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An efficient synthesis of *endo,exo*-furofuranone derivatives

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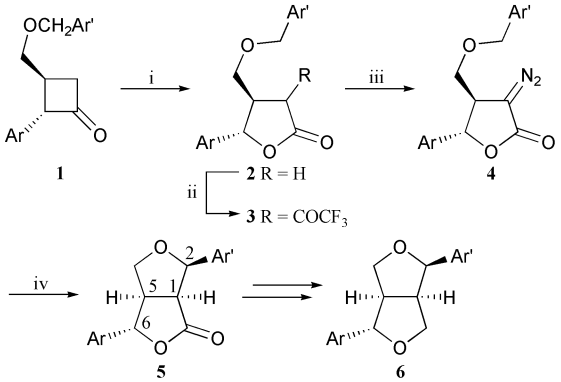
The ring openings of 1-acetyl-4-phenyl-3-oxabicyclo-[3.1.0]hexane afforded α-acetyl-γ-butyrolactones that underwent a novel diazo-transfer reaction, followed by C–H insertion, to provide a series of *endo,exo*-furofuranone analogues.

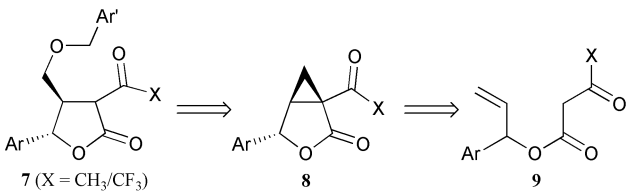
The furofurans are one of the largest subclass of lignans and continue to attract substantial interest due to their varied biological activities.[1] Additionally, the rigid bicyclic framework of the furofuran(one)s could provide a novel scaffold for the assembly of libraries for biological evaluation. Consequently, the preparation of structural analogues is of significant importance.

We have recently reported an approach to the *endo,exo*-furofuran series **6** that utilised an intramolecular C–H insertion reaction to close the C1–C2 σ-bond (Scheme 1).[2,3] Although



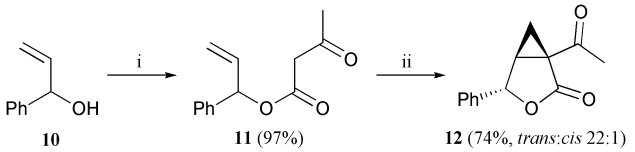
Scheme 1 *Reagents and conditions*: i, H_2O_2, AcOH; ii, LiHMDS, $CF_3CH_2OCOCF_3$; iii, *p*-$NO_2C_6H_4SO_2N_3$, NEt_3; iv, 2 mol % $Rh_2(OAc)_4$.

this original route provided an entry to furofuranones **5** and furofurans **6**, including three lignan natural products, it had some shortcomings. The initial [2 + 2] cycloaddition reaction[4] to form cyclobutanones **1** was low yielding with electron rich aromatic systems. Furthermore, this same step was not readily applicable to the enantioselective synthesis of cyclobutanones.[5] Here we report a new, more robust and higher yielding approach to furofuranone lignan derivatives **5**, centering on the nucleophilic ring openings of a cyclopropane intermediate **8** to afford the key precursors **7** to diazo-lactones **4** (Scheme 2).



Scheme 2

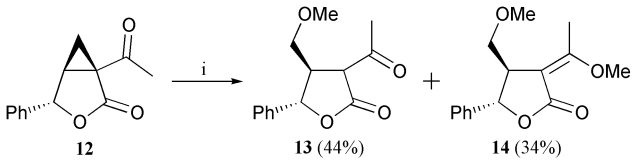
Our investigation began with acetoacetylation[6] of 1-phenyl-prop-2-en-1-ol (**10**) to provide the corresponding acetoacetate ester **11** in excellent yield (Scheme 3).† Mn(III)-mediated



Scheme 3 *Reagents and conditions*: i, 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one, xylenes, 150 °C; ii, $Mn(OAc)_3$, $Cu(OAc)_2$, KOAc, AcOH, 70 °C.

oxidative cyclisation of β-ketoester **11** successfully provided the desired cyclopropane **12** in good yield (74%) and excellent diastereoselectivity (*trans*:*cis*, 22:1).[7] *trans*-Lactone **12** was obtained exclusively after recrystallisation.[8] Surprisingly, there has only been a limited number of similar cyclopropanations to provide related bicyclo[3.1.0]lactones.[9]

We envisioned cyclopropane **12** as a key intermediate towards furofuranone derivatives due to its expected predisposition to undergo nucleophilic ring opening. Indeed, addition of soft nucleophiles (*e.g.* cuprates, thiols, amines) proceeded very smoothly although opening with alcohols proved more problematic.[10,11] We turned our attention to the Lewis acid assisted openings of cyclopropane **12** in neat methanol but, even at reflux for 24 h, conversion to the desired product **13** was low.‡ Fortunately, access to a SmithSynthesizer™ microwave reactor[12] allowed us to investigate a much broader range of conditions with the conclusion that cyclopropane **12** could be opened, with methanol, effectively at 120 °C.[13] Consumption of **12** was observed after just 30 min at this temperature (with a stoichiometric amount of $Zn(OTf)_2$) to provide desired methyl ether product **13** and corresponding enol ether **14** (Scheme 4).



Scheme 4 *Reagents and conditions*: i, MeOH, $Zn(OTf)_2$, 120 °C, microwave radiation.

Microwave conditions were not required for benzylic alcohol additions due to their higher boiling points, and following a survey of metal triflates and other common Lewis acids, $Mg(ClO_4)_2$ provided the best results.§ Ultimately, optimisation of the conditions allowed opening of **12** to be conducted with three equivalents of the appropriate alcohol, neat, at 120 °C with 10 mol% of Lewis acid, providing products **15a–d** in excellent yields with very little enol ether formation (Scheme 5).

Substrates **15a–d** proved completely inert to all attempted deacetylative diazo-transfer procedures reported in the literature, despite the fact that such transformations are well precedented.[3,14] However, a facile and highly reactive one-pot method was devised that successfully transformed these acetyl-activated lactones **15a–d** to their corresponding α-diazo-lactones **16a–d** in good to excellent yields following the *in situ* generation of triflyl azide under phase-transfer catalysis (Scheme 6).[15] Furthermore, these biphasic conditions could find applications in diazo-transfers to particularly difficult substrates

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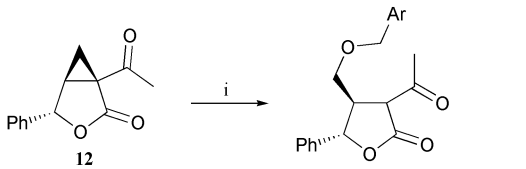
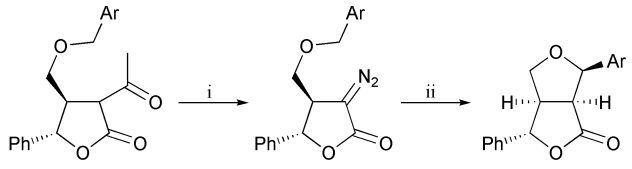


Scheme 5 *Reagents and conditions*: i, $ArCH_2OH$, 10 mol% $Mg(ClO_4)_2$, 120 °C.



Scheme 6 *Reagents and conditions*: i, NaN_3, $(Tf)_2O$, $^nBu_4NBr$, 2 M NaOH/hexane/MeCN (2 : 1 : 1), 0 °C; ii, 2 mol% $Rh_2(OAc)_4$, CH_2Cl_2, rt.

that have previously proved challenging. As expected, the C–H insertion reactions proceeded rapidly and highly diastereoselectively upon treatment of a catalytic quantity of rhodium(II) acetate dimer to provide furofuranones **17a**–**d** bearing aryl substituents with an *endo*,*exo*-configuration.[2,16] Thus, the synthesis of series **a** (Ar = Ph) was complete in 5 steps with 47% overall yield and demonstrates the excellent efficiency of this approach. Furthermore, the convergent nature of this route provides opportunites to assemble diverse sets of structural furofuran lignan derivatives.

In summary, we have achieved a concise and diastereoselective synthesis of a series of *endo*,*exo*-furofuranone analogues. Significant contributions include the microwave assisted optimisation of alcohol additions to cyclopropane **12** under Lewis acidic conditions and development of a highly effective diazo-transfer protocol to afford α-diazo-γ-butyrolactones. Future work in this area will focus on an asymmetric synthesis of γ-butyrolactones and potential furofuranone derivatives.

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Notes and references

† Reaction time of 10 min to avoid [3,3] sigmatropic rearrangement of product.
‡ Ratio of starting cyclopropane : product = 5 : 2 (^{1}H NMR).
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