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Highly efficient indium(III)-mediated cyclisation of 5-hydroxy-1,3-diketones to 2,3-dihydro-4*H*-pyran-4-ones; mechanistic insights from *in situ* Fourier transform infrared spectroscopy†

Philip C. Andrews,*[a] William J. Gee,[a] Peter C. Junk[a] and Harald Krautscheid[b]

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5-Hydroxy-1,3-diketones have been synthesised in a facile one-pot reaction from the treatment of acid chlorides with non-substituted ketones and LiHMDS. Subsequent cyclisation to 2,3-dihydro-4*H*-pyran-4-ones occurs rapidly and in high yield (89–99%) when mediated by anhydrous indium(III) chloride. A spectroscopic study of the reaction using *in situ* Fourier transform infrared (FTIR) spectroscopy has shown the reaction to be highly dependent on temperature, metal complex formation and $InCl_3$ concentration. Since the reaction is deactivated by the precipitation of $[InCl_3{\cdot}(H_2O)_3]$, the concurrent use of a stronger drying agent, such as molecular sieves 4 Å or anhydrous $MgSO_4$, allows the reaction to be successfully carried out at relatively low loadings of $InCl_3$ (1–10%). In their absence, the optimum reaction conditions were found to be a diketone : $InCl_3$ ratio of 3 : 1 in toluene, and a reaction temperature of 80 °C.

Introduction

2,3-Dihydro-4*H*-pyran-4-ones are important biological scaffolds. They are incorporated in several natural products including Prelog–Djerassi lactone and Compactin, a competitive inhibitor in cholesterol biosynthesis,[1,2] as well as serving as intermediates in the synthesis of many other biologically active compounds.[3] Synthetic routes to this class of compound from 5-hydroxy-1,3-diketones are well established, utilising strong acids including hydrochloric, sulfuric, and *p*-toluenesulfonic acids,[4–6] as well as Lewis acids, including $TiCl_4$ and $AlCl_3$.[7,8] However, each of these methods suffers from either by-product formation[4–8] or inconsistent yields.[4–6,9] Recently, indium(III) chloride has been described as an efficient and high yielding Lewis acid for the formation of flavones from 2′-hydroxychalcones[8] and phenol-substituted 1,3-diketones,[9] albeit with a loading requirement of 20–50% $InCl_3$. The mechanism for the indium mediated cyclisation remains unclear, though the latter report implicates an ultimate dehydration pathway.[9]

In situ Fourier transform infrared (FTIR) spectroscopy is a powerful analytical tool for probing reaction mechanisms and is proving invaluable to both the chemical and pharmaceutical industries.[10,11] In recent years, the application of in-line spectroscopy has proved effective in quality control,[12] in understanding kinetic studies,[13–15] in postulating reaction mechanisms,[15] in reaction optimisation, and in the identification of reaction intermediates.[16,17] *In situ* measurements allow reactions to be constantly monitored and evaluated, eliminating the potential for transfer contamination and sample degradation between the source and the spectrometer.

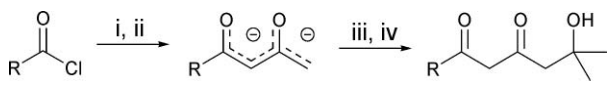
In this paper, we report the rapid, one-pot synthesis of a series of 5-hydroxy-1,3-diketones, and describe their subsequent conversion to 2,3-dihydro-4*H*-pyran-4-ones mediated by $InCl_3$. The 2,3-dihydro-4*H*-pyran-4-ones are generated from acid chlorides and non-substituted ketones, borrowing from a previously described method for generating diketones from acid chlorides and lithium enolates.[18] This constitutes the first synthesis of 2,3-dihydro-4*H*-pyran-4-ones from acid chlorides in a single step, improving efficiency and allowing the rapid isolation of products.

In addition, we describe the optimum reaction conditions, in terms of rate and yield, and a plausible reaction pathway deduced from *in situ* FTIR spectroscopy. We report the need for participation in the reaction mixture of an efficient dehydrating agent for a low level of $InCl_3$ catalyst loading to be effective.

Results and discussion

Synthesis of 2,3-dihydropyranones

Precursor 5-hydroxy-1,3-diketones **1–6** (Table 1), required for cyclisation to 2,3-dihydro-4*H*-pyran-4-ones, were synthesised by a one-pot condensation reaction of a 1,3-dicarbonyl dianion with a ketone (Scheme 1). A nitrogen-flushed reaction vessel was cooled to −78 °C and charged with dry THF. One equivalent of freshly formed lithium propen-2-olate was generated by the addition of lithium hexamethyldisilazide (LiHMDS) to acetone. A single



Scheme 1 *Reagents and conditions*: (i) 1 eq. lithium propen-2-olate, −78 °C, 5 min; (ii) 2 eq. LiHMDS, −78 °C, 5 min; (iii) 1 eq. acetone, −78 → 0 °C, 2 h; (iv) HCl(aq).

[a]*School of Chemistry, Monash University, Clayton, Melbourne, Vic 3800, Australia. E-mail: phil.andrews@sci.monash.edu.au; Fax: +61 3 99054597; Tel: +61 3 99055509*
[b]*Institut für Anorganische Chemie, Universität Leipzig, 04103, Leipzig, Germany*

† Electronic supplementary information (ESI) available: Generated *in situ* IR spectra and waterfall representations. Experimental procedure for assigning conversion percentage for drying agent study. See DOI: 10.1039/b919402a

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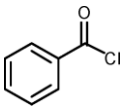
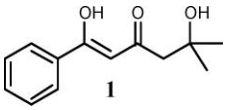
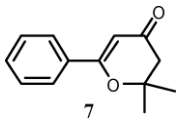
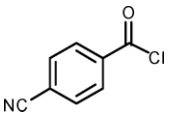
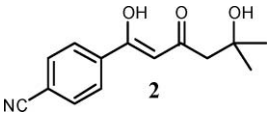
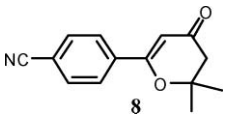
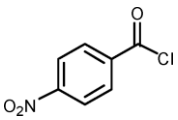
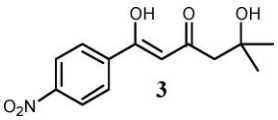
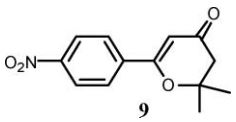
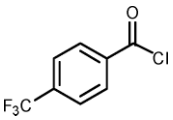
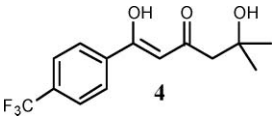
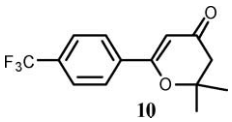
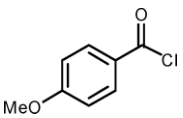
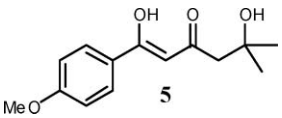
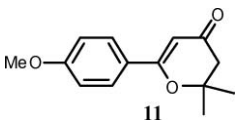
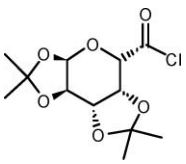
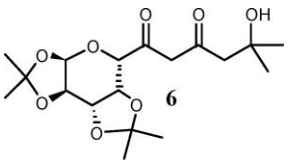
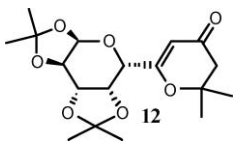
Table 1 5-Hydroxy-1,3-diketones and 2,3-dihydro-4*H*-pyran-4-ones synthesised

Acid chloride	Intermediate	Diketone yield (%)	Product	Pyranone yield (%)
	 **1**	77	 **7**	99
	 **2**	66	 **8**	97
	 **3**	80	 **9**	97
	 **4**	68	 **10**	95
	 **5**	72	 **11**	98
	 **6**	46	 **12**	89

equivalent of acid chloride was then added with rapid stirring to generate the diketone. Addition of a further two equivalents of LiHMDS to the solution gave the dianion, which then reacted with a final equivalent of acetone. The more nucleophilic terminal enolate reacts preferentially, giving the 5-hydroxy-1,3-diketone after acidic workup.

Performing the reaction at −78 °C and using a 1 : 1 ratio of enolate to acid chloride inhibited the possible formation of triketone by-products, improving overall reagent economy. Conducting the reaction at 0 °C results in a sharp increase in triketone species. Table 1 displays the 5-hydroxy-1,3-diketones and 2,3-dihydro-4*H*-pyran-4-ones synthesised in this study, alongside their corresponding isolated yields.

Cyclisation of 1,3-diketo-5-hydroxy moieties was achieved through the addition of 0.33 equivalents of anhydrous $InCl_3$ to a pre-dried toluene solution of each respective hydroxy diketone (**1–6**) at 80 °C. Optimisation of the reaction conditions is described below. After stirring for 30 min the solution was filtered and all volatiles removed *in vacuo* yielding the 2,3-dihydro-4*H*-pyranones (**7–12**).

Optimisation of reaction

An optimisation study was undertaken using *in situ* FTIR spectroscopy to determine the minimum loading of $InCl_3$ required to achieve total conversion of hydroxydiketone to dihydropyranone. Hydroxydiketone **3** was chosen as the representative substrate since it is obtained in high yield and, being solid, is easily purified through simple recrystallisation. Scanning from 4000 to 650 cm^{-1} at one minute intervals commenced from the time indium(III) chloride was added to the reaction mixture. This approach, rather than focusing on one absorption band, allows us to plot continual and cumulative changes in the spectra against time, thereby encompassing rate and conversion changes arising from intermediate species en route to the final product. If each new spectrum differs from its immediate predecessor and the change is significant then a steep incline occurs when this change is plotted relative to time. The converse is also therefore true for spectra that show no or only slight cumulative changes per unit time.

Optimisation reactions were undertaken by varying the ratio of $InCl_3$ relative to a 0.055 M toluene solution of **3**, heated at 80 °C. The most rapid conversion was observed for a molar ratio of 3 : 1 (diketone : $InCl_3$), with the reaction reaching completion after 13 min (Fig. 1). Surprisingly, increasing the amount of $InCl_3$ was found to negatively impact on the conversion rate of cyclisation, with equimolar equivalents more than doubling the time required to effect complete conversion. A reduction in the amount of $InCl_3$ relative to the diketone resulted not only in a drop in conversion rate, but also in incomplete conversion to the pyranone. This corresponds with previous reports in the literature.[8] When a ratio

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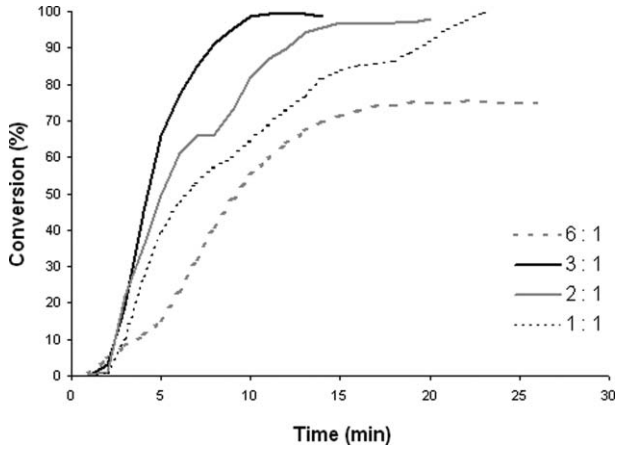

Fig. 1 Rate of change in IR spectra for transformation of diketone **3** into pyran-4-one dependant on diketone : $InCl_3$ ratio. *Reaction conditions*: 0.055 M toluene solution of **3** maintained at 80 °C.

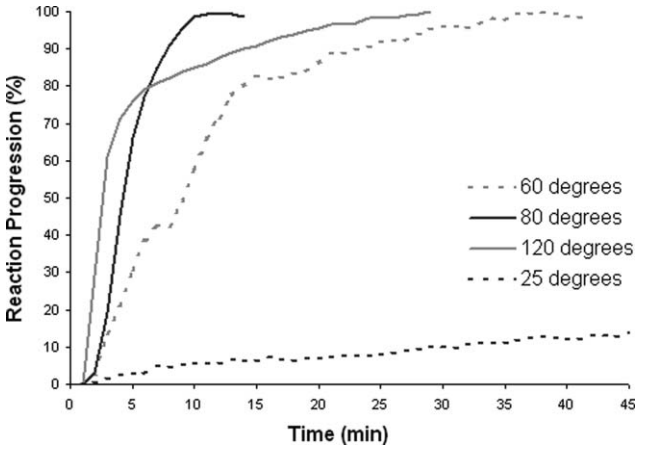

Fig. 2 Rate of change in IR spectra for transformation of diketone **3** into pyran-4-one dependant on reaction temperature.

of 6 : 1 (diketone : $InCl_3$) was employed, the yield of pyran-4-one was only 75%. Extending the reaction time by five hours led to no improvement in the overall yield.

A temperature dependence conversion study was undertaken next. Varying the reaction temperature from 80 °C to 25, 60 and 120 °C, whilst retaining the optimised 3 : 1 diketone : $InCl_3$ ratio, led to interesting variations in conversion rate over the reaction lifetime (Fig. 2). Increasing the temperature to 120 °C initially resulted in an increased rate of conversion relative to the reaction conducted at 80 °C. However, after approximately 75% conversion, a sharp decrease in rate was observed, such that complete conversion was achieved 15 min later than the 80 °C experiment. Analysis of the reaction at 25 °C indicates that the reaction proceeds to completion, but with total conversion only achieved after approximately 12 h (not shown). The kinetic profile of the 80 °C experiment is suggestive of Michaelis–Menton-type kinetics; however, this assumption was invalidated by variations in rate observed for the 60 and 120 °C experiments, implying a multistep reaction mechanism containing multiple species.[19]

Based on these observations it is postulated that the conversion of diketone **3** to dihydropyranone **9** occurs *via* transient intermediate species with variations in rate signifying the transition between species. Identification of the intermediate species is discussed below.

In situ FTIR analyses

To aid in the elucidation of the reaction mechanism for the cyclisation of diketone **3** to dihydropyranone **9**, a peak library was generated for the starting material and product using *in situ* FTIR spectroscopy. Spectra of 0.055M solutions of analyte in toluene were collected. Metal interaction can be expected to have a marked effect on carbonyl stretches; hence, assignment focused on the region of 1700–1200 cm^{-1}. Assigned bands for both **3** and **9** are shown in Table 2.

^1H NMR spectral analysis of **3** identified the conjugated vinylic and enolic protons at 6.26 and 15.82 ppm, respectively, indicating the dominant tautomer in solution to be the enolized form. This is consistent with the IR spectrum, which shows a characteristic very strong and broad band from 1550–1680 cm^{-1}. The location and extreme intensity of this band is attributed to the large increase in charge polarisation of the C=O bond, shifting the absorption to a lower wavenumber and increasing the charge on the carbonylic oxygen.[20] The overall resolution of bands in the IR

Table 2 Assignment of observed wavenumbers for diketone **3**, dihydropyranone **9**, and intermediates **13** and **14**

Wavenumber/cm^{-1}	Assignment	Wavenumber/cm^{-1}	Assignment
Diketone **3**		Intermediate **13**	
1577	C=O, C=C stretch	1727	C=O stretch *trans*
1532	N=O asym. stretch	1693	C=O stretch *cis*
1349	N=O sym. stretch	1657	C=O stretch *cis*
1320	C–H in-plane bend	1637	C=C stretch *cis*
1300	C–H in-plane bend	1618	C=C stretch *cis*
		1586	C=C stretch *trans*
		1538	C=O stretch *diketone*
		1521	N=O asym. stretch
2,3-Dihydropyranone **9**		Intermediate **14**	
1596	C=O stretch	1674	C=O stretch
1570	C=C stretch	1616	C=C aromatic stretch
1533	N=O asym. stretch	1606	C=C aromatic stretch
1505	C=C aromatic stretch	1547	N=O asym. stretch
1484	C=C aromatic stretch	1506	C=C aromatic stretch
1353	N=O sym. stretch	1491	C=C aromatic stretch
1310	C–H in-plane bend	1340	N=O sym. stretch

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spectrum of diketone **3** was poor, attributed to various rotameric isomers giving broadened, overlapping vibrations. The infrared spectrum of dihydropyranone **9** displays greater resolution of bands owing to greater rigidity afforded by the pyranone ring. Both the υ(C=C) and υ(C=O) bands are evident at 1570 and 1596 cm^{-1}, respectively, with well defined aromatic C=C stretching bands observed between 1505 and 1484 cm^{-1}. The appearance of a trisubstituted vinylic C–H out of plane bend at 852 cm^{-1} further confirms the presence of the pyranone ring. Twin nitro asymmetric and symmetric stretches (N=O) are prominent for both **3** and **9** at approximately 1530 and 1349 cm^{-1}.

Intermediate species in the conversion of diketone **3** to pyranone **9** were sought using real-time infrared scanning. Species differentiation by the software ConcIRT™ was improved through reducing the conversion rate by using toluene at 50 °C with the optimised diketone : $InCl_3$ ratio of 3 : 1. Concentration profiles were identified for diketone **3**, dihydropyranone **9** as well as two intermediate species across the 30 min reaction period (Fig. 3).

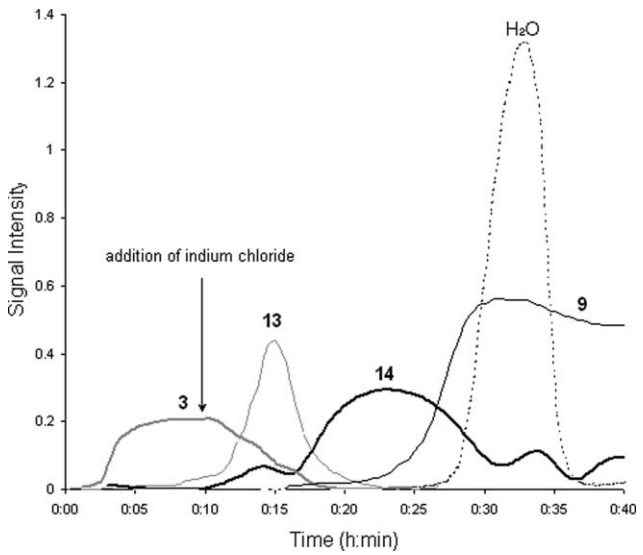
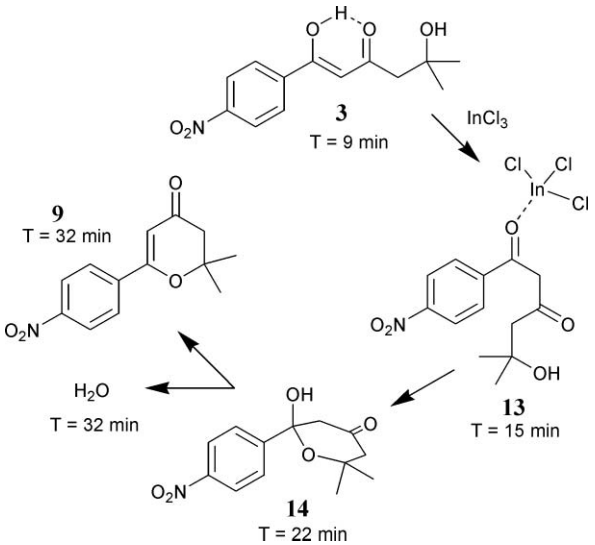


Fig. 3 Identified reaction components (compounds **3**, **9**, **13** and **14**) as a function of time.

The reaction commenced with the addition of $InCl_3$ to a solution of **3** at $T = 9$ min. Delaying the addition of $InCl_3$ was required to allow ConcIRT™ to generate reference spectra and allow the concentration of diketone to equilibrate prior to the reaction commencing. Post addition, free diketone **3** is consumed as the concentration of an indium coordinated intermediate **13** increases, reaching a maximum after 5 min (Scheme 2).

Chelation to the metal by the diketone represents the most stable conformer, seen as an intense υ(C=O) stretch at 1538 cm^{-1}, yet a large number of conformational rotamers are observed in the component IR spectrum as six bands in the double bond stretching region located at 1586, 1618, 1637, 1657, 1693 and 1727 cm^{-1} (Table 2). These bands are characteristic of *cis* and *trans* rotamers of keto enol ethers,[12] arising in this case through disruption of intramolecular hydrogen bonding by indium coordination. These bands can be assigned as an equilibrium of kinetically favoured *cis* β-keto enol ethers and thermodynamically stable *trans* forms. The lifetime of intermediate **13** was 10 min, after which complete conversion to a second pyran-4-one intermediate



Scheme 2 Species observed by *in situ* IR spectroscopy.

14 had occurred. The increase in concentration of **14** was seen to mirror the decline of indium-complexed diketone **13**. The carbonyl region of **14** shows a single dominant υ(C=O) band at 1674 cm^{-1}. Sharp aromatic υ(C=C) pairs are seen at 1606–1616 cm^{-1} and at 1491–1506 cm^{-1} overlapping the asymmetric nitro stretch. Ring closure was determined by the appearance of an intense υ(C–O) stretch at 1061 cm^{-1}. At $t = 20$ min, 11 min after the addition of indium(III) chloride, evidence for the formation of dihydropyranone **9** is obtained. Occurrence of the product again mirrors the decline in intermediate **14** with complete conversion effected after a further 10 min. The component spectrum of **9** correlates well with that of the solid state IR spectrum and peak library determination. The final detectable species is water, identified by an intense hydroxyl band located at 1321 cm^{-1}. Exact correlation with an *in situ* IR reference of deionised water was observed. The appearance of water was seen to coincide with **9**, and existed for approximately 10 min before sharply subsiding. This disappearance is attributed to the coordination of water molecules to indium(III) chloride, which results in loss of water from the solution phase and precipitation of the insoluble hydrate $[InCl_3 \cdot (H_2O)_3]$. A comparison by Raman spectroscopy of indium(III) chloride hydrate, generated *in situ* from a sample of indium(III) chloride exposed to moist air, yielded an identical spectrum, containing a single υ(In–Cl) band at 297 cm^{-1}. Both species also gave a broad hydroxyl band at 3315 cm^{-1}.

Based on these observations, the proposed mechanism initiates with activation of a keto group by coordination to indium(III) chloride. Interaction with the metal disrupts intramolecular hydrogen bonding through binding of the diketone to the indium centre, most probably in the more thermodynamically stable chelate mode but in equilibrium with a proportion bound only in a monodentate fashion. A range of conformers are therefore observed by FTIR as multiple vibrations in the carbonyl region. Significantly, only when the diketone is acting as a monodentate ligand, as epitomised by conformer **13**, can the hydroxyl group be in close proximity to the indium-activated carbonyl group, thus enabling cyclisation through an intramolecular S_N2 attack resulting in an ether linkage and an anionic indate species. Performing the reaction at 120 °C gave an increased conversion rate (Fig. 2), most likely resulting

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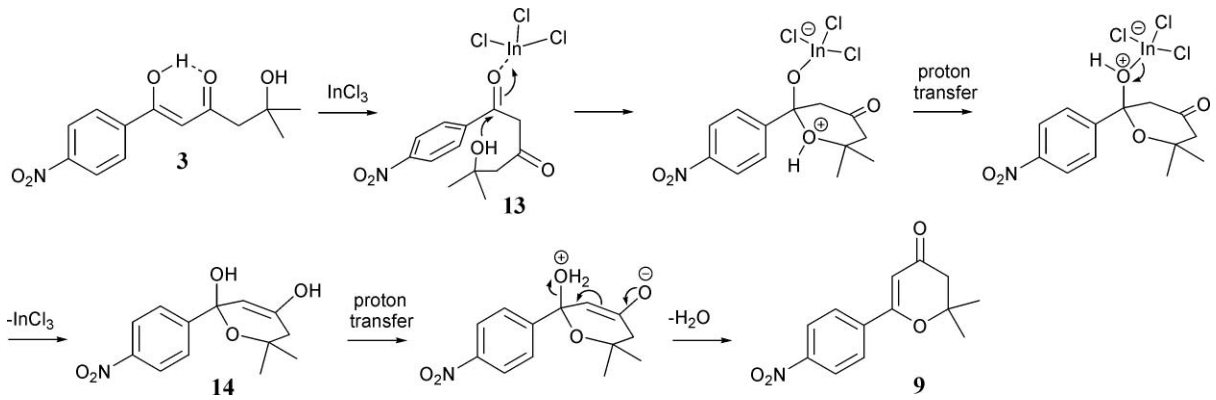

Scheme 3 Proposed mechanism of pyran-4-one formation.

from a shift in the complex equilibrium favouring monodentate binding of the ligand and an increase in kinetic energy promoting the intramolecular S_N2 attack.

Protonation results in cleavage of the unstable indium–oxygen bond, regenerating indium(III) chloride and releasing the hydroxypyranone, **14**. The IR spectrum of intermediate **14** shows retention of the more stable keto form. Elimination of water requires a tautomeric shift to the enol form, constituting the second rate step observed in Fig. 2. At higher temperatures the equilibrium shifts to favour the keto form,[21–23] and as such, the decrease in the rate of cyclisation observed at 120 °C can be justified by the fact that in the keto form, elimination of water is not energetically favourable. Only in the enol form does proton transfer occur, leading to the elimination of water and formation of the conjugated 2,3-dihydro-4*H*-pyranone. Scheme 3 displays the observed species **3**, **9**, **13** and **14** with the proposed mechanism overlayed.

Variation in the rate of conversion induced by differing ratios of indium(III) chloride to 5-hydroxy-1,3-diketone (Fig. 1) can also be understood in light of the mechanism. Incomplete conversion is observed when a molar ratio of less than 3 : 1 (diketone : $InCl_3$) is employed, attributed to the rapid capture of eliminated water by the indium cation to generate hydrated indium(III) chloride. The coordination of three equivalents of water saturates the coordination sphere of indium(III) chloride, binding with greater strength than the diketone. As a result the diketone is denied access to the metal center, resulting in termination of reaction.

In light of this, the addition of molecular 4 Å sieves to a solution loaded with only 10% $InCl_3$ (*i.e.* 10 : 1 molar ratio) led to a near doubling in the observed yield when compared with the analogous reaction conducted in the absence of sieves (43 *vs.* 82%; Table 3). That the conversion is not quantitative may be indicative of competitive binding of water between the sieves and $InCl_3$. Subsequent substitution of the sieves with an evenly distributed suspension of anhydrous magnesium sulfate ($MgSO_4$) did produce a quantitative conversion of diketone to pyranone. However, reducing the catalyst loading to 1% $InCl_3$ resulted in only 72% conversion to the pyranone product, presumably due to slow poisoning of the catalyst by water. The hydrated indium(III) chloride can be easily recovered by filtration and dehydrated through sublimation.

Increased concentrations of indium (*i.e.* greater than 3 : 1 diketone:indium) were found to cause a decline in rate (Fig. 1).

Table 3 Assignment of observed wavenumbers for diketone **3**, dihydropyranone **9** and intermediates **13** and **14**

Drying agent	$InCl_3$ loading (%)	Conversion ratio (diketone : pyranone)
—	10	67 : 43
4 Å molecular sieves	0	100 : 0
4 Å molecular sieves	10	18 : 82
Anhydrous $MgSO_4$	0	100 : 0
Anhydrous $MgSO_4$	10	0 : 100
Anhydrous $MgSO_4$	1	28 : 72

It would be expected that an increase in the concentration of $InCl_3$ would lead to both a rate enhancement and an overall yield improvement since a greater proportion of the diketone is complexed and activated, and excess anhydrous $InCl_3$ would act as a dehydrating agent. One plausible explanation why this is not the case could be that as the $InCl_3$ concentration increases then so does the amount of diketone coordinated to two $InCl_3$ molecules; one on each carbonyl functionality, with the hydroxy group also binding to give a stable six-membered chelate, as illustrated by **15** in Fig. 4. This would inhibit the diketone adopting configurations capable of undergoing intramolecular S_N2 attack. An increase in concentration of $InCl_3$ would also increase the possibility of stabilising the keto tautomer of intermediate **16**, further resulting in a rate decrease.

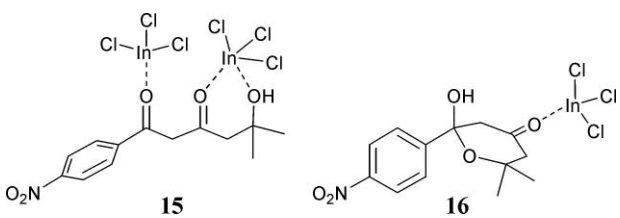

Fig. 4 Possible intermediates **15** and **16** implicated in rate reduction.

Conclusions

We have developed a new one-pot synthetic protocol for the formation of 5-hydroxy-1,3-diketones from acid chlorides, non-substituted ketones and the bulky lithium base, LiHMDS. These can be rapidly and efficiently converted to 2,3-dihydro-4*H*-pyran-4-ones through a cyclisation reaction mediated by anhydrous

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indium(III) chloride. For this latter process, examination and analysis of the reaction by *in situ* FTIR spectroscopy has indicated that the optimum reaction conditions in the absence of a dehydrating agent involve an $InCl_3$: diketone ratio of 1 : 3, heated at 80 °C. The reaction rate and yield are affected favourably by shifting the keto–enol equilibrium in favour of the enol form (lower temperature), and by monodentate binding of the diketone to $InCl_3$ rather than by chelation. The nucleophilic cyclisation and final dehydration step to give the pyranone ring are also favoured by higher temperatures, indicating that a fine balance is required to maximise product yield. A higher concentration of $InCl_3$ leads to a reduced reaction rate, most likely due to formation of an $[(InCl_3)_2 \cdot (diketone)]$ complex with a configuration which prohibits cyclisation.

The discovery that the reaction is deactivated by the precipitation of $[InCl_3 \cdot (H_2O)_3]$ led to the reaction being successfully conducted at low $InCl_3$ loadings (1–10%) when a more competitive drying agent, molecular sieves 4 Å or anhydrous $MgSO_4$, was used in the reaction medium.

Experimental

General

All chemicals were obtained from commercial sources and were used as received unless otherwise stated. Anhydrous solvents were obtained from a MBRAUN MB SPS-800 solvent purification system, and all reaction glassware was oven-dried prior to use. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Varian Unity Nova 500 MHz spectrometer. Chemical shifts were recorded on the δ scale and referenced to deuterated solvent. ^{13}C NMR spectra were recorded at 125 MHz, with resonances referenced to deuterated solvent. Solid-state IR spectra were recorded on a Bruker Equinox 55 Infrared Spectrometer fitted with a Specac Diamond ATR source. Solution RTIR scanning measurements were recorded using a Mettler Toledo ReactIR 10 spectrometer fitted with a DiComp probe and connected to an MCT detector by a K6 Conduit. Scanning was performed in the region of 4000–650 wavenumbers at 8 wavenumber resolution. Elucidation of reaction components was performed using ConcIRT™ software. All positive and negative electrospray ionization mass spectroscopy (ESI(±)-MS) was performed on a Micromass Platform II QMS spectrometer using cone voltages varying from 35–50 V. Melting points were measured on a Stuart Scientific Melting Point Apparatus in an open capillary.

General method for the synthesis of 5-hydroxy-1,3-diketones

To a solution of freshly prepared LiHMDS (1.25 mL, 1.6 M in hexanes, 2.0 mmol) in dry THF (5 mL) at −78 °C was added one equivalent of acetone (142 µL, 2.00 mmol) with rapid stirring for approximately 1 min. After this time, an equimolar quantity of acid chloride was added in one portion with rapid stirring. After approximately 5 min two further equivalents of LiHMDS were added and the solution was stirred for an additional 5 min. A second equivalent of acetone was added and the solution allowed to warm to room temperature. The reaction was quenched with water (~10 mL) and acidified to pH 5 with 1 M HCl. The solution was then extracted with EtOAc (3 × 25 mL) and the organic washes dried ($MgSO_4$) and concentrated to dryness under reduced pressure. The crude product was then purified by column chromatography yielding the 5-hydroxy-1,3-diketone.

General method for the synthesis of 2,3-dihydro-4*H*-pyran-4-ones

The 5-hydroxy-1,3-diketone (1.00 mmol) and indium chloride (22.1 mg, 0.100 mmol) were suspended in dry toluene in a nitrogen-flushed, oven-dried flask. The mixture was stirred at 80 °C for 40 min. After this time, the solution was filtered and evaporated under reduced pressure yielding the 2,3-dihydro-4*H*-pyran-4-one product.

(*Z*)-1,5-dihydroxy-5-methyl-1-phenylhex-1-en-3-one (1). Viscous yellow oil (0.340 g, 77%); IR (KBr) ν 3431 s, 2974 s, 1603 s, 1461 s, 1379 s, 1187 s, 1159 s, 1079 s, 1028 m, 1001 m, 981 m, 950 m, 909 s, 859 w, 813w, 765 s, 699 s, 648 m, 571 m, 498 m cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) δ 1.33 (s, 6H, CH_3), 2.62 (s, 2H, H-4), 3.43 (s, 1H, OH), 6.18 (s, 1H, H-2), 7.46 (t, 2H, J = 7.2 Hz, Ar), 7.54 (t, 1H, J = 7.2 Hz, Ar), 7.88 (d, 2H, J = 7.2 Hz, Ar), 16.14 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) δ 29.5 (CH_3), 51.3 (C-4), 70.4 (C-5), 98.0 (C-2), 127.1 (Ar), 128.7 (Ar), 132.6 (Ar), 134.3 (Ar), 182.6 (C-1), 196.8 (C-3); HRMS (ESI) calcd for (M + H) $C_{13}H_{17}O_3$: 221.1178. Found: 221.1172.

(*Z*)-4-(1,5-dihydroxy-5-methyl-3-oxohex-1-enyl)benzonitrile (2). Colourless oil (0.322 g, 66%); IR (KBr) ν 3445 brm, 2974 m, 2231 m, 1615 s, 1598 s, 1562 s, 1501 m, 1463 m, 1437 m, 1379 m, 1288 s, 1161 m, 1114 m, 909 m, 855 m, 806 m, 776 m, 545 m cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) δ 1.34 (s, 6H, CH_3), 2.67 (s, 2H, H-4), 3.23 (s, 1H, OH), 6.23 (s, 1H, H-2), 7.75 (d, 2H, J = 8.4 Hz, Ar), 7.97 (d, 2H, J = 8.4 Hz, Ar), 15.87 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) δ 29.6 (CH_3), 51.8 (C-4), 70.5 (C-5), 99.1 (C-2), 115.5 (Ar), 118.0 (CN), 127.5 (Ar), 132.2 (Ar), 138.3 (Ar), 179.0 (C-1), 198.6 (C-3); HRMS (ESI) calcd for (M − H) $C_{14}H_{14}NO_3$: 244.0974. Found: 244.0980.

(*Z*)-1,5-dihydroxy-5-methyl-1-(4-nitrophenyl)hex-1-en-3-one (3). Red crystalline solid (0.426 g, 80%); Mp 56.1–56.6 °C; IR (KBr) ν 3276 m, 2979 m, 2929 m, 1584 s, 1520 s, 1382 m, 1344 s, 1319 s, 1297 m, 1157 m, 1110 m, 1074 m, 1010 m, 989 m, 948 w, 912 m, 895 m, 866 w, 814 w, 804 m, 783 m, 764 m, 750 w, 729 m, 707 m, 683 m, 651 w, 583 w, 486 w, 444 w, 416 w cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) δ 1.35 (s, 6H, CH_3), 2.69 (s, 2H, H-4), 3.19 (s, 1H, OH), 6.26 (s, 1H, H-2), 8.04 (d, 2H, J = 8.4 Hz, Ar), 8.30 (d, 2H, J = 8.4 Hz, Ar), 15.82 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) δ 29.7 (CH_3), 51.9 (C-4), 70.5 (C-5), 99.4 (C-2), 123.9 (Ar), 128.0 (Ar), 139.9 (Ar), 149.9 (Ar), 178.4 (C-1), 199.1 (C-3); HRMS (ESI) calcd for (M − H) $C_{13}H_{14}NO_5$: 264.0872. Found: 264.0876.

(*Z*)-1,5-dihydroxy-5-methyl-1-(4-(trifluoromethyl)phenyl)hex-1-en-3-one (4). White powder (0.390 g, 68%); Mp 76.8–77.2 °C; IR (KBr) ν 3515 m, 3099 m, 2987 m, 2927 m, 1617 s, 1576 s, 1518 m, 1444 m, 1390 m, 1379 m, 1329 s, 1261 m, 1162 s, 1129 s, 1113 s, 1080 m, 1064 s, 1016 m, 984 w, 948 w, 913 w, 887 w, 855 m, 822 s, 718 m, 685 w, 598 w, 519 w, 428 w cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) δ 1.34 (s, 6H, CH_3), 2.66 (s, 2H, H-4), 3.24 (s, 1H, OH), 6.21 (s, 1H, H-2), 7.72 (d, 2H, J = 8.0 Hz, Ar), 7.98 (d, 2H, J = 8.0 Hz, Ar), 15.91 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) δ 29.6 (CH_3), 51.9 (C-4), 70.4 (C-5), 98.7 (C-2), 125.6

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(Ar), 125.7 (Ar), 127.3 (Ar), 137.5 (Ar), 180.1 (C-1), 198.1 (C-3); HRMS (ESI) calcd for (M − H) $C_{14}H_{14}F_3O_3$: 287.0895. Found: 287.0900.

(*Z*)-1,5-dihydroxy-1-(4-methoxyphenyl)-5-methylhex-1-en-3-one (5). Colourless oil (0.361 g, 72%); IR (KBr) *ν* 3436 m, 2972 m, 2841 m, 1602 m, 1258 s, 1175 s, 1114 m, 1077 m, 1029 s, 982 m, 951 m, 909 m, 844 m, 806 m, 774 m, 682 w, 633 w cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) δ 1.31 (s, 6H, CH_3), 2.58 (s, 2H, H-4), 3.50 (s, 1H, OH), 3.86 (s, 3H, C*H*$_3$O), 6.11 (s, 1H, H-2), 6.94 (d, 2H, J = 8.5 Hz, Ar), 7.86 (d, 2H, J = 8.5 Hz, Ar), 16.18 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) δ 29.6 (CH_3), 51.9 (C-4), 55.9 (OCH_3), 70.5 (C-5), 99.3 (C-2), 109.1 (Ar), 114.1 (Ar), 126.8 (Ar), 130.5 (Ar), 178.3 (C-1), 199.0 (C-3); HRMS (ESI) calcd for (M + H) $C_{14}H_{19}O_4$: 251.1283. Found: 251.1280.

5-Hydroxy-5-methyl-1-((3α*S*,5*R*,5α*R*,8α*S*,8β*S*)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis[1,3]dioxolo[4,5-*b*:4′,5′-*d*]pyran-5-yl)-hexane-1,3-dione (6). Colourless oil (0.344 g, 46%); IR (KBr) *ν* 3478 s, 2979 s, 1704 s, 1603 s, 1257 s, 901 m, 841 m, 787 m, 678 w, 633 s cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) δ 1.23 (s, 6H, CH_3), 1.28 (s, 3H, $(O)_2C(CH_3)_2$), 1.33 (s, 3H, $(O)_2C(CH_3)_2$), 1.41 (s, 3H, $(O)_2C(CH_3)_2$), 1.52 (s, 3H, $(O)_2C(CH_3)_2$), 2.17 (s, 2H, H-2), 2.51 (s, 2H, H-4), 2.63 (s, 1H, O*H*), 4.33-4.38 (m, 2H, H-3′, H-5′), 4.62 (dd, 1H, J = 7.5 Hz, J_2 = 2.0 Hz, H-2′), 4.67 (dd, 1H, J = 7.5 Hz, J_2 = 2.0 Hz, H-4′), 5.61 (d, 1H, J = 4.5 Hz, H-1′); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) δ 24.7 ($C(CH_3)_2$), 25.1 ($C(CH_3)_2$), 26.1 ($C(CH_3)_2$), 26.3 ($C(CH_3)_2$), 29.5 (CH_3), 29.7 (CH_3), 50.6 (C-4), 70.0 (C-4′), 70.6 (C-5), 70.8 (C-2′), 70.9 (C-3′), 77.0 (C-2), 96.67 (C-5′), 100.01 (C-1′), 109.32 ($C(CH_3)_2$), 110.02 ($C(CH_3)_2$), 191.42 (C-3), 192.40 (C-1); HRMS (ESI) calcd for (M + H) $C_{18}H_{29}O_8$: 373.1862. Found: 373.1862

2,2-Dimethyl-6-phenyl-2*H*-pyran-4(3*H*)-one (7). Yellow oil (0.200 g, 99%); IR (KBr) *ν* 1633 s, 1493 m, 1451 s, 1372 s, 1255 s, 1171 s, 1056 s, 1028 m, 983 m, 935 m, 891 m, 772 m, 692 m cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) δ 1.55 (s, 6H, CH_3), 2.67 (s, 2H, H-3), 6.12 (s, 1H, H-5), 7.43 (t, 2H, J = 8.0 Hz, Ar), 7.48 (t, 1H, J = 8.0 Hz, Ar), 7.74 (d, 2H, J = 8.0 Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) δ 26.3 (CH_3), 47.2 (C-3), 81.6 (C-2), 100.8 (C-5), 126.9 (Ar), 128.8 (Ar), 131.9 (Ar), 133.3 (Ar), 169.8 (C-6), 194.5 (C-4); HRMS (ESI) calcd for (M + H) $C_{13}H_{15}O_2$: 203.1072. Found: 203.1067.

2,2-Dimethyl-6-*p*-(cyanophenyl)-2*H*-pyran-4(3*H*)-one (8). Colourless oil (0.219 g, 97%); IR (KBr) *ν* 2230 m, 1630 s, 1417 m, 1256 m, 1170 m, 1108 m, 1057 m, 1017 m, 983 m, 935 m cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) δ 1.59 (s, 6H, CH_3), 2.85 (s, 2H, H-3), 6.40 (s, 1H, H-5), 7.74 (d, 2H, J = 8.0 Hz, Ar), 7.87 (d, 2H, J = 8.0 Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) δ 26.2 (CH_3), 46.6 (C-3), 83.1 (C-2), 102.1 (C-5), 115.5 (Ar), 118.0 (CN), 127.7 (Ar), 132.6 (Ar), 136.8 (Ar), 169.8 (C-6), 197.0 (C-4); HRMS (ESI) calcd for (M + H) $C_{14}H_{14}NO_2$: 228.1025. Found: 228.1015.

2,2-Dimethyl-6-*p*-(nitrophenyl)-2*H*-pyran-4(3*H*)-one (9). Red crystalline solid (0.240 g, 97%); Mp 154–156 °C; IR (KBr) *ν* 1659 s, 1603 s, 1580 s, 1514 m, 1471 m, 1416 m, 1343 s, 1324 s, 1300 m, 1249 m, 1105 s, 1044 m, 1012 w, 981 m, 862 s, 849 s, 834 s, 815 m, 756 s, 693 s cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) δ 1.56 (s, 6H, CH_3), 2.62 (s, 2H, H-3), 6.06 (s, 1H, H-5), 7.88 (d, 2H, J = 9.0 Hz, Ar), 8.27 (d, 2H, J = 9.0 Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) δ 26.2 (CH_3), 46.4 (C-3), 83.5 (C-2), 102.4 (C-5), 124.0 (Ar), 128.3 (Ar), 138.3 (Ar), 150.1 (Ar), 170.3 (C-6), 197.8 (C-4); HRMS (ESI) calcd for (M + H) $C_{13}H_{14}NO_4$: 248.0923. Found: 248.0915.

2,2-Dimethyl-6-*p*-((trifluoromethyl)phenyl)-2*H*-pyran-4(3*H*)-one (10). Colourless oil (0.255 g, 95%); IR (KBr) *ν* 1633 s, 1417 s, 1324 s, 1115 m, 1069 m, 1015 m, 983 m, 936 m, 809 m cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) δ 1.58 (s, 6H, CH_3), 2.76 (s, 2H, H-3), 6.25 (s, 1H, H-5), 7.69 (d, 2H, J = 8.0 Hz, Ar), 7.86 (d, 2H, J = 8.0 Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) δ 26.3 (CH_3), 47.1 (C-3), 82.6 (C-2), 101.9 (C-5), 125.9 (Ar), 127.4 (Ar), 133.6 (CF_3), 133.8 (Ar), 136.6 (Ar), 169.1 (C-6), 195.5 (C-4); HRMS (ESI) calcd for (M + H) $C_{14}H_{14}F_3O_3$: 271.0946. Found: 271.0942.

2,2-Dimethyl-6-*p*-(methoxyphenyl)-2*H*-pyran-4(3*H*)-one (11). Colourless oil (0.227 g, 98%); IR (KBr) *ν* 1633 s, 1249 s, 1169 s, 1108 s, 983 s, 936 s, 892 m, 842 m, 771 m, 733 s, 679 m cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) δ 1.56 (s, 6H, CH_3), 2.83 (s, 2H, H-3), 3.86 (s, 3H, CH_3O), 6.34 (s, 1H, H-5), 6.93 (d, 2H, J = 9.0 Hz, Ar), 7.86 (d, 2H, J = 9.0 Hz, Ar); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) δ 26.3 (CH_3), 46.2 (OCH_3), 55.7 (C-3), 82.2 (C-2), 99.2 (C-5), 114.4 (Ar), 124.7 (Ar), 129.5 (Ar), 163.6 (Ar), 173.3 (C-6), 196.2 (C-4); HRMS (ESI) calcd for (M + H) $C_{14}H_{17}O_3$: 233.1178. Found: 233.1170.

2,2-Dimethyl-6-((3α*S*,5*R*,5α*R*,8α*S*,8β*S*)-2,2,7,7-tetramethyltetrahydro-3a*H*-bis[1,3]dioxolo[4,5-*b*:4′,5′-*d*]pyran-5-yl)-2*H*-pyran-4(3*H*)-one (12). Colourless oil (0.315 g, 89%); IR (KBr) *ν* 1652 s, 1455 s, 1372 s, 1259 s, 1055 m, 933 w, 898 w, 802 m, 733 w, 692 w cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) δ 1.30 (s, 3H, $(O)_2C(CH_3)_2$), 1.33 (s, 3H, $(O)_2C(CH_3)_2$), 1.37 (s, 3H, $(O)_2C(CH_3)_2$), 1.38 (s, 3H, $(O)_2C(CH_3)_2$), 1.45 (s, 3H, $C(CH_3)_2$), 1.53 (s, 3H, $C(CH_3)_2$), 2.48 (d, 1H, J = 16.5 Hz, H-3a), 2.57 (d, 1H, J = 16.5 Hz, H-3b), 4.27 (m, 1H, H-5′), 4.36 (dd, 1H, J = 5.0 Hz, J_2 = 2.5 Hz, H-3′), 4.42 (dd, 1H, J = 8.0 Hz, J_2 = 2.5 Hz, H-2′), 4.64 (dd, 1H, J = 8.0 Hz, J_2 = 2.5 Hz, H-4′), 5.59 (d, 1H, J = 5.5 Hz, H-1′), 5.66 (s, 1H, H-5); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) δ 24.5 ($C(CH_3)_2$), 24.9 ($C(CH_3)_2$), 25.0 ($C(CH_3)_2$), 26.1 ($C(CH_3)_2$), 26.2 (CH_3), 27.9 (CH_3), 47.9 (C-3), 67.6 (C-4′), 70.7 (C-2′), 70.9 (C-3′), 71.7 (C-5′), 82.0 (C-2), 96.6 (C-1′), 102.7 (C-5), 109.1 ($C(CH_3)_2$), 109.9 ($C(CH_3)_2$), 170.5 (C-6), 192.8 (C-4); HRMS (ESI) calcd for (M + H) $C_{18}H_{27}O_7$: 355.1757. Found: 355.1751.

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