Synthesis of *endo,exo*-furofuranones using a highly diastereoselective C–H insertion reaction

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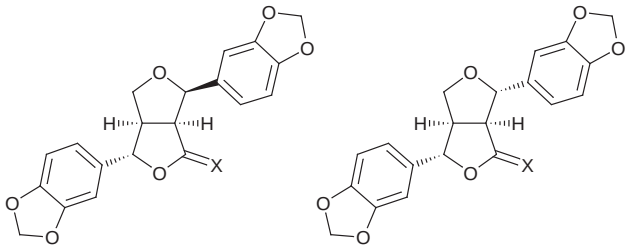
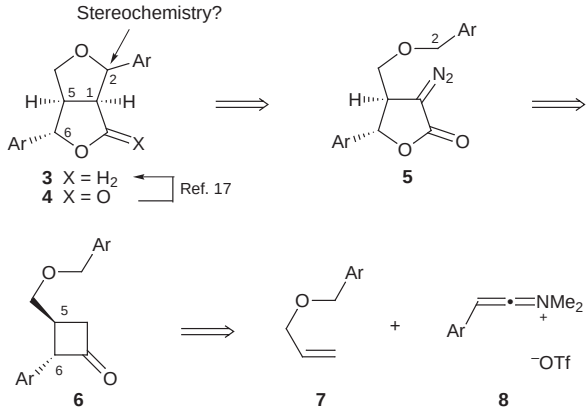
A highly stereoselective ring closure of α-diazo-γ-butyrolactones to form the 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane ring system is reported; a formal synthesis of the furofuran lignan asarinin 1 is also described.

The 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane ring system is a key structural element in a large sub-class of lignan natural products, the furofuranoids (*i.e.* **1**, **2**, sesamin and aptosimon).[1,2] The electron rich aromatic substituents, which are characteristic of lignans, occupy *endo*- or *exo*-orientations on the 3,7-dioxabicyclo[3.3.0]octane core, which itself may be present at various levels of oxidation. The challenge of correctly establishing the four contiguous stereogenic centres present within the furofuranoids combined with their diverse biological activities has provoked substantial interest in their synthesis.[1–3] Our synthetic interest lay in the possibility of employing a C–H insertion reaction of an α-diazo-γ-lactone to form the 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane ring system. By targeting a furofuranone such as **4** as an advanced intermediate (Scheme 1), we hoped to develop a versatile route which could also be applied to the synthesis of other furofuranoids like asarinin **1** and cinnamonol **2**.



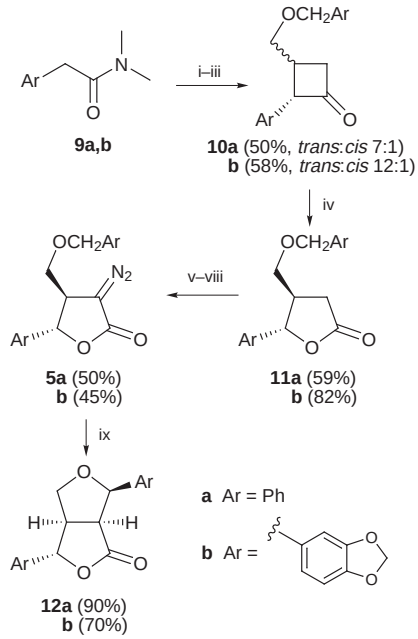
Our retrosynthetic analysis of the furofuranone **4** identified diazolactone **5** as a potential precursor (Scheme 1). Intramolecular C–H insertion into one of the diastereotopic C2–H bonds present in **5** would be expected to provide the furofuranone scaffold. We did not consider that the stereochemistry at the ring junction would be an issue, assuming that the 1,5-*cis*-adduct would be obtained. However, we were more reluctant to predict the stereochemical outcome at C2, hoping that we might control the stereoselectivity at this position through the use of different catalysts and conditions. The *trans*-relationship of the C5 and C6 substituents would be established in the cyclobutanone **6** which would arise from a [2+2] olefin–keteniminium salt cycloaddition reaction between **7** and **8**.



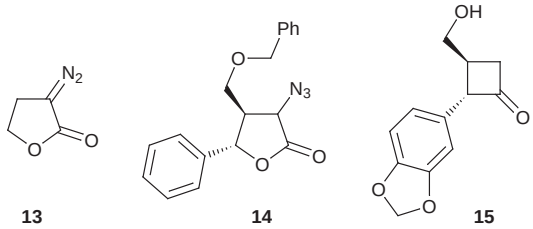
Scheme 1

Initial synthetic studies focused on the synthesis of a simple furofuranone **12a** (Ar = Ph, Scheme 2). According to Ghosez's protocol,[4] amide **9a**[5] was converted *in situ* to the corresponding keteniminium salt which underwent cycloaddition with benzyl allyl ether **7a**.[6] After hydrolysis of the intermediate cyclobutanone iminium salts, a mixture of diastereomeric cyclobutanones **10a** (*trans*:*cis*, 7:1) was obtained which was further enriched in the *trans*-isomer by careful chromatography. Due to the instability of the cyclobutanone **10a** it was immediately oxidised to the γ-lactone **11a**‡ using either MCPBA or H_2O_2 in AcOH.[7]

A search of the literature only revealed one previously reported synthesis of an α-diazo-γ-butyrolactone **13** which does not possess an additional stabilising group adjacent to the diazo functionality.[8] Although the deformylative diazo transfer procedure used to prepare **13** did provide our desired diazolactone **5a**, the yield was very poor, so alternative diazo transfer procedures were investigated. In view of our reluctance to



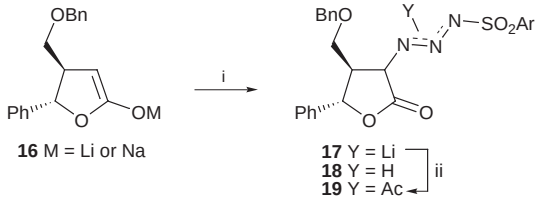
Scheme 2 *Reagents and conditions*: i, Tf_2O, CH_2Cl_2, −20 °C; ii, **7a** or **7b**, 2,6-di-*tert*-butylpyridine, CH_2Cl_2 (followed by 1equiv. K_2CO_3 for **7b**); iii, $NaHCO_3$ (aq.); iv, H_2O_2, AcOH; v, LiHMDS, THF; vi, *p*-$NO_2C_6H_4SO_2N_3$, THF, −78 °C; vii, AcCl; viii, DMAP, THF; ix, 2 mol% $Rh_2(OAc)_4$, CH_2Cl_2, room temp.



13 **14** **15**

pursue other methods of decarbonylative diazo transfer,[9,10] and the existence of encouraging reports of direct diazo transfer to ester and imide enolates, we focused our efforts on the later approach.[11,12]

The conditions reported for direct diazo transfer to ester enolates failed to give satisfactory yields of the diazo lactone **5a**, with azide **14** isolated as the major product. Although disappointing, the isolation of substantial amounts of azide **14** strongly implied that the intermediate triazine anion **17** was being formed efficiently (Scheme 3). An earlier study of the decomposition of triazines had shown that the relative proportions of diazo transfer and azide transfer were influenced by the reaction conditions.[12] In our case the triazine **18** proved to be too unstable to isolate,§ however, treatment of the reaction mixture with AcCl provided a mixture of isomeric *N*-acetyltriazines **19**.[13]¶ When the acetyl triazines **19** were treated with an equivalent of DMAP smooth conversion to a 1:1 mixture of azide **14** and the desired diazo lactone **5a** was observed. The reason for the increased proportion of diazo lactone **5a** are not clear at present although it is tempting to suggest that generation of a metal-free triazine anion, by the nucleophilic deacylation of **19** with DMAP, is important.



16 M = Li or Na

17 Y = Li
18 Y = H
19 Y = Ac

Scheme 3 *Reagents and conditions*: i, *p*-$NO_2C_6H_4SO_2N_3$, THF, −78 °C; ii, AcCl, −78 °C to room temp.

Gratifyingly, the key C–H insertion reaction required to set up the furofuranone framework proceeded extremely cleanly when diazo lactone **5a** was treated with a catalytic amount of $Rh_2(OAc)_4$, providing a single diastereoisomeric product **12a**. The relative stereochemistry of the furofuranone **12a** was assigned as *endo,exo* on the basis of NOE experiments. We were intrigued by the possibility of conducting the same intramolecular C–H insertion reaction under thermal conditions, which might provide altered stereoselectivity. In fact, heating the diazo lactone **5a** in 1,2-dichloroethane cleanly afforded the same cyclised product **12a**, again in excellent yield and stereoselectivity.

Relatively few of the published approaches to the synthesis of furofuranoid lignans have addressed the stereoselective synthesis of the less common *endo,exo* structures.[14–19] To demonstrate the scope of our approach to the synthesis of furofuranoid containing natural products the synthesis of *epi*-aptosimon **12b** was investigated. The conversion of *epi*-aptosimon **12b** to the furofuran lignan asarinin **1** has been reported previously.[17]
Initial attempts to carry out the [2+2] cycloaddition reaction of allyl ether **7b**[6] (Ar = 3,4-methylenedioxyphenyl) with the keteniminium salt derived from amide **9b**[20] failed to provide **10b**. Instead the major isolated product was the alcohol **15** arising from acid-catalysed cleavage of the benzylic ether bond which was assisted by the electron donating methylenedioxy group. The problem was almost certainly due to the formation of di-*tert*-butylpyridinium triflate under the reaction conditions. Fortunately this problem was easily resolved by the addition of anhydrous K_2CO_3 to the reaction mixture, allowing the desired cycloadduct **10b** to be obtained in good yield.

Baeyer–Villager oxidation of **10b** followed by diazo transfer to the resulting lactone **11b** afforded the cyclisation precursor **5b** in a yield of 37% from ketone **4b**. As was the case for the model diazo lactone **5a**, the C–H insertion reaction of **5b** proceeded cleanly to give the known furofuranone (±)-*epi*-aptosimon **12b** in good yield.

In summary, we have achieved a concise and diastereoselective synthesis of the 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane ring system. Significant contributions include: the development of conditions for conducting the keteniminium–olefin [2+2] cycloaddition reaction with alkenes bearing acid-sensitive functionality; and a method for effecting diazo transfer on γ-butyrolactones to provide the α-diazo-γ-butyrolactones **5** in acceptable yield. Finally, (±)-*epi*-aptosimon **12b** has been synthesised using this approach, representing a formal synthesis of the natural product (±)-asarinin **1**.

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Notes and References

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‡ Due to the difficult chromatographic separation of the *cis*- and *trans*-diastereoisomers, γ-lactone **11a** was contaminated with a trace of the *cis*-isomer.

§ Protonation of the triazine anion (ref. 17) (AcOH or pH 7 phosphate buffer) followed by warming to ambient temperature afforded predominantly azide **14** along with a small amount of diazo transfer product **5a**.

¶ The *N*-acetyltriazines **19** exhibited very complex ^1H and ^{13}C NMR spectra, probably due to the presence of regio- and diastereo-isomers.

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