***SHORT PAPER***

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# Synthesis of chiral polyfunctionalised cyclopentanes from the Diels–Alder adduct of furan and maleic anhydride†

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Chiral polyfunctionalised cyclopentanes have been readily obtained in ~65% enantiomeric excess via a stereospecific Wagner–Meerwein rearrangement induced by bromination of derivatives of the *exo-cis* Diels–Alder adduct of furan and maleic anhydride, combined with desymmetrisation of a *meso* intermediate by pig liver esterase.

Chiral precursors are essential in modern synthesis and hence much research effort has been devoted to increasing the chiral pool by treating *meso* compounds with enzymes and other asymmetric reagents. Again, for many years Diels–Alder additions have been widely used as a reliable way of controlling stereochemistry at two or more centres in ring synthesis. Here we describe a synthesis of chiral, functionalised cyclopentanes from achiral starting materials, which combines a stereospecific Wagner–Meerwein rearrangement of the *exo-cis* Diels–Alder adduct of furan and maleic anhydride with desymmetrisation of a *meso* intermediate by pig liver esterase.

Our approach is based on the original work that Woodward and Baer[1] carried out to correct an erroneous report by Diels and Alder[2] that an adduct obtained by reacting furan **1** and maleic anhydride **2** in diethyl ether had *endo-cis* stereochemistry. From a sequence of chemical transformations, Woodward and Baer showed the anhydride to be the *exo-cis* stereoisomer **3**, in contrast to the *endo-cis* product from maleic acid. *Inter alia*, a crucial observation was that reacting the anhydride with alkali and subsequent addition of bromine afforded the tricyclic bromolactonic acid **4** *via* a Wagner-Meerwein rearrangement that was not feasible with the *endo* isomer. Cleavage of the ether ring and esterification with methanol and acid yielded the so-called 'pseudo-ester' **6**. We were intrigued by the array of different functionality and defined stereochemistry around the cyclopentane rings in **4** and **6**, which was reminiscent of natural products such as iridoids, and considered that they were potential precursors to a range of interesting novel cyclopentane structures. Hence we have investigated the potential application of this rearrangement in synthesis and, in particular, explored possible routes for enantioselection.

Repetition of the above work[1] gave in good yield the previously characterised compounds **3**–**6**, whose structures were corroborated by MS, IR and NMR spectra. On one occasion, bromination of **3** gave an additional product, characterised as its methyl ester, mp 175 °C, which was shown by an X-ray structure[5] determination to be the bromolactone **7**. This was evidently derived from an *endo-cis* adduct of furan and maleic acid formed *via* a *retro*-Diels-Alder reaction, which could be avoided by keeping the temperature well below 10 °C throughout.

In order to achieve a chiral synthesis of **5** and **6** we anticipated that a modification to the route would be required by carrying out the bromolactonisation on the salt of a mono-acid rather than the diacid, and this was tested on racemic material. Thus stirring the anhydride **3** in methanol overnight gave the mono-acid **8** in quantitative yield. Bromination of **8** in aqueous alkali as in the literature method[1] gave the bromolactone **5** in moderate yield, but use of chloroform and anhydrous potassium carbonate improved the yield to 86%. Conversion of **5** to the pseudo-ester **6** was then achieved in 73% yield with thionyl chloride in methanol.

Since this modification was satisfactory, we now turned to the task of introducing chirality, and lipase or esterase enzymes seemed to be best suited for our purpose. Indeed, pig liver esterase (PLE) has been used to perform stereoselective transformations in good yield and enantiomeric excess (e.e.) on the prochiral *meso* dimethyl ester to give the 1*R*, 2*S*, 3*R*, 4*S* monoacid **8**.

After some experimentation, the diester **9** was obtained in 47% yield from **3** using sodium methoxide and dimethyl sulphate.[4] It was then treated with PLE in aqueous pH 7 buffer at 30 °C for 24 hours, and the isolated product was recrystallised once from cyclohexane/ethyl acetate to give the optically active mono-acid **8** mp 107–109° $[\alpha]_D^{20}$ –9.1° (45 mg/ml, $CHCl_3$) (lit[3], mp 110° $[\alpha]_D^{20}$ –10.6°) in 65% yield. An X-ray crystal structure[5] confirmed that the *exo* configuration had been retained, and thus that there had been no alteration of stereochemistry *via retro* Diels-Alder reaction to give *endo* adducts such as we had observed above. The optically active bromolactone ester **5** was then formed using both methods described above. Again, the non-aqueous route gave a better yield (78%) than the aqueous (69%) after recrystallisation from methanol, with the same optical rotation $[\alpha]_D^{20}$ –10.0° (100 mg/ml, $CH_2Cl_2$) for the product. Nevertheless, the latter route was more convenient to use on a larger scale, since the bromolactonisation could be carried out directly in the solution used for enzymatic hydrolysis, without the need for isolation of the intermediate mono-ester, and in rather better overall yield. Finally the corresponding pseudo-ester **6** was obtained as above in good yield with an optical rotation of $[\alpha]_D^{20}$ –25°(100 mg/ml, $CHCl_3$).

In all cases the e.e. was estimated at 65% from the the $^1H$ NMR spectrum, using the europium(III) tris[3-(heptafluoropropylmethylene)-(+)-camphorato] chiral shift reagent. In view of the fact that Bloch *et al*.[3] apparently attained 98% do not consider that the optimum e.e. has yet been attained. It appears to depend upon precise maintenance of the pH of the solution at 7.0, since as the reaction proceeds, the solution becomes acidic and this results in loss of optical activity. In these preliminary experiments we attempted to correct this by periodic manual addition of alkali, but it would obviously be better to do this on a continuous basis by use of an automatic pH controller.

The cyclopentane ring of **6** has five chiral centres, each with a different functionality, and some transformations have been

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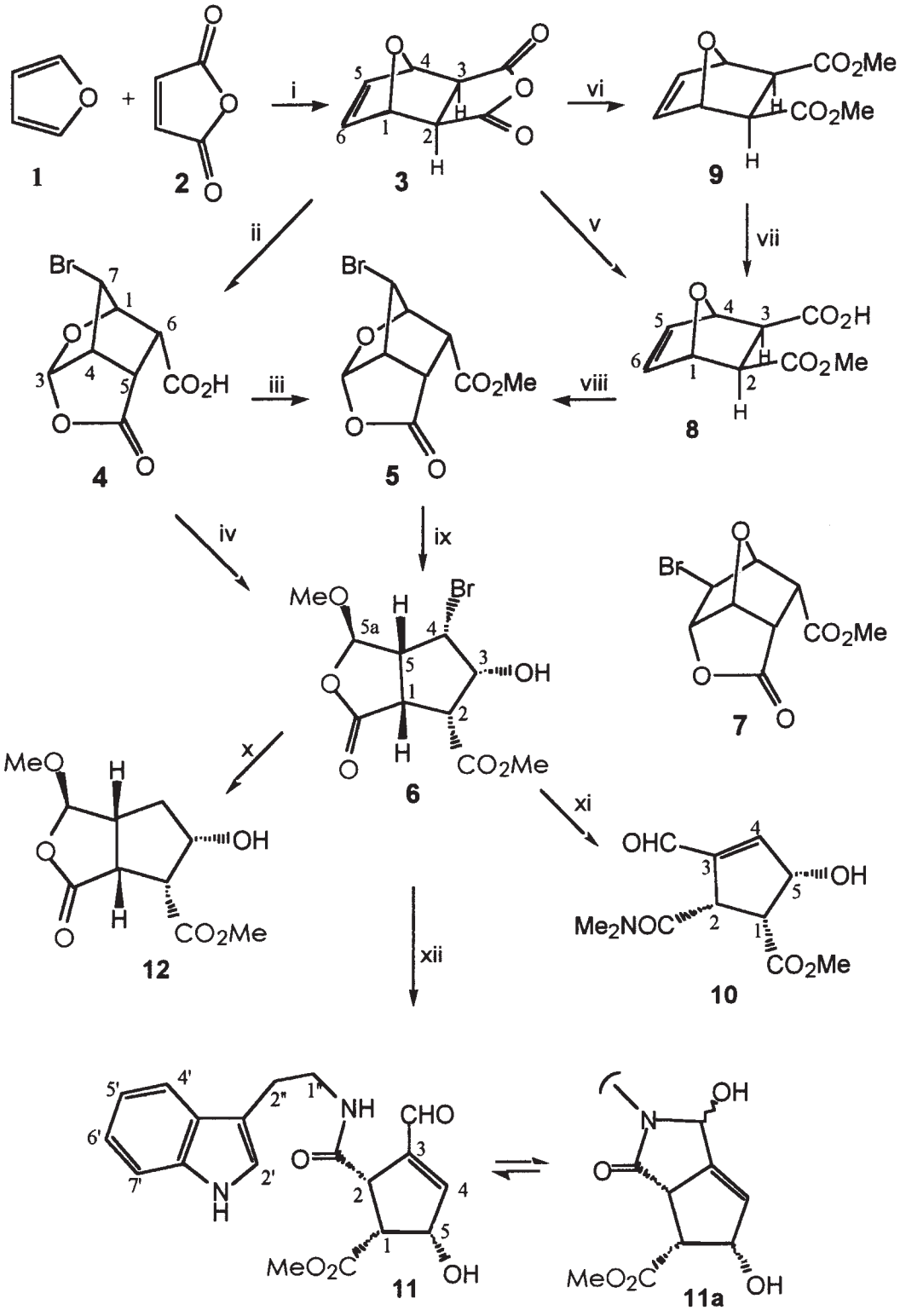

Reagents (yields)
i) $Et_2O$, 4-6°C, 18 h (66%); ii) aq. NaOH, $Br_2$, <10°C, 30 min (92%); iii) MeOH, $SOCl_2$,18 h (81%); iv) MeOH, f. $H_2SO_4$, D, 3 h (73%); v) MeOH, 18 h (100%); vi) NaOMe, MeOH, $Me_2SO_4$, 18 h (47%); vii) PLE, pH 7 aq. buffer, 30∞C, 24 h (86%); viii) $CHCl_3$, $K_2CO_3$, $Br_2$, 0°C, 3 h (78%); ix) MeOH, $SOCl_2$, D, 2 h (77%); x) Raney Ni/$H_2$, MeOH, 48 h (87%); xi) $Me_2NH$, $CHCl_3$, 0°C, 2 h (71%); xii) tryptamine, $CHCl_3$, 5 d (45%).

**Scheme 1**

explored. Not surprisingly, it has been found to be very labile to alkali, with rearrangement to several products after cleavage of the lactone and elimination of hydrogen bromide. However, controlled opening of the lactone occurs with amines such as dimethylamine and tryptamine which give **10** and **11** respectively in fair yields. The latter cyclises reversibly to the aminol **11a** in presence of a trace of acid. Removal of the bromine at C-6 by hydrogenolysis with Raney nickel affords the less labile compound **12**. Use of these products for the synthesis of a range of known and novel structures is under investigation.

## Experimental

exo-cis-*7-oxabicyclo[2.2.1]hept-5-ene-1,2-dicarboxylic anhydride* **3**: Prepared as in ref. 1 (66%), mp 125 °C (lit.[1] 125 °C); $\nu_{max}$(film): 3050, 1860, 1795 cm$^{-1}$; *m/z* (CI): 184 (M+$NH_4^+$); $\delta_H$ (300 MHz, $CDCl_3$): 6.79 (2H, d, *J* 2 Hz, H-5, 6), 5.68 (2H, d, *J* 2 Hz, H-1, 4), 3.42 (2H, s, H-2, 3). Found: C, 57.8; H, 3.6. $C_8H_6O_4$ requires: C, 57.8; H, 3.6.

*5,6,7*-endo-*7-bromo-6-carboxy-2-oxabicyclo[2.2.1]heptane-5,3-carbolactone* **4**: Prepared as in ref. 1 (92%), m.p. 153 °C (lit.[1] 153 °C); $\nu_{max}$(film): 3200-2500, 1765, 1720 cm$^{-1}$; *m/z* (EI): 265/263 ($MH^+$), 246/244, 183, 137, 111; $\delta_H$ (300 MHz, $d_6$-DMSO): 5.95 (1H, d, *J* 5 Hz, H-3), 3.52 (1H, bs, H-5), 3.45 (1H, t, *J* ~2 Hz, H-6), 3.32 (1H, m, H-4), 2.94 (1H, m, H-1), 2.46 (1H, t, *J* ~5 Hz, H7). Found: $M^+$ 262.9551. Calc. for $C_8H_5O_5{}^{79}Br$: 262.9555.

*5,6,7*-endo-*7-Bromo-6-methoxycarbonyl-2-oxabicyclo[2.2.1]heptane-5,3-carbolactone* **5**: Prepared as in ref. 1 (81%), mp 168 °C (lit.[1] 168 °C); $\nu_{max}$(film): 1796, 1736 cm$^{-1}$; *m/z* (EI): 279/277 ($MH^+$), 247/245, 197, 179, 165, 148/146, 137, 125, 113, 109; $\delta_H$ (300 MHz, $CDCl_3$): 6.08 (1H, d, *J* 5 Hz, H-3), 4.73 (1H, bs, H-5), 4.28 (1H, d, *J* 2 Hz, H-6), 3.75 (3H, s, $CO_2$Me), 3.48 (1H, m, *J* 5, 5 Hz H-4), 3.24 (1H, dd, *J* 10, 2 Hz H-1), 3.04 (1H, dd, *J* 10, 5 Hz, H7). Found: $M^+$ 276.9717. Calc. for $C_8H_5O_5{}^{79}Br$: 276.9712.

*1,2,3,4,5*-cis-*5a*-trans-*4-Bromo-3-hydroxy-2-methoxycarbonyl-5-methoxymethylcyclopentane-1,5a-carbolactone ('pseudo-ester')* **6**: Prepared as in ref. 1 (73%), m.p. 162 °C (lit.[1] 163 °C); $\nu_{max}$(film): 3520, 1760, 1723 cm$^{-1}$; *m/z* (EI): 311/309 ($MH^+$), 282/280, 248/246, 193, 165, 137, 111; $\delta_H$ (300 MHz, $CDCl_3$): 5.60 (1H, d, *J* 2 Hz, H-4), 4.52 (1H, dd *J* 9, 4 Hz, H-6), 4.35 (1-H, t, *J* 4 Hz, H-7), 3.75 (3H, s, $CO_2$Me), 3.52 (1H, t, *J* 4 Hz, H-1), 3.51 (3H, s, OMe), 3.35 (1H, t, *J* 4 Hz, H-8), 3.20 (1H, td, *J* 9, 2 Hz, H-5), 2.60 (1H, bs, OH). Found: $M^+$ 308.9976. Calc. for $C_{10}H_{13}O_6{}^{79}Br$: 308.9974.

*1,2,3,4,5*-cis-*5a*-trans-*3-hydroxy-2-methoxycarbonyl-5-methoxymethylcyclopentane-1,5a-carbolactone* **12**: The pseudo-ester **6** (5.0 g) in methanol (50 ml) was treated for 48 hours under hydrogen (60 psi) in presence of Raney nickel catalyst (~1 g). After filtration through Celite, evaporation and chromatography on silica, the debrominated product **12** (3.25 g, 87%) was obtained as white crystals, mp 123 °C; $\nu_{max}$(film): 3500, 1772, 1725 cm$^{-1}$; *m/z* (EI): 230 ($M^+$), 199, 154, 139, 124, 109; $\delta_H$ (300 MHz, $CDCl_3$): 5.29 (1H, d, *J* 3 Hz, H-4), 4.45 (1H, m, H-7), 3.84 (3H, s, $CO_2$Me), 3.50 (3H, s, OMe), 3.43 (1H, t, *J* 9 Hz, H-1), .2.93 (1H, dd, *J* 9, 3 Hz, H-8), 2.84 (1H, tq, *J* 9, 3 Hz, H-5), 1.98 (1H, dd, *J* 15, 5 Hz, H-$6_a$), ), 1.95 (1H, dd, *J* 15, 2 Hz, H-$6_b$). Found: $M^+$ 230.0788. Calc. for $C_{10}H_{14}O_6$: 230.0790.

*Racemic* exo-cis-*3-methoxycarbonyl-7-oxabicyclo[2.2.1]hept-2-ene-2-carboxylic acid* **8**: The adduct **3** (10.0 g, 60 mmol) was stirred with methanol (50 ml) overnight, and the solvent then removed under reduced pressure to afford racemic mono-acid **8** as an amorphous white solid (11.9 g, 100%); $\nu_{max}$(film): 3470, 1750, 1733 cm$^{-1}$; *m/z* (CI): 216 (M+$NH_4^+$), 148, 131; $\delta_H$ (200 MHz, $CDCl_3$): 8.73 (1H, bs, OH), 6.48 (2H, s, H-5, 6), 5.35 (1H, s, H-3), 5.27 (1H, s, H-2), 3.73 (3H, s, $CO_2$Me), 2.88 (2H, s, H-1, 4).

*Chiral* exo-cis-*3-methoxycarbonyl-7-oxabicyclo[2.2.1]hept-2-ene-2-carboxylic acid* **8**: To a stirred solution of the adduct **3** (5.0 g, 30 mmol) in methanol (25 ml), sodium methoxide (1.6 g, 30 mmol) and dimethyl sulphate (3.0 ml, 30 mmol) were added sequentially and the mixture then left overnight. After neutralisation by addition of solid sodium bicarbonate with cooling, most of the solvent was removed *in vacuo*. The residue was taken up in chloroform (25 ml), which was washed with water, dried, filtered and evaporated *in vacuo* to give the dimethyl ester **9** as an amorphous white solid (2.98 g, 47%). ); $\nu_{max}$(film): 1750 cm$^{-1}$; *m/z* (CI): 230 (M+$NH_4^+$), 162, 145; $\delta_H$ (200 MHz, $CDCl_3$): 6.45 (2H, bs, H-5, 6), 5.26 (2H, bs, H-1, 4), 3.7 (6H, s, 2 $CO_2$Me), 2.82 (2-H, bs, H-1, 4).

The dimethyl ester (1.06 g, 5 mmol) was incubated with pig liver esterase (Sigma, ~2 mg) at 30 °C in pH 7 buffer (25 ml). The pH was maintained at 7 by addition of 1M sodium hydroxide at 10 minute intervals for 8 hours, and then the solution was left overnight. By the morning the pH had dropped to 5.7, the solution was acidified to pH 4 and extracted with ethyl acetate (3 × 50 ml). Evaporation of the dried extract under reduced pressure and reprecipitation from ethyl acetate/ cyclohexane afforded the chiral mono-acid **8** (0.64 g, 65%) $[\alpha]_D{}^{20}$ –9.1° (45 mg/ml, $CHCl_3$) with spectroscopic data identical to the above racemate.

*5,6,7*-endo-*7-bromo-6-methoxycarbonyl-2-oxabicyclo[2.2.1]heptane-5,3-carbolactone* **5**: A solution of the racemic mono-acid **8** (0.7 g, 3.5 mmol) in chloroform (10 ml) was stirred at 0 °C with anhydrous potassium carbonate (0.54 g, 3.9 mmol) while bromine (0.20 ml, 3.9 mmol) in chloroform (2 ml) was added dropwise. The stirred reaction mixture was left to warm up to room temperature over 3 hours, with addition of more potassium carbonate (0.5 g). The chloroform solution was washed with water (10 ml), dried and evaporated *in vacuo*. Flash chromatography of the residue on silica with chloroform/methanol 9:1, followed by recrystallistion from methanol afforded a bromolactone (0.84 g, 86%), m.p. 168 °C, identical to the racemic **5** prepared above.

Repetition of this reaction sequence with the optically active mono-acid (1.75 g) gave the corresponding chiral bromolactone (1.91 g, 78%) $[\alpha]_D{}^{20}$ -–10° (100 mg/ml, $CH_2Cl_2$) with 65% e.e.

*Chiral 1,2,3,4,5*-cis-*5a*-trans-*4-bromo-3-hydroxy-2-methoxycarbonyl-5-methoxymethylcyclopentane-1,5a-carbolactone* **6**: The chiral methyl bromolactonate **5** (0.55 g, 2.0 mmol) was dissolved in dry methanol (20 ml), thionyl chloride (0.15 ml) added and the solution heated under reflux for 2 hours. It was then evaporated under reduced pressure and the residue taken up in dichloromethane (50 ml), which was washed with water and dried. Removal of the solvent and recrystallisation from methanol afforded chiral pseudo-ester **6** (0.47 g, 77%) as plates, mp 160–3 °C, $[\alpha]_D{}^{20}$ –25° (100 mg/ml, $CHCl_3$) with 65% e.e. and spectroscopic data identical to the above racemate.

*Methyl 1,2,5*-cis-*3-formyl-5-hydroxy-2-N,N-dimethylaminocarbonyl-cyclopent-3-ene-1-carboxylate* **10**: Dimethylamine (3.2 ml, 48 mmol) was added to pseudo-ester **6** (5.0 g,16 mmol) in chloroform (50 ml) at 0 °C. After 2 hours the solution was evaporated under reduced pressure and the residue flash chromatographed on silica with ethyl acetate/chloroform 3:2. The crude product was taken up in a small volume of ethyl acetate and impurities precipitated by addition of petroleum ether (40-60°). Filtration and evaporation then afforded the dimethylamide **10** (2.77 g, 71%), m.p. 152 °C. $\nu_{max}$(film): 3255, 1739, 1682, 1622 cm$^{-1}$; *m/z* (EI): 242 ($MH^+$), 165, 109; $\delta_H$ (300 MHz, $CDCl_3$): 9.72 (1H, s, CHO), 7.11 (1H, d, *J* 3 Hz, H-4), 5.02 (1H, dd, *J* 6, 3 Hz, H-5), 4.35 (1H, d, *J* 6 Hz, H-3), 3.75 (3H, s, $CO_2$Me), 3.39 (3H, s, NMe), 3.25 (1H, t, *J* 6 Hz, H-1), 3.02 (3H, s, NMe). Found: $MH^+$ 242.1026. Calc. for $C_{11}H_{16}NO_5$: 242.1029.

*Methyl 1,2,5*-cis-*3-formyl-5-hydroxy-2''-(3'-indolyl)ethylaminocarbonylcyclopent-3-ene-1-carboxylate* **11**: A mixture of tryptamine (2.07 g, 12.9 mmol) and pseudo-ester **6** (1.0 g, 3.2 mmol) was left in chloroform (25 ml) under nitrogen for 5 days and the solution was then evaporated under reduced pressure. Chromatography of the residue on silica with chloroform/methanol 4:1 as eluent yielded as the major product the tryptamide **12** (0.52 g, 45%) as an amorphous solid. $\lambda_{max}$(MeOH): 210, 279, 289 nm; $\nu_{max}$(film): 3370, 2780, 1734, 1681, 1643 cm$^{-1}$; *m/z* (FAB): 357 ($MH^+$), 339, 313, 279, 261, 239, 217, 203, 154, 136, 107; $\delta_H$ (300 MHz, $CDCl_3$): 9.72 (1H, s, CHO), 8.08 (1H, bs, NH), 7.65 (1H, d, *J* 8 Hz, H-7′), ), 7.40 (1H, d, *J* 8 Hz, H-4′), ), 7.21 (1H, Td, *J* 8, 1 Hz, H-5′), ), 7.17 (1H, d, *J* 2 Hz, H-4), ), 7.14 (1H, dd, *J* 8, 1 Hz, H-6'), ), 7.05 (1H, d, *J* 3 Hz, H-2'), 6.34 (1H, bs, NH), 5.31 (1H, d, *J* 4 Hz, H-2), 4.99 (1H, dd, *J* 4, 2 Hz, H-5), 3.77 (3H, s, $CO_2$Me), 3.63 (1H, m, H-1″a), 3.45 (1H, m, H-1''b), 3.20 (1H, t, *J* 4 Hz, H-1), 2.95–3.09 (2H, m, $H_2$-2″). Found: $MH^+$ 357.1456. Calc. for $C_{19}H_{21}N_2O_5$: 357.1451.

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5 Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 142201 for structure **7** and 142198 for structure **8**.