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A stepwise lactol carbocyclisation to bridged ethers via a keto–acetal cascade

Sean McCarthy[1,2] and Charles M Marson[1]

Abstract

Lactol carbocyclisations provide a succinct method of constructing the oxabicyclo[3.2.1]octane scaffold, a motif present in various natural products of medicinal interest. Lactols containing an unsaturated ketone or ester were prepared by olefin cross-metathesis; an electrophilic alkene derived from methyl vinyl ketone underwent concomitant terminal α-methylenation and oxa-Michael addition to give a bridged lactol which then underwent oxygen-to-carbon transposition in the presence of titanium (IV) chloride giving the desired unsaturated carbocyclic seven-membered bridged ether via a novel dehydrative cascade considered to involve titanium enolates.

Keywords

bridged ether synthesis, dehydrative rearrangement, enone–lactol cyclisation, keto–acetal cascade, oxa-Michael acetal formation

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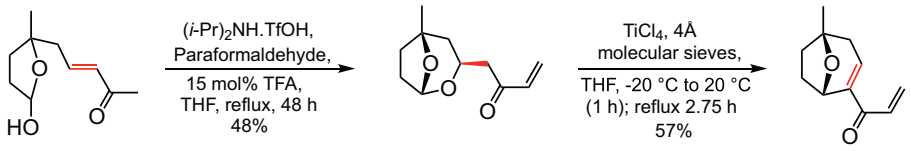
A stepwise enone-lactol carbocyclisation is described. Concomitant α-methylenation and intramolecular oxa-Michael addition afford a bridged acetal which in the presence of $TiCl_4$ undergoes oxygen-to-carbon transposition giving an unsaturated carbocyclic bridged ether.



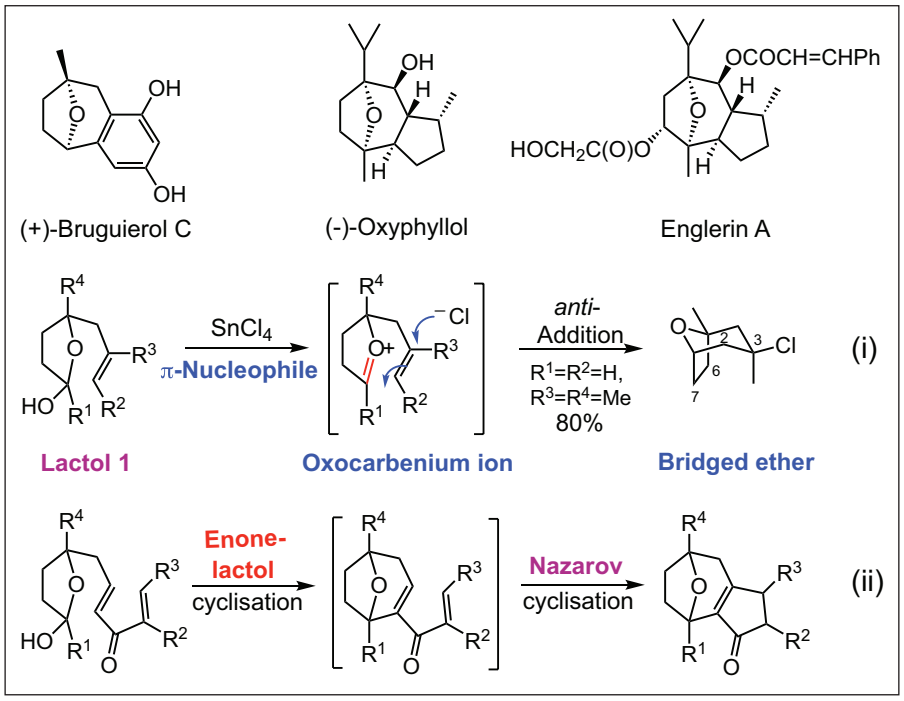
Introduction

Bridged ethers are found in numerous natural products,[1–7] including the potent anti-cancer agent englerin A (Scheme 1).[2,5,6] Recently, oxabicyclo natural products containing the benzo-8-oxabicyclo[3.2.1]octane core (Figure 1) have been identified as Gram-positive antibiotics, anti-parasitic agents and anti-cancer agents,[1,2] adding further incentive to access such bridged systems. Accordingly, general methods of constructing polysubstituted *O*-bridged systems with control of stereochemistry are valuable in the synthesis of natural products and new scaffolds for medicinal chemistry. To this end, we identified lactol carbocyclisations as an effective method of constructing bridged ethers,[8] including the *trans*-addition across an alkene terminus to give a bridged ether (Scheme 1, eq. i). When the π-nucleophile is an aromatic ring, these lactol carbocyclisations have also proved efficient,[1,3,8–13] creating a benzenoid ring fused across the 2,3-positions of the bridged ether positions (numbering as in Scheme 1). Such methodology has become a cornerstone in the synthesis of various bridged-ether natural products.[1,3,9–13]

Although aromatic termini serve effectively as a trap for the lactol-derived oxocarbenium ion, the scope of such lactol cyclisations (Scheme 1, eq. i) would be greatly increased if an alkene π-nucleophile could act as a charge relay, delivering carbocyclisation cascades. For example, the bridged

[1]Department of Chemistry, Christopher Ingold Laboratories, University College London, London, UK
[2]Department of Chemistry, Molecular Sciences Research Hub, Imperial College London, London, UK

Corresponding author:
Charles M Marson, Department of Chemistry, Christopher Ingold Laboratories, University College London, 20 Gordon Street, London WC1E 6BT, UK.
Email: c.m.marson@ucl.ac.uk



Scheme 1. Representative oxabicyclo[3.2.1]octane natural products, a lactol carbocyclisation route to such bridged ethers, and a proposed enone–lactol–Nazarov cyclisation cascade.

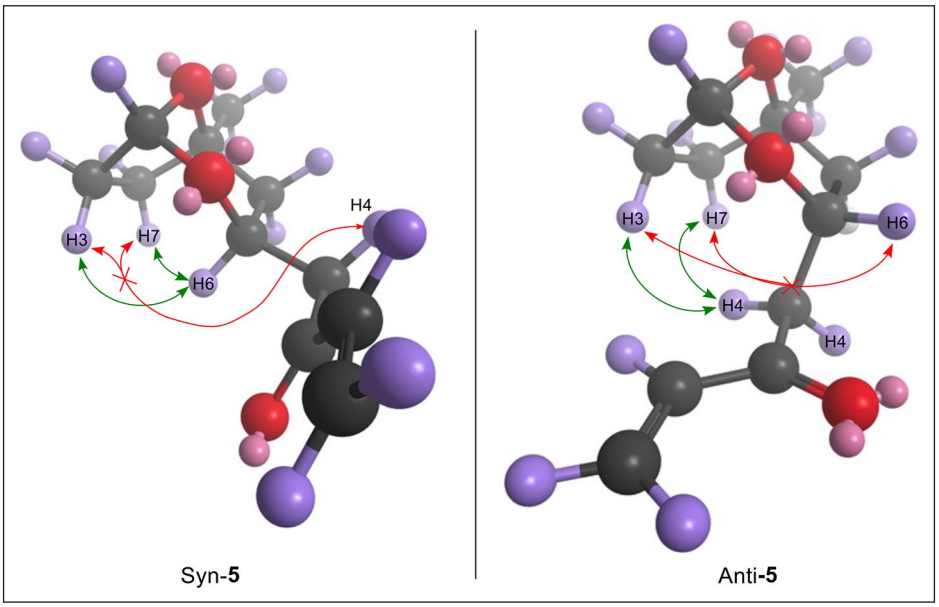
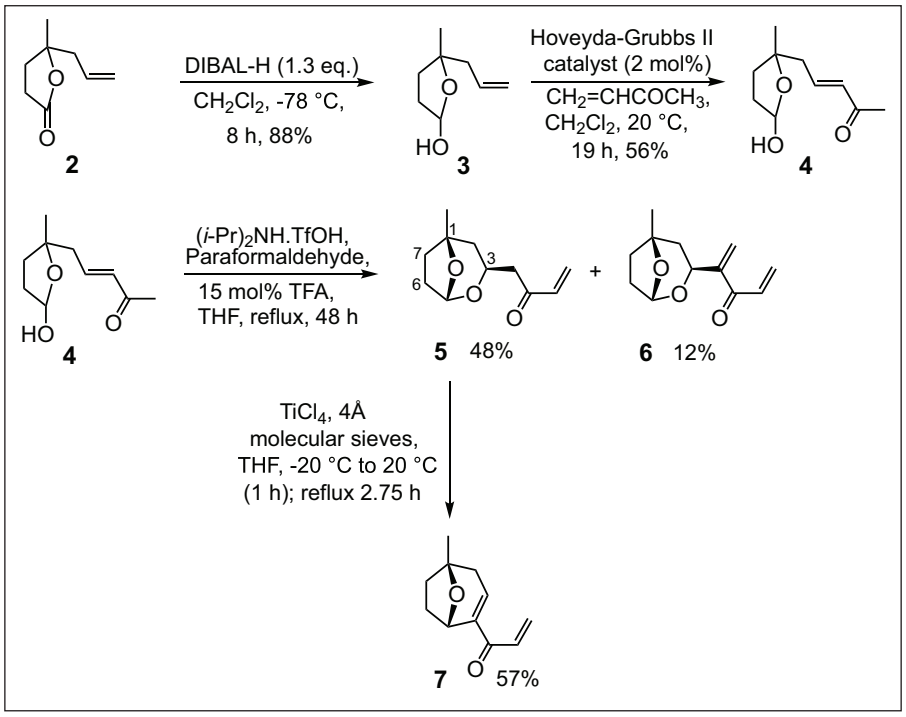


Figure 1. Comparision of syn-and anti-5 expected NOESY cross peaks.
Conformations simulated by Allinger MM2 dynamics (Chem3D 19.1).

perhydroazulene scaffold, present in englerin A and related natural products of therapeutic significance, might be constructed via a sequential lactol–Nazarov cyclisation (Scheme 1, eq ii). This raised the question of whether a direct lactol–enone cyclisation was feasible where R^2 in lactol **1** is an electron-withdrawing group, via at least a formalism, and perhaps mechanism, more akin to Morita–Baylis–Hillman[14–16] addition although involving an acetal. In contrast, the more Prins-like carbocyclisations[17–19] of lactols **1** (eq. ii, where R^2 is not an electron-withdrawing group) require a relatively nucleophilic alkene. Here we report a stepwise lactol carbocyclisation which proceeds via an isolable keto acetal that undergoes an enolic cascade resulting in an unsaturated carbocyclic bridged ether.

Results and discussion

Addition of allylzinc bromide to methyl levulinate afforded the known lactol **2** (Scheme 2);[20] subsequent reduction with diisobutylaluminium hydride (DIBAL-H)[21]



Scheme 2. Synthesis of enone lactol **4** and subsequent sequential cyclisations.

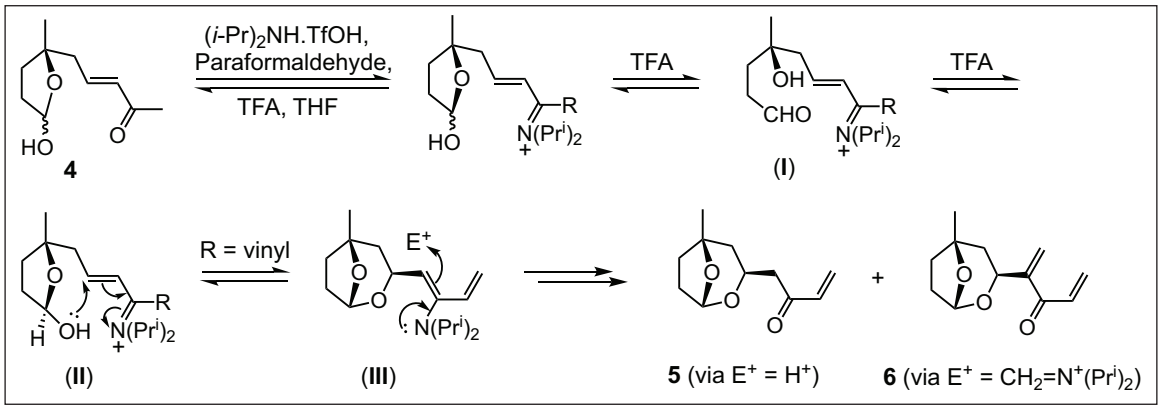
furnished the common lactol intermediate **3** used in making electrophilic alkenes. Synthesis of ketone **4** (53%) and the corresponding methyl ester, methyl (*E*)-4-(5-hydroxy-2-methyltetrahydrofuran-2-yl)but-2-enoate (64%), was achieved by cross-metathesis[20] of **3** using methyl vinyl ketone and methyl acrylate, respectively, in the presence of the Hoveyda–Grubbs II catalyst. Preliminary attempts at a direct cyclisation of enone **4** were made; however, neither $TiCl_4$ (2 equiv.) with 4Å molecular sieves in CH_2Cl_2 (–20 °C to 20 °C over 2 h, then 4 h at 60 °C, then 6 h at reflux), nor trimethylsilyl trifluoromethanesulfonate (TMSOTf) (3 equiv.) with 4Å molecular sieves in CH_2Cl_2 (–20 °C for 3 h, then 4 h at 20 °C) afforded cyclised products. Likewise, attempted cyclisations of methyl (*E*)-4-(5-hydroxy-2-methyltetrahydrofuran-2-yl)but-2-enoate using $SnCl_4$ or $TiCl_4$ at –78 °C were unsuccessful.

Attention was then turned to the synthesis of dienone termini (Scheme 1, eq. ii) since those might first undergo Nazarov cyclisation[22] followed by lactol carbocyclisation induced by an enol intermediate (i.e. the reverse order of that in eq. ii). Accordingly, Mannich α′-methylenation studies were undertaken in the presence of diisopropylammonium trifluoroacetate, using Connell's procedure.[23] α-Methylenation of **4** was indeed observed, but also a concomitant formal oxa-Michael addition to the enone giving predominantly acetal **5** and in addition dienone acetal **6** as the minor product.

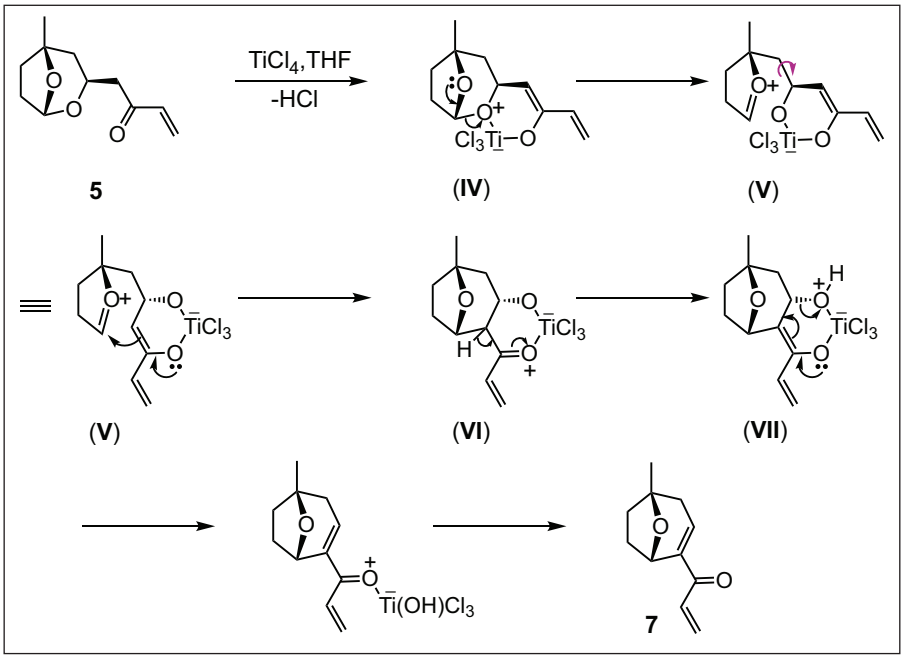
It was noted that the removal of alkene unsaturation through the formation of acetal **5** could still permit the overall desired formation of the bridged ether provided that conditions favouring the enolisation of the ketone also induced acetal cleavage to the 5-membered oxocarbenium species, giving potential for an intramolecular enolic cyclisation. Mindful of the wide application of titanium enolates in organic synthesis,[24] in which their chelating abilities are often crucial, $TiCl_4$ was selected for early study. To our delight, in the presence of $TiCl_4$ (2.2 equiv.), acetal **5** was converted into dienone **7** (57%) as the sole diastereoisomer, during which formal dehydration also occurred (Scheme 2). The formation of potential Nazarov precursors (Scheme 2) is notable, although under the above conditions no Nazarov cyclisation was observed.

The constitution of enone acetal **5** was initially confirmed by (1) the absence of a methyl ketone signal in the ^{1}H NMR spectrum, but the presence of a vinylic ABX system, (2) the absence of a *trans*-alkene but the presence of four methylene groups shown by the DEPT (Distortionless Enhancement by Polarization Transfer) ^{13}C NMR spectrum, in particular, the methylene group adjacent to the ketone (^{1}H: δ 2.56, dd, ^2J = 16.2 Hz, ^3J = 5.7 Hz; ^{13}C: 45.5 ppm), (3) the presence of a deshielded methine group (^{1}H: δ 4.37, m; ^{13}C: 85.0 ppm) and (4) the distinctive signal attributable to the strongly deshielded methine group of the acetal (^{1}H: δ 5.44, d, J = 4.3 Hz; ^{13}C: 100.3 ppm), comparing closely with that of epimeric lactol **4** (^{1}H: δ 5.46, m; ^{13}C: 100.1 and 98.6 ppm). Analysis of all HSQC, HMBC and COSY cross peaks (see the Supporting Information) enabled the full assignment of NMR data, consistent with the structure proposed for **5**. In addition, the relative configuration of **5** was confirmed by ^{1}H–^{1}H NOESY analysis to be the *syn*-isomer (w.r.t. the tetrahydrofuran (THF) ether bridge and the enone substituent), cross peaks being observed for the interaction of the C-3 methine hydrogen atom with each of the hydrogen atoms *anti* to the THF ether in ethylene linkage (C-6 and C-7), as well as the absence of any cross peak attributable to the C-3 *anti*-isomer. (Modelling of stereoisomers is also illustrated in Figure 1).

In the same fashion, confirmation of the constitution of the dienone acetal **6** included (i) the absence of a methyl ketone signal in the ^{1}H NMR, but the presence of a $=CH_2$



Scheme 3. Proposed mechanism for the formation of bridged enone acetals **5** and **6**.

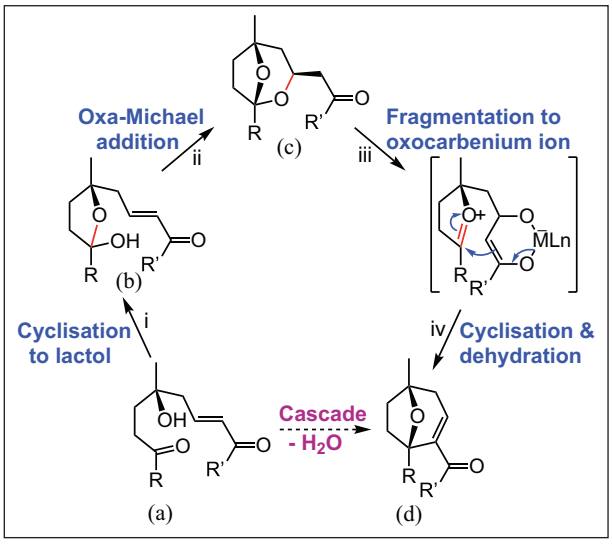


Scheme 4. Proposed mechanism for the transposition of acetal **5** to give *O*-bridged enone **7**.

group (^{1}H: δ 6.26, $^2J_{gem}$ = 1.5 Hz, and δ 6.13, br s; ^{13}C: 124.7 ppm), in addition to a vinylic AMX system, (ii) the absence of a *trans*-disubstituted alkene but the presence of three methylene groups shown by the DEPT ^{13}C NMR spectrum, (iii) the presence of a deshielded methine group (^{1}H: δ 4.89, dd, J = 11.3 Hz, J = 3.5 Hz; ^{13}C: 66.2 ppm) and (iv) the methine group of the acetal (^{1}H: δ 5.60, br d, J = 3.5 Hz; ^{13}C: 100.5 ppm). Again, analysis of HSQC, HMBC and COSY cross peaks (see the Supporting Information) enabled a full assignment of NMR data, and NOESY analysis confirmed that dienone acetal **6** was the *syn*-isomer.

Confirmation of the constitution of dienone ether **7** included (1) the presence of a =CH_2 group (^{1}H: δ 6.76, dd, J = 4.7 Hz, J = 2.9 Hz, ^{13}C: 144.5 ppm), in addition to a vinylic AMX system, (2) the presence of three methylene groups shown by the DEPT ^{13}C NMR spectrum, (3) the presence of an ether possessing a methine bridgehead (^{1}H: δ 5.07, d, J = 6.5 Hz; ^{13}C: 73.2 ppm) and a quaternary bridgehead (^{13}C: 78.6 ppm) and whose data were closely consistent with literature values for other substituted 8-oxabicyclo[3.2.1]oct-2-enes. A COSY correlation of the ring =CH with an adjacent hydrogen atom at C-3, together with the analysis of HSQC data, enabled the full assignment of the NMR data for ether **7**.

The present observations can be accounted for by the mechanistic pathways outlined in Schemes 3 and 4. The combined yield of isolated products **5** (48%) and **6** (12%) was greater than either diastereoisomer of **4** (*dr* = 53:47), consistent with clearance of its oxygenated stereocentre via an hydroxy aldehyde of type (**I**) (Scheme 3), a common example of ring–chain tautomerism[25] that was also required to account for a previous lactol carbocyclisation.[8] No acetal or carbocyclic product was isolated when **4** was treated with trifluoroacetic acid (TFA) alone (15 mol% in THF, 48 h reflux), an observation consistent with the requirement of an amine to induce oxa-Michael reactions,[26] involving the addition of an alcohol to an iminium species such as (**II**). Although the order in which α-methylenations occur is not certain, cyclisation of (**II**) where R = vinyl would give (**III**) which could serve as a common intermediate that leads both to the major product **5** (by β-protonation of the



Scheme 5. Assembly of identified steps into a proposed cascade from acylic reactants.

enamine, followed by hydrolysis of the iminium species), and also to dienone **6** (by α′-methylenation of (**III**), followed by hydrolysis).

Chelated titanium enolates such as (**IV**) and (**V**) are likely pivotal to the efficiency of the transposition of acetal **5** to carbocycle **7** (Scheme 4). Coordination of Ti(IV) to **5** followed by enolisation would afford (**IV**) whose activated acetal can undergo cleavage to the oxocarbenium species (**V**). Subsequent rotation within (**V**) permits the proximity of titanium enolate with the five-membered ring and hence endocylic ring-closure to (**VI**). Subsequent deprotonation and reprotonation would give (**VII**), poised for a unimolecular elimination to generate the endocyclic alkene and hence dienone **7**.

Key features identified in this study can be linked with inferred and known lactol formations to postulate a set of cascade processes from a totally acylic precursor (Scheme 5). A previous lactol carbocyclisation could only be readily accounted for by postulating a *linear* γ-hydroxycarbonyl compound as a key intermediate in the cascade rearrangement of certain 3,4-epoxy alcohols. For example, a bridged ether possessing a 6,7-fused cyclopentane ring (numbering as in Scheme 1) was formed in greater than 80% yield from a putative γ-hydroxyaldehyde.[8] Those observations and the present work confirm that conditions for lactol carbocyclisations are generally compatible with the conversion of a *linear* γ-hydroxycarbonyl compound such as **A** into lactol **B**, and hence, given the present finding that lactol **B** can afford carbocylic enone **D**, a multiple cascade from an acyclic hydroxy carbonyl compound (**A**) to a bridged ether (**D**) could be realised, whose flexibility would significantly enhance the scope and synthetic utility of current lactol carbocyclisations.

Conclusion

Hitherto, lactol carbocyclisations have been confined to the use of relatively electron-rich alkenes such as π-nucleophiles. This study has achieved a formal process corresponding to lactol carbocyclisation using an electrophilic alkene derived from methyl vinyl ketone. Under the conditions of terminal α-methylenation of methyl ketone, oxa-Michael addition of lactol occurred, affording a bridged lactol which then underwent oxygen-to-carbon transposition to give the desired carbocyclic bridged ether via a cascade inferred to involve titanium enolate species. In contrast to the powerful Ferrier type II[27–29] and Petasis–Ferrier reactions,[17,30–33] which involve trapping of oxocarbenium ions by enol ethers, both generated from atoms within the ring that is cleaved, the present oxygen-to-carbon transposition involves remote but concomitant generation of the oxocarbenium ion and its trapping by a presumed metal enolate derived from a *ketone* moiety *external* to the ring cleaved, a process which has not been previously reported, to the best of our knowledge. In addition to these novel transformations, and taken together with previous lactol-forming reactions, the results suggest a route from *acyclic* hydroxy ketones to the bridged ethers might be achieved without the isolation of acetal intermediates. This methodology enhances access to the 8-oxabicyclo[3.2.1]octane scaffold, one found in a range of natural products possessing medicinal properties.

Experimental section

General

Starting materials and reagents were purchased from commercial sources and used without further purification. Diisopropylammonium trifluoroacetate was prepared as previously decribed.[23] Anhydrous THF was purchased from Acros Organics. Anhydrous dichloromethane was produced by distillation over CaH_2, stored over 4 Å molecular sieves and used within 1 week of distillation. Molecular sieves were washed with dichloromethane before use and dried at 180 °C for at least 48 h. All reactions were performed under an argon atmosphere and using glassware pre-dried in an oven (150 °C) and then cooled to room temperature under a nitrogen atmosphere. Flasks for reactions performed under an inert atmosphere were fitted with Suba·Seal rubber septa, sealed with Parafilm, and purged with nitrogen. Flash column chromatography was performed using Merck 0.040–0.063 mm, 230–400 mesh silica gel. Evaporation refers to the removal of solvent under reduced pressure. Thin-layer chromatography (TLC) was performed on Merck 0.2 mm aluminium-backed silica gel 60 F_{254} plates and visualised under UV light (254 nm) either by staining with alkaline potassium permanganate with subsequent heating, or by exposure to an acidic (1% v/v conc. H_2SO_4) ethanolic solution of vanillin (6% wt/vol). Alternatively, the TLC plate was developed in an iodine chamber. Infrared (IR) spectra were recorded on a Perkin−Elmer Spectrum One FTIR spectrometer; absorptions are quoted in wavenumbers. ^1H and ^{13}C NMR spectra were recorded on either a Bruker Avance III 400 MHz spectrometer or a Bruker Avance Neo 700 MHz spectrometer and calibrated using residual undeuterated solvent as an internal reference; chemical shifts are in parts per million (δ) and coupling constants (*J*) are given in Hertz (Hz). The following abbreviations were used in signal assignments: singlet (s), broad singlet (br s), doublet (d), triplet (t), quartet (q), and multiplet (m). Diastereoisomeric

ratios were calculated from ^{1}H NMR peak areas. High-resolution mass spectra (HRMS) were recorded using either an Agilent ESI TOF (time of flight) mass spectrometer at 3500 V emitter voltage or using a Waters LCT Premier QTOF spectrometer connected to a Waters sample manager 2777C at University College London.

Preparation and use of activated zinc

A heterogeneous solution of zinc (1.60 g, 24.4 mmol) in aqueous hydrochloric acid (5%, 20 mL) was stirred for 10 min or until effervescence had subsided. The resulting zinc slurry was then filtered, washed with water (2 × 5 mL), ethanol (2 × 5 mL) and then with diethyl ether (2 × 5 mL). In experiments involving the preparation of allylzinc reagents, the activated zinc was either used directly or oven-dried (180 °C) for at least 24 h. After allowing the washed zinc to cool, it was added to the stirred reaction mixture, and where necessary, the reaction was initiated by the addition of a single crystal of iodine, resulting in a significant exotherm which subsided after 5–10 min.

*5-Allyl-5-methyldihydrofuran-2(3H)-one (**2**)*

According to a literature procedure,[20] modified by the addition of HMPA, a round-bottom flask was charged with a stirred suspension of oven-dried (180 °C) zinc powder (<150 μm, 99.995%) (5.71 g, 87.3 mmol) in THF (90 mL) under a nitrogen atmosphere. To the suspension was added methyl levulinate (4.32 mL, 34.9 mmol), followed by HMPA (0.61 mL, 3.5 mmol) and allyl bromide (7.53 mL, 87.1 mmol). The resulting dark grey suspension was heated to 45 °C. After 8 h, the reaction was complete, as indicated by TLC analysis. The dark grey suspension was evaporated and the residue was quenched with saturated aqueous ammonium chloride (100 mL). The aqueous layer was extracted with diethyl ether (3 × 100 mL) and the combined organic layers were washed with hydrochloric acid (1 M, 75 mL) and brine (100 mL), and then dried ($MgSO_4$) and evaporated. The residue was purified by chromatography on silica gel using hexane: ethyl acetate (90:10 then 85:15, R_f = 0.17) to give **2** (4.31 g, 88%) as a pale-yellow oil; IR (film, ν_{max}) 2977, 2930, 1767, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.79 (1H, ddt, $^3J_{trans}$ = 16.8 Hz, $^3J_{cis}$ = 9.5 Hz, $^3J_{vinyl}$ = 7.3 Hz, CH=CH$_2$), 5.17 (2H, m, CH=C**H$_2$**), 2.67–2.53 (2H, m, O=CC**H$_2$**), 2.43 (2H, ddd, $^2J_{gem}$ = 14.3 Hz,$^3J_{vinyl}$ = 7.3 Hz, $^4J_{allylic}$ = 1.0 Hz, C**H$_2$**CH=CH$_2$), 2.19–2.12 (1H, m, O=CCH$_2$CHH), 1.99–1.92 (1H, m, O=CCH$_2$CHH), 1.40 (3H, s, C**H$_3$**).

*5-Allyl-5-methyltetrahydrofuran-2-ol (**3**)*

A solution of **2** (3.35 g, 23.9 mmol) in anhydrous dichloromethane (120 mL) was cooled to –78 °C under a nitrogen atmosphere. To the stirring solution was added DIBAL-H in dichloromethane (1 M, 31.1 mL) dropwise over the course of 1.5 h. The mixture was stirred vigorously for 8 h, or until all of **2** had been consumed, as indicated by TLC analysis. The cooled reaction mixture was quenched by the dropwise addition of ethyl acetate (3.2 mL) followed by saturated aqueous solution of Rochelle's salt (140 mL). The resulting white emulsion was allowed to warm to room temperature and left stirring overnight, or until two clear layers formed upon standing. The organic layer was separated and the aqueous layer extracted with dichloromethane (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to give **3** as a colourless oil (2.99 g, 88%, *dr* = 1:1). The product was used in olefin metathesis reactions without further purification, but traces of any remaining lactone could be removed by column chromatography on silica gel using an eluent of 15:85 ethyl acetate: dichloromethane to give **3** (R_f = 0.29); IR (film, ν_{max}) 3406, 2970, 2923, 1641, 1453, 1058 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.93–5.75 (1H, m, CH=CH$_2$), 5.51–5.24 (1H, m, CHOH), 5.13–5.03 (2H, m, CH=C**H$_2$**), 2.50–2.33 (1H, m, C**H$_2$**CH=CH$_2$), 2.23–2.20 (1H, m, C**H$_2$**CH=CH$_2$), 2.13–1.76, 1.69–1.54 (4H, m, C**H$_2$**C**H$_2$**COH), 1.38, 1.17 (3H, s, C**H$_3$**); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.2, 134.8 (CH=CH$_2$), 117.4, 117.1 (CH=CH$_2$), 100.3, 100.0 (OCHOH), 83.9 (OCCH$_3$), 47.3, 46.3 (CH-CH=CH$_2$), 34.4, 33.8 (CH$_2$CH$_2$CHOH), 33.0, 32.4 (CH$_2$CHOH), 28.4, 26.3 (CH$_3$); HRMS (ESI$^+$) *m/z* [M+H]$^+$, $C_8H_{15}O_2$ calcd. 143.1072, found 143.1071.

Methyl (E)-4-(5-hydroxy-2-methyltetrahydrofuran-2-yl)but-2-enoate

To a stirring solution of **3** (0.364 g, 2.56 mmol) and methyl acrylate (0.71 mL, 7.8 mmol) in dichloromethane (6 mL) under a nitrogen atmosphere was added a solution of Hoveyda–Grubbs second-generation catalyst (16 mg, 26 μmol) in dichloromethane (1 mL). After stirring the mixture for 17 h, the solvent was evaporated to give a dark brown residue which was purified by chromatography on silica gel using hexane: ethyl acetate (60:40, R_f = 0.23) to give methyl (E)-4-(5-hydroxy-2-methyltetrahydrofuran-2-yl)but-2-enoate (0.328 g, 64%, *dr* = 52:48) as a pale-yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (1H, ddd, $^3J_{trans}$ = 15.6 Hz, $^3J_{vinyl}$ = 7.8 Hz, CH=CHC=O), 5.86 (1H, dt, $^3J_{trans}$ = 15.7 Hz, $^4J_{allylic}$ = 1.4 Hz, CH=CHC=O), 5.50 (1H, m, CHOH), 3.71 (3H, s, OC**H$_3$**), 2.55–2.33 (2H, m, C**H$_2$**CH=CH), 2.08–1.92 (2H, m, C**H$_2$**COH), 1.90–1.65 (2H, m, CH$_2$C**H$_2$**COH), 1.39, 1.17 (s, CC**H$_3$**, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.8, 166.7 (C=O), 145.6, 145.1 (CH=CHC=O), 123.7, 123.5 (CH=CHC=O), 98.9, 98.6 (ROCOH), 83.8 (OCCH$_3$), 51.4 (OCH$_3$), 45.6, 44.3 (CH$_2$CH=CH), 34.4, 34.2 (CH$_2$CH$_2$COH), 33.5, 33.1 (CH$_2$COH), 28.8, 26.5 (CCH$_3$); HRMS (ESI$^+$) *m/z* [M+H]$^+$, $C_{10}H_{17}O_4$ calcd. 201.1127, found 201.1129.

*(E)-5-(5-Hydroxy-2-methyltetrahydrofuran-2-yl)pent-3-en-2-one (**4**)*

To a stirring solution of **3** (0.118 g, 0.830 mmol) and methyl vinyl ketone (0.26 mL, 3.1 mmol) in dichloromethane (2 mL) under a nitrogen atmosphere was added a solution of Hoveyda–Grubbs second-generation catalyst (11 mg, 0.018 mmol) in dichloromethane (1 mL). After stirring the

mixture for 19 h, the solvent was evaporated to give a dark brown residue which was purified by chromatography on silica gel using hexane: ethyl acetate (50:50, R_f = 0.19) to give **4** (0.085 g, 56%, *dr* = 53:47) as a pale-yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz); δ 6.80 (1H, dt, $^3J_{trans}$ = 15.5 Hz, $^3J_{vinyl}$ = 7.4 Hz, CH_2CH=CH), 6.03 (1H, dd, $^3J_{trans}$ = 15.5 Hz, *J* = 6.2 Hz, CH_2CH=CH), 5.46 (1H, m, CH(OH)OR), 2.59–2.31 (2H, m, CH_2CH=CH), 2.20 (3H, s, O=CCH_3), 2.08–1.87 (2H, m, CH_2CHOH), 1.80, 1.65 (2H, m, CH_2CH_2CHOH), 1.35, 1.13 (3H, s, ROCCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.5, 198.4 (C=O), 144.7, 143.9 (CH_2CH=CH), 133.7, 133.5 (CH_2CH=CH), 100.1, 98.6 (C(OH)OR), 83.6, 83.6 (OCCH_3), 45.6, 44.6 (CH_2CH=CH), 34.7, 32.3 (CH_2CH_2C(OR)OH), 28.8, 26.8 (OCCH_3), 26.8, 26.7 (O=CCH_3); HRMS (ESI$^+$) *m/z* $[M+H]^+$, $C_{10}H_{17}O_3$ calcd. 185.1178, found 185.1175.

One-pot α-methylenation-oxa-Michael cyclisation of **4** *to give 1-methyl-3-(buta-1-en-3-one)-4,8-dioxabicyclo[3.2.1]octane (***5***) and 1-methyl-3-(2-(penta-1,4-dien-3-one))-4,8-dioxabicyclo[3.2.1]octane (***6***)*

A mixture of **4** (0.137 g, 0.744 mmol), diisopropylammonium trifluoroacetate (0.165 g, 0.767 mmol),[23] paraformaldehyde (0.057 g, 1.9 mmol) and TFA (0.01 mL, 0.13 mmol) in anhydrous THF (4 mL) was heated at reflux for 24 h under a nitrogen atmosphere. After allowing to cool to room temperature, paraformaldehyde (0.057 g, 1.9 mmol) was added and the mixture again heated at reflux for 24 h. The solvent was then evaporated and the yellow residue was purified by silica gel chromatography on silica gel using hexane: ethyl acetate (60:40, R_f **5** = 0.45, R_f **6** = 0.35) to give **5** (0.070 g, 48%) as a colourless oil and **6** (0.019 g, 12%) as a pale-yellow oil.

For **5**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.36 (1H, dd, $^3J_{trans}$ = 18.0 Hz, $^3J_{cis}$ = 10.5 Hz, CH=CH_2), 6.23 (1H, dd, $^3J_{trans}$ = 18.0 Hz, $^2J_{gem}$ = 1.2 Hz, CH=CHH), 5.87 (1H, dd, $^3J_{cis}$ = 10.5 Hz, $^2J_{gem}$ = 1.2 Hz, CH=CHH), 5.44 (1H, d, *J* = 4.3 Hz, CH(OR)O), 4.37 (1H, m, ROCHCH_2C=O), 2.94 (1H, dd, ^2J = 16.2 Hz, ^3J = 7.0 Hz, CHHC=O), 2.56 (1H, dd, ^2J = 16.2 Hz, ^3J = 5.7 Hz, CHHC=O), 2.16–2.04 (2H, m, CH_2CO), 1.92–1.85 (1H, m, CHHCH_2CO), 1.68–1.58 (1H, m, CHHCH_2CO), 1.56–1.50 (2H, m, C(CH_3)CH_2CHO), 1.36 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 198.4 (C=O), 136.9 (CH=CH_2), 128.9 (CH=CH_2), 100.4 (C(OR)O), 80.1 (OCCH_3), 64.9 (ROCHCH_2C=O), 45.5 (CH_2C=O), 43.1 (CCH_2CH), 33.2 (CH_2CH_2CO), 31.5 (CH_2CH_2CO), 25.7 (CH_3); HRMS (ESI$^+$) *m/z* $[M+H]^+$, $C_{11}H_{17}O_3$ calcd. 197.1178, found 197.1179.

For **6**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.90 (1H, dd, $^3J_{trans}$ = 17.0 Hz, $^3J_{cis}$ = 10.5 Hz, CH=CH_2), 6.30 (1H, dd, $^3J_{trans}$ = 17.0 Hz, $^2J_{gem}$ = 1.5 Hz, CH=CHH), 6.26 (1H, d, $^2J_{gem}$ = 1.5 Hz, C=CHH), 6.13 (1H, br s, C=CHH), 5.82 (1H, dd, $^3J_{cis}$ = 10.5 Hz, $^2J_{gem}$ = 1.5 Hz, CH=CHH), 5.60 (1H, bd, *J* = 3.5 Hz, CH(OR)O), 4.89 (1H, dd, *J* = 11.3 Hz, *J* = 3.5 Hz, ROCHC=CH_2), 2.20–2.15 (2H, m, CH_2CHO), 2.01 (1H, m, CHHCH_2CHO), 1.82 (1H, ddd, *J* = 12.9 Hz, *J* = 3.6 Hz, *J* = 1.1 Hz, OCCHHCH), 1.69 (1H, m, CHHCH_2CHO), 1.45 (1H, m, OCCHHCH), 1.36 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.0 (C=O), 149.0 (C=CH_2), 132.0 (CH=CH_2), 129.4 (CH=CH_2), 124.7 (R-C(C=O)=CH_2), 100.5 (CH(O)O), 80.4 (OCCH_3), 66.2 (ROCHC=CH_2), 43.5 (CCH_2CH), 33.0 (CH_2CH_2CO), 31.7 (CH_2CH_2CO), 25.7 (CH_3); HRMS (ESI$^+$) *m/z* $[M+H]^+$, $C_{12}H_{17}O_3$ calcd. 209.1178, found 209.1173.

Fragmentative carbocyclisation of **5** *to give 1-methyl-4-(prop-3-en-1-one)-8-oxabicyclo[3.2.1]oct-3-ene (***7***)*

A stirring solution of **5** (25 mg, 0.13 mmol) containing 4 Å molecular sieves (40 mg) in anhydrous THF (1 mL) was cooled to –20 °C under a nitrogen atmosphere. Titanium(IV) chloride in dichloromethane (1 M, 0.29 mL, 0.29 mmol) was then added dropwise over 10 min. The stirring mixture was then allowed to warm and was maintained at room temperature for 1 h. Since TLC analysis (hexane: ethyl acetate, 80:20) did not confirm significant product formation, the mixture was then heated at reflux for 2 h 45 min, at which time TLC analysis confirmed that no **5** remained. The reaction mixture was then cooled to –20 °C and quenched with a saturated aqueous solution of sodium carbonate (5 mL). The mixture was then concentrated and the aqeous layer extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated. The residue was purified by chromatography on silica gel using hexane: ethyl acetate (80:20, R_f = 0.24) to give **7** (13 mg, 57%) as a colourless oil; ^{1}H NMR ($CDCl_3$, 700 MHz) δ 6.87 (1H, dd, $^3J_{trans}$ = 17.1 Hz, $^3J_{cis}$ = 10.5 Hz, CH=CH_2), 6.76 (1H, dd, *J* = 4.7 Hz, *J* = 2.9 Hz, CH_2CH=C), 6.30 (1H, dd, $^3J_{trans}$ = 17.1 Hz, $^2J_{gem}$ = 1.7 Hz, CH=CHH), 5.75 (1H, dd, $^3J_{cis}$ = 10.5 Hz, $^2J_{gem}$ = 1.7 Hz, CH=CHH), 5.07 (1H, d, *J* = 6.5 Hz, CH_2CHOR), 2.62 (1H, br d, *J* = 19.2 Hz, CHHCH=C), 2.24–2.19 (1H, m, CH_2CHHCH), 2.17 (1H, dd, *J* = 19.2 Hz, *J* = 2.8 Hz CHHCH=C), 1.97–1.94 (1H, m, CH_2CHHCH), 1.83–1.78 (1H, m, CHHCH_2CH), 1.76–1.71 (1H, m, CHHCH_2CH), 1.46 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$, 176 MHz) δ 186.6 (C=O), 144.5 (CH=C), 137.3 (CH=CC=O), 130.7 (CH=CH_2), 128.5 (CH=CH_2), 78.6 (OCCH_3), 73.6 (CH_2CHOR), 41.4 (CH_2CH=C), 36.1 (CH_2CH_2CHOR), 36.0 (CH_2CH_2CHOR), 26.5 (CH_3); HRMS (ESI$^+$) *m/z* $[M+H]^+$ $C_{11}H_{15}O_2$ calcd. 179.1077, found 179.1072.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest in relation to the research, authorship and publication of this article.

ORCID iDs

Charles M Marson https://orcid.org/0000-0002-1729-5760
Sean McCarthy https://orcid.org/0000-0002-4858-0564

Supplementary material

Supplementary material for this article is available online.

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