Synthesis of the tetrahydroisoquinoline unit in the AB ring system of the novel antitumor-antibiotic tetrazomine

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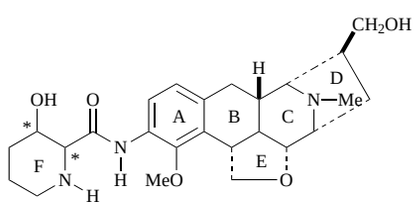
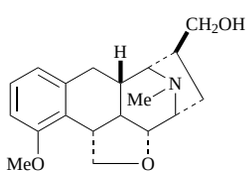
1 PERKIN COMMUNICATION

The elaboration of a polysubstituted 7-amino tetrahydroisoquinoline derivative which embodies the central AB ring system of the novel antitumor-antibiotic tetrazomine, employing a highly selective *ortho* nitration and Jackson tosylamido acetal cyclisation as crucial steps, is reported.

Tetrazomine **1**, a 7-aminotetrahydroisoquinoline derivative which is active against several Gram-positive and Gram-negative bacteria and towards P-388 and L1210 leukemia cell lines,[1] belongs to a rapidly growing group of related compounds which possess potent antitumor or antibiotic properties. These include quinocarcin **2**, the saframycins, naphthyridinomycins, ecteinascidins and bioxalomycins.[2]



1 (proposed structure)



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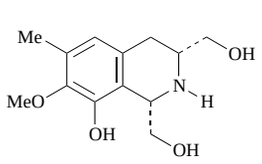
We have reported the total synthesis of MY336-a **3**,[3] structurally related to the AB rings of the natural isoquinoline-based antitumor-antibiotics, employing an extension of the Jackson tosylamido acetal cyclisation.[4] To expand the scope of this synthetic route and taking into account the recent isolation of simple 7-aminotetrahydroisoquinolines,[5] we have focused our attention on the elaboration of compound **4** which contains the



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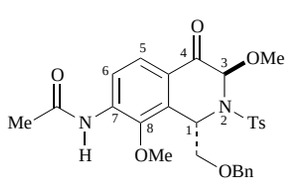

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AB ring system of **1** and may constitute a key intermediate for its total synthesis. Compound **4** possesses protected 7-amino and 1-hydroxymethyl groups, together with appropriate substituents for C-3 functionalisation and stereochemical control at this position through the neighbouring oxo moiety.[6] This is important since there are only scattered references to the preparation of 7-aminotetrahydroisoquinoline derivatives and even less on the synthesis of its congeners bearing the less common and more difficult to elaborate 7,8-difunctional substitution pattern.[7]

Initial efforts towards the installation of the protected 1-hydroxymethyl side chain by our epoxide ring-opening methodology[4a] gave poor results when applied to 2-methoxystyrene oxide **6** (Scheme 1);[6b] however, one-pot addition of benzyloxymethyllithium[8] to *o*-anisaldehyde **5**, followed by trapping of the resulting alkoxide with acetic anhydride, gave 90% of acetate **7**.

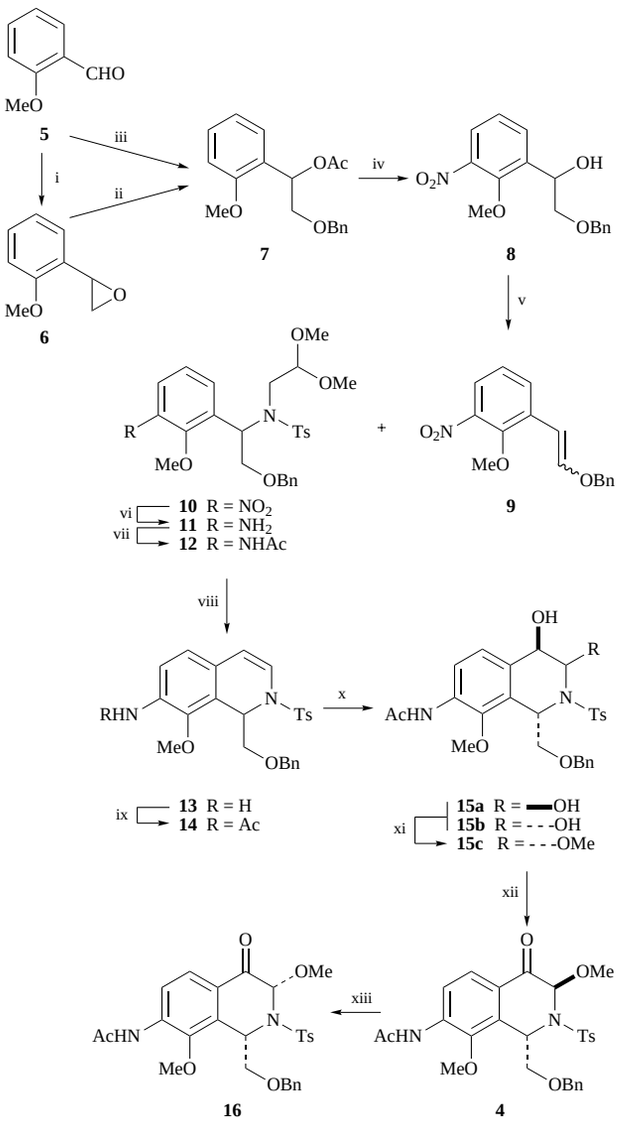
Submission of the latter to nitration with potassium nitrate–trifluoroacetic anhydride in dry chloroform[9] at −20 °C, afforded 92% of nitro alcohol **8** after basic hydrolysis. A reaction temperature of −20 °C was crucial for the high yield and selectivity observed, whilst avoiding undesirably long reaction times; at 0 °C considerable amounts of products resulting from *para* nitration of both aromatic rings were observed and when the transformation was performed at 10 °C the required *o*-nitroanisole became a minor component of a complex mixture.

Building of the heterocyclic ring was accomplished by Mitsunobu amination of benzylic alcohol **8** following García *et al.*[10] with the DIAD–PPh_3 couple, providing tosyl acetal **10** in 69% yield together with 20% of a 3:1 (*E*/*Z*) mixture of elimination products **9**. The formation of these could not be suppressed or even diminished by the addition of pyridine.[11]

Next, catalytic hydrogenation of **10**, with Pd/C, smoothly gave 87% of the readily oxidisable amine **11**, conveniently activated for cyclisation. This was immediately exposed to Jackson cyclisation conditions to afford 1,2-dihydroisoquinoline **13** in 98% yield when 3 equivalents of aqueous 6 mol dm^{-3} HCl were employed; this transformation seems to be general, since related model compounds obtained by the same synthetic scheme were also efficiently cyclised.

Noteworthy is the fact that unlike other routes reported for the elaboration of aminoisoquinolines, such as the Bischler–Napieralski strategy, this Jackson-based sequence did not require previous protection of the amino function;[12] moreover, cyclisation of acetanilide **12** occurred with complete amide hydrolysis, furnishing 94% of **13**.

Acylation of the light and air sensitive 1,2-dihydroisoquinoline **13** furnished 86% of acetanilide **14**, suitable for the required double bond functionalisation by way of a catalytic dihydroxylation with osmium tetraoxide, employing NMO as re-oxidant. This afforded a 3:1 inseparable mixture of compounds, **15a** and **15b**. Molecular mechanics calculations of **14** revealed that the 1-benzyloxymethyl side chain has to adopt a quasi-axial orientation in order to relieve strain with the neighbouring toluene-*p*-sulfonyl group. Therefore, structures **15a** and **15b** were assigned to the mixture of easily interconverting hemiamidals arising from osmium attack on the less hindered face of the double bond.



Scheme 1 *Reagents and conditions*: i, $Me_3S^+HSO_4^-$, CH_2Cl_2–50% NaOH, TBAI (cat.), reflux, 95%; ii, 1. NaBnO, BnOH, 100 °C, overnight; 2. Ac_2O, TEA, CH_2Cl_2 (34%); iii, 1. Bu_3SnCH_2OBn, BuLi, THF, −78 °C, 5 min, then **5**; 2. Ac_2O, −78 °C→RT overnight, 90%; iv, 1. KNO_3, $(F_3CCO)_2O$, $CHCl_3$, −20 °C, 29 h; 2. SMe_2, −20 °C; 3. K_2CO_3, MeOH–H_2O, RT, 92%; v, $TsHNCH_2CH(OMe)_2$, DIAD, PPh_3, THF, reflux, 3 h, **9**, 20%, **10**, 69%; vi, H_2 (4 atm), 10% Pd/C, 2-PrOH, 87%; vii, Ac_2O, TEA, CH_2Cl_2, 0 °C, 92%; viii, 6 mol dm^{-3} HCl, dioxane, reflux, 15 min, **12**→**13**, 94%, **11**→**13**, 98%; ix, Ac_2O, TEA, CH_2Cl_2, 0 °C, 86%; x, 1. OsO_4 (cat.), NMO, acetone–Bu^{t}OH–H_2O (4:2:1), overnight; 2. $NaHSO_3$, 88%; xi, $HC(OMe)_3$, MeOH–CH_2Cl_2, TsOH (cat.), RT, 100%; xii, DMSO, $(F_3CCO)_2O$, −60 °C, 15 min, then TEA, 98%; xiii, BF_3·Et_2O, CH_2Cl_2, −60 °C, 88%

Not surprisingly, however, their acetalisation with methyl orthoformate[4a] quantitatively afforded **15c** as a single product, in agreement with results of molecular mechanics calculations and exhaustive NMR experiments.

Finally, **15c** reacted under Swern conditions (TFAA–DMSO) to give ketone **4** almost quantitatively. The ability of the carbonyl to allow stereochemical inversion of the adjacent center, providing 1,3-*cis*-disubstituted compounds, was demonstrated through the synthesis of **16** by Lewis acid-promoted isomerisation of **4**. Comparative analysis of NOE data of both epimeric ketones and **15c** confirmed their proposed structures and that epimerisation took place during the oxidation step.

In conclusion, we have readily synthesised compound **4** through high-yielding chemistry, and have shown the ability of the Jackson isoquinoline synthesis efficiently to provide polysubstituted 7-aminoisoquinoline derivatives. Compound **4** possesses the AB ring system of tetrazomine and it is a potential key intermediate for its total synthesis. Further study of the C-3 functionalisation of compound **4** is in progress.

Experimental

_N_-[1-Benzyloxymethyl-8-methoxy-2-(_p_-tolylsulfonyl)-1,2-dihydroisoquinolin-7-yl]acetamide 14

A solution of tosylamide **11** (364 mg, 0.708 mmol) in a mixture of anhydrous dioxane (3 cm^3) and 6 mol dm^{-3} HCl (0.35 cm^3, 2.1 mmol), was heated under reflux for 15 min. Then, the reaction was cooled to room temperature, neutralised with saturated $NaHCO_3$ (3 cm^3) and extracted with EtOAc (4 × 25 cm^3). The extract was washed with brine (5 cm^3), dried (Na_2SO_4), concentrated under reduced pressure and chromatographed through a short column, affording **13** (312 mg, 98%) as a highly photosensitive and readily oxidisable oil; ν_{max}(film)/cm^{-1} 3480, 3370, 2920, 2850, 1620, 1500, 1350, 1180, 920 and 750; δ_H(200 MHz, $CDCl_3$) 2.29 (3 H, s, $ArCH_3$), 3.36 (1 H, dd, *J* 4.6, 10.7, CH_2OBn), 3.57 (1 H, dd, *J* 8.3, 10.7, CH_2OBn), 3.62 (3 H, s, 8-OCH_3), 3.78 (2 H, br s, $w_{1/2}$ 14, NH_2), 4.48 (1 H, d, *J* 12.1, OCH_2Ar), 4.59 (1 H, d, *J* 12.1, OCH_2Ar), 5.66 (1 H, ddd, *J* 1.4, 4.6, 8.3, 1-H), 5.94 (1 H, d, *J* 7.4, 4-H), 6.50 (1 H, dd, *J* 1.4, 7.4, 3-H), 6.52 (1 H, d, *J* 8, 5-H), 6.58 (1 H, d, *J* 8, 6-H), 7.10 (2 H, d, *J* 8.3, ArH of toluene-*p*-sulfonyl), 7.25–7.35 (5 H, m, ArH of benzyl) and 7.65 (2 H, d, *J* 8.3, ArH of toluene-*p*-sulfonyl);† δ_C(50 MHz, $CDCl_3$) 21.20, 51.67, 59.61, 69.45, 72.53, 113.45, 115.08, 120.56, 121.40, 121.57, 121.92, 126.51 (2 × C), 127.15, 127.44 (2 × C), 128.00 (2 × C), 129.11 (2 × C), 136.91, 138.05, 139.40, 142.73 and 143.17. Without further purification, a solution of amine **13** (300 mg, 0.67 mmol) in CH_2Cl_2 (12 cm^3) containing triethylamine (0.8 cm^3, 1.96 mmol) was treated at 0 °C with Ac_2O (0.2 cm^3, 0.98 mmol) until complete conversion of the starting material was achieved. Then the reaction was diluted with EtOAc (45 cm^3) and washed successively with 1 mol dm^{-3} HCl (5 cm^3), saturated $NaHCO_3$ (5 cm^3) and brine (5 cm^3). The organic phase was dried, concentrated and chromatographed to afford **14** (282 mg, 86%) as an oil (Found: C, 66.01; H, 5.59; N, 5.74; S, 6.38. $C_{27}H_{28}N_2O_5S$ requires C, 65.84; H, 5.73; N, 5.69; S, 6.51); ν_{max}(film)/cm^{-1} 3380, 3300, 2890, 1690, 1530, 1350, 1180, 1040 and 700; δ_H(200 MHz, $CDCl_3$) 2.18 (3 H, s, CH_3CO), 2.31 (3 H, s, $ArCH_3$), 3.36 (1 H, dd, *J* 5.0, 10.4, CH_2OBn), 3.56 (1 H, dd, *J* 7.9, 10.4, CH_2OBn), 3.60 (3 H, s, 8-OCH_3), 4.44 (1 H, d, *J* 12.2, OCH_2Ar), 4.52 (1 H, d, *J* 12.2, OCH_2Ar), 5.62 (1 H, ddd, *J* 1.3, 5.0, 7.9, 1-H), 5.97 (1 H, d, *J* 7.4, 4-H), 6.66 (1 H, dd, *J* 1.3, 7.4, 3-H), 6.76 (1 H, d, *J* 8.3, 5-H), 7.12 (2 H, d, *J* 8.2, ArH of toluene-*p*-sulfonyl), 7.19–7.35 (5 H, m, ArH of benzyl), 7.53 (1 H, s, NH), 7.64 (2 H, d, *J* 8.2, ArH of toluene-*p*-sulfonyl) and 8.07 (1 H, d, *J* 8.3, 6-H); δ_C(50 MHz, $CDCl_3$), 21.24, 24.45, 51.59, 61.18, 69.47, 72.66, 112.18, 120.56, 121.00, 121.14, 123.30, 126.44 (2 × C), 126.76, 127.25, 127.35 (2 × C), 128.02 (2 × C), 129.32 (2 × C), 130.42, 136.66, 137.79, 143.60, 144.89 and 168.08.

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† *J* Values are given in Hz.

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