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Stereoselective tetrahydropyrido[2,1-*a*]isoindolone synthesis via carbanionic and radical intermediates: a model study for the Tacaman alkaloid D/E ring fusion

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Abstract

Stereoselective cyclisation of malic acid-derived α-sulfanyllactam (**1**) via radical and carbanionic intermediates affords stereo-defined tetrahydropyrido[2,1-*a*]isoindolones as model compounds for the D/E *cis*-ring fusion of the Tacaman indole alkaloid skeleton. A transition-state model to explain the stereoselectivity is presented.

Keywords: radical and carbanionic cyclisation; indole alkaloid; isoindolone synthesis.

The isoindolone ring system has featured in recent years as a desirable synthetic target in view of its presence in both natural products and synthetic pharmaceuticals with biological activity.[1] Synthetic methodology for C–C bond formation at the isoindolone benzylic position has been dominated by procedures based on the nucleophilic interception of iminium ions,[1c,2] while carbanionic and radical approaches have received far less attention. We recently reported on the stereoselective formation of a substituted tetrahydropyrido[2,1-*a*]isoindolone via intramolecular cyclisation of a benzylic α-benzoylamino radical onto an enoate ester, and this was used as a model for synthesising the Tacaman indole alkaloid D/E ring system.[3] In the latter study, a D-ribose-derived *cis*-isopropylidene grouping in the tether was used as the stereo-directing auxiliary to afford an incorrect *trans* D/E ring fusion for the Tacaman system.[4] We have now extended our original study by synthesising precursor (**1**) in which the tether is derived from L-malic acid, and in this communication we report on stereoselective cyclisation of (**1**) via both radical and carbanionic intermediates to afford model compounds with the desired *cis*-stereochemistry (Fig. 1).

The synthesis of the cyclisation precursor (**1**) proceeded from L-malic acid as follows. Fischer esterification followed by chemoselective reduction according to literature procedures[5] furnished diol (**2**), which was protected as its ketal, and its ester reduced to the known alcohol (**3**).[5,6] Mitsunobu coupling with phthalimide, hydrolysis (ketal) and chemoselective disilylation gave (**4**). Routine conversion of (**4**)

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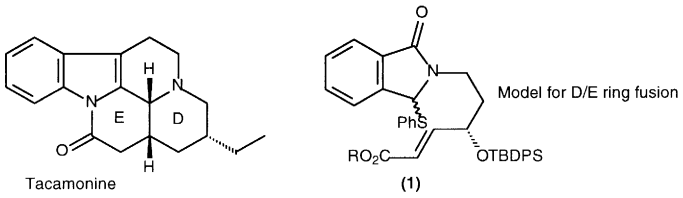
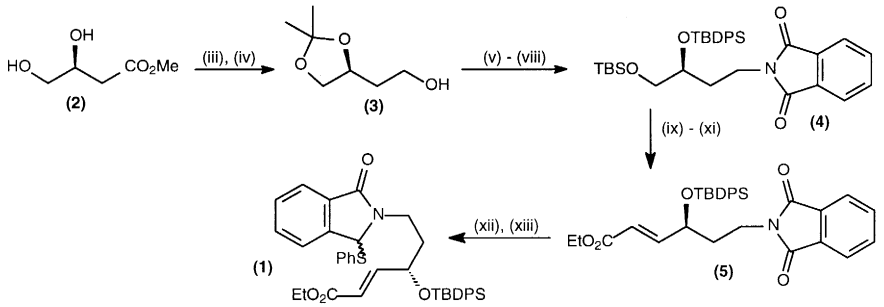


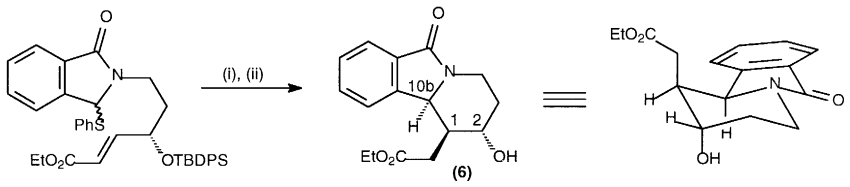
Fig. 1.

(TBS removal, Swern oxidation, Wittig) yielded exclusively the (*E*)-enoate ester (**5**). Chemoselective reduction of the imide ($NaBH_4$) followed by Lewis acid-promoted sulfenylation with thiophenol at low temperature afforded (**1**) in good overall yield for the 13 steps (Scheme 1).



Scheme 1. *Reagents and conditions*: (iii) $(CH_3)_2C(OMe)_2$/*p*-TsOH; (iv) $LiAlH_4$/THF; (v) phthalimide/PPh_3/DEAD/THF (94%); (vi) HCl (1 M)/THF/Δ (85%); (vii) TBSCl/imidazole/CH_2Cl_2 (97%); (viii) TBDPSCl/imid/CH_2Cl_2/DMF; (ix) HF (40%)/CH_3CN (89% for two steps); (x) Swern; (xi) Ph_3PCHCO_2Et/CH_2Cl_2 (96% for two steps); (xii) $NaBH_4$/THF/−40°C (92%); (xiii) PhSH (2 equiv.)/$BF_3 \cdot Et_2O$ (2 equiv.)/CH_2Cl_2/−78°C (92% as two epimers)

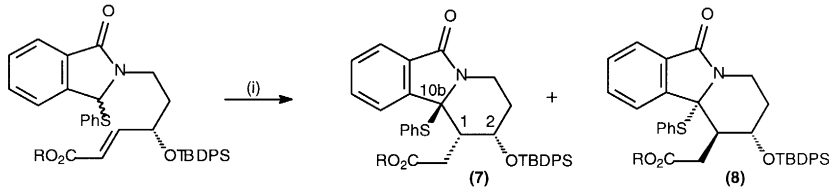
Cyclisation of α-acylamino radicals was introduced in the 1980s and pioneered by Hart and co-workers as a versatile methodology for rapid construction of pyrrolizidine and indolizidine nitracycles.[7] Exposure of (**1**) to standard radical cyclisation[8] conditions (Bu_3SnH/AIBN (cat.)/toluene/Δ) resulted in rapid conversion to a more polar product which was isolated by chromatography in near quantitative yield (97%). Scrutiny of this product by 400 MHz ^1H NMR revealed it to be an inseparable mixture of three diastereomers in an approximate ratio of 4:2:1. Treatment of the mixture with tetrabutylammonium fluoride (TBAF) in THF furnished the desilylated alcohol (**6**) in 55% yield over the two steps as the dominant diastereomer and in crystalline form. The stereochemical assignments at the newly formed asymmetric centres at C-1 and C-10b were made on the basis of the two small vicinal coupling constants between C-1 and its neighbours, C-2 (3.2 Hz) and C-10b (4 Hz), indicating *gauche* relationships. Since a pseudo-axial configuration for the hydrogen at C-10b is obligatory, it followed that the hydrogens at C-1 and C-10b were *cis*. Failure of (**6**) to form a lactone under the TBAF conditions (see carbanionic case) resulted in the ethoxycarbonylmethyl substituent being assigned as β- (Scheme 2).



Scheme 2. *Reagents and conditions*: (i) Bu_3SnH (3 equiv.)/AIBN (cat.)/toluene/Δ; (ii) TBAF/THF (55% as major diastereomer)

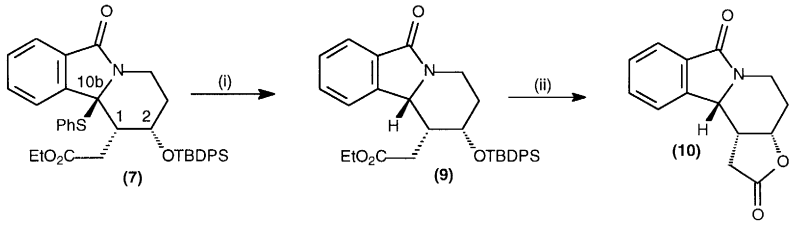
We next examined carbanionic-promoted cyclisation,[9] which was prompted, in part, by the observation that such a process could be brought about by TBAF. In this case the diastereoselectivity was only

modest so we opted for a lower temperature using a stronger base. Furthermore, during the course of the present study Luzzio[10] published his results on a very similar system to ours that lacked the chiral auxiliary (OTBDPS group) as well as having phenylsulfonyl in place of phenylsulfanyl. The Luzzio study utilised NaH/DMSO at rt as the base to afford a modest overall yield (50% for two steps) of product as a 1:1 mixture of diastereomers following desulfonylation. Gratifyingly, addition of (**1**) to LDA (3 equiv.) in THF at −78°C promoted a highly diastereoselective closure producing the two *anti*-isomers (**7**) and (**8**) in 77 and 18% yield, respectively, after column chromatography. Once again, assignment of stereochemistry was based on vicinal coupling constants and the assumption that the phenylsulfanyl group adopts a pseudo-axial configuration in view of the requirement for the N–C and C–C attachment bonds of the five-membered ring to be virtually coplanar (Scheme 3).



Scheme 3. *Reagents and conditions*: (i) LDA (3 equiv.)/THF/−78°C; (**7**):(**8**)=77:18

Reductive desulfurisation of the major diastereomer (**7**) using nickel boride[11] afforded isoindolone (**9**) in high yield (92%) and with retention of configuration at C-10b, thus offering a complementary route to the alternative diastereomer in which the C-1 and C-10b hydrogens are *cis*. Desilylation of (**9**) afforded lactone (**10**), thus vindicating the configurational assignments of the C-1 substituents in compounds (**6**) and (**7**) (Scheme 4).



Scheme 4. *Reagents and conditions*: (i) $NiCl_2/NaBH_4$/aq. EtOH, 92%; (ii) HF (40%)/CH_3CN, 90%

A transition-state model to account for the diastereoselectivity of formation of the major diastereomers (**6**) and (**7**) from the two methodologies identifies two orientational features. Firstly, in both cases the enoate ester adopts an *endo* orientation with respect to the new ring being formed. Secondly, the facial approaches are opposite; in the radical reaction the sterically unencumbered radical at C-10b approaches the enoate ester from its underneath face proximal to the chiral auxiliary (OTBDPS group and α-), whereas the more congested carbanion is forced to approach from the top face so as to minimise steric strain between groups around sulfur and silicon (Fig. 2).

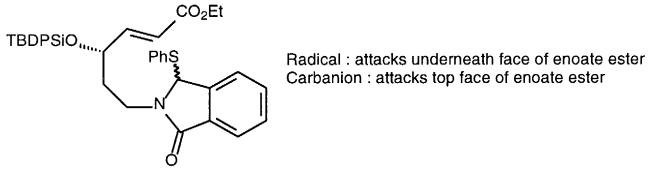


Fig. 2.

Research is in progress on the application of these findings to alkaloid synthesis.

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