A total synthesis of (±)-α-cyclopiazonic acid using a cationic cascade†

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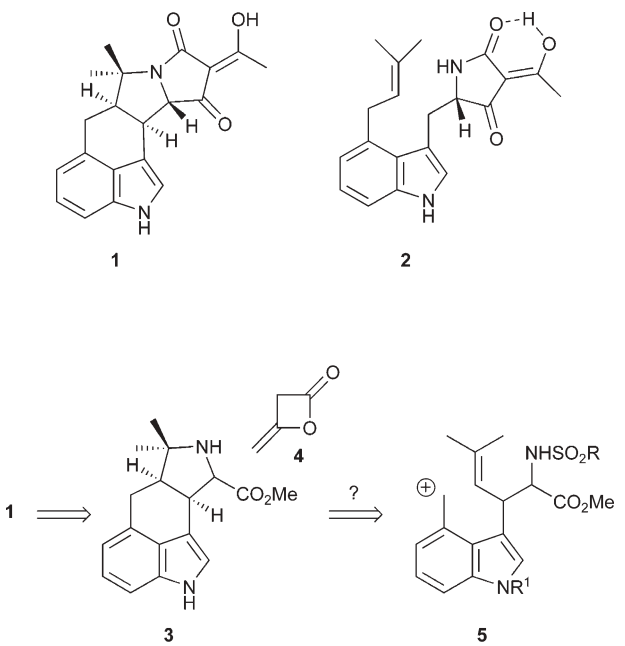
The indolic terpene alkaloid α-cyclopiazonic acid 1 has been prepared in 11 steps from indole-4-methanol 6; the key step is a carbocationic cascade, terminated by a 4-nitrosulfonamide group and initiated by benzylic carbocation formation directly from the intermediate 9, which gives the tetracyclic product 10 in 74% yield.

α-Cyclopiazonic acid (α-CPA) **1** is a major toxic principle of the fungus *Penicillin cyclopium* Westling, which has a world wide distribution and which is often found in stored grain and cereal.[1] Its structure was elucidated some thirty five years ago;[2] since then, its biosynthesis has been the subject of many studies[3] which have shown that β-cyclopiazonic acid **2** is its immediate biological precursor. More recently, it has enjoyed a heightened profile, by reason of its ability to specifically inhibit the Ca^{2+}-ATPase of the sarcoplasmic reticulum, the very origin of its toxicity.[4] This renders it useful as a biological standard: in 2002, some 193 papers were published which featured this application.

α-Cyclopiazonic acid **1** is distinguished by a pentacyclic array containing a 3,4-disubstituted indole and a highly substituted tetramic acid residue, together with a central *cis*-ring fusion. To date, only two total syntheses of α-CPA **1** have been reported. In the first, by the Kozikowski group,[5] the central carbocyclic ring was established using an intramolecular Michael addition of a suitable 3,4-disubstituted indole. The pyrrolidine ring was then elaborated followed by the tetramic acid motif from the corresponding pyrrolidine-2-carboxylate and diketene. A final base-catalysed epimerization led to the correct stereochemistry at the C-9 (tetramic acid) stereogenic centre. A second synthesis by Muratake and Natsume featured formation of a suitable 4-substituted indole from *N*-Moc-pyrrole by the less common tactic of constructing the benzene ring.[6] The central ring system was again generated using an intramolecular Michael addition, followed by formation of a 2-methyl-l-pyrroline and the addition of nucleophilic methyl to produce the *gem*-dimethyl feature. The tetramic acid was again elaborated using diketene and the stereochemistry adjusted by epimerisation. Both routes are relatively brief (16 and 19 steps respectively), but both suffer from a few rather inefficient steps.

Our idea was to synthesise the basic ring structure of α-CPA **1** using a cationic cascade cyclisation, terminated by a sulfonamide function, which we have recently demonstrated to be an efficient tactic for pyrrolidine synthesis.[7] Both previous syntheses have successfully constructed the tetramic acid residue from a pyrrolidine-2-carboxylate **3** and diketene **4**, by a Dieckmann cyclisation (Scheme 1).[5,6] The key intermediate **3** could, we reasoned, be generated rapidly by a cascade cyclisation, initiated by formation of the benzylic carbocation **5**. Concerns about its eventual removal led us to substitute the original toluenesulfonyl group, which was used throughout our initial studies to attenuate the reactivity of the cascade terminator,[7] with a nitrophenylsulfonyl function, in the anticipation that this would be much more readily cleaved when necessary.[8] The stereochemical outcome of the cascade cyclisation(s), if observed, was clearly also of concern. Fortunately, Dreiding models showed both diastereomers of the intermediates [*cf.* **5**] to be rather crowded and strongly suggested that access to a transition state conformation which would lead to the desired *cis*-ring fusion would be much easier than that leading to *trans*-ring fusion.

Our synthesis began with indole-4-methanol **4**,[9] which was protected selectively at oxygen using TBDPSCl in THF containing imidazole, then formylated under standard Vilsmeier conditions[10] and further protected by tosylation of the indolic nitrogen. The resulting aldehyde **7** was then homologated by a Horner–Wadsworth–Emmons reaction,[11] which gave an acceptable yield of the unsaturated ester **8** (Scheme 2) which was then subjected to a Michael addition of 2-methylpropenylmagnesium bromide in the presence of phenylthiocopper.[12] This gave the expected product in an unoptimised isolated yield of 53%. Subsequent enolization, specifically using KHMDS at low temperature, followed by brief



Scheme 1

† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b4/b417625c/

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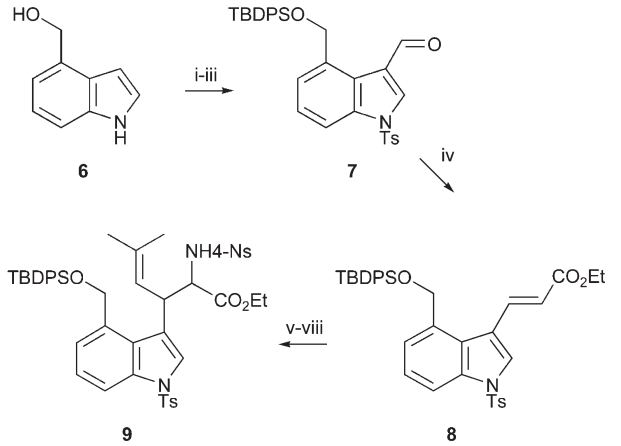
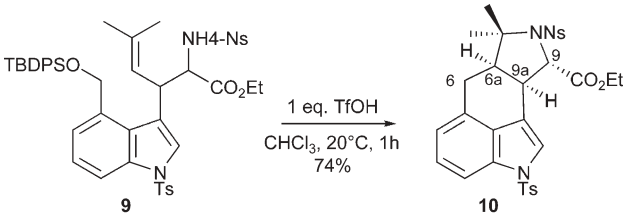


Reagents: i) TBDPSCl (1.1 eq.), imidazole (0.1 eq), THF 20°C, 16h (95%); ii) $POCl_3$ (1.1 eq.), DMF (4.5 eq.), pyridine (1.2 eq), 0°C then add indole (1.0 eq.) in DMF, then 35°C, 0.75h, quench with ice, add 0.5M aqueous NaOH, reflux 2 min. (82%); iii) TsCl (1.2. eq), DMAP (cat.), Et_3N (1.2 eq.), CH_2Cl_2, 20°C, 16h (85%); iv) $(EtO)_2P(O)CH_2CO_2Et$ (1.2 eq.), LiCl (1.2eq.), MeCN, add DBN (1.0 eq.), 20°C, 0.25h, add **7** (1.0eq.) in MeCN, 20°C, 2h (62%); v) Me_2C:CHMgBr, PhSCu, THF, -40°C warmed to 0°C over 1h, cool to -40°C, add enoate **8**, warm to 20°C (53%); vi) KHMDS (1.1eq.), THF, -78°C, add trisyl azide, -78°C, 5 min, add HOAc (62%); vii) Ph_3P (2 eq.), H_2O (2eq.), THF, 60°C. 6h, viii) 4-$NO_2C_6H_4SO_2Cl$ (1.2 eq.), pyridine (1.2 eq.), DMAP (cat.), $CHCl_3$, 20°C, 16h (43% for vii and viii).

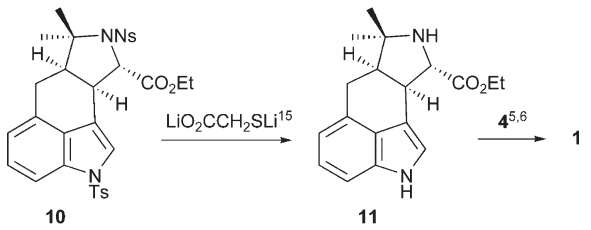
Scheme 2

exposure to trisyl azide then engendered introduction of the necessary nitrogen functionality, as the azide.[13] Conversion into the corresponding free amino-ester was then achieved under standard conditions.[14] Finally, this approach work was completed by immediate *N*-nosylation[8] to give the precursor **9** in 43% overall and unoptimised yield for these last two steps, as a *ca.* 60 : 40 mixture of diastereoisomers.

We reasoned that the desired benzylic carbocation (*cf.* **5**, Scheme 1) might be generated directly from the *O*-silyl derivative **9** although, of course, the corresponding alcohol could still be an intermediate. We were therefore delighted to find that, after some optimization, compound **9** was converted cleanly into the advanced tetracyclic precursor **10**, in 74% isolated yield, upon exposure to one equivalent of triflic acid at ambient temperature in chloroform for 1 h (Scheme 3). Furthermore, our stereochemical conjectures proved correct: the product **10** possessed entirely the desired *cis*-ring fusion ($J_{6a,9a}$ = 4.1 Hz) and was mostly the epimer shown ($J_{9,9a}$ = 9.5 Hz) along with a small amount (*ca.* 8%) of the β-ethoxycarbonyl epimer ($J_{9,9a}$ = 4.2 Hz).[5,6] Although we had anticipated obtaining the correct stereochemistry at C_9 during formation of the tetramic acid ring,[5,6] evidently steric crowding was sufficiently severe that almost complete epimerization at this



Scheme 3



Scheme 4

centre also had occurred during exposure to acid. While we have previously observed such an equilibration to a more thermodynamically stable isomer in simpler models,[7] the ease with which this occurred here was unexpected. We then benefited from a novel observation: while removing the nosyl group using thioglycolate,[8] the indolic tosyl function was also cleaved, leading directly to the fully deprotected pyrrolidino-indole **11** in an excellent 82% yield. The ratio of epimers remained essentially unchanged. We have subsequently shown that this is a relatively general and convenient method for the *N*-detosylation of indoles.[15]

Completion of the synthesis followed the chemistry described above:[5,6] treatment of the deprotected indole **11** with diketene and potassium *t*-butoxide in dichloromethane led smoothly to α-CPA **1** (Scheme 4). The sample proved to be identical, except for its lack of optical rotation, to an authentic sample (Tocris) according to its m.p. of 238–242 °C [authentic: m.p. 244–245 °C (Tocris sample); mixed m.p. 240–242 °C], ^1H and ^{13}C NMR data, mass spectra and tlc mobility (EtOAc : petrol 3 : 2). A trace (*ca.* 5%) of an epimer was detectable in our synthetic sample by ^1H NMR [δ_H 4.45, d, J = 3.9 Hz] which was probably isomeric at C-9 (*i.e.* the all-*cis*-isomer); α-CPA itself shows the C-9 proton at δ_H 4.00 (d, J = 11.1 Hz).

Despite some unoptimised and not especially efficient steps in the approach work, the relatively spectacular yield of 74% from the key cascade cyclisation step, together with the relative brevity of this synthesis (14 steps from 2-methyl-3-nitrobenzoate) suggests that this type of chemistry should find many other useful applications.

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