COMMUNICATION

Highly *cis*- or *trans*-selective oxygen to carbon rearrangements of anomerically linked 6-substituted tetrahydropyranyl enol ethers

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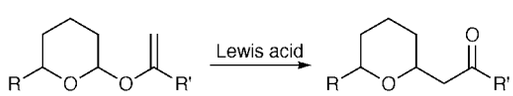
Low temperature Lewis acid catalysed oxygen to carbon rearrangements of anomerically linked 6-substituted tetrahydropyranyl enol ethers lead to the corresponding *trans*-ketones in a highly diastereoselective manner, whereas at higher temperatures the *cis*-ketones are formed with a high degree of selectivity under thermodynamic control.

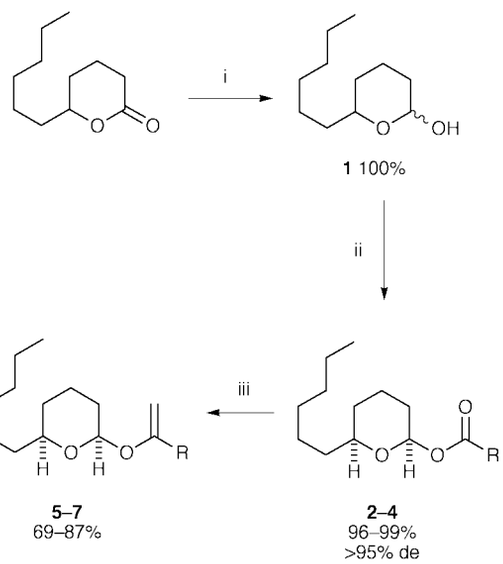
The profusion of bioactive natural products containing tetrahydropyran and/or tetrahydrofuran rings bearing carbon substituents in the 2-position has provided the impetus for the development of methods for the formation of such systems.[1] We have recently investigated a number of reactions exploiting oxygen to carbon rearrangement of an anomerically linked nucleophile to introduce a carbon substituent directly at the anomeric centre. To date these nucleophiles include electron-rich alkenes,[2–4] alkynyl stannanes[5] and silyl enol ethers,[6] and the latter has been successfully used as the key step in the total synthesis of the anti-cancer agent (+)-goniodiol.[7] Here we present our discoveries on the next in this series of nucleophiles, the general concept for which is the utilisation of anomerically linked 6-substituted tetrahydropyranyl enol ethers to effect Lewis acid promoted stereoselective carbon–carbon bond formation at the 2-position (Scheme 1).[8]



Scheme 1

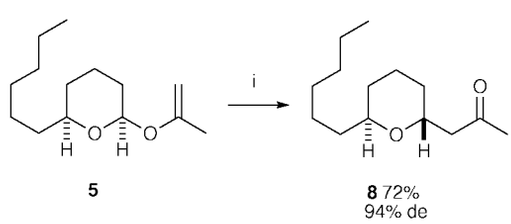
We have developed an efficient and flexible route towards anomerically linked enol ethers bearing an alkyl side chain in the 6-position, starting from commercially available undecanoic δ-lactone (Scheme 2). Quantitative reduction to lactol **1** using diisobutylaluminium hydride (1.05 equiv.) at −78 °C in toluene, followed by formation of the anomeric alkoxide with potassium hexamethyldisilylamide (KHMDS) in tetrahydrofuran (THF) at −78 °C and subsequent acylation with acetic anhydride or an acid chloride, yielded anomeric esters **2**–**4** in excellent yield after purification on silica gel deactivated with triethylamine.† Interestingly, these esters are formed almost exclusively as the *cis* isomers (>95% de). In order to complete the sequence, these esters were treated with Tebbe reagent in THF–toluene 1 : 1 at −30 °C, which after 30 minutes gave the corresponding enol ethers **5**–**7** in good yield after filtration through alumina.[9]

With a general route to the anomerically linked 6-substituted tetrahydropyranyl enol ethers established, investigations into the conditions required for the rearrangement were then undertaken. Initially, it was found that when anomeric enol ether **5** was treated with a catalytic quantity (5 mol%) of trimethylsilyl trifluoromethanesulfonate (TMSOTf) in dichloromethane at −78 °C for 5 minutes, it underwent the desired anomeric oxygen to carbon rearrangement to *trans*-methyl ketone **8** in 72% yield



Scheme 2 R = Me (**2**, **5**), Ph (**3**, **6**), C_4H_9 (**4**, **7**). *Reagents and conditions*: (i) 1.05 equiv. diisobutylaluminium hydride, toluene, −78 °C, 30 min; (ii) 1.05 equiv. potassium hexamethyldisilylamide, THF, −78 °C, Ac_2O or RCOCl, 120 min; (iii) 1.2 equiv. Tebbe reagent (0.5 M in toluene), THF–toluene (1 : 1), −30 °C, 30 min.

and 94% de (Scheme 3), which was easily separated from its *cis* counterpart by flash column chromatography.[10]

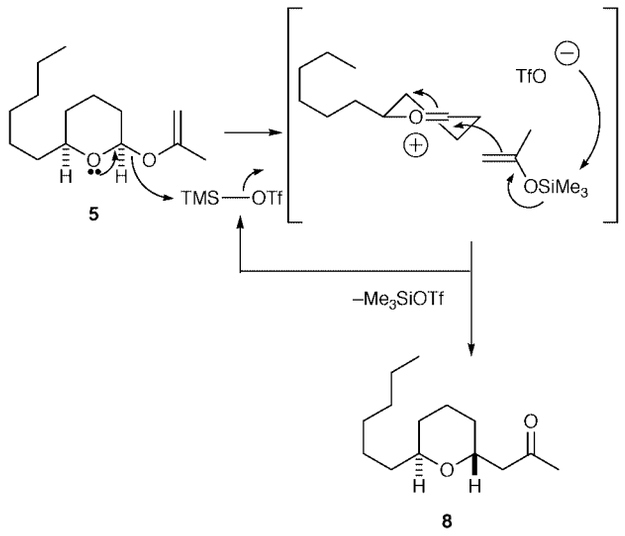


Scheme 3 *Reagents and conditions*: (i) 5 mol% TMSOTf, −78 °C, CH_2Cl_2, 5 min.

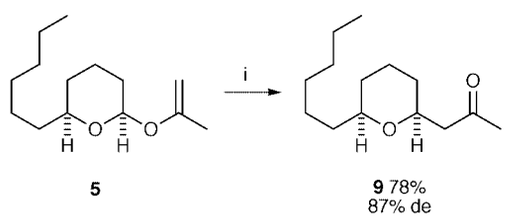
Evidently TMSOTf is activating the leaving group leading to an oxonium ion and formation of a silyl enol ether *in situ* (Scheme 4). These components recombine under kinetic control to give *trans*-ketone **8**, with concurrent loss of the trimethylsilyl group which rejoins the catalytic cycle.

In contrast, when enol ether **5** was exposed to 1 equivalent of TMSOTf at room temperature for 30 minutes the selectivity of the reaction was reversed, and *cis*-methyl ketone **9** was isolated in 78% yield and 87% de (Scheme 5).

This powerful control of selectivity by a simple modification of the reaction conditions is the result of two factors. At low temperatures and with catalytic amounts of Lewis acid, an initial highly diastereoselective reaction occurs under kinetic



Scheme 4



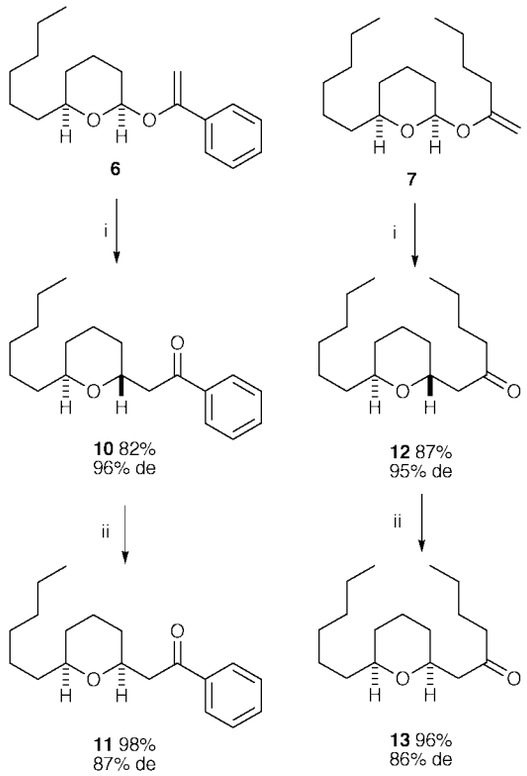
Scheme 5 *Reagents and conditions*: (i) 1 equiv. TMSOTf, room temp., CH_2Cl_2, 30 min.

control, directed by the alkyl chain in the 6-position, to give the *trans*-product.[11] At higher temperatures and in the presence of larger amounts of Lewis acid a reversible β-elimination ensues, leading to an equilibrium where the thermodynamically favoured *cis*-product predominates.[12] This mechanism is supported by the observation that pure *cis*-ketone **9** or pure *trans*-ketone **8** both gave an identical *cis*/*trans* mixture on treatment with 1 equivalent of TMSOTf at room temperature in dichloromethane.

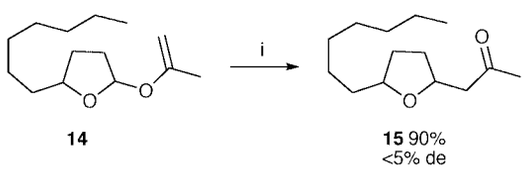
We have also shown that it is possible to extend these reactions to anomerically linked enol ethers **6** and **7**. When these substrates were treated with catalytic quantities of TMSOTf at −78 °C in dichloromethane for 5 minutes they were converted to the *trans*-ketones **10** (82% yield, 96% de) and **12** (87% yield, 95% de) respectively (Scheme 6). The *trans*-products, when treated with 1 equivalent of TMSOTf at room temperature in dichloromethane, gave the *cis*-ketones **11** (98% yield, 87% de) and **13** (96% yield, 86% de) respectively.

This rearrangement was also applicable to 5-substituted tetrahydrofuran ring systems, such as enol ether **14** (prepared in 56% overall yield from undecanoic γ-lactone) (Scheme 7). In this case, reaction under kinetic control resulted in ketone **15** in 90% yield, but with low de (<5%). Subsequent attempts to isomerise under the conditions described above did not affect the de of the product; this lower de is in accordance with our previous observations on the selectivity of rearrangement reactions on related tetrahydrofuranyl systems.[5,6]

We believe that the methodology described above significantly extends the scope of anomeric oxygen to carbon rearrangements in organic synthesis. Depending on the choice of reaction conditions, treatment of the readily formed anomerically linked 6-substituted tetrahydropyranyl enol ethers with Lewis acid allows access to either *cis*- or *trans*-substituted tetrahydropyranyl ring systems, in high yields and with good to excellent diastereoselectivities. We are presently conducting further research into the scope of this rearrangement, including its application in the total synthesis of natural products, and our findings will be reported in due course.



Scheme 6 *Reagents and conditions*: (i) 5 mol% TMSOTf, −78 °C, CH_2Cl_2, 5 min; (ii) 1 equiv. TMSOTf, room temp., CH_2Cl_2, 30 min.



Scheme 7 *Reagents and conditions*: (i) 5 mol% TMSOTf, −78 °C, CH_2Cl_2, 5 min.

Acknowledgements

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Notes and references

† Satisfactory accurate mass and/or microanalysis data was obtained for all new compounds.

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3 For related examples see: (*a*) J. Herscovici, S. Delatre and K. Antonakis, *J. Org. Chem.*, 1987, **52**, 5691; (*b*) K. Mikami and H. Kishino, *Tetrahedron Lett.*, 1996, **37**, 3705.
4 For related rearrangements at benzylic positions see: (*a*) J. Wennerberg, L. Eklund, M. Polla and T. Frejd, *Chem. Commun.*, 1997, 445; (*b*) J. Wennerberg and T. Frejd, *Acta Chem. Scand.*, 1998, **52**, 95.
5 M. F. Buffet, D. J. Dixon, S. V. Ley and E. W. Tate, *Synlett*, 1998, 1091.
6 D. J. Dixon, S. V. Ley and E. W. Tate, *Synlett*, 1998, 1093.
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52, 5700; (*c*) H. Frauenrath and J. Runsink, *J. Org. Chem.*, 1988, **53**, 1860; (*d*) A. Ricci, A. Degl'Innocenti, A. Capperucci, C. Faggi, G. Seconi and L. Favaretto, *Synlett*, 1990, 471; (*e*) D. G. Bourke, D. J. Collins, A. I. Hibbered and M. D. McLeod, *Aust. J. Chem.*, 1996, **49**, 425; (*f*) M. Sollogoub, J.-M. Mallet and P. Sinaÿ, *Tetrahedron Lett.*, 1998, **39**, 3471.

9 Fresh Tebbe reagent (purchased from Sigma-Aldrich Chemical Co.) is required for this reaction to proceed smoothly. It was found that if an older batch of Tebbe reagent was used the Lewis acidity of the degraded reagent was sufficient to cause some decomposition during the methylenation reaction.

10 Typical experimental procedure for the transformation of **5** into **8** and **9**: To a stirred solution of **5** (0.100 g, 0.44 mmol) in dichloromethane (1.5 mL) at −78 °C was added TMSOTf (0.004 mL, 0.022 mmol). After stirring at −78 °C for 5 min the reaction mixture was quenched by the addition of phosphate buffer (pH 7.4, 3 mL), the aqueous layer extracted with diethyl ether (3 × 5mL) and the combined organic extracts dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a slightly yellow oil. ^{1}H NMR spectroscopic analysis of this crude product showed a 3:97 ratio of **9**:**8**. Purification by silica column chromatography, eluting with 20% diethyl ether–light petroleum (bp 40–60 °C), gave **9** (0.002 g, 2%) and **8** (0.070 g, 70%) as colourless oils. Characterisation data for **9**: ν_{max} (thin film)/cm^{-1} 2930, 2858, 1717, 1458, 1356, 1197, 1080; δ_H(400 MHz; $CDCl_3$) 3.74–3.68 (1H, m, OC*H*CH_2CO), 3.26–3.22 (1H, m, C*H*OCH-CH_2CO), 2.64 (1H, dd, *J* 15.1 and 8.1, C*H*H$COCH_3$), 2.38 (1H, dd, *J* 15.1 and 4.8, CH*H*$COCH_3$), 2.16 (3H, s, $COCH_3$), 1.82–1.11 (16H, m, 8 × CH_2), 0.86 (3H, t, *J* 7.0, CH_2CH_3); δ_C(100 MHz; $CDCl_3$) 207.8 (*C*OCH_3), 78.0 (O*C*HCH_2CO), 74.4 (*C*HOCHCH_2CO), 50.4 (*C*H_2CO), 36.4, 31.8, 31.6, 31.3, 31.0 (CO*C*H_3), 29.3, 25.5, 23.5, 22.6, 14.0 (CH_2CH_3); *m*/*z* (FAB) 109 (62%), 113 (53%), 136 (60%), 154 (54%), 169 (100%), 227 (40%) (Found: MH^+, 227.2015. $C_{14}H_{27}O_2$ requires 227.2011) (Found: C, 74.79; H, 11.58. $C_{14}H_{26}O_2$ requires: C, 74.96; H, 11.60%). Characterisation data for **8**: ν_{max}(thin film)/cm^{-1} 2930, 2858, 1715, 1460, 1357, 1203, 1162, 1095, 1041; δ_H(400 MHz; $CDCl_3$) 4.42–4.19 (1H, m, OC*H*CH_2CO), 3.69–3.61 (1H, m, C*H*OCHCH_2CO), 2.75 (1H, dd, *J* 15.1 and 8.3, C*H*H-$COCH_3$), 2.42 (1H, dd, *J* 15.1 and 7.4, CH*H*$COCH_3$), 2.17 (3H, s, $COCH_3$), 1.71–1.26 (16H, m, 8 × CH_2), 0.87 (3H, t, *J* 6.4, CH_2CH_3); δ_C(100 MHz; $CDCl_3$) 207.4 (*C*OCH_3), 71.7 (O*C*HCH$_2$CO), 67.5 (*C*HOCHCH_2CO), 48.2 (*C*H_2CO), 33.0, 31.8, 30.5 (CO*C*H_3), 30.2, 29.6, 29.3, 25.7, 22.6, 18.4, 14.0 (CH_2CH_3); *m*/*z* (FAB) 109 (71%), 169 (100%), 227 (78%) (Found: MH^+, 227.2016. $C_{14}H_{27}O_2$ requires 227.2011) (Found: C, 74.86; H, 11.57. $C_{14}H_{26}O_2$ requires: C, 74.96; H, 11.60%).

11 For a transition-state discussion of this phenomenon, see P. Deslongchamps, *Pure Appl. Chem.*, 1993, **65**, 1161.

12 Base-induced reversible β-elimination as a method for forming *cis*-tetrahydropyrans is well-established in synthesis, for example: E. D. Bergman, D. Ginsburg and R. Pappo, *Org. React.* (*N.Y.*), 1959, **10**, 179.

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