Synthesis of benzolactams by 11-*endo* selective aryl radical cyclisation of 2-iodobenzamides

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Regioselective 11-*endo* aryl radical cyclisation of methyl 4-*O*-allyl-2,3-di-*O*-benzyl-6-deoxy-6-(2-iodobenzoylamino)-α-D-glucopyranoside **4** and *N*-(3-allyloxypropyl)-2-iodobenzamide **9** with tri-*n*-butyltin hydride provided the benzolactams **5** and **10**, respectively. The unequivocal structures of **5** and **10** were supported by ^{1}H and ^{13}C NMR spectroscopy and by PENDANT or DEPT, COSY and HMQC experiments.

Introduction

Bu_3SnH-mediated aryl radical cyclisations are now widely used in organic synthesis for the construction of fused aromatic compounds.[1] There are several examples of fused aromatic compounds obtained by Bu_3SnH-mediated aryl radical cyclisation from *ortho*-halogen compounds bearing a carbon–carbon double bond in the side chain. Most of them have a five- or six-membered ring fused to a benzene ring.[1–9] Some of these compounds are γ- or δ-lactams fused to the aromatic ring.[1–6] To the best of our knowledge, there are only two reports to date of Bu_3SnH-mediated aryl radical cyclisation to give fused aromatic compounds in which the carbocyclic rings have more than six members,[8,9] and there are no benzolactams with lactam rings larger than six members obtained by the same method. One possible explanation for this involves an assumption that, in the *ortho*-halogenobenzamides bearing a hydrogen on the saturated carbon at the 5-position relative to the aryl radical centre, generation of the aryl radical is followed by intramolecular hydrogen-atom transfer to the aryl group with formation of an amidoyl radical which undergoes a variety of new radical addition and cyclisation reactions.[10]

Despite our knowledge of 1,5-hydrogen-atom transfer, we decided to explore the possibility of using Bu_3SnH-mediated radical cyclisation to create benzomacrolactams such as **A** and **B** by 11-*endo* and/or 10-*exo* cyclisation, respectively, from methyl 4-*O*-allyl-2,3-di-*O*-benzyl-6-deoxy-6-(2-iodobenzoylamino)-α-D-glucopyranoside **4**. We were somewhat encouraged by the possibility of the carbohydrate unit of the aryl radical precursor adopting a conformation in which the cyclisation reaction would occur prior to 1,5-hydrogen-atom transfer. This hypothesis was also supported by the observation of ring closure of radicals derived from precursors with an oxygen atom in the chain, such as in **4**. These radicals cyclise much more rapidly than do their carbon analogues.[11–13] The effect of an oxygen atom in the chain on the rate of cyclisation has been attributed to a decrease in the strain energy of the cyclisation transition structures resulting from the replacement of a carbon atom by oxygen, a hypothesis supported by molecular mechanics calculations.[14]

Results and discussion

We began our investigations by examining the cyclisation of the *o*-iodobenzamide **4**, which was obtained from methyl α-D-glucopyranoside in eight conventional synthetic steps (Scheme 1). The C-4 and C-6 hydroxy groups of the starting material were protected as a benzylidene acetal[15] and the C-2 and C-3 hydroxy groups were *O*-benzylated.[16] After removal of the benzylidene group under mild acidic conditions[17] the hydroxy group at C-6 of methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside was selectively replaced by an iodine atom[18] to give methyl 2,3-di-*O*-benzyl-6-deoxy-6-iodo-α-D-glucopyranoside. Treatment of the 6-iodo derivative with sodium azide in DMF

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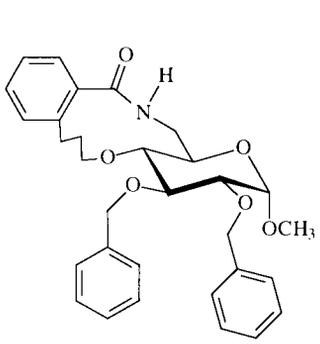
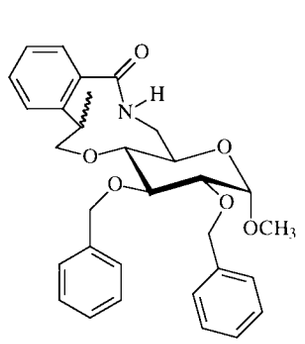


A 11-*endo* cyclisation



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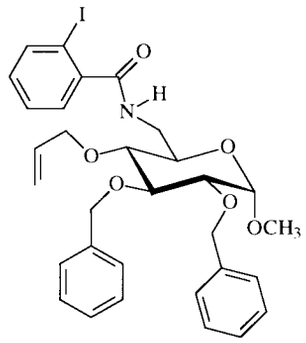

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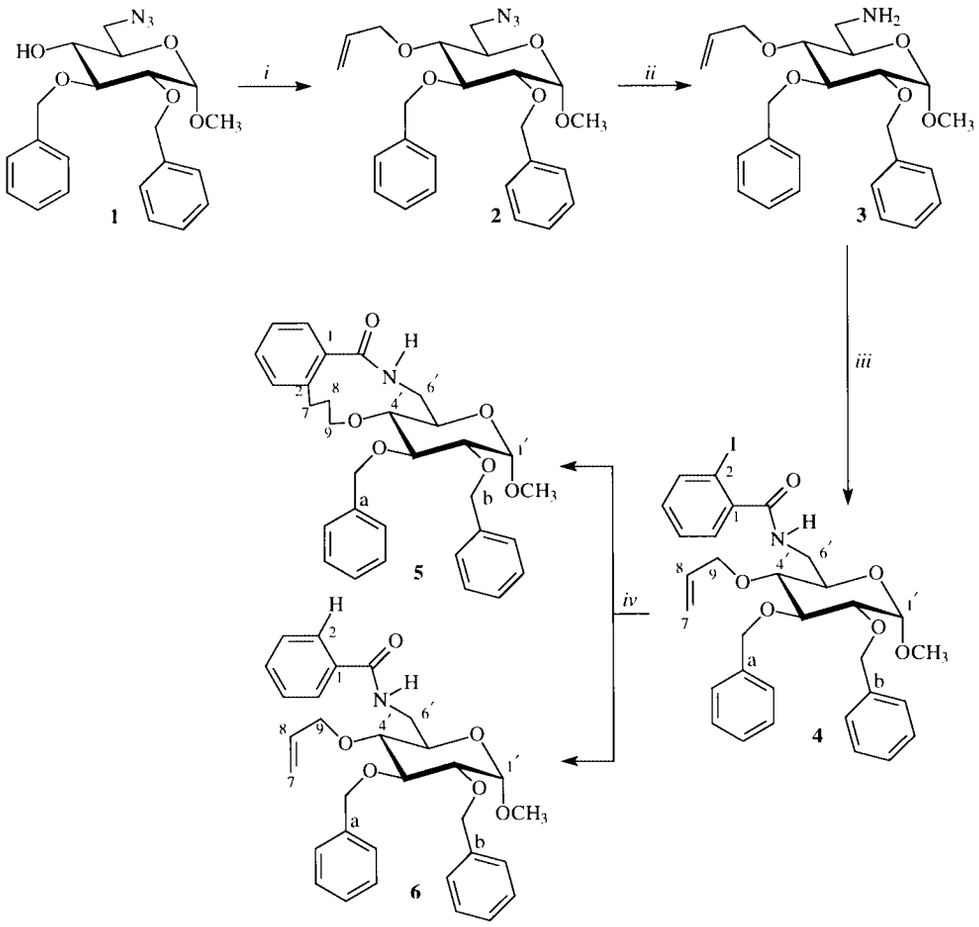
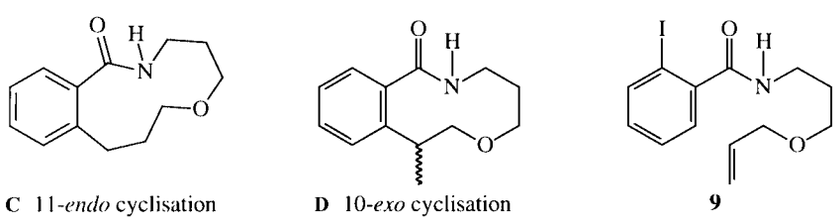


Scheme 1 *Reagents, conditions and yields*: *i*, 3 equiv. NaH, 2.4 equiv. allyl bromide, DMF, rt, 93%; *ii*, 1.5 equiv. triphenylphosphine, toluene, water, reflux, 85%; *iii*, 1 equiv. 2-iodobenzoyl chloride, 10% aq. NaOH, CH_2Cl_2, rt, 51%; *iv*, 1.5 equiv. Bu_3SnH, benzoyl peroxide (cat.), benzene, reflux, **5** 40%, **6** 42%.



C 11-*endo* cyclisation **D** 10-*exo* cyclisation **9**

gave the 6-azido derivative **1**,[19] which was treated with allyl bromide in the presence of sodium hydride in DMF to give methyl 4-*O*-allyl-6-azido-2,3-di-*O*-benzyl-6-deoxy-α-D-glucopyranoside **2**. Selective reduction of the azido group using the Staudinger reaction[20] gave methyl 4-*O*-allyl-6-amino-2,3-di-*O*-benzyl-6-deoxy-α-D-glucopyranoside **3**. Compound **4** was obtained by reaction of **3** with 2-iodobenzoyl chloride.

Consideration of the competing reactions available to the radicals involved in this cyclisation suggested that the formation of cyclised products should be improved by conducting the experiment with very low concentrations of both the 4-*O*-allyl-2,3-di-*O*-benzyl-6-deoxy-6-(2-iodobenzoylamino)-α-D-glucopyranoside **4** and Bu_3SnH and slow addition of Bu_3SnH/benzoyl peroxide in benzene solution, thus respectively decreasing the intermolecular reactions and the rate of hydrogen-atom transfer to uncyclised radicals.[6,14,21] Thus, a mixture of Bu_3SnH (1.5 mol equiv.) and benzoyl peroxide (catalytic amount) in nitrogen-saturated anhydrous benzene was added over a period of one hour to a solution of the *o*-allyloxyiodobenzamide **4** in nitrogen-saturated anhydrous benzene maintained at 80 °C to give a reaction mixture 0.012 mol dm^{-3} in Bu_3SnH. The reaction mixture was heated under reflux for a further one hour. Subsequent solvent removal and column chromatography on silica gel gave two main crystalline products identified as the benzomacrolactam **5**, resulting from 11-*endo* aryl radical cyclisation in 40% yield and the hydrogenolysis product **6** in 42% yield (Scheme 1).

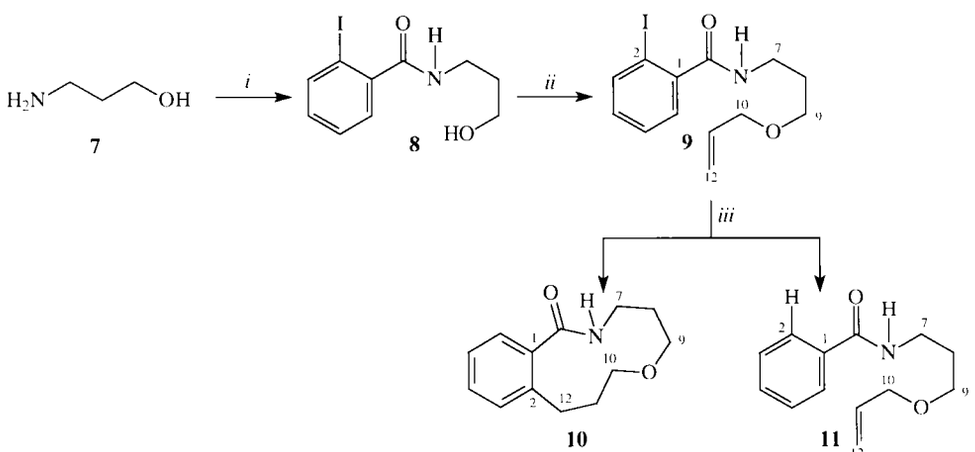
Encouraged by the success of the Bu_3SnH-mediated radical cyclisation reaction of **4**, we then applied this methodology to the synthesis of benzomacrolactams such as **C** and **D** from *N*-(3-allyloxypropyl)-2-iodobenzamide **9** to examine whether or not this methodology would be applicable to other systems where the conformational restraints imposed by the carbohydrate unit are lacking.

The 2-iodobenzamide **9** was readily prepared by condensation of 3-aminopropan-1-ol **7** with 2-iodobenzoyl chloride, followed by *O*-alkylation of the resulting *N*-(3-hydroxypropyl)-2-iodobenzamide **8** with allyl bromide. Similar treatment of compound **9** as described above for **4**, but using AIBN as radical initiator, gave an oil identified as the hydrogenolysis product **11** (85% yield) and a crystalline substance identified as the macrolactam **10** (14% yield), resulting from 11-*endo* aryl radical cyclisation (Scheme 2).

The structures of lactams **5** and **10**, hydrogenolysis products **6** and **11**, and precursors **4** and **9** were supported by ^1H and ^{13}C NMR spectroscopy. The unequivocal structures of **5** and **10**

Table 1 Selected ^{13}C NMR ($CDCl_3$) data for compounds **4**, **5**, **6**, **9**, **10** and **11**

Compound	Carbon	δ (ppm)	MHz
4	1-C	142.24	100
	2-C	92.26	
	8-C	134.62	
	7-C	117.30	
5	1-C, 2-C	One of 4 signals between 139.04 and 137.38	100
	8-C	31.79	
	7-C	28.00	
6	1-C	134.93	100
	2-C	One of 9 signals between 129.06 and 127.27	
	8-C	135.08	
	7-C	117.80	
9	1-C	142.27	50
	2-C	92.40	
	11-C	134.37	
	12-C	116.88	
10	1-C	140.2	100
	2-C	137.4	
	11-C	28.3 or 31.3	
	12-C	29.6	
11	1-C	134.52	50
	2-C	128.34 or 126.81	
	11-C	134.34	
	12-C	117.27	



Scheme 2 *Reagents*, *conditions and yields*: *i*, 2 equiv. 2-iodobenzoyl chloride, 1 equiv. triethylamine CH_2Cl_2, rt, 67%; *ii*, 0.2 equiv. Bu_4NBr, 5% aq. NaOH, 3 equiv. allyl bromide, rt, 29%, *iii*, 1.5 equiv. Bu_3SnH, AIBN (cat.), benzene, reflux, **10** 14%, **11** 85%.

were also confirmed by PENDANT or DEPT, COSY and HMQC experiments. Selected ^{13}C NMR data for these six compounds are listed in Table 1.

The unsatisfactory elemental analysis of **5**, **10** and **11** could be due of the presence of tri-*n*-butyltin compounds as impurities, since it is well known that a major drawback in employing the tri-*n*-tributyltin reagent can be the poor separation of the products from tin residues.[22] Attempts to obtain compounds **5**, **10** and **11** with correct analytical data were not successful. The NMR spectra of **5** and **10** do not indicate the presence of significant quantities of tri-*n*-butyltin residues and the elemental analyses for these compounds are almost good. On the other hand, the analytical data for the uncyclised product **11** are incorrect and the signals relative to the butyl group in its NMR spectra indicate the presence of tri-*n*-butyltin compounds. These results can be attributed to the difficulty of purifying **11**, which is an oil.

Thus we found that the Bu_3SnH-induced aryl radical cyclisation of the *o*-iodobenzamides **4** and **9** provided exclusively the lactams **5** and **10**, respectively, resulting from 11-*endo* aryl radical cyclisation. Our results are in agreement with the guideline for radical macrocyclisation that '*endo* cyclisation modes are favored'[23] and with other literature data of macrocyclisations.[8,9] Comparison of the ratio lactam : hydrogenolysis product isolated from the Bu_3SnH-mediated reaction of the benzamide **4** (1 : 1) with the ratio lactam:hydrogenolysis product isolated from the reaction of the benzamide **9** (1.5 : 8.5) suggests that our previous hypothesis might be correct: conformational restraints imposed by the sugar unit in the carbohydrate aryl radical precursor favoured the cyclisation. On the other hand, in the reaction of the benzamide **9**, where the conformational restraints are lacking, direct hydrogen-atom transfer to the initially formed aryl radical, or 1,5-hydrogen-atom transfer to give the amidoyl radical and, subsequently, the uncyclised product, occurred prior to the cyclisation.

In conclusion, the present investigation shows the potential of aryl radical macrocyclisation from *o*-iodobenzamides bearing a hydrogen atom on the saturated carbon in position 5 relative to the halogen atom in the synthesis of condensed lactams incorporating large rings. We have also found that the 11-*endo* cyclisation mode is preferred over a 10-*exo* ring closure in those systems having an allyloxy group at the 7 position relative to the aryl radical centre.

Experimental

General procedures

Mps were determined on a Kofler Sybron apparatus and are uncorrected. Optical rotations were determined at 25 °C with a

Bellingham & Stanley P20 Polarimeter; $[\alpha]_D$-values are given in units of 10^{-1} deg cm^2 g^{-1} NMR spectra were measured in deuteriochloroform with TMS as the internal standard with a Bruker Avance DRX-400 or a Bruker Avance-200 instrument; chemical shifts are given on the δ-scale, and J-values are given in Hz. Column chromatography was performed with silica gel 60, 70–230 mesh (Merck). The term 'standard work-up' means that the organic layer was washed with water, dried over anhydrous sodium sulfate, filtered and the solvent was removed under reduced pressure.

Methyl 4-*O*-allyl-6-azido-2,3-di-*O*-benzyl-6-deoxy-α-D-glucopyranoside 2

A solution of allyl bromide (1.7 cm^3, 2.3 g, 19 mmol) in DMF (10 cm^3) was added to a mixture of sodium hydride (0.6 g, 24 mmol) and methyl 6-azido-2,3-di-*O*-benzyl-6-deoxy-α-D-glucopyranoside **1** [19] (3.8 g, 7.9 mmol) in DMF (10 cm^3). The mixture was stirred for 18 h at room temperature (rt). Distillation under reduced pressure gave a residue. Addition of water, extraction with CH_2Cl_2 and standard work-up gave the product **2** (3.3 g, 93%) as an oil; $[\alpha]_D$ +73.2 (*c* 2.0 in $CHCl_3$); δ_H(200 MHz, $CDCl_3$) 7.35–7.28 (10 H, m, Ph), 5.93–5.79 (1 H, m, CH_2=C*H*), 5.23 (1 H, dd, one of C*H*$_2$=CH, J_{trans} 17.2, J_{gem} 1.4), 5.16 (1 H, dd, one of C*H*$_2$=CH, J_{cis} 11.4, J_{gem} 1.4), 4.95 (1 H, d, J_{gem} 10.7, one of PhC*H*$_2$), 4.79 (1 H, d, J_{gem} 12.4, one of PhC*H*$_2$), 4.77 (1 H, d, J_{gem} 10.7, one of PhC*H*$_2$), 4.64 (1 H, d, J_{gem} 12.4, one of PhC*H*$_2$), 4.60 (1 H, d, $J_{1,2}$ 3.8, 1-H), 4.34 (1 H, dd, J_{gem} 12.3, *J* 5.6, one of OC*H*$_2$), 4.10 (1 H, dd, *J* 12.3, *J* 5.8, one of OC*H*$_2$), 3.91 (1 H, t, $J_{3,2} = J_{3,4} = 9.2$, 3-H), 3.77–3.71 (1 H, m, 5-H), 3.54–3.36 (3 H, m, 6-H$_2$, 2-H), 3.39 (3 H, s, MeO), 3.29 (1 H, t, 4-H); δ_C(50 MHz, $CDCl_3$) 138.47 (one of Ph *ipso*), 137.91 (other Ph *ipso*), 134.36 (H*C*=CH$_2$), 128.37, 128.30, 127.96, 127.88, 127.56 (Ph), 117.17 (HC=*C*H$_2$), 97.92 (1-C), 81.57 (3-C), 79.65 (2-C), 78.09 (4-C), 75.63, 73.82, 73.31 (2 × Ph*C*H$_2$O and OC*H*$_2$), 69.84 (5-C), 55.25 (MeO), 51.26 (6-C) (Found: C, 65.4; H, 6.7; N, 9.4. Calc. for $C_{24}H_{29}N_3O_5$: C, 65.6; H, 6.6; N, 9.6%).

Methyl 4-*O*-allyl-6-amino-2,3-di-*O*-benzyl-6-deoxy-α-D-glucopyranoside 3 [20]

To a solution of methyl 4-*O*-allyl-6-azido-2,3-di-*O*-benzyl-6-deoxy-α-D-glucopyranoside **2** (3.5 g, 7.9 mmol) in toluene (100 cm^3) was added triphenylphosphine (3.2 g, 12 mmol). The solution was stirred for 18 h at reflux. Water (2 cm^3) was added and the solution was stirred under reflux for 2 h. Distillation of the toluene gave a residue, which was submitted to column chromatography. Elution with $CHCl_3$–CH_3OH 9.8 : 0.2 gave methyl 4-*O*-allyl-6-amino-2,3-di-*O*-benzyl-6-deoxy-α-D-glucopyranoside **3** (2.8 g, 85%).

Methyl 4-*O*-allyl-2,3-di-*O*-benzyl-6-deoxy-6-(2-iodobenzoylamino)-α-D-glucopyranoside 4

To a solution of 2-iodobenzoyl chloride (1.0 g, 3.9 mmol) in dichloromethane (10 cm^3) were added 10% aq. NaOH (5 cm^3) and a solution of methyl 4-*O*-allyl-6-amino-2,3-di-*O*-benzyl-6-deoxy-α-D-glucopyranoside **3** (1.6 g, 3.9 mmol) in CH_2Cl_2. The mixture was stirred for 12 h at rt. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. Standard work-up gave a residue, which was submitted to column chromatography. The iodobenzamide **4** (1.3 g, 51%), eluted with hexane–ethyl acetate 7 : 3, was obtained as a white solid; mp 150–153 °C; $[\alpha]_D$ +22.3 (*c* 0.9 in $CHCl_3$); δ_H(400 MHz, $CDCl_3$) 7.85 (1 H, d, $J_{6,5}$ 7.9, 6-H), 7.37–7.26 (12 H, m, ArH), 7.09 (1 H, m, ArH), 6.03 (1 H, br s, NH), 5.94 (1 H, m, 8-H), 5.27 (1 H, dd, $J_{7,8}$ 17.2, J_{gem} 1.4, one of 7-H), 5.15 (1 H, d, $J_{7,8}$ 10.3, one of 7-H), 4.95 (1 H, d, J_{gem} 10.8, one of PhC*H*$_2$), 4.81 (1 H, d, J_{gem} 10.8, one of PhC*H*$_2$), 4.79 (1 H, d, J_{gem} 12.1, one of PhC*H*$_2$), 4.64 (1 H, d, J_{gem} 12.1, one of PhC*H*$_2$), 4.59 (1 H, d, $J_{1',2'}$ 3.5, 1′-H), 4.36 (1 H, dd, J_{gem} 12.0, $J_{9,8}$ 5.6, one of 9-H), 4.25 (1 H, dd, J_{gem} 12.0, $J_{9,8}$ 5.9, one of 9-H), 3.95 (1 H, t, $J_{3',2'} = J_{3',4'} = 9.63$, 3′-H), 3.87 (1 H, qd, J_{gem} 13.60, $J_{6',5'}$ 6.94, $J_{6',NH}$ 5.31, one of 6′-H), 3.80–3.76 (1 H, m, 5′-H), 3.64 (1 H, dt, $J_{6',5'} = J_{6',NH} = 4.03$, one of 6′-H), 3.44 (1 H, dd, 2′-H), 3.38 (3 H, s, MeO), 3.31 (1 H, t, 4′-H); δ_C(100 MHz, $CDCl_3$) 169.11 (C=O), 142.24 (1-C), 139.83 (3-C), 138.50, 138.00 (a- and b-C), 134.62 (H*C*=CH$_2$), 131.02 (4-C), 128.43, 128.41, 128.38, 128.31, 128.27, 128.25, 128.23, 128.17, 128.07, 127.97, 127.94, 127.89, 127.86, 127.58 (6-C, 5-C, Ar), 117.30 (HC=*C*H$_2$), 98.07 (1′-C), 92.26 (CI), 81.61 (3′-C), 79.61 (2′-C), 78.94 (4′-C), 75.69, 74.09, 73.31 (2 × Ph*C*H$_2$ and 9-C), 68.93 (5′-C), 55.43 (MeO), 40.18 (6′-C) (Found: C, 57.9; H, 5.4; N, 2.6. Calc. for $C_{31}H_{34}INO_6$: C, 57.9; H, 5.3; N, 2.2%).

Radical cyclisation of compound 4 [21]

To a stirred, boiling solution of compound **4** (0.1 g, 0.155 mmol) in nitrogen-saturated benzene (15 cm^3) was added a solution of Bu_3SnH (0.06 cm^3, 0.07 g, 0.25 mmol) and benzoyl peroxide (0.002 g) in nitrogen-saturated benzene (5 cm^3) *via* an addition funnel during 1 h. The reaction mixture was heated under reflux and a nitrogen atmosphere for a further 1 h. Subsequent solvent removal and column chromatography (hexane–ethyl acetate 6 : 4) gave, successively, the uncyclised product **6** (0.034 g, 42%) and the lactam **5** (0.032 g, 40%).

The lactam **5** was obtained as a solid; mp 218–220 °C; $[\alpha]_D$ +20.4 (*c* 1.7 in $CHCl_3$); δ_H(400 MHz, $CDCl_3$) 7.39–7.27 (12 H, m, ArH), 7.20–7.16 (2 H, m, ArH), 6.30 (1 H, br s, NH), 4.96 (1 H, d, J_{gem} 10.9, one of PhC*H*$_2$), 4,76 (1 H, d, J_{gem} 12.3, one of PhC*H*$_2$), 4.73 (1 H, d, J_{gem} 10.9, one of PhC*H*$_2$), 4.54 (1 H, d, J_{gem} 12.3, one of PhC*H*$_2$), 4.55 (1 H, d, $J_{1',2'}$ 3.3, 1′-H), 4.09 (1 H, m, 5′-H), 3.97 (1 H, dd, $J_{3',2'}$ 9.9, $J_{3',4'}$ 8.3, 3′-H), 3.92–3.86 (2 H, m, one of 6′-H and one of 9-H), 3.44 (1 H, dd, 2′-H), 3.42 (3 H, s, MeO), 3.28–3.14 (4 H, m, 4′-H, one of 6′-H, one of 9-H, one of 7-H), 2.59 (1 H, dt, J_{gem} 13.88, $J_{7,8}$ 4.52, one of 7-H), 1.99–1.92 (1 H, m, one of 8-H), 1.58–1.52 (1 H, m, one of 8-H); δ_C(100 MHz, $CDCl_3$) 170.65 (C=O), 139.04, 138.62, 138.07, 137.38 (1-, 2-, a- and b-C), 130.74, 129.85, 128.45, 128.38, 128.22, 128.03, 127.97, 127.89, 127.61, 126 65, 126.00 (Ar), 98.07 (1′-C), 82.14 (3′-C), 81.65 (4′-C), 79.39 (2′-C), 75.68, 73.16 (2 × Ph*C*H$_2$), 68.54 (9-C), 65.80 (5′-C), 55.54 (MeO), 43.51 (6′-C), 31.79 (8-C), 28.00 (7-C) (Found: C, 70.8; H, 6.8; N, 2.7. Calc. for $C_{31}H_{35}NO_6$: C, 71.9; H, 6.8; N, 2.7%).

The uncyclised product **6** was obtained as a white solid; mp 148–151 °C; $[\alpha]_D$ +19 (*c* 2.7 in $CHCl_3$); δ_H(400 MHz, $CDCl_3$) 7.74–7.72 (2 H, m, 2- and 6-H), 7.51–7.47 (1 H, m, Ph), 7.44–7.39 (2 H, m, Ph), 7.34–7.27 (10 H, m, Ph), 6.40 (1 H, br s, NH), 5.98–5.89 (1 H, m, 8-H), 5.27 (1 H, dd, $J_{7,8}$ 17.2, J_{gem} 1.3, one of 7-H), 5.15 (1 H, dd, $J_{7,8}$ 10.1, J_{gem} 1.3, one of 7-H), 4.93 (1 H, d, J_{gem} 10.7, one of PhC*H*$_2$), 4.80 (1 H, d, J_{gem} 12.1, one of PhC*H*$_2$), 4.79 (1 H, d, J_{gem} 10.7, one of PhC*H*$_2$), 4.65 (1 H, d, J_{gem} 12.1, one of PhC*H*$_2$), 4.57 (1 H, d, $J_{1',2'}$ 3.5, 1′-H), 4.33 (1 H, dd, J_{gem} 12.1, $J_{9,8}$ 5.58, one of 9-H), 4.19 (1 H, dd, J_{gem} 12.1, $J_{9,8}$ 5.96, one of 9-H), 3.94 (1 H, t, $J_{3',2'} = J_{3',4'} = 9.26$, 3′-H), 3.85 (1 H, qd, J_{gem} 13.49, $J_{6',5'}$ 6.72, $J_{6',NH}$ 5.59, one of 6′-H), 3.79–3.74 (1 H, m, 5′-H), 3.64 (1 H, dt, $J_{6',5'} = J_{6',NH} = 4.07$, one of 6′-H), 3.46 (1 H, dd, 2′-H), 3.37 (3 H, s, MeO), 3.23 (1 H, t, 4′-H); δ_C(100 MHz, $CDCl_3$) 167.66 (C=O), 138.96, 138.52 (a-C and b-C), 135.08 (H*C*=CH$_2$), 134.93 (1-C), 131.86 (4-C), 129.06, 128.95, 128.86, 128.78, 128.46, 128.41, 128.32, 128.06, 127.27 (Ph), 117.80 (HC=*C*H$_2$), 98.49 (1′-C), 82.12, 80.28, 79.36 (2′-, 3′- and 4′-C), 76.19, 74.40, 73.80 (2 × Ph*C*H$_2$ and 9-C), 69.50 (5′-C), 55.69 (MeO), 40.75 (6′-C) (Found: C, 71.8; H, 6.8; N, 2.5. Calc. for $C_{31}H_{35}NO_6$: C, 71.9; H, 6.8; N, 2.7%).

N-(3-Hydroxypropyl)-2-iodobenzamide 8

To a solution of 3-aminopropan-1-ol **7** (2 cm^3, 2.02 g, 26.7 mmol) and triethylamine (3.7 cm^3, 2.75 g, 27.2 mmol) in anhydrous CH_2Cl_2 (115 cm^3) was added a solution of 2-iodo-

benzoyl chloride (14.11 g, 53 mmol) in CH_2Cl_2 (40 cm^3). The mixture was stirred for 20 h at room temperature. Water was added, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. Standard work-up gave a residue, which was submitted to column chromatography. The iodobenzamide **8** (5.42 g, 67%), eluted with ethyl acetate, was obtained as a syrup; δ_H(200 MHz, $CDCl_3$) 7.80 (1 H, d, $J_{6,5}$ 7.9, 6-H), 7.39–7.25 (2 H, m, ArH), 7.05 (1 H, m, ArH), 6.86 (1 H, br s, NH), 3.68 (2 H, t, $J_{9,8}$ 5.6, 9-H_2), 3.80 (1 H, br s, OH), 3.48 (2 H, q, $J_{7,NH} = J_{7,8} = 6.1$, 7-H_2), 1.72 (2 H, quintet, $J_{8,7} = J_{8,9} = 5.9$, 8-H_2); δ_C(50 MHz, $CDCl_3$) 170.43 (C=O), 141.78 (1-C), 139.70 (3-C), 131.01, 128.02 (Ar), 92.45 (CI), 59.41 (9-C), 36.88 (7-C), 31.62 (8-C) (Found: C, 38.9; H, 4.1; N, 4.3. Calc. for $C_{10}H_{12}INO_2$: C, 39.4; H, 3.9; N, 4.6%).

N-(3-Allyloxypropyl)-2-iodobenzamide 9

To a solution of the iodobenzamide **8** (2.04 g, 6.69 mmol) in CH_2Cl_2 (40 cm^3) were added, under magnetic stirring, 5% aq. NaOH (15 cm^3) and Bu_4NBr (0.43 g, 1.33 mmol), as phase-transfer catalyst. The mixture was stirred for 30 min. Allyl bromide (1.7 cm^3, 2.4 g, 20 mmol) was added and the mixture was stirred for 68 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. Standard work-up gave a residue, which was submitted to column chromatography. The allyloxyiodobenzamide **9** (0.67 g, 29%), eluted with hexane–ethyl acetate 1:1, was obtained as a syrup; δ_H(200 MHz, $CDCl_3$) 7.82 (1 H, d, 6-H), 7.39–7.32 (2 H, m, ArH), 7.07 (1 H, m, ArH), 6.55 (1 H, br s, NH), 5.87 (1 H, m, 11-H), 5.27–5.08 (2 H, m, 12-H_2), 3.96 (2 H, dt, $J_{10,11}$ 5.2, $J_{10,12}$ 1.33, 10-H_2), 3.62–3.49 (4 H, m, 7- and 9-H_2), 1.90 (2 H, quintet, $J_{8,7} = J_{8,9} = 6.1$, 8-H_2); δ_C(50 MHz, $CDCl_3$) 169.28 (C=O), 142.27 (1-C), 139.66 (3-C), 134.37 (H*C*=CH_2), 130.83, 127.97 (Ar), 116.88 (HC=*C*H_2), 92.40 (CI), 71.84, 69.11 (9- and 10-C), 38.55 (7-C), 28.77 (8-C) (Found: C, 44.1; H, 4.6; N, 3.9. Calc. for $C_{13}H_{16}INO_2$: C, 45.2; H, 4.7; N, 4.1%).

Radical cyclisation of compound 9 [21]

To a stirred, boiling solution of compound **9** (0.345 g, 1 mmol) in nitrogen-saturated benzene (70 cm^3) was added a solution of Bu_3SnH (0.42 cm^3, 0.44 g, 1.5 mmol) and AIBN (0.01 g) in nitrogen-saturated benzene (12 cm^3) *via* an addition funnel during 1 h. The reaction mixture was heated under reflux and a nitrogen atmosphere for a further 1 h. Subsequent solvent removal and column chromatography (hexane–ethyl acetate) gave, successively, the uncyclised product **11** (hexane–ethyl acetate 8:2; 0.19 g, 85%) and the lactam **10** (hexane–ethyl acetate 3:7; 0.030 g, 14%).

The macrolactam **10** was obtained as a solid; mp 143–147 °C; δ_H(400 MHz, $CDCl_3$) 7.40 (1 H, d, $J_{6,5}$ 7.5, 6-H), 7.30 (1 H, m, ArH), 7.21–7.17 (2 H, m, ArH), 6.17 (1 H, br s, NH), 3.66 (2 H, t, $J_{9,8}$ 4.9, 9-H_2), 3.61 (2 H, q, $J_{7,NH} = J_{7,8} = 5.8$, 7-H_2), 3.40 (2 H, t, $J_{10,11}$ 5.3, 10-H_2), 3.00 (2 H, t, $J_{12,11}$ 6.4, 12-H_2), 1.85 (4 H, m, 8- and 11-H_2); δ_C(100 MHz, $CDCl_3$) 171.0 (C=O), 140.2 (1-C), 137.4 (2-C), 130.8, 129.7, 127.2, 126.0 (Ar), 70.9 (9-C), 69.1 (10-C), 39.5 (7-C), 31.3, 28.3 (8- and 11-C), 29.6 (12-C) (Found: C, 70.8; H, 8.6; N, 5.9. Calc. for $C_{13}H_{17}NO_2$: C, 71.2; H, 7.8; N, 6.4%).

The uncyclised product **11** was obtained as an oil; δ_H(200 MHz, $CDCl_3$) 7.76 (2 H, d, $J_{2,3}$ 7.2, *o*-H), 7.54–7.35 (3 H, m, Ph), 7.18 (1 H, br s, NH), 6.02–5.82 (1 H, m, 11-H), 5.32–5.17 (2 H, m, 12-H_2), 4.00 (2 H, d, $J_{10,11}$ 5.6, 10-H_2), 3.65–3.53 (4 H, m, 9- and 7-H_2), 1.90 (2 H, quintet, $J_{8,7} = J_{8,9} = 5.8$, 8-H_2); δ_C(50 MHz, $CDCl_3$) 167.25 (C=O), 134.52 (1-C), 134.34 (H*C*=CH_2), 131.16 (4-C), 128.34, 126.81 (2- and 3-C), 117.27 (HC=*C*H_2), 72.05, 69.93 (9- and 10-C), 39.14 (7-C), 28.73 (8-C) (Found: C, 65.4; H, 7.0; N, 5.2. Calc. for $C_{13}H_{17}NO_2$: C, 71.2; H, 7.8; N, 6.4%).

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