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Synthesis of a model DEF-ring core of hexacyclinic acid†

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Received (in Cambridge, UK) 3rd April 2003, Accepted 13th May 2003
First published as an Advance Article on the web 3rd June 2003

The first synthesis of a DEF-ring system of hexacyclinic acid is reported. The key steps being an intramolecular Pd(0) π-allyl substitution reaction, followed by a transannular iodocyclisation with acetyl hypoiodite.

Recently the structure of hexacyclinic acid **1**, a new polyketide natural product, was reported (Fig. 1).[1] This compound was isolated from *Streptomyces cellulosa* subsp. *griserubiginosus* (strain S1013) and shown to have some cytotoxic activity when tested in 3 cell lines.[1] It was due to its complex hexacyclic ring system with its unusual 'knotted' DEF-rings, coupled with the biological potential, that we became interested in developing chemistry for the synthesis of the hexacyclinic acid ring systems. In this communication we disclose the first successful synthesis of a DEF-ring system of hexacyclinic acid and report an interesting solvent effect on the key iodocyclisation reaction.

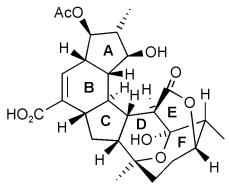
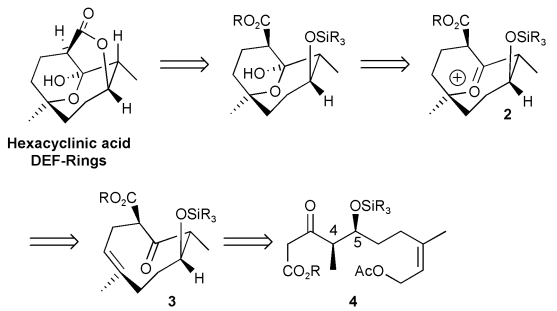


Fig. 1 Hexacyclinic acid **1**.

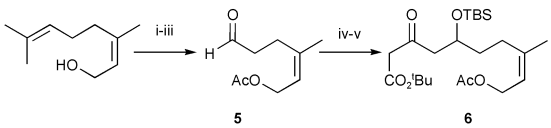
We envisaged that the DEF-rings of hexacyclinic acid would be accessible from the nucleophilic addition to an oxonium ion intermediate **2**, which in turn would arise from the transannular cyclisation of the ketone carbonyl of a β-ketoester onto a cation equivalent generated from a double bond containing 9-membered ring **3**. Carbocycle **3** was to be obtained by a cyclisation of an acyclic precursor such as **4** (Scheme 1).



Scheme 1 Retrosynthesis of the DEF rings.

Before, however, we embarked upon an asymmetric total synthesis of hexacyclinic acid we desired to test our DEF-ring forming hypothesis. To this end we elected to synthesise a hexacyclinic acid model system without the methyl group at C4 in a racemic series. This would expedite the synthesis of our key 9-membered ring precursor as it would i) allow the installation of the β-ketoester in one step from an aldol reaction of a β-ketoester with an appropriate aldehyde and ii) obviate the potential problem of the relative stereochemistry between the C4 methyl group and the C5 hydroxyl group inherent in the Mukaiyama aldol reaction of γ-substituted β-ketoesters.‡

Our DEF-ring synthesis (Scheme 2) started from nerol, which was acylated with acetic anhydride in pyridine with catalytic DMAP and then epoxidised at the most electron rich double bond with *m*CPBA; this was followed by oxidative cleavage of the epoxide with periodic acid to give aldehyde **5**.[3] Mukaiyama aldol reaction of the bis-TMS enol ether of *tert*-butyl acetoacetate with **5** followed by TBS protection of the resulting alcohol yielded cyclisation precursor **6**.

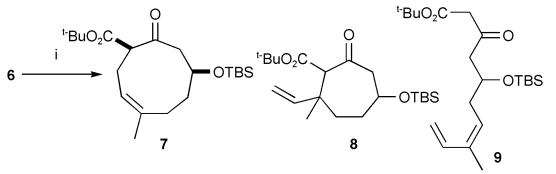


Scheme 2 *Reagents and conditions*: i) Ac_2O, py, DMAP, 100%; ii) mCPBA, CH_2Cl_2, 89%; iii) HIO_4, THF, H_2O, 76%; iv) tBuO-C(OTMS)=CHC(OTMS)=CH_2, $TiCl_4$, CH_2Cl_2, −78 °C, 79%; v) TBSOTf, py, −30 °C, 78%.

Formation of the 9-membered carbocycle **7** was achieved using a Pd(0) catalysed intramolecular π-allyl substitution reaction.[4] We found that the efficiency of this reaction was dependent upon the additional phosphine ligands employed (Table 1), with the optimum being 2 equiv. of dppe, which provided **7** in a 61% isolated yield.[5] The relative stereochemistry of the substituents on the 9-membered ring was determined as *cis* by gradient nOe experiments. Interestingly, this also highlighted that the 9-membered ring existed in a chair–boat conformation (Fig. 2).

As can be seen from Table 1, two other products could also be formed under the reaction conditions, depending on the

Table 1 Optimisation of the Pd(0) π-allyl cyclisation reaction



Reagents and conditions: i) NaH, $Pd(Ph_3P)_4$ (5 mol%), ligand (10 mol%), THF, reflux.

Entry	Ligand	Yield (%)[a]	Ratio **7** : **8** : **9**[b]
1	Ph_3P	91	0 : 1 : 4
2	dppm	97	0 : 1 : 8
3	dppe	93[c]	2 : 0 : 1
4	dppp	94	1 : 1 : 2
5	dppf	90	3 : 2 : 8

[a] Combined yield. All compounds co-ran and exhaustive flash column chromatography provided only small amounts of purified products. [b] By ^{1}H NMR (400 MHz). [c] Isolation of **7** (61%) and **9** (32%) proved possible by flash column chromatography on $AgNO_3$ impregnated silica gel.[5,6]

† Electronic supplementary information (ESI) available: experimental procedures and characterisation data. See http://www.rsc.org/suppdata/cc/b3/b303706a/

DOI: 10.1039/b303706a

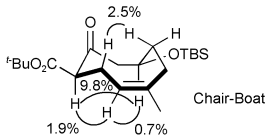
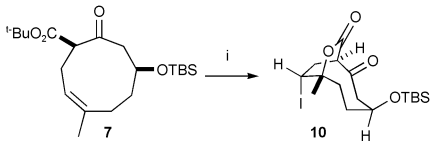


Fig. 2 Conformation of 9-membered ring **7**.

diphosphine ligands used: the 7-membered ring **8**, arising from attack of the acetoacetate anion on the other side of the π-allyl complex,§ and the diene **9**, resulting from elimination of the π-allyl complex.

With carbocycle **7** in hand we next studied the key iodocyclisation reaction. We decided to use AcOI for the formation of the iodonium ion,[7] as previous studies in the group showed that use of I_2 resulted in the deprotection of pendant silyl ethers and competing modes of cyclisation. We were also optimistic that the acetate ion generated would be sufficiently nucleophilic to add to the oxonium ion and thus introduce the masked hemi-ketal needed for a synthesis of the hexacyclinic acid DEF-ring system.

When **7** was treated with AcOI in $CHCl_3$ a single product was formed, which was identified as iodolactone **10** (Scheme 3). Iodolactone **10** is obviously generated by the cyclisation of the ester carbonyl onto the α-iodonium ion *via* a chair–chair conformation of the 9-membered ring (Fig. 3), with loss of a *tert*-butyl cation as isobutene.



Scheme 3 *Reagents and conditions:* i) AcOI, $CHCl_3$, 49%.

Gratifyingly, treatment of **7** with AcOI in AcOH resulted in the cyclisation of the ketone carbonyl onto the desired β-iodonium ion *via* a boat–boat conformation (Fig. 3), and led to the formation of hexacyclinic acid DF-ring unit **11** (Scheme 4), where the intermediate oxonium ion was trapped by the AcOH solvent.[5]¶ We first thought that the differential modes of cyclisation were due to either formation of some of the enol form of the β-ketoester or due to a change in the conformation of the 9-membered ring brought about by the change in solvent

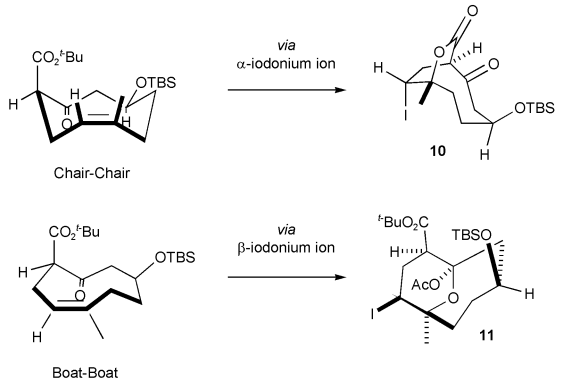
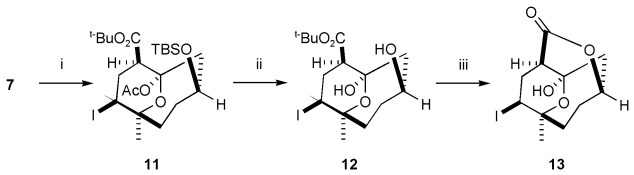


Fig. 3 Proposed reactive conformations of **7**.



Scheme 4 *Reagents and conditions*: i) AcOI, AcOH, 61%; ii) 40% HF (aq.), MeCN, 97%; iii) TFA, CH_2Cl_2, 63%.

from $CHCl_3$ to AcOH. However, ^{1}H NMR (400 MHz) and gradient nOe experiments in d3-acetic acid showed that not only was there no enol form detectable, but the 9-membered ring remained in the same chair–boat conformation as indicated by the ^{1}H NMR experiments conducted previously in $CDCl_3$. We rationalise that, as neither of the reaction pathways occurs *via* the detected chair–boat conformation, and iodonium ion formation is reversible, the change in the reaction pathway must therefore be due to a change in the reacting iodonium ion (either α or β), brought about by solvent effects.‖ At present we are unable to provide any further explanation of this remarkable solvent effect, but we are investigating it further.

Treatment of **11** with aqueous HF in MeCN resulted in the removal of both the TBS and acetate groups to give **12** in 97% yield.[5] The structure of **12** was confirmed by single crystal X-ray analysis,** which showed that cyclisation had occurred through the ketone oxygen of the β-ketoester onto the β-iodonium ion. Removal of the *tert*-butyl ester and lactonisation was achieved by reaction of **12** with TFA in CH_2Cl_2, which furnished a model DEF-ring system of hexacyclinic acid **13** in a yield of 63% (Scheme 4).[5]

In summary, we have developed a new route for the synthesis of the DEF-ring system of hexacyclinic acid utilising a transannular iodocyclisation approach. Application of this route to a total synthesis of hexacyclinic acid is underway.

We thank the EPSRC and AstraZeneca for studentship funding under the CASE Award for New Academics Scheme, AstraZeneca for an unrestricted research support grant and the EPSRC National Mass Spectrometry Service, Swansea for accurate mass determination. We also thank Dr Adrienne Davis (Nottingham) for NMR technical advice and support and Dr Hitesh Sanganee (AstraZeneca) for helpful discussions.

Notes and references

‡ Formation of the *syn* or *anti* aldol product is controlled by the geometry of the silyl enolether. At present there are no reliable methods for the exclusive formation of the desired *Z*-silyl enolether.[2] Therefore, while this strategy may be employed for the synthesis of the actual DEF-ring system, separation of the *syn* and *anti* aldol product diastereomers would be required.

§ It is a feature of these reactions that when differently substituted π-allyl systems are employed, it is the larger ring system which is preferred over the smaller one, especially when there is an increase in the steric encumbrance of the system. See reference 4*a*.

¶ Studies using d3-acetic acid as solvent showed that d3-acetate was introduced exclusively into the cyclised product.

‖ These other conformations are presumably within about 2 kcal mol^{-1} of the ground state chair–boat conformation.

** $C_{15}H_{25}IO_5$, M = 412.25, triclinic, a = 6.5249(5), b = 11.3828(9), c = 13.3018(10) Å, α = 65.415(1), β = 77.402(1), γ = 81.897(1)°, U = 875.35(12) Å^3, T = 150 K, space group *P*-1 (no. 2), Z = 2, μ(Mo-Kα) = 1.846 mm^{-1}, 7666 reflections measured, 3876 unique (R_{int} = 0.028) which were used in all calculations. The final $wR(F^2)$ was 0.077 for all data, $R_1(F)$ was 0.035 for 3298 observed data where $I > 2\sigma(I)$. CCDC 207876. See http://www.rsc.org/suppdata/cc/b3/b303706a/ for crystallographic data in .cif or other electronic format.

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