C, 65.85; H, 7.9; N, 3.3. Found: C, 65.75; H, 7.9; N, 3.4; mp 60–61 °C (pentane/Et_2O); $[\alpha]_D^{25} = +10.1$ (*c* 0.5 in $CHCl_3$); ν_{max} (film) 1733 (C=O), 1726 (C=O), 1602 (C=C); δ_H (400 MHz, $CDCl_3$) 1.33 (3H, s, *Me*CMe), 1.43 (9H, s, CMe_3), 1.52 (3H, s, MeC*Me*), 2.00 (3H, s, CO*Me*), 2.42 (1H, dd, *J* 16.4, 3.9, C$H_AH_BCO_2{}^tBu$), 2.63–2.71 (2H, m, C(2)*H*, $CH_AH_BCO_2{}^tBu$), 2.82–2.87 (1H, m, C(5)*H*), 3.77 (2H, app s, NCH_2), 4.17 (1H, dd, *J* 11.1, 7.4, CH_AH_BOAc), 4.25 (1H, dd, *J* 11.1, 4.8,

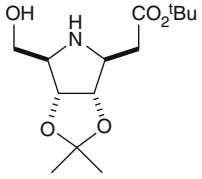
CH_AH_BOAc), 4.61 (1H, dd, *J* 6.5, 4.9, C(3)*H*), 4.69 (1H, dd, *J* 6.5, 4.9, C(4)*H*), 7.21–7.31 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.0 (CO*Me*), 25.6, 26.2 (C*Me*$_2$), 28.1 (C*Me*$_3$), 34.2 (*C*$H_2CO_2{}^t$Bu), 54.9 (NCH_2), 62.5 (*C*H_2OAc), 64.3 (*C*(5)), 66.0 (*C*(2)), 78.8 (*C*(3)), 79.2 (*C*(4)), 80.4 (*C*Me$_3$), 111.4 (*C*Me$_2$), 126.9 (*p-Ph*), 128.1, 128.2 (*o-*, *m-Ph*), 138.6 (*i-Ph*), 170.8, 171.4 (*C*OMe, *C*$O_2{}^t$Bu); *m/z* (ESI$^+$) 442 ([M+Na]$^+$, 80%), 420 (89), 364 (100); HRMS (ESI$^+$) $C_{23}H_{34}NO_6{}^+$ ([M+H]$^+$) requires 420.2381; found 420.2387. Further elution gave **40** as a colourless oil (21 mg, 10%, >98% de); R_f 0.11 (pentane/Et_2O, 4:1); $[\alpha]_D^{24} = -11.1$ (*c* 0.7 in $CHCl_3$); ν_{max} (film) 1733 (C=O); δ_H (400 MHz, $CDCl_3$) 1.36 (3H, s, *Me*CMe), 1.46 (9H, s, C*Me*$_3$), 1.59 (3H, s, MeC*Me*), 2.08 (3H, s, CO*Me*), 2.40 (1H, dd, *J* 12.3, 3.9, C(6)H_A), 2.65 (1H, dd, *J* 16.3, 5.6, $CH_AH_BCO_2{}^t$Bu), 2.75 (1H, dd, *J* 16.3, 7.6, $CH_AH_BCO_2{}^t$Bu), 2.91 (1H, dd, *J* 12.3, 8.3, C(6)H_B), 3.29–3.33 (1H, m, C(2)*H*), 3.57 (1H, d, *J* 14.0, NCH_AH_BPh), 3.85 (1H, d, *J* 14.0, NCH_AH_BPh), 4.41–4.46 (2H, m, C(3)*H*, C(4)*H*), 4.95–4.99 (1H, m, C(5)*H*), 7.22–7.35 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.3 (CO*Me*), 24.8, 26.2 (C*Me*$_2$), 28.1 (C*Me*$_3$), 36.1 (*C*$H_2CO_2{}^t$Bu), 46.9 (*C*(6)), 56.0 (*C*(2)), 57.7 (NCH_2Ph), 66.9 (*C*(5)), 71.9, 75.0 (*C*(3), *C*(4)), 80.7 (*C*Me$_3$), 109.4 (*C*Me$_2$), 127.1 (*p-Ph*), 128.1, 128.6 (*o-*, *m-Ph*), 138.9 (*i-Ph*), 170.5, 171.6 (*C*OMe, *C*$O_2{}^t$Bu); *m/z* (ESI$^+$) 442 ([M+Na]$^+$, 20%), 420 (100); HRMS (ESI$^+$) $C_{23}H_{34}NO_6{}^+$ ([M+H]$^+$) requires 420.2381; found 420.2374.

4.2.16. (2*R*,3*R*,4*S*,5*S*)-2-Acetoxymethyl-3,4-*O*-isopropylidene-5-(*tert*-butoxycarbonylmethyl)pyrrolidine 41



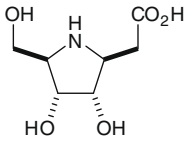
Compound **35** (370 mg, 0.88 mmol) was dissolved in MeOH (15 mL), and the resultant solution was degassed. $Pd(OH)_2$/C (120 mg) was added and the mixture was placed under H_2 (1 atm). After stirring for 15 h, the reaction mixture was filtered through Celite (eluent MeOH) and concentrated in vacuo. Purification via flash column chromatography (eluent pentane/Et_2O, 2:1; containing 2% Et_3N) gave **41** as a colourless oil (191 mg, 66%, >98% de); R_f 0.2 (pentane/Et_2O, 1:1); $[\alpha]_D^{24} = -19.2$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3355 (N–H), 1743 (C=O), 1729 (C=O); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, s, *Me*CMe), 1.45 (9H, s, C*Me*$_3$), 1.51 (3H, s, MeC*Me*), 2.08 (3H, s, CO*Me*), 2.38 (1H, dd, *J* 16.4, 9.1, $CH_AH_BCO_2{}^t$Bu), 2.66 (1H, dd, *J* 16.4, 4.1, $CH_AH_BCO_2{}^t$Bu), 3.38–3.44 (2H, m, C(2)*H*, C(5)*H*), 4.02 (1H, dd, *J* 11.4, 7.1, C(3)*H*), 4.21–4.27 (2H, m, C(4)*H*, CH_AH_BOAc), 4.35 (1H, dd, *J* 6.8, 4.4, CH_AH_BOAc); δ_C (100 MHz, $CDCl_3$) 21.3 (CO*Me*), 25.8, 27.8 (C*Me*$_2$), 28.5 (C*Me*$_3$), 40.1 (*C*$H_2CO_2{}^t$Bu), 60.9 (*C*(5)), 62.7 (*C*(2)), 66.5 (*C*H_2OAc), 81.4 (*C*Me$_3$), 82.2 (*C*(4)), 84.4 (*C*(3)), 114.4 (*C*Me$_2$), 171.3, 171.7 (*C*OMe, *C*$O_2{}^t$Bu); *m/z* (CI$^+$) 330 ([M+H]$^+$, 100%), 274 (42); HRMS (CI$^+$) $C_{16}H_{28}NO_6{}^+$ ([M+H]$^+$) requires 330.1911; found 330.1914.

4.2.17. (2*R*,3*R*,4*S*,5*S*)-2-Hydroxymethyl-3,4-*O*-isopropylidene-5-(*tert*-butoxycarbonylmethyl)pyrrolidine 42



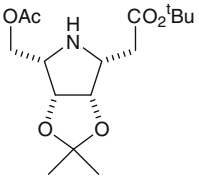
K_2CO_3 (55 mg, 0.4 mmol) was added to a stirred solution of **41** (130 mg, 0.4 mmol) in MeOH (12 mL). After stirring for 2 h, satd aq NH_4Cl (12 mL) was added. The mixture was extracted with EtOAc (2 × 15 mL), and the combined organic layers were dried and concentrated in vacuo. Purification via flash column chromatography (eluent $CHCl_3$/MeOH/Et_3N, 80:1:1) gave **42** as a white crystalline solid (94 mg, 82%, >98% de); mp 55–60 °C ($CHCl_3$/MeOH); $[\alpha]_D^{22} = -37.2$ (*c* 1.6 in $CHCl_3$); ν_{max} (KBr) 3444 (O–H), 3130 (N–H), 1721 (C=O); δ_H (400 MHz, $CDCl_3$) 1.30 (3H, s, *Me*CMe), 1.44 (9H, s, C*Me*$_3$), 1.50 (3H, s, MeC*Me*), 2.43 (1H, dd, *J* 16.3, 9.6, $CH_AH_BCO_2{}^t$Bu), 2.66 (1H, dd, *J* 16.3, 4.5, $CH_AH_BCO_2{}^t$Bu), 3.41–3.47 (3H, m, C(2)*H*, O*H*, N*H*), 3.49–3.55 (1H, m, C(5)*H*), 3.60 (1H, app dd, *J* 11.4, 4.8, CH_AH_BOH), 3.69 (1H, app dd, *J* 11.4, 4.1, CH_AH_BOH), 4.26 (1H, app t, *J* 6.4, C(4)*H*), 4.52 (1H, dd, *J* 6.7, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 25.2, 27.3 (C*Me*$_2$), 28.1 (C*Me*$_3$), 39.5 (*C*$H_2CO_2{}^t$Bu), 60.7 (*C*(5)), 62.1 (*C*H_2OH), 64.6 (*C*(2)), 81.2 (*C*Me$_3$), 81.6 (*C*(3)), 84.0 (*C*(4)), 113.5 (*C*Me$_2$), 171.1 (*C*$O_2{}^t$Bu); *m/z* (APCI$^+$) 288 ([M+H]$^+$, 35%), 232 (100); HRMS (ESI$^+$) $C_{14}H_{26}NO_5{}^+$ ([M+H]$^+$) requires 288.1805; found 288.1812.

4.2.18. (2′*R*,3′*R*,4′*S*,5′*S*)-(2′-Hydroxymethyl-3′,4′-dihydroxypyrrolidin-5′-yl)ethanoic acid 43



Compound **42** (130 mg, 0.45 mmol) was dissolved in TFA (5 mL). The resultant solution stirred for 3 h, diluted with H_2O (3.3 mL), stirred for a further 1 h and concentrated in vacuo. Ion-exchange chromatography (DOWEX 50WX8-200, eluent 1 M aq NH_4OH) gave **43** as a white solid (67 mg, 78%, >98% de); mp 166–167 °C (H_2O); $[\alpha]_D^{24} = +20.3$ (*c* 0.9 in H_2O); ν_{max} (KBr) 3370–2337 (O–H, N–H), 1651 (N–H bend), 1560 ($CO_2{}^-$); δ_H (500 MHz, D_2O) 2.51 (1H, dd, *J* 17.2, 6.9, $CH_AH_BCO_2H$), 2.63 (1H, dd, *J* 17.2, 4.9, $CH_AH_BCO_2H$), 3.55–3.57 (1H, m, C(2′)*H*), 3.66–3.74 (2H, m, C(5′)*H*, CH_AH_BOH), 3.80–3.83 (1H, m, CH_AH_BOH), 3.97–3.99 (1H, m, C(4′)*H*), 4.11–4.14 (1H, m, C(3′)*H*); δ_C (125 MHz, D_2O) 35.3 (*C*H_2CO_2H), 58.5 (*C*H_2OH), 60.2 (*C*(5′)), 64.3 (*C*(2′)), 70.4 (*C*(3′)), 73.1 (*C*(4′)), 177.8 (*C*O_2H); *m/z* (ESI$^+$) 192 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_7H_{14}NO_5{}^+$ ([M+H]$^+$) requires 192.0866; found 192.0880.

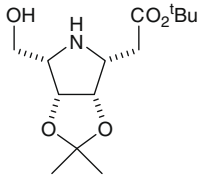
4.2.19. (2*S*,3*R*,4*S*,5*R*)-2-Acetoxymethyl-3,4-*O*-isopropylidene-5-(*tert*-butoxycarbonylmethyl)pyrrolidine 44



Compound **39** (32 mg, 0.08 mmol) was dissolved in MeOH (5 mL), and the resultant solution was degassed. $Pd(OH)_2$/C (15 mg) was added and the mixture was placed under H_2 (1 atm). After stirring for 15 h, the reaction mixture was filtered through Celite (eluent MeOH) and concentrated in vacuo to give **44** as a colourless oil (25 mg, 99%, >98% de); $[\alpha]_D^{25} = +4.0$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3439 (N–H), 1732 (C=O); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, s, *Me*CMe), 1.43 (3H, s, MeC*Me*), 1.44 (9H, s, C*Me*$_3$), 2.06

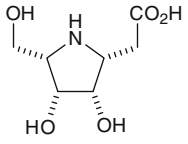
(3H, s, CO*Me*), 2.10 (1H, br s, N*H*), 2.53–2.64 (2H, m, C$H_2CO_2{}^t$Bu), 3.03–3.08 (1H, m, C(2)*H*), 3.10–3.14 (1H, m, C(5)*H*), 4.17 (1H, dd, *J* 11.4, 7.6, CH_AH_BOAc), 4.33 (1H, dd, *J* 11.4, 5.3, CH_AH_BOAc), 4.57–4.61 (2H, m, C(3)*H*, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 21.0 (CO*Me*), 24.3, 25.7 (CMe_2), 28.1 (CMe_3), 34.9 (C$H_2CO_2{}^t$Bu), 58.1 (*C*(5)), 60.3 (*C*(2)), 63.5 (CH_2OAc), 80.5, 81.3 (*C*(3), *C*(4)), 80.7 (*C*Me$_3$), 111.4 (*C*Me$_2$), 170.9, 171.6 (*C*OMe, $CO_2{}^t$Bu); *m/z* (ESI$^+$) 352 ([M+Na]$^+$, 20%), 330 (100), 274 (30); HRMS (ESI$^+$) $C_{16}H_{28}NO_6{}^+$ ([M+H]$^+$) requires 330.1911; found 330.1916.

4.2.20. (2*S*,3*R*,4*S*,5*R*)-2-Hydroxymethyl-3,4-*O*-isopropylidene-5-(*tert*-butoxycarbonylmethyl)pyrrolidine 45



K_2CO_3 (36 mg, 0.26 mmol) was added to a stirred solution of **44** (85 mg, 0.26 mmol) in MeOH (5 mL). After stirring for 2 h, satd aq NH_4Cl (5 mL) was added. The mixture was extracted with EtOAc (2 × 15 mL), and the combined organic layers were dried and concentrated in vacuo to give **45** as a colourless oil (73 mg, 94%, >98% de); $[\alpha]_D^{25} = -12.8$ (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3350 (br, O–H, N–H), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, s, *Me*CMe), 1.44 (9H, s, C*Me*$_3$), 1.49 (3H, s, MeC*Me*), 2.66 (1H, dd, *J* 16.9, 6.4, C$H_AH_BCO_2{}^t$Bu), 2.74 (1H, dd, *J* 16.9, 7.8, C$H_AH_BCO_2{}^t$Bu), 3.13 (1H, app q, *J* 4.6, C(2)*H*), 3.32 (1H, app td, *J* 7.2, 3.3, C(5)*H*), 3.90 (1H, dd, *J* 12.2, 4.7, CH_AH_BOH), 3.97–4.01 (3H, m, CH_AH_BO*H*, N*H*), 4.69–4.73 (2H, m, C(3)*H*, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 23.8, 25.5 (CMe_2), 28.1 (CMe_3), 33.8 (C$H_2CO_2{}^t$Bu), 58.2 (*C*(5)), 60.2 (CH_2OH), 62.8 (*C*(2)), 81.0 (*C*Me$_3$), 81.2, 81.5 (*C*(3), *C*(4)), 111.5 (*C*Me$_2$), 170.7 ($CO_2{}^t$Bu); *m/z* (ESI$^+$) 310 ([M+Na]$^+$, 20%), 288 (100), 232 (30); HRMS (ESI$^+$) $C_{14}H_{26}NO_5{}^+$ ([M+H]$^+$) requires 288.1805; found 288.1820.

4.2.21. (2′*S*,3′*R*,4′*S*,5′*R*)-(2′-Hydroxymethyl-3′,4′-dihydroxypyrrolidin-5′-yl)ethanoic acid 46



Compound **45** (45 mg, 0.16 mmol) was dissolved in TFA (2 mL). The resultant solution was stirred for 3 h, diluted with H_2O (1.3 mL), stirred for a further 1 h and concentrated in vacuo. Ion-exchange chromatography (DOWEX 50WX8-200, eluent 1 M aq NH_4OH) gave **46** as a white solid (14 mg, 47%, >98% de); mp 168–170 °C (H_2O); $[\alpha]_D^{23} = -30.3$ (*c* 0.8 in H_2O); ν_{max} (KBr) 2368–3322 (O–H, N–H), 1626 (N–H bend), 1569 ($CO_2{}^-$); δ_H (500 MHz, D_2O) 2.65 (1H, dd, *J* 16.8, 7.5, C$H_AH_BCO_2H$), 2.74 (1H, dd, *J* 16.8, 6.7, C$H_AH_BCO_2H$), 3.78 (1H, app td, *J* 7.0, 5.0, C(2′)*H*), 3.82–3.88 (2H, m, C(5′)*H*, CH_AH_BOH), 3.94 (1H, dd, *J* 12.2, 4.9, CH_AH_BOH), 4.36 (1H, app t, *J* 4.7, C(4′)*H*), 4.50 (1H, dd, *J* 6.8, 4.7, C(3′)*H*); δ_C (125 MHz, D_2O) 34.2 (CH_2CO_2H), 58.3 (*C*(5′)), 58.5 (CH_2OH), 61.4 (*C*(2′)), 70.4 (*C*(3′)), 71.0 (*C*(4′)), 178.0 (CO_2H); *m/z* (ESI$^-$) 190 ([M–H]$^-$, 100%); HRMS (ESI$^-$) $C_7H_{12}NO_5{}^-$ ([M–H]$^-$) requires 190.0721; found 190.0714.

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