Stereoselective benzylic α-acylamino radical cyclisation: a model study for the Tacaman indole alkaloid skeleton

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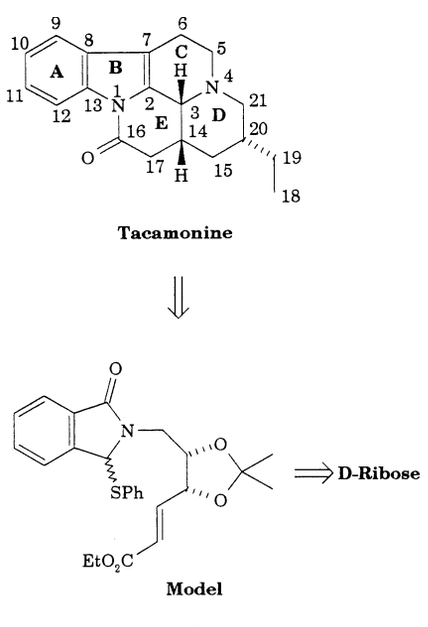
1 PERKIN

Radical cyclisation with tributyltin hydride of the α-phenylsulfanyl lactam 6, prepared in nine steps from D-ribose *via* the corresponding phthalimide, gives the all-*cis* tetrahydropyrido[2,1-*a*]isoindolone 7 stereoselectively as the major diastereomer. The structure of the product is established by ^{1}H NMR spectroscopy and corroborated by formation of the *cis*-lactone 8. The diastereoselectivity is shown to be controlled by the allylic/homoallylic *cis*-ketal group, and a transition state is proposed. The sequence constitutes the first simple model study for C/D ring fusion of the Tacaman indole alkaloid skeleton *via* the relatively unexplored C-3–C-14 bond disconnection.

Introduction

In the last decade or so, the cyclisation of α-acylamino radicals has developed into a powerful methodology for nitracycle synthesis, following the pioneering studies by Hart and co-workers in the 1980s. Synthetic targets involving the methodology include pyrrolizidine and indolizidine alkaloids,[1a–e] functionalised β-lactams,[2] cyclic α-amino acids,[3] the oxoindole gelsemine[4] and the synthetic vitamin (+)-biotin.[5] In all of the cases reported to date in which the α-acylamino radical has been derived from an imide, the latter has been based on succinimide. In this paper, we present the first study of cyclisation of α-acylamino radicals derived from phthalimide. The purpose of the study was to gain information on factors controlling the diastereoselectivity of ring closure onto a chiral D-ribose-derived chain. This was carried out as a simple model study of C/D ring fusion of the Tacaman[6] indole alkaloid skeleton *via* the C-3–C-14[7] bond (see Scheme 1 for Tacaman numbering[8]).



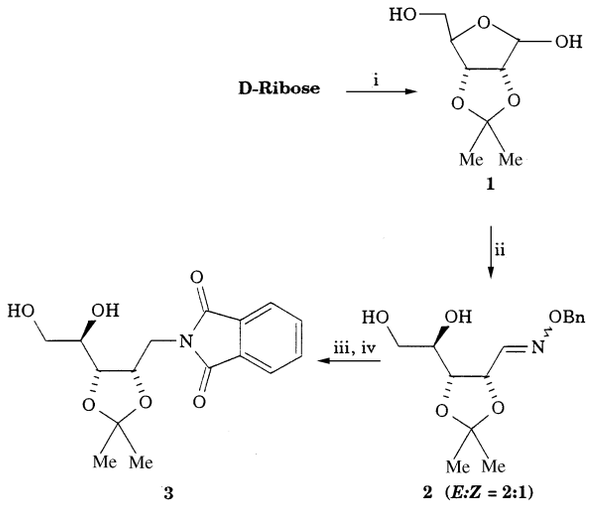
Scheme 1

Results and discussion

Our retrosynthetic analysis identified D-ribose as a suitable starting material for construction of the chiral enoate chain. The acid-catalysed ketalisation of the 2,3-hydroxy groups of D-ribose to its 2,3-*O*-isopropylidene derivative[9] was routinely carried out in around 65% yield by using a stoichiometric amount of conc. H_2SO_4 in dry acetone at 0 °C for about 2 h. A non-aqueous isolation procedure similar to that of Hughes and Speakmann,[10] involving quenching with KOH (2 equiv.) in MeOH together with some anhydrous K_2CO_3 to help coagulation of the precipitated salts, was then used. Filtration of the mixture and evaporation of solvent gave a quantitative yield of products which could be chromatographed or used directly in the next step.

Oxime derivatives of carbohydrates from hydroxylamine were first reported in 1887[11] as a means of characterisation. As with the thioketalisation of sugars, oximation results in ring opening to afford chiral, acyclic chains useful in synthesis. Recently, in this regard, the groups of Bartlett[12] and Marco-Contelles[13] have used this to good effect in the radical cyclisation of carbohydrate-derived oxime ethers to aminocyclitols. Oximation of 2,3-*O*-isopropylidene-D-ribofuranose with *O*-benzylhydroxylamine hydrochloride in pyridine gave the organically soluble crystalline oxime-diol **2** in 85% yield after the normal work-up and chromatography. Crystallisation of the crude product from ethyl acetate–hexane afforded a 70% yield (2 crops). Alternatively, a 50% overall yield of **2** for the two steps after fractional crystallisation could be achieved using the crude product from step 1. The product gave satisfactory spectral and analytical data and was isolated initially as a 2:1 *E*:*Z* mixture. Repeated crystallisation furnished the pure (*E*)-isomer for characterisation. Oxime to amine reduction could be accomplished smoothly by $LiAlH_4$–THF at room temperature. However, not unexpectedly, the amino-diol product was too water soluble for isolation *via* two phase organic extraction, and a derivatisation–isolation procedure was developed. Careful quenching of the $LiAlH_4$ reaction mixture at 0 °C with an NEt_3–H_2O (5:1) mixture resulted in the formation of a flocculent white precipitate after about 30 min which could be filtered off. Evaporation of solvent using benzene to remove any residual water furnished the amine-diol which was immediately derivatised to the phthalimide **3** using *N*-ethoxycarbonylphthalimide[14] with triethylamine in CH_2Cl_2. Column chromatography of the crude mixture (no work-up required) consistently gave a 60% overall yield of the desired imide for the two steps. The imide **3** gave satisfactory analytical and spectral data with an ABX spin system for the diastereotopic protons at C-1 (sugar numbering) and the methine proton at C-2 (Scheme 2).

With the crystalline imide-diol in hand, the scene was set for conversion to the radical precursor. 1,2-Diol cleavage of **3** with $NaIO_4$ in water proceeded uneventfully in high yield, and was superior to $Pb(OAc)_4$ in terms of practical handling. The alde-

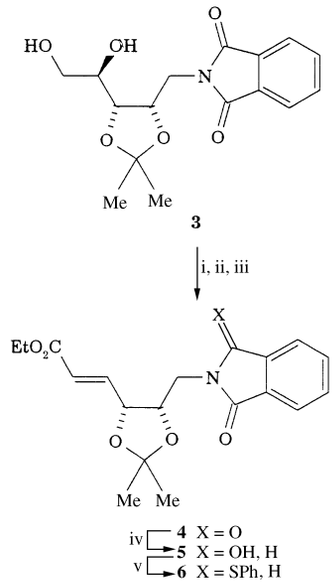


Scheme 2 *Reagents and conditions:* i, acetone, H_2SO_4, 65%; ii, BnO-$NH_3^+Cl^-$, pyridine, 85%; iii, $LiAlH_4$, THF; iv, *N*-ethoxycarbonylphthalimide, NEt_3, CH_2Cl_2, 60% over 2 steps

hyde gave satisfactory NMR data but eluded microanalytical characterisation and was therefore converted directly to the homologated enoate ester **4** in 85% yield for the two steps ($E:Z = 20:80$) using the stabilised Wittig ylide (ethoxycarbonylmethylene)triphenylphosphorane in CH_2Cl_2 at 0 °C. The high (*Z*)-stereoselectivity encountered in this Wittig reaction is well established[15] for α-alkoxyaldehydes.

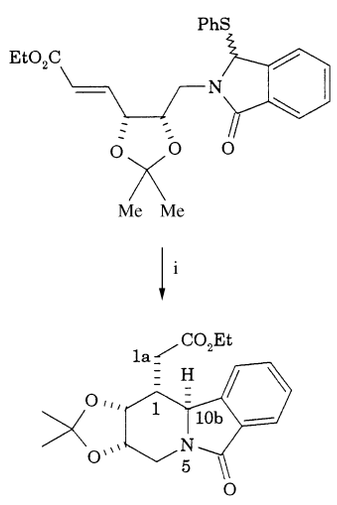
At this point in the synthesis we were aware of the divergence from our approach because of the Wittig result. Since the stereochemical configuration of double bond acceptors is known to play an important role in the stereoselectivity of radical cyclisations,[16] we decided to isomerise the (*Z*)-isomer to the (*E*)-isomer in order to bring the route back on track. This decision was later justified when we established that the (*Z*)-isomer converts to its (*E*)-isomer during radical cyclisation. Various reagents have been developed for thermodynamic *Z* to *E* isomerisation, with radical based procedures[17] involving the benzenethiyl and tris(trimethylsilyl)silyl radicals as the methods of choice. For isomerising the mixture of enoate esters ($Z:E = 80:20$), we found that overnight refluxing in benzene with Bu_3SnH (1 equiv.) and azoisobutyronitrile (AIBN) (cat.) gave a 70% isolated yield of pure (*E*)-isomer **4** after column chromatography. No cyclisation product involving the β-position of the double bond and the imide carbonyl carbon was identified. We also discovered that the titanate complex $LiTi(OPr^i)_4(SPh)$,[18] easily prepared from PhSLi (BuLi–PhSH) and $Ti(OPr^i)_4$ in THF at 0 °C, isomerised **4** at −25 °C over 18 h to a 98:2 $E:Z$ mixture in 66% isolated yield. Details of this new procedure for low temperature isomerisation will be published elsewhere.

To complete the synthesis, the imide of the (*E*)-enoate ester **4** was chemoselectively reduced with $NaBH_4$ to the alcohol-amide **5** in a MeOH–THF mixture at −20 °C without reduction of the double bond. We found it unnecessary to use HCl-saturated EtOH which has been used by other workers[19] in reducing imides. The alcohol-amide **5** was isolated as a crystalline solid in very high yield (>90%) and, interestingly, as a single diastereoisomer. For final conversion to the radical precursor **6**, standard methods developed by other workers in the field, such as PhSH–*p*-TsOH[1a,b] and PhSSPh–Bu_3P,[1c] did not result in clean substitution. Ultimately, we found low temperature (<−20 °C) treatment with PhSH (3 equiv.) and $BF_3{\cdot}OEt_2$ (3 equiv.) in CH_2Cl_2 to serve the purpose, producing the desired product as a mixture of diastereoisomers (*ca.* 1:1) as an oil in 75% isolated yield after flash chromatography. The final target was the only compound in the series which required a high resolution mass for characterisation. All the other intermediates were crystalline solids and gave satisfactory combustion microanalyses. Scheme 3 summarises the conversion of **3** to **6**.



Scheme 3 *Reagents and conditions:* i, $NaIO_4$, EtOH, H_2O; ii, $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 85% over 2 steps; iii, Bu_3SnH, AIBN, reflux, 70%; iv, $NaBH_4$, MeOH, −20 °C, 94%; v, PhSH (3 equiv.), $BF_3{\cdot}Et_2O$, 80%

α,β-Unsaturated esters frequently have been used as radical acceptors for regiocontrolled ring cyclisation[20] in six-membered ring synthesis since for simple heptenyl radicals the 6-*exo* process is only 7 times faster than the 7-*endo* alternative.[21] Of particular interest to our work was the demonstration, by the Marco-Contelles group,[13] that a glucose-derived precursor undergoes radical cyclisation to a six-membered carbocycle using an enoate radical acceptor. Furthermore, the cyclisation proceeded with good stereoselectivity under the directing influence of an allylic/homoallylic ketal functionality. Cyclisation of our precursor **6** was realised under the normal conditions of slow addition (10 h addition, 48 h reflux) of Bu_3SnH (3.5 equiv.) and AIBN (cat.) to a dry, deoxygenated benzene solution of **6** at reflux temperature. Chromatography of the product furnished the tricyclic isoindolone in 60% yield (Scheme 4). It was then

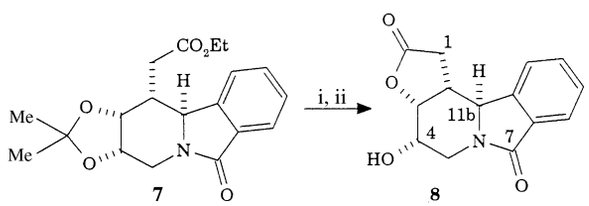


Scheme 4 *Reagents and conditions:* i, Bu_3SnH, AIBN, reflux, 60%

established that essentially the same result (56% yield after chromatography) could be realised using less reagent (1.5 equiv.

Bu_3SnH) and a shorter reaction time (10 min addition, 4 h reflux). No product due to hydrogen reduction of the phenylsulfanyl group could be isolated in any of the reactions, indicating that the cyclisation is much faster than reduction and that, consequently, a relatively high concentration of tin hydride may be tolerated. HPLC analysis of the chromatography fraction revealed it to be a 8:2 mixture of diastereoisomers. A single recrystallisation from ethyl acetate–hexane afforded the major component, which was pure by HPLC. From ^{1}H and ^{13}C NMR spectra it was evident that **7** was a single, cyclised diastereoisomer from the loss of the phenylsulfanyl and enoate ester double bond protons and the appearance of three new signals corresponding to protons at C-1, -1a and -10b (see Scheme 4 for numbering). In order to decide which of the four possible diastereoisomers was actually produced, the protons were configurationally assigned using vicinal coupling constants from 2D COSY and decoupling experiments. Assuming a chair conformation for the new piperidine ring, from the doublet for H-10b (J^3 11.2 Hz) it became clear that H-1 and H-10b, both flanking the new σ-bond from the cyclisation, are in a *trans*-diaxial relationship. Furthermore, since H-1 and H-2 are in a *gauche* relationship (J 3.2 Hz) by NMR spectral analysis, the absolute configurations at C-1 and C-10b could be established as (1*R*,10b*S*) as shown in the diagram, with the C-10b hydrogen, the ethoxycarbonylmethylene group at C-1 and the two D-ribose-derived oxygens at carbons 2 and 3 in an all *cis*-orientation.

In order to provide unequivocal support in favour of *cis*-stereochemistry between the C-1 and C-2 substituents, a *cis*-lactone was prepared. To this end, the cyclisation product **7** underwent successive hydrolytic treatment with acid and base, for cleavage of the ketal and ester groups respectively, to afford the acid-diol which was isolated but not characterised. Lactonisation with dicyclohexylcarbodiimide (DCC) in refluxing CH_2Cl_2 afforded (3a*R*,4*S*,11b*S*,11c*R*)-3a,4,5,11c-tetrahydro-4-hydroxyfuro[3′,2′:3,4]pyrido[2,1-*a*]isoindol-2(1*H*), 7(11b*H*)-dione **8** in 34% overall yield for the three steps. Compound **8** gave an anticipated large *trans*-diaxial coupling constant (J^3 9.6 Hz) between H-11b and H-11c as well as a carbonyl stretch in the IR spectrum at 1770 cm^{-1} for the lactone ring, thus confirming the *cis*-stereochemistry as postulated (Scheme 5).



Scheme 5 *Reagents and conditions:* i, H_3O^+, reflux, HO^-; ii, DCC

Gratified with the high level of stereoselectivity of cyclisation, albeit to give an unwanted *cis*-relationship between the benzylic hydrogen and ethoxycarbonylmethylene group (translating to an undesired *trans* D/E ring fusion in the Tacaman skeleton), we focused our attention on the importance of the allylic/homoallyic ketal grouping. Marco-Contelles has recently[13] demonstrated high stereoselectivity (93:7) in the cyclisation of chiral carbohydrate-derived chains to furnish six-membered carbocycles. Of note regarding our work was the use of both of the crucial structural elements, the enoate ester radical acceptor terminus and a *trans*-1,3-dioxolane ketal grouping attached to the allylic/homoallylic positions of the chain. The stereoselectivity was rationalised in terms of a chair-like transition state with the substituents, including the all-important radical terminus, occupying quasi-equatorial positions. Extending these ideas to our own system, the question of conformational preference in the transition state and the possible mediating effect of the ketal grouping arises. Analysis of the two conformers in which the ethoxycarbonylmethylene group is quasi-equatorial suggests that an H ··· H *gauche* 1,2-allylic relationship leading to the observed product is preferred to an H ··· C–O interaction (Fig. 1).

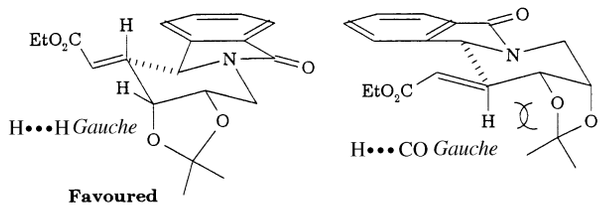
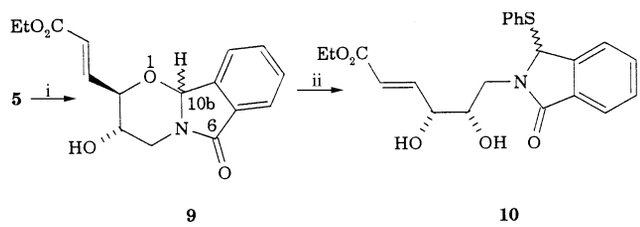


Fig. 1

As an extension of this line of thinking, it was decided to study the stereoselectivity of cyclisation of **6** as its unprotected 1,2-diol. To this end, the ketal-alcohol-amide **5** was deprotected in refluxing acidified EtOH to afford the [1,3]oxazino[2,3-*a*]-isoindolone derivative **9** *via* intramolecular cyclisation involving the liberated allylic hydroxy group. The configuration at C-10b was not assigned, but is likely to be *S* (α-H). Treatment with an excess of PhSH (5 equiv.) and *p*-TsOH (1 equiv.) furnished a low yield (44%) of the target **10** as a single diastereoisomer (Scheme 6). Radical cyclisation with Bu_3SnH (1.5 equiv.) and



Scheme 6 *Reagents and conditions:* i, H_3O^+, reflux, 66%; ii, PhSH, *p*-TsOH, 44%

AIBN (cat.) in refluxing benzene as before gave a cyclised product (60%) after column chromatography which proved to be a 1:1:1 mixture of three diastereoisomers by HPLC and ^{1}H NMR spectral analysis, thus confirming the importance of the isopropylidene ketal as a stereo-directing auxiliary.

Conclusion

In conclusion, this study reports the first application of benzylic α-acylamino radicals in nitracycle synthesis for potential application in the indole and isoquinoline alkaloid arena. Furthermore, it highlights the potential of an allylic/homoallylic ketal grouping for controlling the diastereoselectivity of 6-*exo*-*trig* radical cyclisations to nitracycles. Regarding the Tacaman skeleton, although this study translates to an undesired *trans*-relationship at the D/E ring junction, it has succeeded in demonstrating that the absolute configuration of the benzylic position translating to C-3 in the alkaloid may be controlled. Reduction of the lactam carbonyl group of the cyclised product **7** would provide an efficient entry into stereoselectively functionalised benzo[*a*]indolizidines.[22]

Future research will focus on applying the methodology to a more advanced model for the Tacaman skeleton.

Experimental

IR spectra were recorded on a Perkin-Elmer Paragon 1000 IR spectrophotometer in chloroform. High performance liquid chromatography (HPLC) was carried out on a Waters 510 instrument with a 440 Absorbance Detector. ^{1}H and ^{13}C NMR spectra were recorded on either a Varian VXR-200 (at 200.06 MHz for ^{1}H and 50.31 MHz for ^{13}C) or a Varian Unity 400 (at

399.95 MHz for ^{1}H and 100.58 MHz for ^{13}C) spectrometer in the solvent specified. Chemical shifts (δ) are quoted using residual chloroform (δ 7.24) or tetramethylsilane as an internal standard; *J* values are given in Hz. Mass spectra were recorded on a VG micromass 16F mass spectrometer at 70 eV or at the mass spectrometry unit in the Cape Technicon. Thin layer chromatography (TLC) was performed on aluminium plates coated with Merck silica gel $60F_{254}$. Compounds were visualised with iodine, or by spraying with either ceric ammonium nitrate in 9 M H_2SO_4 or a 2.5% solution of anisaldehyde in H_2SO_4–EtOH (1:10) followed by heating at 100 °C. Column chromatography was carried out on silica gel 60 (Merck 7734) using ethyl acetate–hexane mixtures. Mps were recorded on a Reichert Jung hot-stage melting point apparatus and are uncorrected. Elemental analyses for C, H and N were carried out using a Heraeus CHN rapid combustion analyser. Optical rotations were determined in the solvents indicated at 20 °C using a Perkin-Elmer 141 polarimeter. For the radical cyclisation reactions, the benzene solvent was distilled from sodium and deoxygenated with nitrogen prior to use. *O*-Benzylhydroxylamine hydrochloride and tributyltin hydride were purchased from Aldrich Chemical Company.

2,3-*O*-Isopropylidene-D-ribofuranose 1 [9,10]

To a suspension of D-ribose (5.0 g, 33.4 mmol) in acetone (150 cm^3) at 0 °C was added conc. H_2SO_4 (2 cm^3, 37.5 mmol) dropwise. The reaction was stirred for a further 2 h before being quenched with KOH (4.5 g, 80.2 mmol) in MeOH (50 cm^3) at 0 °C. To the suspension was added K_2CO_3 (2.5 g, 18.1 mmol), and the mixture left stirring for 0.5 h. After the solids had been filtered off and washed with acetone, the solvent was removed under reduced pressure, leaving a syrup of **1** (6.2 g, 32.6 mmol, 98%) which could be used without further purification. For characterisation purposes a sample was chromatographed (500 mg) to give pure **1** as a syrup (0.33 g, 66%); δ_H(200 MHz, $CDCl_3$) major epimer: 1.23 and 1.48 (6 H, 2 × s), 3.55 (2 H, br s, OH), 3.68 (2 H, d, *J* 3.3, H-5), 4.36 (1 H, t, *J* 3.3, H-4), 4.50 (1 H, d, *J* 6.0, H-3), 4.79 (1 H, d, *J* 6.0, H-2), 5.48 (1 H, s, H-1); δ_C (50 MHz, $CDCl_3$) major epimer: 24.6, 26.0, 63.0 (C-5), 81.0 (C-4), 86.5 (C-3), 87.4 (C-2), 102.5 (C-1), 112.0 (ketal).

1-Benzyloxyimino-2,3-*O*-isopropylidene-D-ribose 2

To a solution of crude **1** (4.61 g, 24.3 mmol) in CH_2Cl_2 (25 cm^3) and pyridine (10 cm^3) was added *O*-benzylhydroxylamine hydrochloride (3.95 g, 24.7 mmol) at 0 °C. The mixture was stirred for 15 h after which time an ice-cold solution of dilute aqueous HCl was added until the mixture became acidic. The product was extracted into ethyl acetate and the organic phases washed with saturated aqueous $NaHCO_3$ and brine. Drying and evaporation of solvent afforded crude **2** which was recrystallised from ethyl acetate–hexane to give pure **2** (3.5 g, 11.9 mmol, 50% for 2 steps), mp 95–96 °C [(*E*)-isomer] (Found: C, 61.30; H, 7.27; N, 4.77. $C_{15}H_{21}NO_5$ requires C, 61.0; H, 7.17; N, 4.74%); $[\alpha]_D$ −32.2 (*c* 4.9 in EtOH); ν_{max}($CHCl_3$)/cm^{-1} 3585, 3015, 1600; δ_H(200 MHz, $CDCl_3$) (*E*)-isomer: 1.32 (3 H, s,), 1.43 (3 H, s), 2.6–3.4 (2 H, br s, OH), 3.5–3.8 (3 H, m, H-4 and H-5), 4.12 (1 H, dd, *J* 6.2, 8.4, H-3), 4.74 (1 H, dd, *J* 6.2, 7.2, H-2), 5.07 (2 H, s, $PhCH_2$), 7.2–7.4 (5 H, m), 7.50 (1 H, d, *J* 7.2, H-1); δ_C(50 MHz, $CDCl_3$) (*E*)-isomer: 25.9, 28.2, 64.6 (C-5), 70.2 (C-4), 75.6 (C-2), 76.7 ($PhCH_2$), 78.3 (C-3), 110.7 (ketal), 128.8, 128.9, 129.0, 137.7 (aromatic), 149.5 (C-1); *m/z* 295 (M^+, 1%), 280 ($M^+ - 15$, 2.6), 91 (100), 43 (39).

1-Phthalimido-2,3-*O*-isopropylidene-D-ribose 3

To a solution of **2** (4.0 g, 13.6 mmol) in dry THF was added $LiAlH_4$ (2.1 g, 54.3 mmol) in small portions at 0 °C. The reaction was left stirring for 24 h after which time water (8 cm^3) was added slowly at 0 °C followed by triethylamine (45 cm^3). The slurry was stirred for an additional 0.5 h and the white precipitate then filtered off using Celite. After copious washing of the precipitate with Et_3N–MeOH–EtOAc (20:70:10, 3 × 50 cm^3), removal of the solvent under reduced pressure, with azeotropic removal of H_2O with benzene, furnished crude 1-amino-2,3-*O*-isopropylidene-D-ribose (2.05 g). The latter was then dissolved in dichloromethane (25 cm^3), cooled to 0 °C and triethylamine (10 cm^3) and *N*-ethoxycarbonylphthalimide (3.06 g, 14 mmol) added. After 18 h the volume of solvent was reduced and the residue chromatographed directly with ethyl acetate–hexane to give crystalline **3** (2.8 g, 8.2 mmol, 60% for 2 steps), mp 129–133 °C (Found: C, 59.56; H, 5.92; N, 4.20. $C_{16}H_{19}NO_6$ requires C, 59.81; H, 5.96; N, 4.36%); $[\alpha]_D$ −66 (*c* 0.5 in MeOH); ν_{max}($CDCl_3$)/cm^{-1} 3600, 2988, 2938, 1773, 1716; δ_H(400 MHz, $CDCl_3$) 1.26 (3 H, s), 1.46 (3 H, s), 3.0 (1 H, br s, OH), 3.60 (1 H, br s, OH), 3.73 (1 H, dd, *J* 6.3, 11.9, H-5), 3.86–3.95 (2 H, m, H-4, H-5), 3.92 (1 H, dd, *J* 3.6, 13.8, H-1), 3.99 (1 H, dd, *J* 9.8, 13.8, H-1), 4.14 (1 H, dd, *J* 5.8, 8.9, H-3), 4.62 (1 H, ddd, *J* 3.6, 5.8, 9.8, H-2), 7.6–7.8 (4 H, aromatic); δ_C(100 MHz, $CDCl_3$) 25.8, 27.8, 38.8 (C-1), 64.7 (C-5), 69.5 (C-4), 74.3 (C-2), 76.4 (C-3), 109.5 (ketal), 123.3, 132.1, 133.9 (aromatic), 168.5 (CO); *m/z* 306 ($M^+ - CH_3$, 7%), 161 (22), 160 (33), 59 (100), 43 (40).

Ethyl (4*R*,5*S*)-6-phthalimido-4,5-(propane-2,2-diyldioxy)hex-2-enoate 4

To a solution of **3** (2.0 g, 6.23 mmol) in ethanol (100 cm^3) was added sodium periodate (2.0 g, 9.32 mmol) in water (50 cm^3) at 0 °C. The solution was stirred for 18 h after which time the volume of solvent was reduced and the crude product extracted with ethyl acetate. The organic phase was washed with brine, dried and the solvent evaporated to afford crude (2*S*,3*S*)-4-phthalimido-2,3-(propane-2,2-diyldioxy)butanal (1.71 g, 5.9 mmol, 95%) which was dissolved in dichloromethane (100 cm^3), cooled to 0 °C and (ethoxycarbonylmethylene)triphenylphosphorane (2.46 g, 7.08 mmol) added. The mixture was stirred overnight at room temperature, the solvent removed under reduced pressure and the residue chromatographed with ethyl acetate–hexane (4:6) to afford **4** (1.9 g, 5.30 mmol, 85% for 2 steps) as a mixture (*E*:*Z* = 20:80 by ^{1}H NMR) of isomers.

Isomerisation of (*E*)/(*Z*)-4 to (*E*)-4

To a solution of (*E*)/(*Z*)-**4** (1.0 g, 2.8 mmol) in benzene (25 cm^3) was added tributyltin hydride (0.8 cm^3, 2.97 mmol) and azoisobutyronitrile (AIBN) (25 mg, 0.15 mmol) and the mixture refluxed for 18 h. After removal of solvent under reduced pressure the residue was chromatographed to give pure (*E*)-**4** (0.7 g, 70%), mp 123–124 °C (Found: C, 63.28; H, 5.86; N, 3.73. $C_{19}H_{21}NO_6$ requires C, 63.50; H, 5.89; N, 3.90%); $[\alpha]_D$ −110.4 (*c* 0.5 in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3022, 1774, 1717, 1662, 1615; δ_H(400 MHz, $CDCl_3$) 1.28 (3 H, t), 1.31 (3 H, s), 1.55 (3 H, s), 3.40 (1 H, dd, *J* 3.3, 13.8, H-6), 3.79 (1 H, dd, *J* 10.4, 13.8, H-6), 4.19 (2 H, q), 4.68 (1 H, ddd, *J* 3.3, 6.6, 10.4, H-5), 4.86 (1 H, ddd, *J* 1.6, 5.1, 6.6, H-4), 6.24 (1 H, dd, *J* 1.6, 15.6, H-2), 6.93 (1 H, dd, *J* 5.1, 15.6, H-3), 7.66–7.84 (4 H, m); δ_C(100 MHz, $CDCl_3$) 14.2, 25.7, 27.7, 39.6 (C-6), 60.7 (CH_2 of Et), 74.5 and 75.9 (C-4 and C-5), 110.0 (ketal), 123.3, 123.8 (C-2), 132.0, 134.0, 140.3 (C-3), 165.6 and 168.1 (2 × CO); *m/z* 359 (M^+, 1.2%), 344 ($M^+ - 15$, 22), 199 (51), 160 (100), 141 (19).

Ethyl (2*E*,4*R*,5*S*)-6-(1,3-dihydro-3-hydroxy-1-oxoisoindol-2-yl)-4,5-(propane-2,2-diyldioxy)hex-2-enoate 5

To a solution of **4** (0.78 g, 2.19 mmol) in THF (12 cm^3) and MeOH (30 cm^3) cooled to −40 °C was added sodium boranuide (0.5 g, 14 mmol). The reaction temperature was kept below −20 °C for 1.5 h, after which time the reaction was quenched with aqueous NH_4Cl and the product extracted into ethyl acetate following removal of the methanol under reduced pressure. The organic phase was washed with brine, dried and the solvent evaporated to give crystalline **5** (0.74 g, 2.05 mmol, 94%) pure enough by TLC for the next step. For characterisation purposes a sample was recrystallised from CCl_4–hexane, mp 121–126 °C (Found: C, 62.81; H, 6.42; N, 3.76. $C_{19}H_{23}NO_6$ requires C,

63.15; H, 6.42; N, 3.87%); $[\alpha]_D$ −33.6 (*c* 0.5 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3557, 3368, 1703; δ_H(200 MHz, $CDCl_3$) 1.27 (3 H, t), 1.34 (3 H, s), 1.60 (3 H, s), 3.31 (1 H, dd, *J* 10.2, 14.3, H-6), 3.70 (1 H, br s, OH), 3.77 (1 H, dd, *J* 2.5, 14.3, H-6), 4.16 (2 H, q), 4.59 (1 H, ddd, *J* 2.5, 7.1, 10.2, H-5), 4.82 (1 H, ddd, *J* 1.6, 5.6, 7.1, H-4), 6.07 (1 H, d, *J* 9.9, benzylic H), 6.15 (1 H, dd, *J* 1.6, 15.6, H-2), 6.90 (1 H, dd, *J* 5.6, 15.6, H-3), 7.4–7.8 (4 H, m); δ_C(50 MHz, $CDCl_3$) 14.2, 25.4, 27.8, 40.3 (C-6), 60.7 (Et), 76.2, 77.0 (C-4 and C-5), 82.7 (benzylic), 109.8 (ketal), 123.4 (2 C), 123.6 (C-2), 129.8, 131.5, 132.3, 141.7 (C-3), 144.0, 165.8 and 167.3 (2 × CO); *m/z* 361 (M^+, 0.9%), 346 ($M^+ - 15$, 7), 133 (100).

Ethyl (2*E*,4*R*,5*S*)-6-(1,3-dihydro-3-phenylsulfanyl-1-oxoisoindol-2-yl)-4,5-(propane-2,2-diyldioxy)hex-2-enoate 6

Thiophenol (0.47 cm^3, 4.6 mmol) was added to a solution of **5** (553 mg, 1.53 mmol) in CH_2Cl_2 (12 cm^3) followed by boron trifluoride–diethyl ether complex (0.56 cm^3, 4.60 mmol) which was added dropwise at −78 °C. The reaction was stirred for 4 h at a temperature below −20 °C, after which time it was quenched by adding aqueous sodium carbonate. The crude product was extracted into ethyl acetate, dried and the solvent evaporated to give **6** (490 mg, 1.08 mmol, 2 epimers, 80% based on 70 mg recovered starting material) as an oil after chromatography; δ_H(400 MHz, $CDCl_3$) major epimer: 1.2–1.4 (6 H, m, Me), 1.50 (3 H, s, Me), 3.41 (1 H, dd, *J* 4.0, 14.2, H-6), 3.52 (1 H, dd, *J* 10.6, 14.2, H-6), 4.16 (2 H, q), 4.51 (1 H, m, H-5), 4.79 (1 H, ddd, *J* 1.6, 5.2, 6.4, H-4), 5.82 (1 H, s, benzylic), 6.18 (1 H, dd, *J* 1.6, 15.6, H-2), 6.8–7.7 (10 H, m, H-3 and aromatic); δ_C(100 MHz, $CDCl_3$) major epimer: 14.2 (Me of Et), 25.6, 27.8, 40.4 (C-6), 60.6 (CH_2 of Et), 66.6, 76.1 and 77.4 (C-4, C-5 and benzylic), 109.8 (ketal), 123.1–135.3 (C-2 and aromatics), 140.9 (C-3), 142.7 (aromatic), 165.7 and 167.7 (2 × CO) (Found: M^+, 453.1591. $C_{25}H_{27}NO_5S$ requires *M*, 453.1610).

(1*R*,2*R*,3*S*,10b*S*)-1,2,3,10b-Tetrahydro-1-ethoxycarbonylmethyl-2,3-(propane-2,2-diyldioxy)pyrido[1,2-*a*]isoindol-6(4*H*)-one 7

To a refluxing solution of **6** (490 mg, 1.08 mmol) in benzene (30 cm^3) was added a solution of tributyltin hydride (0.44 cm^3, 1.64 mmol) and AIBN (10 mg, 0.06 mmol) in benzene (20 cm^3) dropwise over 10 min. The solution was refluxed until no more starting material remained by TLC (4 h), the solvent was removed under reduced pressure and the residue chromatographed with ethyl acetate–hexane. The product fraction (225 mg, 0.65 mmol, 60%) was recrystallised from ethyl acetate–hexane to furnish HPLC pure (1*R*,2*R*,3*S*,10b*S*)-1,2,3,10b-tetrahydro-1-ethoxycarbonylmethyl-2,3-(propane-2,2-diyldioxy)pyrido[2,1-*a*]isoindol-6(4*H*)-one **7** (130 mg, 0.38 mmol, 35%), mp 149–152 °C (Found: C, 65.98; H, 6.95; N, 4.02. $C_{19}H_{23}NO_5$ requires C, 66.07; H, 6.70; N, 4.05%); $[\alpha]_D$ 26.2 (*c* 1.0 in EtOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 3053, 2986, 1730, 1690, 1617; δ_H(400 MHz, $CDCl_3$) 1.23 (3 H, t), 1.37 (3 H, s), 1.54 (3 H, s), 2.02 (1 H, m, *J* 3.2, 3.2, 6.8, 11.2, H-1), 2.88 (1 H, dd, *J* 3.2, 15.9, H-1a), 2.93 (1 H, dd, *J* 6.9, 15.9, H-1a), 3.32 (1 H, dd, *J* 6.6, 13.8, H-4), 4.12 (2 H, q), 4.28 (1 H, dd, *J* 6.4, 13.8, H-4), 4.38 (1 H, q, *J* 3 × 6.4, H-3), 4.45 (1 H, d, *J* 11.2, H-10b), 4.47 (1 H, dd, *J* 3.2, 6.4, H-2), 7.49 (3 H, m), 7.85 (1 H, m); δ_C(100 MHz, $CDCl_3$) 14.2, 25.5, 27.8, 33.1 (C-1a), 39.8 (C-1), 40.4 (C-4), 56.3 (C-10b), 60.8 (CH_2 of Et), 71.1 (C-3), 74.2 (C-2), 109.2 (ketal), 123.3, 124.2, 128.6, 131.2, 132.6 and 144.1 (aromatics), 166.9 and 171.2 (2 × CO); *m/z* 345 (M^+, 73), 330 ($M^+ - 15$, 5), 287 (45), 200 (100), 145 (43), 43 (99).

(3a*R*,4*S*,11b*S*,11c*R*)-3a,4,5,11c-Tetrahydro-4-hydroxyfuro-[3′,2′:3,4]pyrido[2,1-*a*]isoindol-2(1*H*),7(11b*H*)-dione 8

To a solution of **7** (98 mg, 0.28 mmol) in EtOH (10 cm^3) and water (1 cm^3) was added conc. H_2SO_4 (0.04 cm^3, 0.72 mmol) and the solution refluxed for 3 h. Potassium hydroxide (121 mg, 2.16 mmol) was added and the solution stirred for 12 h at room temperature. The pH was adjusted to 8 with conc. HCl and the volume of solvent reduced *in vacuo* to produce a residue which was filtered and washed copiously with acetone and acetic acid. The solvent of the filtrate was then removed under reduced pressure with the acetic acid azeotroped off with toluene. A portion of the crude product (52 mg, 0.19 mmol) was dissolved in THF–CH_2Cl_2 (6 cm^3, 1:1) and dicyclohexylcarbodiimide (415 mg, 2.01 mmol) added. The solution was refluxed for 7 h and stirred for a further 12 h at room temperature. The solids were then filtered off and washed with hot ethyl acetate. Removal of solvent followed by chromatography gave **8** (25 mg, 0.096 mmol, 51% based on portion taken), mp 223–230 °C (ethyl acetate–acetone) (Found: C, 64.89; H, 5.14; N, 5.42. $C_{14}H_{13}NO_4$ requires: C, 64.86; H, 5.05; N, 5.40%); $[\alpha]_D$ +37.1 (*c* 0.64 in EtOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 1770, 1700; δ_H(400 MHz, CD_3COCD_3) 2.75 (1 H, m, *J* 5.1, 7.2, 8.8, 9.6, H-11c), 2.93 (1 H, dd, *J* 5.1, 17.4, H-1), 3.04 (1 H, dd, *J* 8.8, 17.4, H-1), 3.42 (1 H, dd, *J* 6.0, 13.3, H-5), 4.10 (1 H, dd, *J* 4.4, 13.3, H-5), 4.25 (1 H, m, H-4), 4.69 (1 H, d, *J* 9.6, H-11b), 4.73 (1 H, dd, *J* 3.0, 7.2, H-3a), 4.98 (1 H, d, *J* 5.4, OH), 7.50–7.74 (4 H, m, aromatic); δ_C(100 MHz, CD_3COCD_3) 34.7 (C-1), 40.2 (C-5), 42.8 (C-11c), 59.3 (C-11b), 66.6 (C-4), 80.0 (C-3a), 123.1, 123.9, 129.2, 132.4, 133.0 and 146.7 (aromatic), 167.1 and 176.3 (2 × CO); *m/z* 259 (M^+, 100%), 217 (68), 132 (97).

(2*R*,3*S*)-3,4-Dihydro-2-[(*E*)-2-ethoxycarbonylethenyl]-3-hydroxy-2*H*-[1,3]oxazino[2,3-*a*]isoindol-6(10b*H*)-one 9

Water (1 cm^3) and conc. H_2SO_4 (0.10 cm^3, 1.88 mmol) were added to a solution of **5** (606 mg, 1.68 mmol) in EtOH (7 cm^3). The solution was refluxed for 12 h, after which time it was neutralised by adding aqueous sodium carbonate. After removal of EtOH under reduced pressure, the mixture was extracted with ethyl acetate and the organic extracts dried and the solvent evaporated. Chromatography of the residue yielded **9** (335 mg, 1.10 mmol, 66%), mp 170–173 °C (ethyl acetate–hexane) (Found: C, 63.46; H, 5.69; N, 4.62. $C_{16}H_{17}NO_5$ requires C, 63.34; H, 5.65; N, 4.62%); $[\alpha]_D$ −80 (*c* 0.7 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3410, 1710, 1660, 1618; δ_H(400 MHz, CD_3SOCD_3) 1.20 (3 H, t), 3.09 (1 H, dd, *J* 10.1, 12.5, H-4), 3.22 (1 H, ddd, *J* 5.4, 9.4, 10.1, H-3), 4.12 (2 H, q), 4.32 (1 H, dd, *J* 5.4, 12.5, H-4), 4.38 (1 H, ddd, *J* 1.7, 4.4, 9.4, H-2), 5.79 (1 H, d, *J* 5.6, OH), 5.94 (1 H, s, H-10b), 6.00 (1 H, dd, *J* 1.7, 15.8, H-2b), 7.01 (1 H, dd, *J* 4.4, 15.8, H-2a), 7.58–7.74 (4 H, m); δ_C(100 MHz, CD_3SOCD_3) 14.1, 44.3 (C-4), 60.7, 66.0 (C-3), 79.5 (C-2), 84.5 (C-10b), 122.9, 123.6, 123.8, 130.3, 132.3 (2 × C), 140.3 and 142.9 (C-2a, C-2b and aromatic), 166.3 (2 × CO); *m/z* 258 ($M^+ - 45$, 9%), 175 (100), 146 (26), 132 (94).

Ethyl (2*E*,4*R*,5*S*)-6-(1,3-dihydro-3-phenylsulfanyl-1-oxoisoindol-2-yl)-4,5-dihydroxyhex-2-enoate 10

Thiophenol (0.37 cm^3, 3.57 mmol), toluene-*p*-sulfonic acid (130 mg, 0.75 mmol) and magnesium sulfate (1 g) were added to a solution of **9** (214 mg, 0.71 mmol) in CH_2Cl_2 (6 cm^3) at room temperature. After stirring the solution for 24 h, aqueous sodium carbonate was added and the product extracted into CH_2Cl_2. Drying of the organic extracts, removal of solvent and chromatography furnished **10** (128 mg, 0.31 mmol, 44%) as an oil and a single diastereomer; δ_H(200 MHz, $CDCl_3$) 1.25 (3 H, t), 3.53 (1 H, br s, OH), 3.97 (1 H, dd, *J* 3.1, 14.8, H-6), 4.05 (2 H, m, H-4 and H-5), 4.14 (2 H, q), 4.27 (1 H, dd, *J* 3.6, 14.8, H-6), 4.83 (1 H, br d, *J* 4.1, OH), 6.04 (1 H, s), 6.18 (1 H, dd, *J* 1.8, 15.7, H-2), 6.95–7.67 (10 H, m, H-3 and aromatic); δ_C(50 MHz, $CDCl_3$), 14.2, 42.0 (C-6), 60.5 (CH_2 of Et), 69.4 (benzylic), 71.6 and 74.3 (C-4 and C-5), 122.6, 123.9, 124.6, 128.3, 129.4 (3 C), 130.0, 131.3, 132.9, 136.1 (2 C), 144.5 and 147.4 (C-2, C-3 and aromatic), 167.8 and 170.9 (2 × CO) (HRMS: Found M^+, 413.1290. $C_{22}H_{23}NSO_5$ requires for *M*, 413.1297).

Radical cyclisation of 10

To a refluxing solution of **10** (92 mg, 0.22 mmol) in benzene (20

cm^3) was added a solution of tributyltin hydride (0.10 cm^3, 0.37 mmol) and AIBN (10 mg, 0.06 mmol) in benzene (10 cm^3) over a period of 3 h. Refluxing was continued for a further 12 h. After removal of solvent under reduced pressure, the residue was chromatographed to afford the cyclised product as an oil (40 mg, 0.13 mmol, 60%). ^{1}H NMR spectral analysis indicated that cyclisation had occurred to give more than one isomer. HPLC analysis indicated a total of three isomers in equal proportions.

Acknowledgements

We thank the Foundation for Research and Development (FRD) Pretoria for financial support.

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Paper 6/02932I
Received 26*th April* 1996
Accepted 21*st August* 1996