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PAPER

Concise formal synthesis of (–)-7-deoxyloganin *via N*-heterocyclic carbene catalysed rearrangement of α,β-unsaturated enol esters†

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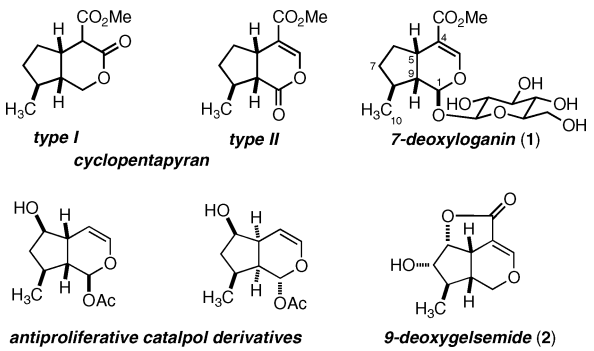
NHC catalysed rearrangement of α,β-unsaturated enol esters derived from formyl acetates and cyclopentyl annulated α,β-unsaturated acids provides the cyclopentapyranone core of (–)-7-deoxyloganin (**1**) with diastereo- and chemoselectivity in 6 steps starting from (–)-citronellal. The elaboration to the natural product has been investigated using two new approaches. The most successful intercepts our previous work on (–)-7-deoxyloganin (**1**) allowing completion of a formal total synthesis in 10-steps.

Introduction

Iridoids are a diverse family of natural products with over 250 members of marine and terrestrial origins.[1] Structurally a cyclopentapyran core of type **I** or **II**, with a *cis* relationship between H-5 and H-9 is common (Scheme 1), although stereoisomeric examples, and *seco* derivatives, are known. Their role in biosynthesis has been extensively investigated, with pivotal involvement as the non-nitrogeous component in alkaloid biosynthesis established.[2] In addition iridoids have received attention as bioactive entities, with recent studies demonstrating that, for example, 9-deoxygelsemide (**2**) and catalpol derivatives have anticancer activity.[1d,e,3] The compact and structurally rich nature of iridoids, together with their numerous biological roles, continue to stimulate investigations focused on their chemical synthesis.[4]



Scheme 1 Iridoid natural products.

While investigating Lewis base mediated reaction cascades, we recently discovered a *N*-heterocyclic carbene (NHC) catalysed dihydropyranone synthesis.[5,6] We postulated that this reaction should provide access to the cyclopentapyran core of (–)-7-deoxyloganin (**1**), and ultimately the natural product itself. This was realised with the total synthesis of (–)-7-deoxyloganin (**1**) completed last year.[6b] While these studies were successful they suffered from a number of limitations, resulting in an 18-step linear sequence and concomitant low overall yield. To demonstrate the enabling role of reaction discovery on target oriented synthesis, we chose to re-examine this sequence, to improve the step count and overall yield. Herein we provide a full-account of our studies on the synthesis of (–)-7-deoxyloganin, with optimisation of the key NHC catalysed rearrangement, improved preparation of the rearrangement precursor (*S*)-**3c** and alternate end-game strategies. These refinements allow a formal total synthesis of (–)-7-deoxyloganin (**1**) to be completed in 10-steps.

Results and discussion

The use of NHCs as organocatalysts for non-carbonyl umpolung reactions has received limited attention.[6,7] In 2009 we found that NHCs catalyse the rearrangement of α,β-unsaturated enol esters to dihydropyranones (Scheme 2) *via* normal polarity intermediates.[6a]

To investigate the utility of this transformation studies into the chemical synthesis of (–)-7-deoxyloganin (**1**) were undertaken, with the key transformation involving isomerisation of enol ester **3** to the cyclopentapyranone **4**. The chemoselectivity of such a transformation was identified as a potential challenge, since NHC catalysed transesterification has been reported.[8] In addition the reaction must tolerate annulation across the α- and β-positions of the α,β-unsaturated motif. Finally, substrate directed diastereoselectivity, to deliver the *cis* arrangement of H5, H9 and the methyl at C-8, would need to be realised (Scheme 2).

Optimisation of the NHC catalysed isomerisation

Since the key challenges associated with the synthesis of **1** relate to the proposed NHC catalysed isomerisation of **3**→**4**

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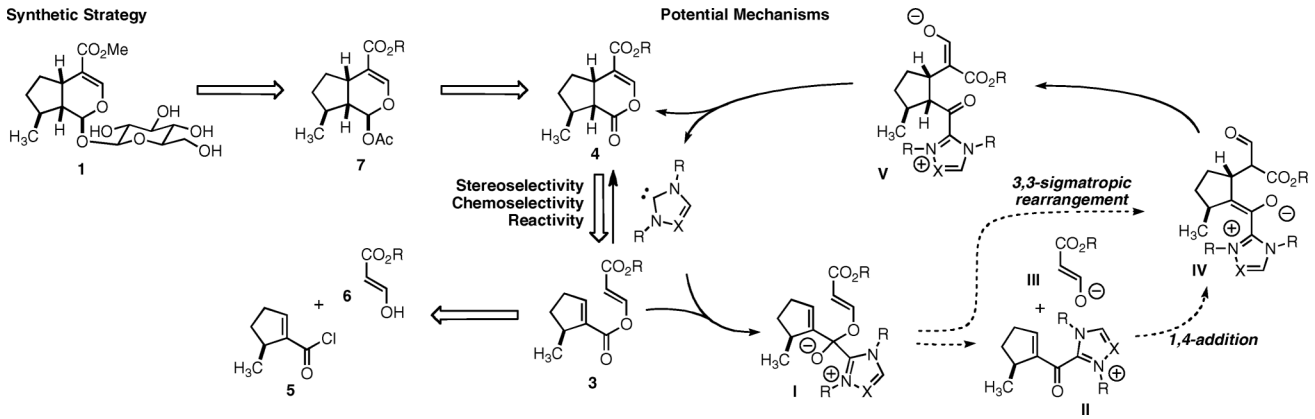


Scheme 2 Synthetic strategy and potential reaction mechanism.

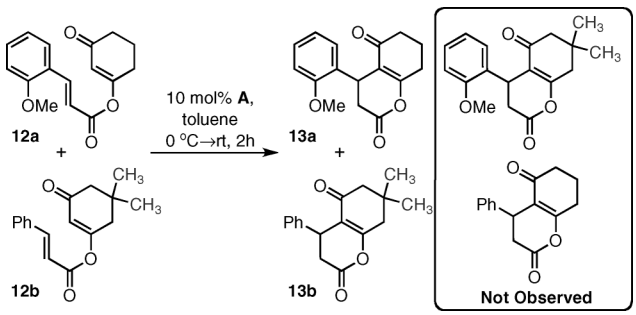
model studies were undertaken to establish the viability of this event. Investigations commenced with the preparation of diesters **8a** and **8b** (R = ^{t}Bu or Et) from formyl acetates **6a–b**[9] and cinnamoyl chloride. Their rearrangements to lactone **9a** and **9b**, were undertaken to examine the impact, if any, of the type of ester on the reaction. The methyl ester was not prepared due to reported difficulties in the synthesis of methyl formyl acetate **6c** (R = Me)[10] (*vide infra*). When the ethyl ester **8b** (R = Et) was rearranged forcing conditions were required, and only a modest yield of lactone **9b** was obtained (Table 1, entry 1b). In contrast the *t*-butyl ester **8a** gave lactone **9a** after 1 h at 0 °C and in excellent yield (Table 1, entry 1a).

Having demonstrated the viability of diester containing substrates in the rearrangement, cyclopentyl ester **10** was prepared, to examine substrates bearing annulation across the α,β-unsaturated portion. In this case an acceptable yield, albeit with modest stereoselectivity, was achieved only when the reaction was heated in toluene at reflux for 14 h (Table 1, entry 2a). The diastereoselectivity could be moderately improved by employing homochiral triazolium derived carbene **B**, however this catalyst provided only a trace of the desired product (Table 1, entry 2b). Unfortunately, and as observed with other NHC catalysed reactions exploiting substrates in the carboxylic acid oxidation state, triazolium derived NHCs display modest reactivity.[6,11]

While these studies demonstrate the viability of assembling (–)-7-deoxyloganin (**1**) using the NHC catalysed rearrangement of **3**→**4**, in addition they highlight potential difficulties with substrates annulated across the α,β-unsaturation.

Based on the greater yields obtained with **8a** compared to **8b** *t*-butyl ester **3a** (R = ^{t}Bu) was identified as the most suitable subtarget for the total synthesis. Unfortunately, when this substrate was exposed to NHC **A** in refluxing toluene for 14 h none of the desired cyclopentapyran **4a** (R = ^{t}Bu) formed (Table 1, entry 3a). The lack of reactivity mirrored the results observed with other annulated substrates (*i.e.* **10**).

For the rearrangement to occur formation of hemiacetal **I** must occur and be followed by formation of acyl azolium **II**/enolate **III** ion pair or a Claisen rearrangement (Scheme 2).[12] To clarify which mechanism is operative in this reaction a cross-over study with substrates **12a** and **b** was undertaken (Scheme 3). This reaction provided **13a** and **b** with none of the crossed-product, thereby implicating the Claisen pathway.



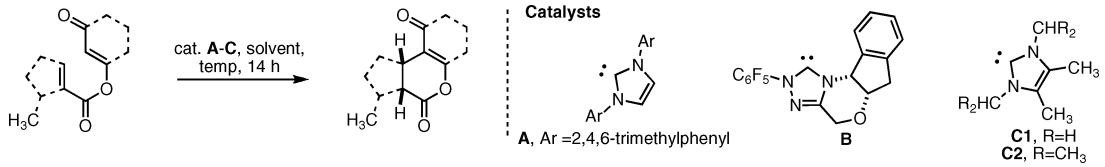
Scheme 3 Cross-over studies of enol ester **12a** and **b**.

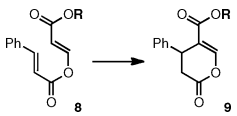
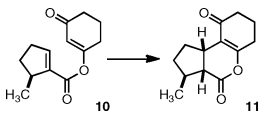
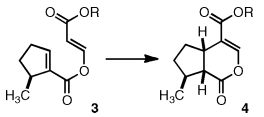
The lack of reactivity with annulated α,β-unsaturated compounds was attributed to difficulties accessing hemiacetal **I**. To facilitate its formation the smaller, but comparably nucleophilic[13] tetramethyl imidazol-2-ylidene carbene **C1** was trialled. To our satisfaction when using this catalyst **4a** formed in 40% isolated yield (Table 1, entry 3b). While this catalyst gave the most useful result it is difficult to handle, and can provide unreliable results. Changing to the more stable, albeit slightly more hindered, diisopropyl dimethyl (IPrMe) NHC **C2** provided lactone **4a** in 74% yield and with an improved 3 : 1 diastereoselectivity (Table 1, entry 3c). Switching the solvent to toluene increased the stereoselectivity (4.4 : 1), although the yield suffered (Table 1, entry 3d).

The rearrangement of ethyl ester **3b** (R = Et), and methyl ester **3c** (R = Me) using IPrMe **C2** was trialled. In these cases comparable yields to those obtained using *t*-butyl ester **3a** were achieved (Table 1, entry 3c *cf.* e and f). This result allows greater flexibility in the end-game of the synthesis (*vide infra*).

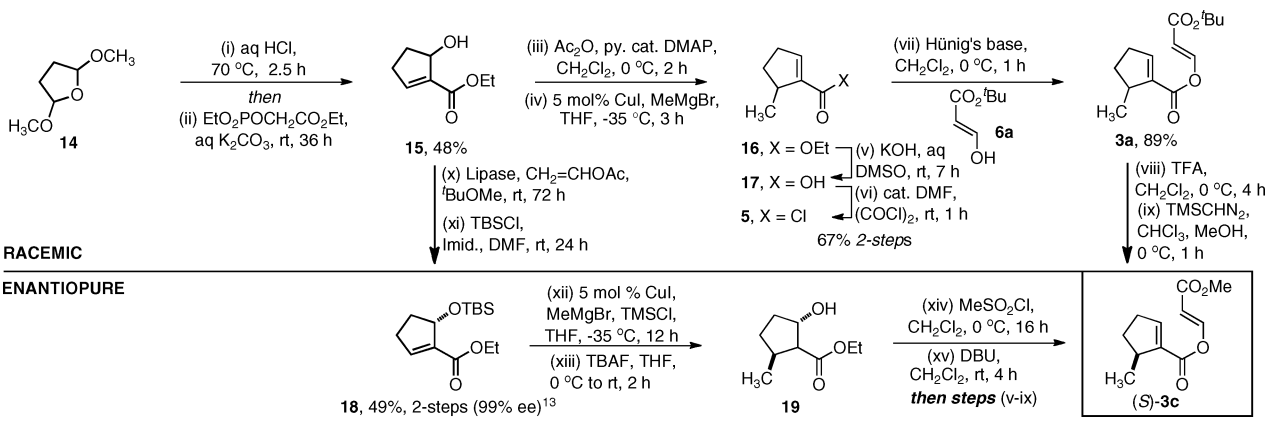
For the optimisation studies detailed above cyclopentyl substrates **3a–c** were assembled from 2,5-dimethoxytetrahydrofuran (**14**) in seven to nine steps *via* the *t*-butyl ester **3a** (Scheme 4, steps (i)→(ix)).[6b] In the first generation total synthesis lipase-based resolution of cyclopentanol **15**[14] followed by TBS protection was employed to provide homochiral allylic alcohol **18** in 99% ee, which was elaborated in 10-steps to the rearrangement precursor (*S*)-**3c** (Scheme 4). The laborious assembly of (*S*)-**3c** is due to a number of factors, specifically, the requirement of a TBS group in alcohol **18** to ensure good stereochemical relay in the methylation reaction, use of a kinetic resolution, and indirect formation of the methyl ester (*S*)-**3c** *via* the *t*-butyl ester (*S*)-**3a**. To increase the efficiency

Table 1 Development of the NHC catalysed rearrangement of α,β-unsaturated enol esters



Entry	Catalyst	Temperature	Solvent	Starting material/product	*R*	dr[a]	Yield[b]
1a	10 mol% **A**[c]	0 °C[d]	Toluene		**a**, ^{t}Bu	—	84
b	10 mol% **A**[c]	Reflux	Toluene		**b**, Et	—	33
2a	10 mol% **A**[c]	Reflux	Toluene		—	2 : 1[e]	64
b	10 mol% **B**[c]	Reflux	Toluene		—	3 : 1[e]	Trace
3a	10 mol% **A**[c]	Reflux	Toluene		**a**, ^{t}Bu	—	—
b	40 mol% **C1**[f]	−78 °C→rt	THF		**a**, ^{t}Bu	2 : 1	40
c	30 mol% **C2**[f]	−78 °C→rt	THF		**a**, ^{t}Bu	3 : 1	74
d	30 mol% **C2**[f]	−78 °C→rt	Toluene		**a**, ^{t}Bu	4.4 : 1	38
e	20 mol% **C2**[f]	−78 °C→rt	THF		**b**, Et	3.2 : 1	78
f	20 mol% **C2**[f]	−78 °C→rt	THF		**c**, Me	3.4 : 1	82

[a] Stereoisomeric ratio determined by ^{1}H-NMR. [b] Isolated yield following flash column chromatography. [c] Carbene generated using 20 mol% KO^{t}Bu. [d] One hour reaction time. [e] Prepared as an inseparable mixture of diastereoisomers. [f] Carbene generated by reduction of the thiourea and isolated.

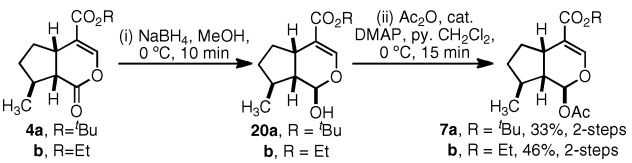


Scheme 4 First generation synthesis of (*S*)-**3c**.

of the synthesis of (–)-7-deoxyloganin (**1**), either improved access to (*S*)-**3c**, or an alternate end-game exploiting the more easily accessed (*S*)-**3a** or (*S*)-**3b** were required. These approaches are discussed in the following section.

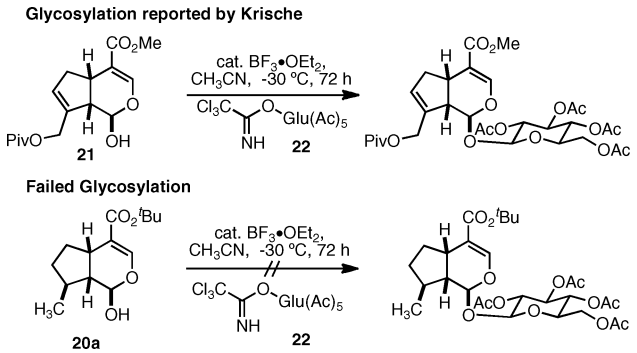
Modified end-game, late stage transesterification

Initial studies focused on employing the more accessible (*S*)-**3a** or (*S*)-**3b**, and exploiting a late-stage transesterification to access the natural product. To examine this strategy lactones **4a** (R = ^{t}Bu) and **b** (R = Et) were reduced using $NaBH_4$[15] to produce the lactols **20a** and **b**, then acetylated to provide **7a** and **b** (Scheme 5). For these studies the racemic materials were exploited.



Scheme 5 Reduction and acetylation of **4a** and **4b**.

Direct glycosylation of lactol **21** has been reported using pentaacetoxyl trichloroacetimidate **22** by Krische in a synthesis of geniposide[4e] (Scheme 6). When the related transformation of **20a** was attempted using the reported conditions, or with alternate Lewis acids, no reaction was observed. The origin of this difference in reactivity is not obvious, although it may relate to subtle stereoelectronic differences due to the pivaloyl protected alcohol within **21**.

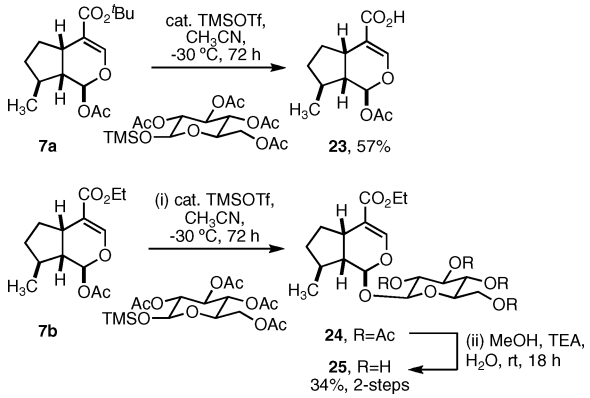


Scheme 6 Attempted glycosylation of lactol **20a**.

The lack of reactivity with lactol **20a** directed attentions to the more commonly used lactol acetates, i.e **7**, as substrates for glycosylation. Using procedures developed by Tietze,[16] and modified by MacMillan for the synthesis of brasoside and littoralisone,[4d] the glycosylation of *t*-butyl lactol acetate **7a** was attempted. Unfortunately, cleavage of the *t*-butyl ester gave acid **23** which failed to undergo glycosylation (Scheme 7). Screening a number of Lewis acids failed to improve this situation. By changing to ethyl ester **7b** ester cleavage was eliminated and glycone **24** could be prepared. Unfortunately, while the subsequent deacetylation proceeded smoothly, the ethyl group proved resistant to transesterification, thereby providing the undesired ethyl ester variant of the natural product **25**. The use of extended reaction times, more forcing reaction conditions, and alternate transesterification catalysts, failed to address this lack of reactivity, and led to decomposition of the substrate. Due to these difficulties attention was directed to improving access to methyl ester (*S*)-**3c**.

Synthesis of cyclopentapyrans 4 from citronellal (18)

In studies by Jacobsen on the synthesis of type I iridolactones the preparation of aldehyde **26** in two steps from citronellal has



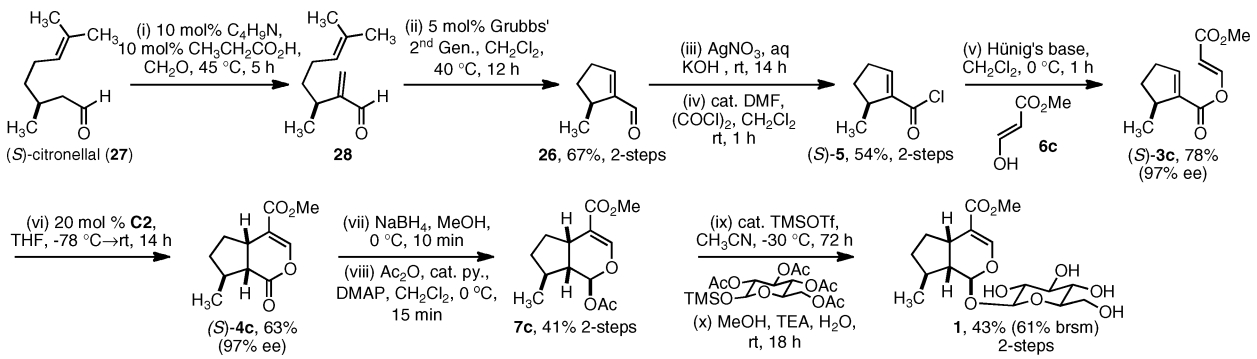
Scheme 7 Glycosylation studies of lactol acetates **7a** and **7b**.

been developed.[4b] Building upon these results it would simply be a matter of oxidizing this material to deliver enantioenriched acid (*S*)-**17**. Finally, it should be possible to eliminate two further operations by acylating methyl formyl acetate **6c** rather than *t*-butyl formyl acetate **6a**.

To execute this synthesis we commenced with *exo* methylenation of (*S*)-citronellal (**27**) to provide **28** in excellent yield (Scheme 8).[17] Ring closing metathesis proceeded in good yield when conducted at high dilution to afford the somewhat volatile cyclopentenal **26**. Oxidation using silver nitrate furnished the acid, which was immediately converted to the acid chloride (*S*)-**5**. Esterification with methyl formyl acetate **6c** proved challenging due to difficulties accessing the required starting material. While the preparation of *t*-butyl formyl acetate **6a** and ethyl formyl acetate **6b** is readily achieved from Meldrum's acid,[9] attempts to prepare the methyl ester **6c** using this approach led to polymerisation. By ozonolysing methyl butenoate, as reported by Cossy,[10] it was possible to access methyl formyl acetate **6c**, which following partial purification, could be converted to the methyl ester (*S*)-**3c** in 78% isolated yield. Thus in 5-steps it is possible to intercept an intermediate, that in our first generation synthesis of 7-deoxyloganin,[6b] was elaborated to the natural product in a further 5-steps.

Conclusions

We have examined two new approaches to the synthesis of (–)-7-deoxyloganin (**1**). In the first, and ultimately unsuccessful strategy, a transesterification was investigated to convert the ethyl ester of **24** to the required methyl ester during final acetate deprotection.



Scheme 8 Improved 10-step synthesis of 7-doxyloganin **1**.

This transformation proved impossible to achieve, thus prompting the development of a strategy in which the required methyl ester was installed at the beginning of the synthesis. Using this approach a number of transformations can be removed from our first generation synthesis allowing a 10-steps formal total synthesis of (–)-7-deoxyloganin (**1**) to be achieved in 5-steps. This shortened synthesis highlights the potential reaction discovery has on enhancing efficiency in multistep synthesis. Furthermore, its short nature in principle allows the preparation of alternate type II iridoids using modified strategies.

Experimental

General Experimental

Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Bruker DRX400 operating at 400 MHz for proton and 100 MHz for carbon nuclei. Infrared spectra (ν_{max}) were recorded on a Perkin-Elmer RXI FTIR Spectrometer. Low resolution mass spectrometry (ESI) was performed on a Micromass Platform QMS spectrometer. High resolution mass spectra (HRMS) were recorded on a Bruker BioApex 47e FTMS fitted with an Analytical electrospray source using NaI for accurate mass calibration. Melting points were measured on a Stuart hot-stage microscope apparatus. Flash column chromatography was performed on silica gel (Davisil LC60A, 40–63 μm silica media) using compressed air or nitrogen. Thin layer chromatography (TLC) was performed using aluminum-backed plates coated with 0.2 mm silica (Merck, DC-Platten, Kieselgel; 60 F_{254} plates). Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable stain followed by heating. Starting materials and reagents were purchased from Sigma-Aldrich and were used as supplied or, in the case of some liquids, distilled. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Ethanol and dichloromethane were distilled from calcium hydride. Acetonitrile, *t*-butanol (*t*-BuOH), and toluene was purified using SPS (Alumina column using an mBraun system) and degassed. Trimethylsilyl trifluoromethanesulfonate was distilled twice from CaH_2 immediately prior to use. Imidazolium salt from which NHC **A** was prepared was prepared using the procedure of Arduengo.[18] Carbene **C1** was prepared using the procedure of Kuhn,[19] and **C2** using the procedure of Yamaguchi.[20]

(*E*)-3-(*tert*-Butoxy)-3-oxoprop-1-enyl cinnamate (8a)

To a stirring solution of cinnamoyl chloride (0.916 g, 5.5 mmol) and DMAP (1.5 mmol, 0.183 g) in THF (10 ml) was added *tert*-butyl formyl acetate **6a** (0.720 g, 5 mmol) in THF (5 ml). The reaction was stirred at rt for 1 h, and then diluted with CH_2Cl_2 (40 ml) and washed with H_2O (5 ml), HCl (5 ml of a 1 M aqueous solution), $NaHCO_3$ (5 ml of a saturated aqueous solution), and H_2O (5 ml). The organic phase was dried ($MgSO_4$) and concentrated. The crude material was purified by flash chromatography (1 : 9, v/v EtOAc:hexane) to yield the pure enol ester as a white solid (0.617 g, 45%). R_f 0.3 (1 : 9, v/v EtOAc:hexane); IR ν_{max} 3069, 2979, 1763, 1699, 1630, 1451, 1370, 1128 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.51 (s, 9H), 5.73 (d, J = 12.5 Hz, 1H), 6.47 (d, J = 16.0 Hz, 1H), 7.43–7.42 (m, 3H), 7.58–7.56 (m, 2H), 7.85 (d, J = 16.0 Hz, 1H), 8.34 (d, J = 12.5 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 28.2, 80.8, 107.7, 115.5, 128.5, 129.0, 131.2, 133.7, 148.3, 149.0, 162.8, 165.5; HRMS Found $(M+NH_4)^+$ 292.1549, $C_{16}H_{18}O_4$ requires $(M+NH_4)^+$ 292.1549.

(*E*)-3-Ethoxy-3-oxoprop-1-enyl cinnamate (8b)

Compound **8b** was prepared as a clear and colourless oil from ethyl formyl acetate **6b** using the procedure for the synthesis of **8a** (0.615 g, 50%). R_f 0.3 (1 : 9, v/v EtOAc:hexane); IR ν_{max} 3066, 2981, 1738, 1702, 1629, 1450, 1367, 1141 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.31 (t, J = 7.0 Hz, 3H), 4.23 (q, J = 7.0 Hz, 2H), 5.81 (d, J = 12.5 Hz, 1H), 6.47 (d, J = 16.0 Hz, 1H), 7.42–7.44 (m, 3H), 7.57–7.56 (m, 2H), 7.86 (d, J = 16.0 Hz, 1H), 8.45 (d, J = 12.5 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.2, 60.5, 105.9, 115.3, 128.5, 129.0, 131.2, 133.7, 148.5, 149.7, 162.7, 166.3; HRMS Found $(M+H)^+$ 247.0964, $C_{14}H_{14}O_4$ requires $(M+H)^+$ 247.0965.

(*S*/*R*)-*tert*-Butyl 2-oxo-4-phenyl-3,4-dihydro-2*H*-pyran-5-carboxylate (9a)

To a stirring solution of IMes·HCl (17 mg, 0.05 mmol) in toluene (2 ml) was added ^{t}BuOK (11 mg, 0.1 mmol). The cloudy suspension was stirred at rt for 1 h resulting in a clear yellow solution of NHC **A**. This was cooled to 0 °C and a solution of enol ester **8a** in toluene (1 ml) was added dropwise. The reaction was allowed to slowly warm to rt and was stirred for a further 1 h. The mixture was concentrated and the crude residue purified by flash column chromatography (3 : 7, v/v EtOAc:hexane) to provide the title compound **9a** as a white solid (0.144 g, 84%). R_f 0.2 (3 : 7, v/v EtOAc:hexane); IR ν_{max} 3112, 2978, 1786, 1693, 1651, 1453, 1368, 1159 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.42 (s, 9H), 2.86 (dd, J = 16.0, 1.5 Hz, 1H), 3.05 (dd, J = 16.0, 7.5 Hz, 1H), 4.15 (dd, J = 7.5, 1.5 Hz, 1H), 7.16–7.32 (m, 5H), 7.67 (s, 1H) ^{13}C-NMR (125 MHz, $CDCl_3$) δ 28.0, 36.0, 36.5, 81.7, 115.7, 126.5, 127.6, 129.1, 140.2, 150.2, 164.0, 165.9; EI-LRMS Found $(M-(CH_3)_3)^+$ 217.1, $C_{16}H_{18}O_4$ requires $(M-(CH_3)_3)^+$ 217.1.

(*S*/*R*)-Ethyl 2-oxo-4-phenyl-3,4-dihydro-2*H*-pyran-5-carboxylate (9b)

Lactone **9b** was prepared following the procedure for the synthesis of **9a**, however the reaction was heated at reflux for 16 h to afford the title compound as a pale yellow oil (0.041 g, 33%). R_f 0.3 (1 : 5, v/v EtOAc:hexane); IR ν_{max} 3108, 2986, 1790, 1713, 1650, 1453, 1382, 1160 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.27 (t, J = 7.0 Hz, 3H), 2.90 (dd, J = 16.0, 1.5 Hz, 1H), 3.05 (dd, J = 16.0, 8.0 Hz, 1H), 4.19–4.25 (m, 3H), 7.20–7.36 (m, 5H), 7.79 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.1, 35.9, 36.3, 61.0, 114.4, 126.5, 127.7, 129.1, 139.9, 150.7, 164.8, 165.6; HRMS Found $(M+H)^+$ 247.0969, $C_{14}H_{14}O_4$ requires $(M+H)^+$ 247.0965.

(*S*/*R*)-3-Oxocyclohex-1-enyl 5-methylcyclopent-1-enecarboxylate (10)

To a stirring solution of 1,3-cyclohexanedione (0.11 g, 1 mmol) and pyridine (0.082 ml, 1 mmol) in CH_2Cl_2 (5 ml) was added acid chloride **5** (0.16 g, 1.1 mmol) in CH_2Cl_2 (1 ml). The mixture was stirred at rt for 2 h then diluted with CH_2Cl_2 (40 ml) and washed with H_2O (5 ml), HCl (5 ml of a 1 M aqueous solution), $NaHCO_3$ (5 ml of a saturated aqueous solution), and H_2O

(5 ml). The organic phase was dried ($MgSO_4$) and concentrated. The crude material was purified by flash chromatography (1 : 4, v/v EtOAc:hexane) to yield the enol ester **10** as a clear and colourless oil (0.125 g, 57%). R_f 0.3 (3 : 7, v/v EtOAc:hexane); IR ν_{max} 2871, 1734, 1678, 1644, 1618, 1456, 1125 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.14 (d, J = 6.5 Hz, 3H), 1.59 (oct, J = 4.0 Hz, 1H), 2.05 (quint, J = 6.5 Hz, 2H), 2.18–2.24 (m, 1H), 2.37–2.42 (m, 2H), 2.42–2.48 (m, 1H), 2.52–2.60 (m, 3H), 2.99–3.04 (m, 1H), 5.92 (s, 1H), 6.89–6.91 (m, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 19.7, 21.3, 28.4, 31.7, 32.0, 36.7, 38.6, 117.3, 139.7, 147.3, 161.2, 170.1, 199.6; HRMS Found $(M+H)^+$ 221.1166, $C_{13}H_{16}O_3$ requires $(M+H)^+$ 221.1179.

(3*S*,3a*R*,9b*S*)-3-Methyl-1,3,3a,7,8,9b-hexahydrocyclopenta[*c*]-chromene-4,9(2*H*,6*H*)-dione *and* (3*R*,3a*S*,9b*R*)-3-methyl-1,3,3a,7,8,9b-hexahydrocyclopenta[*c*]chromene-4,9(2*H*,6*H*)-dione

(3*S*,3a*S*,9b*R*)-3-Methyl-1,3,3a,7,8,9b-hexahydrocyclopenta[*c*]-chromene-4,9(2*H*,6*H*)-dione *and* (3*R*,3a*R*,9b*S*)-3-methyl-1,3,3a,7,8,9b-hexahydrocyclopenta[*c*]chromene-4,9(2*H*,6*H*)-dione (11)

Lactone **11** was prepared as an inseparable mixture of diastereoisomers using the procedure reported for the synthesis of **9a** as a clear and colourless oil (0.050 g, 45%). R_f 0.2 (1 : 4, v/v EtOAc : hexane); IR ν_{max} 2959, 1773, 1654, 1457, 1375, 1168 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (major) 1.07 (d, J = 6.8 Hz, 3H), 1.20–1.24 (m, 1H), 1.38–1.43 (m, 1H), 1.80 (dq, J = 12.4, 6.8 Hz, 2H), 1.96–2.18 (m, 2H), 2.15–2.34 (m, 1H), 2.37–2.43 (m, 2H), 2.48–2.54 (m, 2H), 2.60 (q, J = 6.8 Hz, 1H), 3.17–3.20 (m, 1H) (minor) 1.18 (d, J = 6.8 Hz, 3H), 1.57–1.66 (m, 2H), 1.89–1.95 (m, 1H), 1.96–2.18 (m, 2H), 2.25–2.34 (m, 1H), 2.35–2.41 (m, 2H), 2.48–2.54 (m, 2H), 2.52–2.54 (m, 1H), 3.15–3.23 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 16.4, 20.5, 20.6, 20.8, 27.3, 27.4, 32.6, 32.7, 33.4, 33.5, 34.4, 34.5, 36.9, 37.1, 39.0, 39.6, 46.3, 49.1, 117.5, 117.6, 164.6, 164.7, 167.7, 167.9, 197.4, 197.6; HRMS Found $(M+H)^+$ 221.1171, $C_{13}H_{16}O_3$ requires $(M+H)^+$ 221.1172.

(*E*)-3-Ethoxy-3-oxoprop-1-en-1-yl 5-methylcyclopent-1-enecarboxylate (3b)

A magnetically stirred solution of acid chloride **5** (1.08 g, 7.5 mmol) in CH_2Cl_2 (5 ml) was cooled to 0 °C then treated dropwise with Hünig's base (1.6 ml 9 mmol) followed by ethyl formyl acetate (**6b**) (5 ml of a 1.4 M solution in CH_2Cl_2, 7 mmol). The reaction was stirred at 0 °C for 1 h then diluted with Et_2O (15 ml) and washed with H_2O (5 ml), HCl (5 ml of a 1 M aqueous solution) and $NaHCO_3$ (5 ml of a saturated aqueous solution). The organic phase was dried ($MgSO_4$), concentrated *in vacuo* and purified *via* flash column chomatography (1 : 5, v/v EtOAc:hexane) to furnish the title compound **3b** as a clear and colourless oil (1.53 g, 91%). R_f 0.3 (1 : 5, v/v EtOAc:hexane) IR ν_{max} 2953, 1741, 1442, 1651, 1620, 1436, 1110 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.13 (d, J = 6.9 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H), 1.53–1.63 (m, 1H), 2.13–2.26 (m, 1H), 2.37–2.64 (m, 2H), 2.99–3.09 (m, 1H), 4.19 (q, J = 7.2 Hz, 2H), 5.71 (d, J = 12.6 Hz, 1H), 6.96–6.98 (m, 1H), 8.36 (d, J = 12.6 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.2, 19.6, 31.8, 31.9, 38.6, 60.3, 105.3, 138.8, 148.1, 149.7, 160.3, 166.3; HRMS Found $(M+Na)^+$ 247.0942, $C_{12}H_{16}O_4$ requires $(M+Na)^+$ 247.0941.

(4a*S*,7*S*,7a*R*)-Ethyl 7-methyl-1-oxo-1,4a,5,6,7,7a hexahydrocyclo penta[*c*]pyran-4-carboxylate *and* (4a*R*,7*R*,7a*S*)-Ethyl 7-methyl-1-oxo-1,4a,5,6,7,7a hexahydrocyclo penta[*c*]pyran-4-carboxylate (4b)

Using the procedure reported for the synthesis of **4c**[6b] the title compound **4b** was prepared as a clear and colourless oil (0.175 g, 78%). R_f 0.5 (1 : 4, v/v EtOAc:hexane) IR ν_{max} 2967, 1778, 1715, 1657, 1465, 1333, 1274, 1156 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.16 (d, J = 6.6 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H), 1.30–1.44 (m, 2H), 1.86–1.95 (m, 1H), 2.21–2.31 (m, 1H), 2.44–2.53 (m, 2H), 3.07–3.15 (m, 1H), 4.15–4.23 (m, 2H), 7.38 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.1, 20.4, 33.1, 33.2, 35.9, 39.3, 48.3, 60.6, 113.6, 147.8, 165.6, 169.0; HRMS Found $(M+H)^+$ 225.1120, $C_{12}H_{16}O_4$ requires $(M+H)^+$ 225.1121.

(*E*)-3-Oxocyclohex-1-en-1-yl 3-(2-methoxyphenyl)acrylate 12a

Using the procedure reported for the synthesis of **12b**[6a] the title compound **12a** was prepared as a white solid (0.424 g, 78%). R_f 0.3 (1 : 3, v/v EtOAc:hexane); IR ν_{max} 2951, 1735, 1673, 1624, 1598, 1466, 1118 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.08 (p, J = 6.0 Hz, 2H), 2.43 (t, J = 6.0 Hz, 2H), 2.62 (t, J = 6.0 Hz, 2H), 3.90 (s, 3H), 6.00 (s, 1H), 6.59 (d, J = 16.0 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 6.98 (t, J = 8.0 Hz, 1H), 7.39 (t, J = 8.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 8.07 (d, J = 16.0 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 21.3, 28.4, 36.7, 55.5, 111.2, 116.7, 117.2, 120.7, 122.6, 129.4, 132.3, 143.3, 158.6, 163.8, 170.3, 199.7; HRMS Found $(M+H)^+$ 273.1121, $C_{16}H_{16}O_4$ requires $(M+H)^+$ 273.1121.

Crossover experiment

To a stirring solution of IMes·HCl (17 mg, 0.05 mmol) in toluene (2 ml) was added ^{t}BuOK (11 mg, 0.1 mmol). The cloudy suspension was stirred at rt for 1 h resulting in a clear yellow solution of NHC A. This was cooled to 0 °C and a solution of enol esters **12a** (61 mg, 0.25 mmol) and **12b** (68 mg, 0.25 mmol) as a 1 : 1 mixture in toluene (1 ml) was added dropwise. The reaction was allowed to slowly warm to rt and was stirred for a further 1 h. The mixture was concentrated and the crude residue purified by flash column chromatography (3 : 7, v/v EtOAc : hexane) to provide the title compounds **13a** and **13b**[6a] as white solids (46 mg, 75%) and (56 mg, 82%) respectively. **4-(2-Methoxyphenyl)-3,4,7,8-tetrahydro-2*H*-chromene-2,5(6*H*)-dione 13a**. R_f 0.2 (1 : 3, v/v EtOAc:hexane); IR ν_{max} 2952, 1783, 1651, 1492, 1374, 1112 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 2.03–2.08 (m, 2H), 2.39 (t, J = 6.5 Hz, 2H), 2.60–2.65 (m, 2H), 2.85–2.86 (m, 2H), 3.76 (s, 3H), 4.37–4.39 (m, 1H), 6.81–6.86 (m, 2H), 7.12 (dd, J = 8.0, 2.0 Hz, 1H), 7.19 (dt, J = 8.0, 1.5 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 20.6, 27.4, 31.3, 34.4, 36.8, 54.4, 110.6, 114.8, 120.5, 128.2, 128.6, 129.2, 156.9, 165.8, 167.1, 196.4; HRMS Found $(M+H)^+$ 273.1119, $C_{16}H_{16}O_4$ requires $(M+H)^+$ 273.1121.

(*S*)-5-Methylcyclopent-1-enecarboxylic acid ((*S*)-17)

To a stirring solution of silver nitrate (0.24 g, 1.4 mmol) in H_2O (0.5 ml) was added sodium hydroxide (0.5 ml of a 5.6 M aqueous solution, 2.8 mmol). After stirring for 5 min, aldehyde **26** (0.11 g, 1 mmol) was added in one portion. The solution had stirred

for 14 h at rt then filtered and the residue was washed with H_2O (2 × 2 ml). The combined aqueous layer was washed with Et_2O and then cooled to 0 °C and acidified with HCl (3 ml of a 2 M aqueous solution). The aqueous layer was then extracted with Et_2O (3 × 5 ml), dried ($MgSO_4$) and concentrated. The crude material was purified by flash column chromatography (3 : 10, v/v EtOAc : hexane) to afford (*S*)-**17** as a white solid (0.066 g, 63%) whose spectral data matched that reported.[6b]

(1*R*,4a*S*,7*S*,7a*R*)-*tert*-Butyl 1-hydroxy-7-methyl-1,4a,5,6,7,7a-hexahydrocyclopenta [*c*]pyran-4-carboxylate *and* (1*S*,4a*R*,7*R*,7a*S*)-*tert*-Butyl 1-hydroxy-7-methyl-1,4a,5,6,7,7a-hexahydrocyclopenta [*c*]pyran-4-carboxylate (20a)

Using the procedure reported for the synthesis of **20c**[6b] the title compound **20a** was prepared as a clear and colourless oil (0.069 g, 54%). R_f 0.2 (1 : 3, v/v EtOAc : hexane) IR ν_{max} 3409, 2957, 1704, 1631, 1434, 1096 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.08 (d, J = 6.9 Hz, 3H), 1.33–1.54 (m, 2H), 1.47 (s, 9H), 1.58–1.78 (m, 1H), 1.82–2.00 (m, 2H), 2.22–2.31 (m, 1H), 2.79–2.87 (m, 1H), 3.82 (s, 1H), 4.88 (d, J = 6.9 Hz, 1H), 7.32 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 20.8, 28.3, 33.0, 33.2, 34.6, 35.7, 49.1, 79.9, 95.5, 112.5, 150.9, 167.1; HRMS Found $(M+H)^+$ 255.1587, $C_{14}H_{22}O_4$ requires $(M+H)^+$ 255.1591.

(1*S*,4a*S*,7*S*,7a*R*)-*tert*-butyl 1-Acetoxy-7-methyl-1,4a,5,6,7,7a-hexahydrocyclo penta[c]pyran-4-carboxylate *and* (1*R*,4a*R*,7*R*,7a*S*)-*tert*-butyl 1-Acetoxy-7-methyl-1,4a,5,6,7,7a-hexahydrocyclo penta[*c*]pyran-4-carboxylate (7a)

Using the procedure reported for the synthesis of **7c**[6b] the title compound **7a** was prepared as a clear and colourless oil (8 mg, 61%). R_f 0.5 (1 : 3, v/v EtOAc : hexane) IR ν_{max} 2978, 1745, 1721, 1666, 1495, 1120 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.07 (d, J = 6.3 Hz, 3H), 1.11–1.23 (m, 1H), 1.41–1.54 (m, 1H), 1.47 (s, 9H), 1.68–1.90 (m, 2H), 2.12 (s, 3H), 2.16–2.27 (m, 2H), 2.85–2.94 (m, 1H), 5.95 (d, J = 4.5 Hz, 1H), 7.24 (d, J = 1.5 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 19.8, 20.2, 28.1, 31.8, 32.0, 33.1, 34.8, 47.7, 81.1, 91.0, 112.3, 150.9, 167.6, 169.0; HRMS Found $(M+H)^+$ 297.1699, $C_{16}H_{24}O_5$ requires $(M+H)^+$ 297.1697.

(1*S*,4a*S*,7*S*,7a*R*)-Ethyl 1-acetoxy-7-methyl-1,4a,5,6,7,7a-hexahydrocyclopenta[*c*]pyran-4-carboxylate *and* (1*R*,4a*R*,-7*R*,7a*S*)-Ethyl 1-acetoxy-7-methyl-1,4a,5,6,7,7a-hexahydrocyclopenta[*c*]pyran-4-carboxylate (7b)

Using the procedure reported for the synthesis of **7a**[6b] the title compound **7b** was prepared in two steps from lactone **4b** without purification following the reduction (19 mg, 46%). R_f 0.5 (1 : 3, v/v EtOAc : hexane) ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.07 (d, J = 6.0 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H), 1.18–1.27 (m, 1H), 1.41–1.51 (m, 1H), 1.72–1.91 (m, 2H), 2.10 (s, 3H), 2.16–2.17 (m, 2H), 2.89–2.96 (m, 1H), 4.11–4.23 (m, 2H), 5.94 (d, J = 4.8 Hz, 1H), 7.33 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.2, 19.9, 20.9, 31.8, 33.0, 33.1, 35.2, 47.2, 59.9, 91.5, 112.2, 150.2, 167.0, 169.6; HRMS Found $(M+H)^+$ 269.1382, $C_{14}H_{20}O_5$ requires $(M+H)^+$ 269.1384.

(4a*S*,7*S*,7a*R*)-1-acetoxy-7-methyl-1,4a,5,6,7,7a-hexahydrocyclopenta[*c*]pyran-4-carboxylic acid *and* (4a*R*,7*R*,7a*S*)-1-acetoxy-7-methyl-1,4a,5,6,7,7a-hexahydrocyclopenta[*c*]pyran-4-carboxylic acid (23)

A solution of acetate **7a** (0.020 g, 0.067 mmol) in benzene was transferred to a Schlenk flask containing 1-*O*-(trimethylsilyl)-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (0.086 g, 0.2 mmol, prepared following the method of Allevi).[21] The solution was frozen and benzene removed by sublimation. The remaining solid was dissolved in CH_3CN (0.5 ml) and the mixture cooled to −30 °C. TMSOTf (0.14 ml of a 5% solution in CH_3CN, 0.039 mmol) was then added dropwise. The reaction was stirred at −30 °C for 3 days after which time phosphate buffer (2 ml of a 0.1 M pH 7 solution) was added and the mixture extracted with ether (3 × 3 ml). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the crude material *via* flash column chromatography (3 : 7, v/v EtOAc : hexane) provided the title acid **23** as a yellow oil (9 mg, 57%). R_f 0.2 (3 : 7, v/v EtOAc : hexane) ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.08 (d, J = 6.0 Hz, 3H), 1.17–1.22 (m, 1H), 1.42–1.53 (m, 1H), 1.76–1.93 (m, 3H), 2.12 (s, 3H) 2.18–2.28 (m, 1H), 2.92 (q, J = 7.2 Hz, 1H), 5.97 (d, J = 5.1 Hz, 1H), 7.45 (s, 1H); HRMS Found $(M+H)^+$ 241.1070, $C_{12}H_{16}O_5$ requires $(M+H)^+$ 241.1071.

(1*S*,4a*S*,7*S*,7a*R*)-Ethyl 7-methyl-1-(((2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)-1,4a,5,6,7,7a-hexahydrocyclopenta[*c*]pyran-4-carboxylate (25)

Using the procedure reported for the synthesis of **1**[6b] the title compound **25** was prepared by glycosylation followed by deacetylation as a gum which was separable from the alternate diastereoisomer (9 mg, 34%). R_f 0.1 (20 : 1 v/v EtOAc : MeOH) ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.01 (d, J = 6.3 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H), 1.24–1.29 (m, 1H), 1.38–1.50 (m, 1H), 1.86–1.99 (m, 3H), 2.16–2.25 (m, 1H) 2.97 (q, J = 7.8 Hz, 1H), 3.36 (dd, J = 9.3, 8.1 Hz, 1H), 3.44–3.65 (m, 3H), 3.50 (dd, J = 12.3, 5.6 Hz, 1H), 3.96, (dd, J = 12.3, 2.1 Hz, 1H), 4.22–4.29 (m, 2H), 4.91 (q, J = 8.1 Hz, 2H), 5.38 (d, J = 4.5 Hz, 1H), 7.48 (d, J = 1.2 Hz, 1H); HRMS Found $(M+Na)^+$ 411.1624, $C_{18}H_{28}O_9$ requires $(M+Na)^+$ 411.1626.

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