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A mild entry to isoindolinones from furfural as renewable resource†

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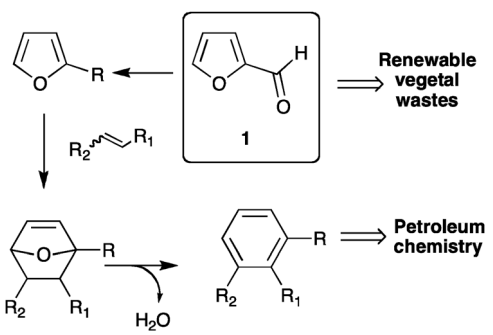
A convenient transformation of furfural and derivatives into arene compounds is described. This process provides a straightforward access to isoindolinones from a renewable resource *via* the sequence of a tandem Ugi–Diels–Alder process followed by a ring-opening, dehydrating aromatisation. Five bonds are created and water is the sole by-product during this two-step sequence.

Introduction

Furfural **1** (from the Latin *furfur*, bran) is a compound directly derived from C5 sugars that are extracted from otherwise unexploited plant wastes such as those of wheat bran, corncobs or sugarcane.[1–3] Current large-scale uses of furfural mostly involve simple processes like hydrogenation, leading to widely-used compounds such as furan itself, tetrahydrofuran (THF) and 2-methyltetrahydrofuran (MeTHF).[4] Although well-established, these processes are still under investigation in order to increase their efficiency and enhance their E-factors.[5] This clearly illustrates the significant degree of optimisation required to establish an environmentally sustainable industrial process. Considering that petroleum resources are dwindling, and that the use of petroleum in energy production might be prioritised over petrochemicals manufacturing, we have engaged in a program aimed at enabling building-block production from renewable resources such as furfural. It is noteworthy that although a wide array of furan scaffolds (at different levels of hydrogenation) may be accessed from furfural, processes giving rise to other scaffolds (such as arenes) starting from furfural are scarce. This is surprising, since furan derivatives are known to react with activated double bonds in [4+2] cycloadditions, leading to bicyclic structures possessing six-membered carbocyclic sub-units. These oxabicyclic adducts can in theory lead to benzenic products through aromatisation with loss of a single molecule of water. Such access to aromatic scaffolds (typically produced from petroleum), starting from a renewable starting material like furfural, would represent an overall process fulfilling a number of green chemistry principles (use of renewable feedstocks, carbon-atom economy, waste prevention). Indeed, pericyclic reactions are highly atom-efficient, and proceed with excellent levels of regio- and stereo-control. The regioselectivity combined with a simple ring opening–dehydration domino sequence shall therefore give a sustainable access to structurally defined polyfunctionalised arenes (Scheme 1). One would expect the reaction to proceed smoothly if it was carried out in an intramolecular fashion.[6] For that purpose, the dienophile could be tethered to the pendant arm of the furan arising from the initial aldehyde function of the furfural. Such a tether and further molecular complexity could be achieved by taking advantage of multi-component reactions (MCR) such as the well described Ugi reaction.[7–10] This would then represent a very step-efficient conversion of the initial five-membered ring to the six-membered ring. The overall process would complement nicely the tandem processes involving a Ugi reaction, yielding heterocycles.[11] Also, it would be an efficient process in terms of taking advantage of every



Scheme 1 Arenes from furfural, an alternative access to petrochemicals from ''renewable wastes.''

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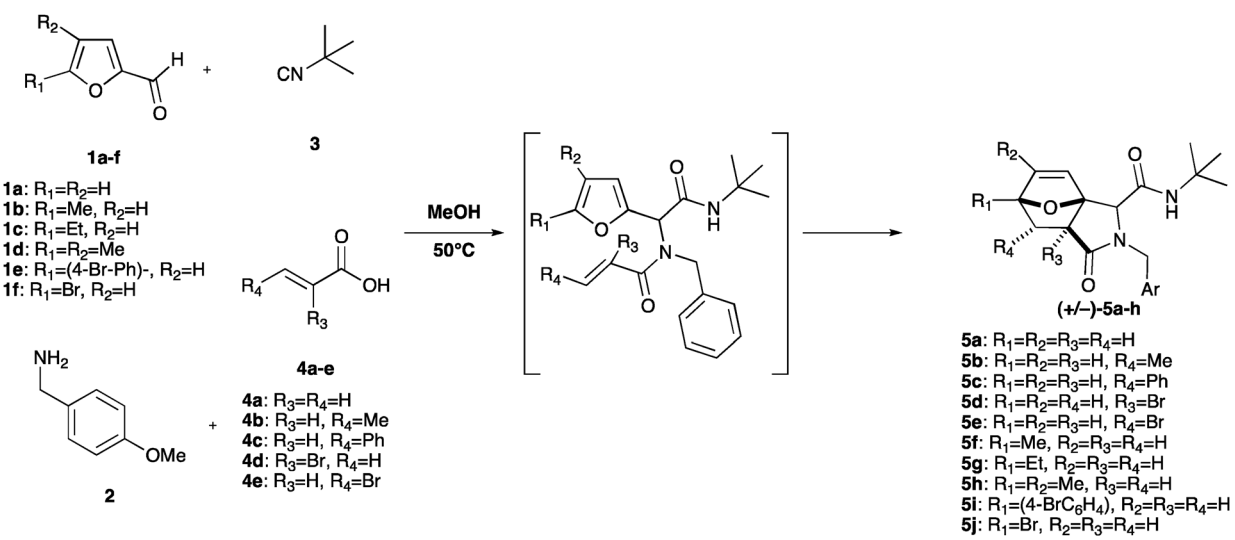
chemical function of furfural (aldehyde involved in MCR to anchor the dienophile, diene involved in the Diels–Alder cycloaddition, oxygen released in the final water elimination). We disclose here our recent results toward this approach.

Results and discussion

Based on previous reports using maleic and fumaric derivatives,[12–15] we first carried out the Ugi reaction on furfural with *tert*-butyl isocyanide, 4-methoxybenzylamine and differently substituted acrylic acids in methanol at 50 °C, as protic solvents are known to favor the Ugi reaction.[16] We also showed that substituted furan carboxaldehydes can be successfully engaged in this reaction, as illustrated below (Scheme 2). Our first attempt (Table 1, entry 1) was performed with acrylic acid. We noticed that a slight heating of the reaction medium was required for complete consumption of the starting furfural, and we observed after one day a single reaction product exhibiting the bicyclic core of the expected product of the tandem process in a satisfying yield of 54% for the four-component, five-bond-forming process. This result contrasts with the previous reports from McCluskey and co-workers, who showed that the Ugi reaction of furfural occurs within 30 minutes at room temperature.[17,18]

Yet, in our case, the ethylene moiety proved more reactive than the previously reported acetylene analogue, since the Diels–Alder reaction proceeded spontaneously under the reaction conditions, therefore avoiding the need for solvent exchange and more forcing conditions. No uncyclised product could be isolated (the only intermediate observed by TLC analysis is thought to be the imine, as it appears to be hydrolysed back to furfural on preparative scale). No intermolecular Diels–Alder reaction was observed under these reaction conditions, clearly indicating the order of reactions during the cascade. From a sustainable development perspective the lower temperature (compared to the 200 °C in a sealed tube reported by McCluskey *et al.*) is a significant improvement; and the lack of the requirement for a second electron-withdrawing group (compared to previous reports[12–15]) enhances the versatility of this reaction. In order to shorten the reaction time, we explored the use of microwave irradiation (Table 1, entry 2). Although the reaction time was indeed shortened, we observed no significant enhancement of the reaction efficiency. Having established that one single electron-withdrawing group is sufficient for the reaction to proceed smoothly, we explored the effect of further substitution of the double bond, as it is well known to strongly affect the reversibility of the Diels–Alder reaction of furans.[19] The introduction of a methyl group appeared rather detrimental, allowing the isolation of the oxabicycle in only 26% yield, together with 47% of the uncyclised product **6** (Table 1, entry 3; see Fig. 1). Interestingly, the cyclised product was obtained as a single diastereoisomer, corresponding to an *exo* approach. The isolation of this thermodynamic adduct fits well with the known reversibility of Diels–Alder reactions with furans,[20] and the epimerisable nature of the carbon α to the amide, since no stereocontrol is expected in the course of the Ugi reaction.

In contrast, in the presence of a phenyl group, no uncyclised compound was obtained and a better isolated yield of the polycyclic structure was achieved (Table 1, entry 4). Again, only the *exo* diastereoisomer was isolated. Finally, the best yields were obtained for reactions involving bromine-substituted acrylic acids. Interestingly, introducing the bromine atom at position 2 of the acrylic partner promoted a scrambling of the diastereoselectivity of the reaction, a mixture of both diastereoisomers being obtained in 80% overall yield. Contrastingly, using the bromoacrylic acid of E geometry allowed the isolation of the cyclised adduct in 90% yield as a single diastereoisomer. This enhanced efficiency has been nicely correlated with a higher exergonic reaction profile.[21] Having established the usefulness of the tandem process using unactivated acrylic derivatives, we also explored the effect of the substitution pattern of the furan ring on the reaction profile. Introduction of substituents at the 5-position of the furan did not hamper the



Scheme 2 Tandem Ugi–Diels–Alder involving differently substituted furyl aldehydes and various acrylic acids.

Table 1 Tandem Ugi–Diels–Alder reaction of furyl aldehydes with *tert*-butyl isocyanide, 4-methoxybenzylamine and various acrylic acids

Entry	Aldehyde **1**	Acrylate **4**	Reaction time (h)	Product and isolated yield (%)
1	**1a**	**4a**	25	**5a** 54
2	**1a**	**4a**	4[a]	**5a** 59
3	**1a**	**4b**	24	**5b** 26 (47[b])
4	**1a**	**4c**	31	**5c** 69
5	**1a**	**4d**	4.5	**5d** 80[c]
6	**1a**	**4e**	24	**5e** 90
7	**1b**	**4a**	24	**5f** 44
8	**1c**	**4a**	24	**5g** 56
9	**1d**	**4a**	24	**5h** 54
10	**1e**	**4a**	24	**5i** 54
11	**1f**	**4a**	24	**5j** 68

[a] The reaction was conducted under microwave irradiation (CEM Explorer). [b] Uncyclised product. [c] A 1 : 1 mixture of the two diastereoisomers was obtained.

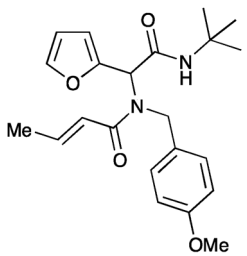


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Fig. 1 Uncyclised product from the reaction involving crotonic acid.

overall efficiency of the process: the desired cyclised adducts were systematically obtained as single diastereoisomers, with moderate yields similar to those obtained with furfural and acrylic acid (Table 1, entries 7, 8, 10, and 11). Disubstitution of the furan at positions 4 and 5 was also tolerated in this process.

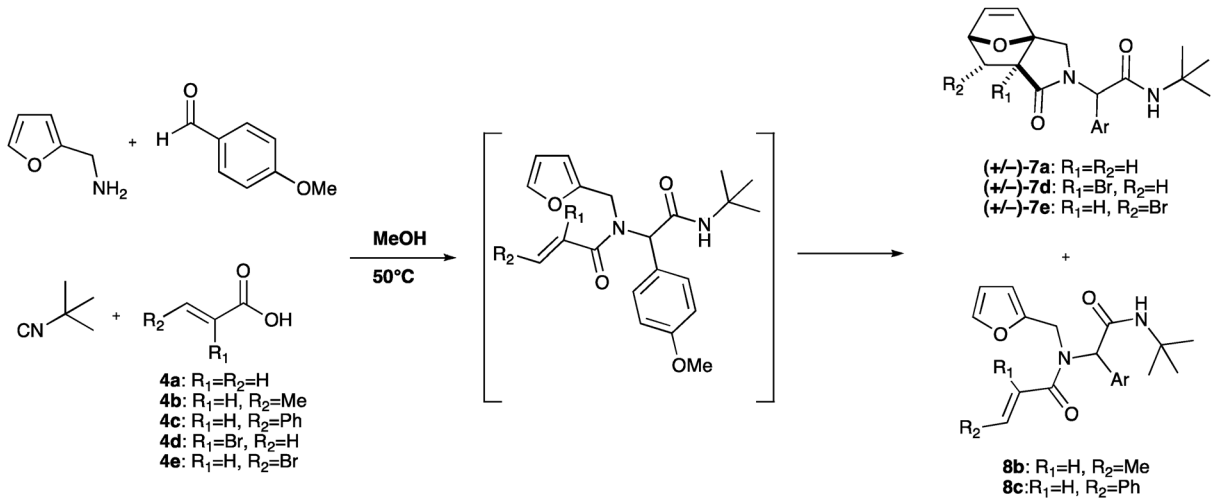
In addition to the studies described above, we sought to develop similar tandem processes involving furfurylamine, another derivative of furfural. Furfurylamine is routinely produced from furfural under heterogeneous catalytic conditions, and is another interesting renewable building-block. It may be engaged similarly in a tandem Ugi–Diels–Alder reaction to give cyclised adducts exhibiting an alternative substitution pattern (compounds **7a**, **7d** and **7e**) as shown in Scheme 3. Under the same reaction conditions using furfurylamine, 4-methoxybenzaldehyde, *tert*-butyl isocyanide and acrylic acid, we obtained the expected bicyclic adduct (Table 2, entry 1) in a yield similar to that achieved previously with furfural (see Table 1, entry 1). Increasing the substitution of the acrylic reagent proved to be detrimental in this case, as reactions involving crotonic and cinnamic acid gave good yields of the Ugi adduct, but no Diels–Alder cycloaddition was observed (Table 2, entries 2 and 3).

Contrastingly, when bromoacrylic acids were involved the bridged bicyclic adducts were obtained in good yields but with low diastereoselectivities (Table 2, entries 4 and 5). It should be pointed out that in every case only the isolated product was detected. We believe that in the less efficient reactions decomposition may occur and that the by-products are eliminated during the work-up/purification procedure.

Having shown that the tandem process using unactivated acrylate can be efficiently performed on furfural and furfurylamine, we explored the transformation of the oxabridged bicycle into an aromatic ring. Various strategies have been reported for the conversion of oxabicyclic adducts to the corresponding aromatic moiety. Treatment with concentrated sulfuric acid has been shown to perform this ring opening-dehydration process albeit with variable efficiencies.[22,23] One recent report has shown that a Lewis acid can promote a deselenisation–aromatisation sequence from selenated oxabridge bicycles.[24] This approach did not meet our aim of developing an environmentally friendly process. An alternative approach may be envisaged, in which an electron-withdrawing group is attached to the oxabridge bicycle by performing the ring opening-dehydration process under basic conditions in the presence of LiI.[25] With the acidic treatment appearing as the most mass-efficient one, we explored the use of various acids and found that one equivalent of hydrated PTSA promoted the desired transformation within a few minutes in toluene under reflux (Scheme 4).[26] As expected, the substitution of the oxabicycle strongly affected not only the reaction time but also its outcome. The unsubstituted oxabicycle arising from the Ugi–Diels–Alder tandem required two hours to reach full conversion and although the crude reaction mixture appeared relatively clean, the isolated yield remained moderate though reproducible (Table 3, entry 1).

A shorter reaction time was necessary to fully convert the phenyl-substituted oxabicycle (Table 3, entry 2). Although the yields are still low, this method is an interesting approach to the 1,2,3-trisubstituted biphenyl moieties in a metal-free process beginning from a renewable resource. Higher yields and shorter reaction times were achieved from oxabicycles arising from diversely substituted furans.

Thus, introduction of a methyl on the bridgehead cut the reaction time to 30 minutes, resulting in an average isolated yield of 51% (Table 3, entry 3). A 62% yield was achieved in the case of the more inductive electron-donating ethyl substitution at the bridgehead (Table 3, entry 5), with the reaction time decreased further. Disubstitution of the bicyclic moiety allowed another increase in yield (Table 3, entry 4). Introduction of a 4-bromo-substituted phenyl ring on the bridgehead also allowed the access to a biphenyl adduct, now 1,3,4,4′ substituted (Table 3, entry 6). Interestingly, introducing a bromine on the bridgehead led to the formation of the corresponding phenol (Table 3, entry 7). Finally, among the oxabicyclic adducts obtained from furfurylamine only **7a** underwent the ring opening-dehydrative aromatisation process, although the isolated yield was 95%. The other substrates obtained from the Ugi–Diels–Alder tandem reaction were shown to be either unreactive (**5d** and **7d** bearing a bromine atom α to the C=O bond) or underwent degradation (**7e**). Although rather disappointing, these results provide evidence for the reaction mechanism of the process. Acidic activation of the oxabicycle likely promotes the ring opening by elimination. Among the two hydrogen atoms available for this elimination, the one α to



Scheme 3 Tandem Ugi–Diels–Alder involving furfurylamine and various acrylic derivatives.

Table 2 Tandem Ugi–Diels–Alder reaction of furfurylamine with *tert*-butyl isocyanide, 4-methoxybenzaldehyde and various acrylic acids

Entry	Acrylate **4**	Reaction time (h)	Product and isolated yield (%)
1	**4a**	24	**7a**, 57
2	**4b**	24	**8b**, 70
3	**4c**	16	**8c**, 81
4	**4d**	24	**7d**, 87[a]
5	**4e**	24	**7e**, 70[b]

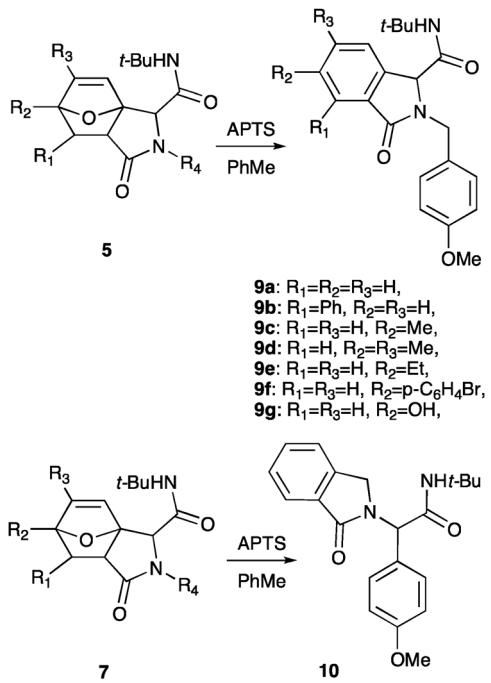
[a] A 1 : 1 mixture of diastereoisomers was obtained. [b] A 2 : 1 mixture of diastereoisomers was obtained.

Table 3 Ring opening-dehydrative aromatisation yielding isoindolinones

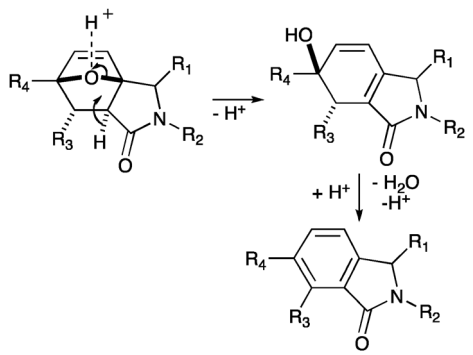
Entry	Reactant	Reaction time (min)	Product and isolated yield (%)
1	**5a**	120	**9a**, 39
2	**5c**	60	**9b**, 21
3	**5f**	30	**9c**, 51
4	**5h**	40	**9d**, 75
5	**5g**	10	**9e**, 62
6	**5i**	10	**9f**, 31
7	**5j**	30	**9g**, 54
8	**7a**	100	**10**, 95

the C═O bond is the one involved (being more acidic and giving access to a tetrasubstituted doubly conjugated double bond). The lack of reactivity of the compounds in which this hydrogen is replaced by a bromine atom accounts for this first step. From this point, the alcohol obtained undergoes an acid-catalysed elimination to yield the desired arene as shown in Scheme 5.

This second elimination appears to be favored when R_4 promotes the formation of a carbocation. This effect might not be observed from **5i**, as the bromine atom on the phenyl substituent deactivates it, such that the process is only as efficient as in the unsubstituted cases. In contrast, when R_3 is a phenyl group and R_4 a hydrogen atom, its position *trans* to the leaving oxygen disfavours the elimination and makes the



Scheme 4 Aromatisation of Ugi–Diels–Alder adducts.



Scheme 5 Mechanism of the ring opening-aromatisation sequence.

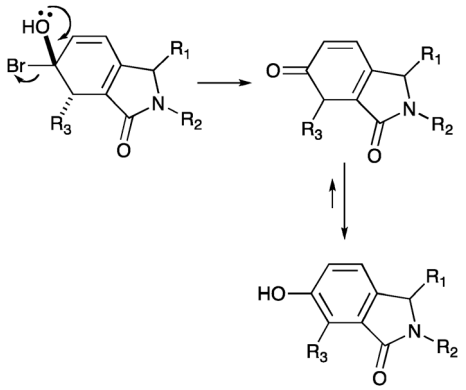


Fig. 2 Direct phenol formation from **5j**.

process less efficient (as it must go through a secondary carbocation). Finally when R_4 is a bromine, the ring opening leads directly to the phenol *via* its tautomeric keto form (see Fig. 2).

Conclusions

We have shown that a two-step approach to arenes can be achieved *via* a tandem Ugi–Diels–Alder/acid-catalysed aromatisation sequence from furfural and derivatives. This represents an interesting entry to isoindolinone, a moiety found in various biologically active compounds. Moreover, differently substituted biphenyl moieties have been reached without using any transition metal catalysis under mild conditions and from a renewable resource. This approach is therefore a cost-effective access to polysubstituted arenes (including biphenyls) and represents an interesting starting point for further investigations required to make the process not only economically – but also environmentally – friendly; this is the goal of our current investigations since only the combination of these two factors can make a process truly sustainable.

Representative experimental details

General procedure for the tandem Ugi–Diels–Alder reactions

Methanol (6 mL) was heated at 50 °C in a two-necked round-bottomed flask equipped with a condenser, then furfural (2 mmol), *p*-methoxybenzylamine (2 mmol), acrylic acid (2 mmol) and *tert*-butylisocyanide (2.4 mmol) were added successively. The mixture was stirred at 50 °C until completion of the reaction (monitored by TLC and GC), then cooled back to RT and diluted with dichloromethane (60 mL). The solution was washed with saturated aqueous sodium bicarbonate (30 mL), saturated aqueous ammonium chloride (30 mL) and brine (30 mL); the organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography with ethyl acetate–cyclohexane as system of eluents to yield the pure polycyclic adducts. Spectroscopic data for **5a:** ^{1}H NMR (d^6-DMSO, 300 MHz, ppm): 8.16 (s, 1H); 7.10 (m, 2H); 6.88 (m, 2H); 6.44 (dd, 1H, *J* 5.9 *J* 1.6); 6.20 (d, 1H, *J* 5.9); 5.06 (dd, 1H, *J* 4.5 *J* 1.6); 4.62 (d, 1H, *J* 15.2); 4.25 (s, 1H); 3.83 (d, 1H, *J* 15.2); 3.72 (s, 3H); 2.49 (m, 1H); 1.87 (ddd *J* 11.5 *J* 4.5 *J* 3.8); 1.49 (dd, 1H, *J* 11.5 *J* 8.9); 1.26 (s, 9H). ^{13}C NMR (d^6-DMSO, 100 MHz, ppm): 174.1; 167.0; 159.0; 137.6; 132.6; 129.3; 128.8; 114.3; 91.1; 78.7; 62.6; 55.6; 51.2; 46.4; 44.7; 28.7; 28.4. IR (ATR, cm^{-1}): 3314; 3083; 2966; 1686; 1663; 1553; 1517; 1453; 1249; 1224; 1189; 1030; 929; 791; 714; 709. MS (DCI, NH_3, *m*/*z*): 371 (MH^+), 388 (MNH_4^+); HRMS (ESI) expected for $C_{21}H_{27}N_2O_4$ (MH^+): 371.1971; found: 371.1966.

General procedure for aromatisation

To a 0.1 M solution of cycloadduct in toluene in a two-necked round-bottomed flask equipped with a reflux condenser was added PTSA·H_2O (1 eq.). The mixture was heated to reflux until completion of the reaction (indicated by disappearance of the starting material on TLC), then cooled back to RT and poured in a 3 : 2 mixture of dichloromethane and saturated aqueous sodium bicarbonate. The organic layer was separated, washed again with saturated aqueous sodium bicarbonate and brine, dried over anhydrous sodium sulfate and evaporated to dryness. When required, the product was purified by flash chromatography using ethyl acetate–cyclohexane mixtures. Spectroscopic data for **9c**: ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): 7.67 (d, 1H, *J* 0.9); 7.48 (d, 1H, *J* 7.8); 7.37 (dd, 1H, *J* 7.8 *J* 0.9); 7.27 (m, 2H); 6.87 (m, 2H); 5.40 (s_{br}, 1H); 5.06 (d, 1H, *J* 14.6); 4.69 (s, 1H); 4.37 (d, 1H, *J* 14.6); 3.80 (s, 3H); 2.46 (s, 3H); 1.19 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): 170.1; 166.8; 159.4; 139.2; 139.0; 133.5; 130.7; 130.1; 129.5; 128.7; 124.2; 114.4; 65.2; 55.4; 51.4; 45.8; 28.4; 21.4. IR (ATR, cm^{-1}): 3304; 2957; 2929; 1694; 1663; 1543; 1515; 1444; 1307; 1244; 1207; 1188; 1029; 849; 832; 818; 768; 741. MS (DCI, NH_3, *m*/*z*): 367 (MH^+). HRMS (DCI, CH_4) expected for $C_{22}H_{27}N_2O_3$ (MH^+): 367.2022; found: 367.2024

Further analytical data are provided in the ESI.†

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