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Pyridinium chlorochromate mediated oxidative cyclisation of sterically crowded γ,δ-unsaturated alcohols

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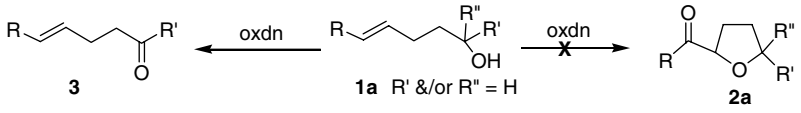
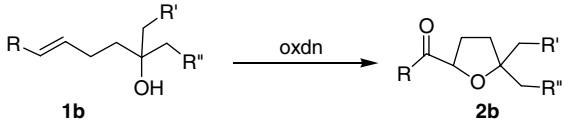
Abstract—Pyridinium chlorochromate (PCC) mediated oxidative cyclisation of sterically crowded γ,δ-unsaturated alcohols (primary, secondary, allylic, benzylic as well as tertiary) is described.

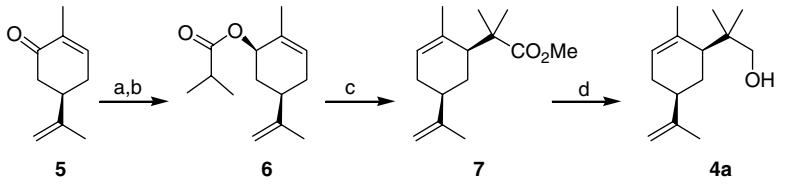
γ,δ-Unsaturated alcohols **1** have been employed as starting materials for the construction of 2-acyltetrahydrofurans **2** in natural product synthesis, either via the corresponding epoxide or by employing a haloetherification (or its equivalent) reaction. However, there is no report in the literature on the direct one-step oxidative conversion of γ,δ-unsaturated primary and secondary alcohols **1a** to generate 2-acyltetrahydrofurans **2a**, as oxidation to the corresponding aldehyde or ketone **3** is preferred (Eq. 1). A few scattered examples of oxidative cyclisation of γ,δ-unsaturated tertiary alcohols **1b** to the corresponding 2-acyltetrahydrofurans **2b** (Eq. 2) have been reported in the literature.[1] Pyridinium chlorochromate (PCC) is a versatile oxidising agent, which has been employed in the selective oxidation of a variety of alcohols.[2] It has also been utilised in the transposition of tertiary alcohols and cyclopropyl methanols.[2] During our investigations on the synthesis of enantiopure bicyclo-[n.3.1]alkanes from derivatives of carvone, we have discovered a novel PCC mediated oxidative cyclisation of sterically crowded γ,δ-unsaturated alcohols, which is the subject of this Letter.



(1)



(2)



Scheme 1. Reagents and conditions: (a) $LiAlH_4$, Et_2O, −70 °C, 2 h, 96%; (b) Me_2CHCO_2H, DCC, DMAP, CH_2Cl_2, rt, 3 h, 94%; (c) (i) LDA, THF, TMSCl, NEt_3, −70 °C, 30 min; rt, 2 h; reflux, 8 h; (ii) dil HCl, 30 min; (iii) CH_2N_2, Et_2O, 0 °C, 30 min, 92%; (d) $LiAlH_4$, Et_2O, 0 °C, 2 h, 97%.

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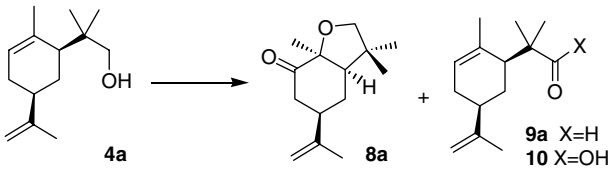
Neopentyl alcohol **4a** was prepared from (*R*)-carvone **5** as depicted in Scheme 1 via the Ireland ester Claisen rearrangement[3] of carvyl 2-methylpropanoate **6**, followed by reduction of the resulting ester **7**. Oxidation of neopentyl alcohol **4a** with 2.5 equiv[4] of PCC and silica gel in methylene chloride at room temperature for 40 minutes furnished the bicyclic ketone **8a** in addition to aldehyde **9a**, in a combined 85% yield and 1:1 ratio.

Compounds **8a** and **9a** were separated by column chromatography on silica gel. The structure of the bicyclic ketone **8a** was established from its spectral data,[†] in particular, from the presence of a carbonyl absorption band at 1724 cm^{-1} in the IR spectrum, the absence of signals due to the trisubstituted olefin and aldehyde protons and carbons in the NMR spectra, and the presence of a quaternary carbon resonance at δ 211.4 due to the ketone carbon and two oxygen bearing carbons (one quaternary at 86.6 and one methylene at 78.1 ppm) in the ^{13}C NMR spectrum. The reaction was further investigated, Scheme 2. The bicyclic ketone **8a** was formed on oxidation of alcohol **4a** under various conditions, viz. pyridinium dichromate (PDC) in methylene chloride, PCC in the absence of silica gel and PCC and sodium acetate. However, Jones' reagent failed to generate ketone **8a**, and furnished only a mixture of aldehyde **9a** and the corresponding acid **10**, which ruled out the role of the acidity of PCC in the formation of the bicyclic ketone **8a** from alcohol **4a**.



reagent	yield	ratio of **8a** and **9a**
PCC, silica gel	85%	1:1
PCC	90%	1:1.2
PCC, NaOAc	81%	1:1.2
PDC	76%	1:6
Jones' reagent	90%	only **9a** and **10**

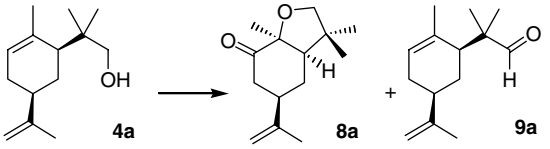
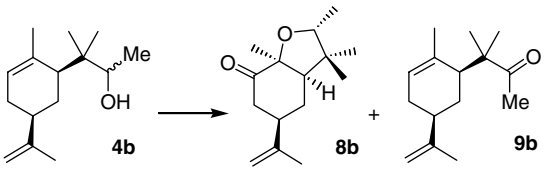
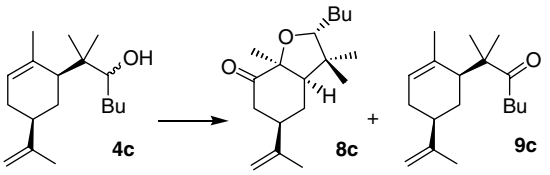
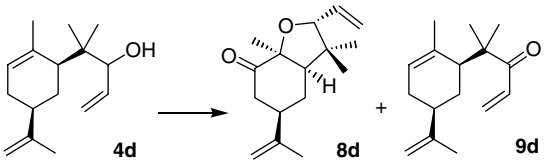
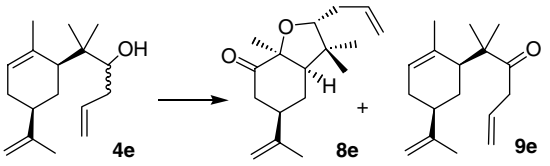
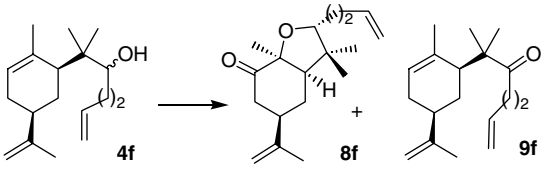
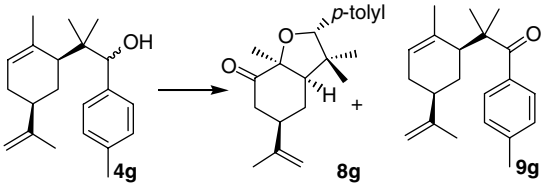
Scheme 2.

The PCC mediated oxidative cyclisation was further investigated with several secondary alcohols **4b–g** and the results are summarised in Table 1. The alcohols **4b–g** were prepared from aldehyde **9a**. Oxidation was carried out with PCC in methylene chloride at room temperature.[5] It is worth noting that even the allyl alcohol (entry d) and benzyl alcohol (entry g) furnished the bicyclic ketones. The *exo* isomer was found to predominate (>8:1) in all the bicyclic compounds **8b–g**, indicating that one of the isomers of **4b–g** preferentially cyclises and the other generates both the bicyclic ketone **8** and aldehyde **9**.

Since it is already well established that the primary alcohol **11a** undergoes smooth oxidation to the corresponding aldehyde[6] with PCC, it is obvious that the presence of the quaternary carbon (thereby increasing the steric crowding) in alcohol **4a** is responsible for the generation of ketone **8a**, perhaps due to the Thorpe–Ingold (or reactive rotamer) effect.[7] The oxidative cyclisation was carried out with an epimeric mixture of propyl alcohol **12** in the presence of PCC and silica gel in methylene chloride in order to establish the role of the two methyl groups in **4a** in the cyclisation. Alcohol **12** was readily available from carvone **5** and the stereochemistry of the secondary methyl group has been established.[8] It was observed that the major isomer (*R*)-**12** leads to a mixture of the bicyclic ketone[†] **13** and aldehyde **14**, whereas the minor isomer (*S*)-**12** exclusively gives aldehyde **14**. This was further established by the oxidation of the tertiary alcohols **11b** and **15**. The reaction was found to be very slow with alcohol **11b** (only 20% conversion after 5 h) and produced the bicyclic ketone[†]

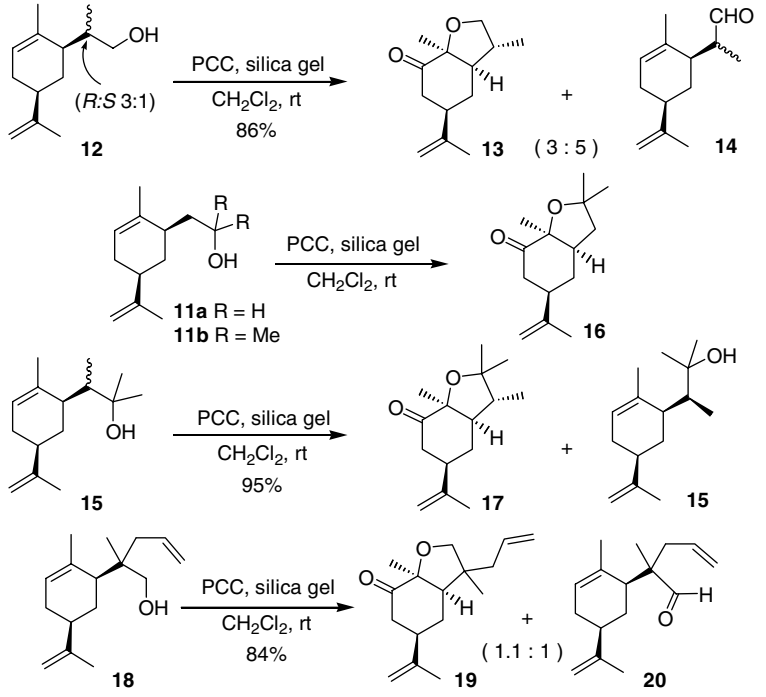
[†] Yields refer to isolated and chromatographically pure compounds. All the compounds exhibited spectral data (IR, ^1H and ^{13}C NMR and mass) consistent with their structures. Selected spectral data for the bicyclic ketone **8a**: $[\alpha]_D^{23}$ +7.4 (*c* 2.6, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1724, 1646, 1072, 891; ^1H NMR (300 MHz, $CDCl_3$): δ 4.76 (2H, s), 3.49 and 3.41 (2H, 2 × d, *J* 9.0 Hz), 2.75–2.60 (2H, m), 2.20–1.95 (2H, m), 1.85–1.70 (1H, m), 1.74 (3H, s), 1.46 (3H, s), 1.40–1.00 (1H, m), 1.12 (3H, s), 0.89 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.4 (C), 146.9 (C), 110.3 (CH_2), 86.6 (C), 78.1 (CH_2), 56.5 (CH), 42.2 (C), 41.5 (CH_2), 39.8 (CH), 29.6 (CH_2), 27.1 (CH_3), 26.3 (CH_3), 21.2 (CH_3), 20.1 (CH_3); HRMS: *m*/*z* calcd for $C_{14}H_{22}O_2Na$ (M+Na): 245.1517. Found: 245.1515. For the bicyclic ketone **8d**: $[\alpha]_D^{22}$ +11.0 (*c* 1.2, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3081, 1723, 891; ^1H NMR (300 MHz, $CDCl_3$): δ 5.77 (1H, ddd, *J* 17.4, 10.2 and 6.6 Hz), 5.26 (1H, d, *J* 17.4 Hz), 5.22 (1H, d, *J* 10.2 Hz), 4.75 (2H, s), 3.66 (1H, d,*J* 6.3 Hz), 2.73–2.58 (2H, m), 2.25–2.00 (2H, m), 1.90–1.70 (1H, m), 1.73 (3H, s), 1.51 (3H, s), 1.25–1.10 (1H, m), 0.98 (3H, s), 0.85 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.9 (C), 147.2 (C), 133.7 (CH), 118.1 (CH_2), 110.3 (CH_2), 86.4 (CH), 85.5 (C), 57.6 (CH), 44.5 (C), 41.5 (CH_2), 39.9 (CH), 31.0 (CH_2), 26.5 (CH_3), 25.6 (CH_3), 20.1 (CH_3), 20.0 (CH_3); HRMS: *m*/*z* calcd for $C_{16}H_{24}O_2Na$ (M+Na): 271.1675. Found: 271.1675. For the bicyclic ketone **8g**: $[\alpha]_D^{24}$ −17.9 (*c* 5.5, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1723, 1071, 764; ^1H NMR (300 MHz, $CDCl_3$): δ 7.15 and 7.05 (4H, 2 × d, *J* 8.1 Hz), 4.76 (2H, s), 4.26 (1H, s), 2.80–2.50 (2H, m), 2.32 (3H, s), 2.20–2.10 (2H, m), 1.90–1.70 (1H, m), 1.74 (3H, s), 1.59 (3H, s), 1.40–1.25 (1H, m), 0.89 (3H, s), 0.72 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.3 (C), 147.1 (C), 136.5 (C), 134.0 (C), 128.1 (2C, CH), 126.5 (2C, CH), 110.2 (CH_2), 86.1 (CH), 84.8 (C), 57.7 (CH), 44.5 (C), 41.4 (CH_2), 39.8 (CH), 31.2 (CH_2), 26.4 (CH_3), 26.0 (CH_3), 21.2 (CH_3), 20.2 (CH_3), 20.0 (CH_3); HRMS: *m*/*z* calcd for $C_{21}H_{28}O_2Na$ (M+Na): 335.1987. Found: 335.1986. For the bicyclic ketone **13**: $[\alpha]_D^{25}$ +4.5 (*c* 1.5, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1717, 1015, 893; ^1H NMR (300 MHz, $CDCl_3$): δ 4.80 (1H, br s), 4.74 (1H, s), 4.02 (1H, dd, *J* 8.1 and 8.1 Hz), 3.48 (1H, dd, *J* 9.9 and 8.1 Hz), 2.80–2.60 (1H, m), 2.55–2.39 (3H, m), 2.16 (1H, quintet, *J* 6.6 Hz), 1.80–1.65 (1H, m), 1.75 (3H, s), 1.35–1.21 (1H, m), 1.27 (3H, s), 1.01 (3H, d, *J* 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.0 (C), 147.3 (C), 110.3 (CH_2), 85.1 (C), 72.6 (CH_2), 50.1 (CH), 42.9 (CH), 42.5 (CH_2), 36.7 (CH), 29.0 (CH_2), 22.1 (CH_3), 20.4 (CH_3), 11.6 (CH_3); HRMS: *m*/*z* calcd for $C_{13}H_{20}O_2Na$ (M+Na): 231.1361. Found: 231.1360. For the bicyclic ketone **16**: $[\alpha]_D^{24}$ +20.0 (*c* 3.0, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 1722, 891; ^1H NMR (300 MHz, $CDCl_3$): δ 4.71 (2H, s), 2.60–2.25 (4H, m), 2.10–1.90 (2H, m), 1.69 (3H, s), 1.58 (1H, dd, *J* 12.3 and 7.2 Hz), 1.50–1.40 (1H, m), 1.36 (3H, s), 1.26 (3H, s), 1.23 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.5 (C), 147.0 (C), 110.7 (CH_2), 85.8 (C), 81.3 (C), 47.6 (CH), 46.2 (CH_2), 42.1 (CH_2), 41.5 (CH), 34.0 (CH_2), 30.5 (CH_3), 30.1 (CH_3), 26.1 (CH_3), 20.8 (CH_3); HRMS: *m*/*z* calcd for $C_{14}H_{22}O_2Na$ (M+Na): 245.1517. Found: 245.1509.

Table 1. PCC mediated oxidative cyclisation of neopentyl alcohols **4a–g**

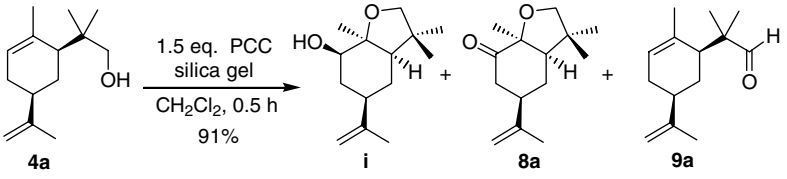
Entry	Alcohol **4**	Products[a] **8** and **9**	Yield/% (ratio[b] of **8**:**9**)
a			85 (1:1)
b			93 (1:1.2)
c			79 (1.6:1)
d			86 (1:1.6)
e			81 (1.2:1)
f			94 (1.5:1)
g			84 (1.8:1)

[a] All the compounds were separated by column chromatography on silica gel.
[b] Ratio is based on the isolated pure compounds.

16. On the other hand, the major isomer of alcohol (*R*)-**15** was cyclised to the bicyclic ketone **17** and the minor isomer (*S*)-**15** remained unreacted under these conditions. The reaction was also investigated with alcohol **18** containing two competing olefins at the γ-position for the alcohol to cyclise. As expected, bicyclic ketone **19** was formed, clearly establishing the preference for the electron rich olefin to cyclise.



In conclusion, we have reported a novel oxidative cyclisation of sterically crowded alcohols (primary, secondary, allyl, homoallyl, benzyl, tertiary) to generate annulated tetrahydrofurans. Currently, we are investigating the utility of this oxidative cyclisation in the synthesis of perhydrobenzofuran based natural products.



Acknowledgements

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4. It was found that a minimum of 2 equiv of PCC was required for completion of the reaction. For example, reaction of alcohol **4a** with 1.5 equiv of PCC furnished the bicyclic alcohol **i** in addition to the bicyclic ketone **8a** and aldehyde **9a** (**i**:**8a**:**9a** 3:2:5), suggesting the secondary alcohol **i** (or its equivalent chromium containing species) as the intermediate in the sequence.
5. *General experimental procedure*: To a magnetically stirred solution of alcohol **4a** (250 mg, 1.2 mmol) in anhydrous CH_2Cl_2 (4 ml) was added a homogeneous mixture of PCC (775 mg, 3.6 mmol) and silica gel (775 mg), and the reaction stirred for 30 min at rt. The reaction mixture was then filtered through a small silica gel column using CH_2Cl_2 as eluent. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1:20) as eluent furnished aldehyde **9a** (106 mg, 43%) as an oil. Further elution of the column with ethyl acetate–hexane (1:10) furnished the ketoether **8a** (134 mg, 42%) as an oil.
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