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A tandem C–H insertion—acetal cleavage sequence: stereocontrolled synthesis of substituted tetrahydrofurans

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Abstract—A short sequence involving Rh(II) mediated carbene insertion followed by Lewis acid promoted reductive acetal cleavage with Et_3SiH provides a stereoselective method for the construction of 2,3,5-trisubstituted tetrahydrofuran rings.

Substituted tetrahydrofuran ring systems are a common structural unit found in many bioactive natural products. Consequently, the development of strategies for the stereocontrolled synthesis of substituted tetrahydrofurans is an area of considerable ongoing interest.[1] In particular, the 3-hydroxy-2,5-disubstituted tetrahydrofuran skeleton is found in a number of natural products isolated from various marine sources (Fig. 1).[2] These exhibit a broad range of biological profiles and therefore have been the targets of a number of synthetic programmes.

In this letter, we describe a tandem reaction sequence, involving an intramolecular C–H insertion reaction on an acetal template followed by a reductive Lewis acid mediated ring opening, that provides access to this core structure (Scheme 1). Whilst both components of this sequence have been the subject of a number of studies, this combination represents a new strategy for the stereocontrolled access to these valuable heterocycles.[3–5]

In preliminary experiments, the desired acetal template could be constructed by the condensation of diol **5a** with pyruvic acid according to the procedure of Newman.[6] Consistent with the simple principles of anomeric stabilisation, the acetal **6a** adopted a conformation placing the carboxylate group preferentially in the axial position.[7] The formation of the mixed anhydride and

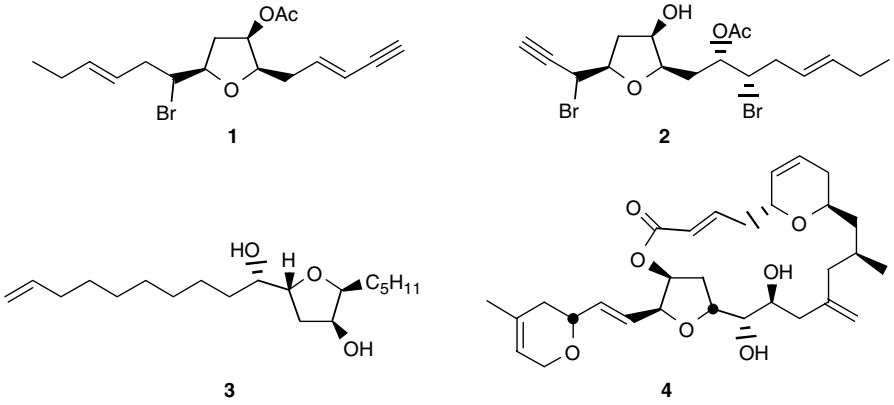

Figure 1.

Keywords: Rhodium; C–H insertion; Reductive cleavage; Acetal; Tetrahydrofuran.
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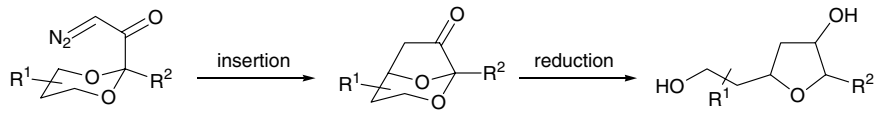
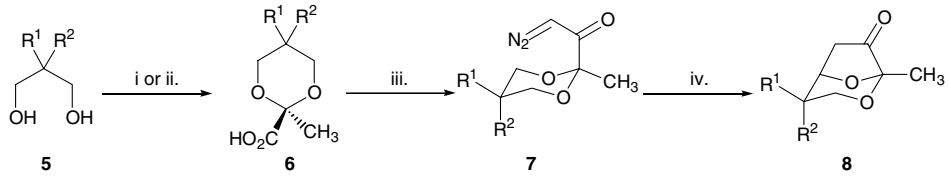


Scheme 1.



Entry	R^1	R^2	6	7	8
a	Me	Me	38%	79%	27%
b	Ph	H	73%	84%	45%
c	H	Ph	---[a]	82%	15%
d	$PhCH_2$	H	70%	85%	50%
e	4-$NO_2C_6H_4$	H	68%	75%	20%
f	H	4-$NO_2C_6H_4$	---[a]	70%	11%
g	4-$AcNHC_6H_4$	H	---[b]	79%	33%

a Minor epimer isolated from the reaction mixture (**6b:6c** 3.5:1; **6e:6f** 4:1). b. Obtained from **6b** by nitration, reduction and acetylation (63%)

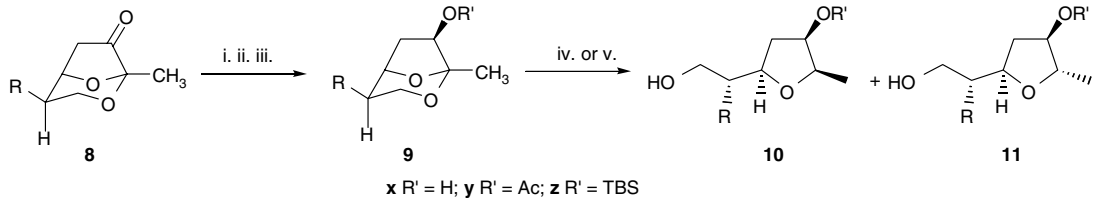
Scheme 2. Reagents and conditions: (i) CH_3COCO_2H, PhH, Dowex 50WX8, Δ; (ii) CH_3COCO_2Me, $BF_3{\cdot}OEt_2$, MeCN then NaOH, THF, H_2O; (iii) EtO_2CCl, Et_3N, THF, −15 °C, then CH_2N_2, Et_2O/THF, −5 °C; (iv) $Rh_2(OAc)_4$, DCM, rt.

subsequent treatment with diazomethane then afforded the desired diazoketone **7a**. Slow addition of this to a solution of $Rh_2(OAc)_4$ in DCM gave the desired bicyclic acetal **8a**, albeit in low yield (Scheme 2). Attempts to optimise this result were complicated by the volatility of this acetal and the lack of a chromophore for easy analysis of reaction progress.

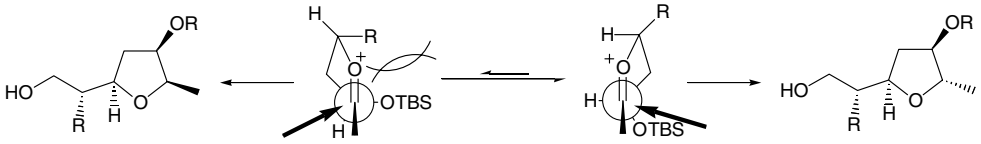
Consequently, the synthesis was repeated using 2-phenylpropane-1,3-diol, and in this case it proved more efficient to utilise the sequence reported by Wardrop involving acetalisation of pyruvate ester and subsequent hydrolysis. With the corresponding diazoketone **7b** in hand, attempts to optimise the insertion sequence explored the reaction variables including catalyst, solvent, concentration and the rate of addition. From these studies it proved possible to achieve the insertion reaction with the dioxanes with equatorial substituents at C-4 in modest but reproducible yields of 35–45% (Scheme 2). Variation of the electronic effect of the aryl group had limited effect on the process. Attempts to extend this result to the C-4 epimers (**7c** and **7f**) were considerably less efficient, presumably reflecting an unfavourable conformation of the dioxane template.

Initial attempts to undertake Lewis acid promoted acetal ring opening using the bicyclic ketone **8b** failed, and consequently this was reduced with $NaBH_4$ to give the *endo* alcohol **9bx** as a single diastereoisomer. The formation of the *endo* alcohol was confirmed by NOE experiments on the corresponding acetate, which showed strong correlations between the acetate CH_3 and the axial 4-H. Treatment of **9bx** with Et_3SiH and $BF_3{\cdot}OEt_2$ at 0 °C afforded the tetrahydrofurans **10bx** and **11bx** as a 3:7 mixture of isomers at C-2. These reactions are believed to proceed via nucleophilic attack on an intermediate oxocarbenium with the balance of retentive and invertive pathways being controlled by factors including the life-time of the initial ion pair and steric hindrance to the approach of the nucleophile.[8] Attempts to control this selectivity through the use of DIBAL-H, which is believed to reduce acetals via a retentive ring opening mechanism via a coordinated complex, were not successful, affording a complicated mixture of products. Similarly, variation of Lewis acid or reaction temperature did not provide a significant enhancement in selectivity. Consequently, we explored the effect of steric bulk at C3 and prepared a range of simple derivatives to probe the effect of controlling additions to the intermediate oxocarbenium ion. Satisfyingly, the use of a TBS ether in the presence of $TiCl_4$ as Lewis acid enabled the ring opening reaction to be achieved in high yield and high selectivity affording the 2,3-*anti*-3,5-*syn* product **11** in good yields and selectivities ($\geqslant$95:$\leqslant$5). The stereochemistry was established by NOE experiments on the corresponding acetates **10by** and **11by** (Scheme 3).

This result can be rationalised by coordination of Lewis acid to the more accessible oxygen atom to generate a five-membered ring oxocarbenium ion. Subsequent delivery of the hydride occurs to the 'inside face' of this oxocarbenium ion in such a conformation that both substituents reside in a pseudoequatorial orientation. Importantly, this approach maintains a staggered



Scheme 3. Reagents and conditions: (i) $NaBH_4$, MeOH (**9b** 87%, **9d** 70%, **9e** 84%, **9g** 80%); (ii) AcCl, Et_3N, DMAP, DCM (**9by** 75%); (iii) TBSOTf, 2,6-lutidine, DCM (**9bz** 60%, **9dz** 85%, **9ez** 65%, **9gz** 89%); (iv) Et_3SiH, $BF_3{\cdot}OEt_2$, −78 °C (**10bx**:**11bx** 7:3, 60%); (v) Et_3SiH, $TiCl_4$, −78 °C (**10bz**:**11bz** 5:95, 77%; **10dz**:**11dz** 5:95, 80%; **10ez**:**11ez** 3:97, 79%; **10gz**:**11gz** 13:87, 50%).



Scheme 4.

arrangement between the C-1 CH_3 and C-2 $OSiR_3$ in the transition state structure and leads to the observed 2,3-*anti* stereochemistry.[9] The alternative conformation leading to attack *anti* to the C–OSi bond is additionally disfavoured by steric interactions between the C-5 substituent and the bulky OTBS group (Scheme 4).

Having established the basic methodology, we then probed the effect of different groups at C-5 of the bicyclic acetal on both the insertion and ring fragmentation steps. Both aryl and alkyl groups work equally efficiently. Whilst an electron withdrawing group on the aryl ring or the alternative stereochemistry at this C-4 of the acetal lowered the efficiency of the insertion process neither variation has significant effect on the stereochemical outcome of the ring cleavage reaction. In all cases, the sequence produces the 2,3-*anti*-3,5-*syn* tetrahydrofuran with good levels of stereocontrol.

In conclusion, we have demonstrated a short stereoselective sequence for the synthesis of 2,3,5 substituted tetrahydrofurans.[10] Work towards extending this methodology to produce other stereochemistries and its application towards the synthesis of target structures containing this motif are in progress and will be reported in due course.

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References and notes

1. Elliott, M. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2301–2323; Harmange, J. C.; Figadere, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711–1754.
2. (**1**) Capon, R. J.; Barrow, R. A.; Rochfort, S.; Jobling, M.; Skene, C.; Lacey, E.; Gill, J. H.; Friedel, T.; Wadsworth, D. *Tetrahedron* **1998**, *54*, 2227–2242; (**2**) Norte, M.; Fernandez, J. J.; Ruano, J. Z. *Tetrahedron* **1989**, *45*, 5987–5994; (**3**) Suzuki, T.; Koizumi, K.; Suzuki, M.; Kurosawa, E. *Chem. Lett.* **1983**, 1643–1644; (**4**) Quinoa, E.; Kakou, Y.; Crews, P. *J. Org. Chem.* **1988**, *53*, 3642–3644.
3. For recent overviews on intramolecular C–H insertion processes see: Sulikowski, G. A.; Cha, K. L.; Sulikowski, M. M. *Tetrahedron: Asymmetry* **1998**, *9*, 3145–3169; Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: from Cyclopropanes to Ylides*; Wiley: Chichester, 1998; Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861–2903; Doyle, M. P. Chiral dirhodium(II) carboxamidates for catalytic asymmetric synthesis. In *Methodologies in Asymmetric Catalysis*; 2004; Vol. 880; pp 1–13.
4. For examples of the application of reductive cleavage of bicyclic acetals as a route to heterocyclic systems see: Ishihara, K.; Mori, A.; Yamamoto, H. *Tetrahedron* **1990**, *46*, 4595–4612; Kotsuki, H. *Synlett* **1992**, 97–106; Rychnovsky, S. D.; Dahanukar, V. H. *Tetrahedron Lett.* **1996**, *37*, 339–342; Fujiwara, K.; Amano, A.; Tokiwano, T.; Murai, A. *Tetrahedron* **2000**, *56*, 1065–1080; Bogaczyk, S.; Brescia, M. R.; Shimshock, Y. C.; DeShong, P. *J. Org. Chem.* **2001**, *66*, 4352–4355; Barrero, A. F.; Roldan, E.; Santiago, J. L. R.; Chahboun, R. *Synlett* **2003**, 2313–2316; Crimmins, M. T.; Siliphalvanh, P. *Org. Lett.* **2003**, *5*, 4641–4644.
5. Concurrent with our early endeavours, Wardrop reported an identical C–H insertion approach en route to the synthesis of the squalestatin and sordidin skeleton: Wardrop, D. J.; Velter, A. I.; Forslund, R. E. *Org. Lett.* **2001**, *3*, 2261–2264; Wardrop, D. J.; Forslund, R. E. *Tetrahedron Lett.* **2002**, *43*, 737–739; Wardrop, D. J.; Forslund, R. E.; Landrie, C. L.; Velter, A. I.; Wink, D.; Surve, B. *Tetrahedron: Asymmetry* **2003**, *14*, 929–940.
6. Newman, M. S.; Chen, C. H. *J. Org. Chem.* **1973**, *38*, 1173–1177.
7. Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer: New York, 1983.
8. Yamamoto, Y.; Nishii, S.; Yamada, J. *J. Am. Chem. Soc.* **1986**, *108*, 7116–7117; Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1991**, *113*, 8089–8110; Mori, I.; Ishihara, K.; Flippin, L. A.; Nozaki, K.; Yamamoto, H.; Bartlett,

P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 6107–6115; Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1992**, *114*, 10998–10999; Sammakia, T.; Smith, R. S. *J. Org. Chem.* **1992**, *57*, 2997–3000; Harada, T.; Oku, A. *Synlett* **1994**, 95–104, and references cited therein.

9. Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208–12209; Shaw, J. T.; Woerpel, K. A. *Tetrahedron* **1999**, *55*, 8747–8756; Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521–15528; Smith, D. M.; Woerpel, K. A. *Org. Lett.* **2004**, *6*, 2063–2066; Shenoy, S. R.; Woerpel, K. A. *Org. Lett.* **2005**, *7*, 1157–1160.
10. Typical experimental procedures: 1-methyl-4-phenyl-2,8-dioxabicyclo[3.2.1]octan-7-one **8b**: To a solution of rhodium acetate dimer ($Rh_2[OAc]_4$) (22.1 mg, 0.05 mmol) in CH_2Cl_2 (50 mL, 1 mmol/L, 2 mol %), a solution of diazoketone (**6b**) (0.615 g, 2.5 mmol) in CH_2Cl_2 (100 mmol/L) was added dropwise over 24 h via a syringe pump at room temperature. When the addition was complete, silica gel was added and the reaction mixture was concentrated. The residue was then immediately purified by flash chromatography (cyclohexane/EtOAc: 9/1), to give the title ketone (**8b**) (0.245 g, 45%) as a white solid. Mp: 78–80 °C. ν_{max} (ATR) : 3000–2838, 1763 (C=O), 1259, 1183, 1086, 1021, 862, 799, 759, 699, 668 cm^{-1}. δ_H (400 MHz): 7.35–7.15 (3H, m, Ar–CH), 7.07 (2H, d, $J = 7.0$ Hz, Ar–CH), 4.83 (1H, dd, $J = 7.1$, 3.3 Hz, 5-H), 4.25–4.15 (2H, m, 3-H_{ax}, 3-H_{eq}), 3.80 (1H, ddd, $J = 10.2$, 7.7, 3.3 Hz, 4-H), 2.50 (1H, dd, $J = 18.7$, 7.1 Hz, 6-H_a), 2.35 (1H, d, $J = 18.7$ Hz, 6-H_b), 1.4 (3H, s, CH_3). δ_C (100.5 MHz): 210.7 (CO), 136.3, 129.1, 127.6, 127.2, 98.2 (C-1), 76.1 (C-5), 64.1 (C-3), 42.2 (C-6), 36.4 (C-4), 18.1 (CH_3). *m/z* (CI, NH_3): 236 ($[MH+NH_3]^+$, 50%), 219 ($[MH]^+$, 100%), 201 (25%), 187 (62%), 173 (60%), 157 (9%), 130 (62%), 117 (19%), 104 ($[PhCHCH_2]^+$, 34%), 91 ($[PhCH]^+$, 17%), 77 ($[Ph]^+$, 12%). HRMS (ES^+): 218.0865 ($C_{13}H_{14}O_3$ requires 218.0941). 2-[4′-(*tert*-Butyldimethylsilanyloxy)-5′-methyltetrahydrofuran-2′-yl]-2-phenylethanol **10bz**, **11bz**: To a solution of the TBDMS protected alcohol (**9bz**) (70 mg, 0.21 mmol) in CH_2Cl_2 (15 mL), triethylsilane (Et_3SiH, 0.05 mL, 0.315 mmol, 1.5 equiv) was added at −78 °C followed by the dropwise addition of a 1 M solution of titanium tetrachloride ($TiCl_4$) in CH_2Cl_2 (0.030 mL, 0.252 mmol, 1.2 equiv). The reaction mixture was stirred at −78 °C. After 8 h, the solvent was evaporated in vacuo and without any work up, the crude residue, containing a mixture of two tetrahydrofuran isomers (**11bz**, **10bz**) in a 95:5 ratio, was purified by flash chromatography (cyclohexane/EtOAc: 9:1) to give the title tetrahydrofurans as an inseparable mixture (54 mg, 77%). Data for major isomer **11bz** ν_{max} (ATR): 3480–3000 (br OH) 2980–2850 (CH–OSi), 1245+835 (Si–CH_3), 1111, 1044, 881,835, 730, 699, 667 cm^{-1}. δ_H (500 MHz): 7.32–7.17 (5H, m, Ar–CH), 4.44 (1H, ddd, $J = 8.8$, 6.5, 6.2 Hz, 5-H), 4.02 (1H, dd, $J = 11.0$, 6.2 Hz, 2′-H), 3.90–3.82 (2H, m, 2′-H+3-H), 3.66 (1H, qd, $J = 6.2$, 6.2 Hz, 2-H), 3.07 (1H, ddd, $J = 6.2$, 6.2, 6.2 Hz, 1′-H), 2.27 (1H, br s, OH), 2.07 (1H, ddd, $J = 12.4$, 6.5, 6.2 Hz, 4-H_a), 1.76 (1H, ddd, $J = 12.4$, 8.8, 6.8 Hz, 4-H_b), 1.13 (3H, d, $J = 6.2$ Hz, CH_3), 0.86 (9H, s, $SiC(CH_3)_3$), 0.36+0.30 (6H, 2×s, $Si(CH_3)_2$). δ_C (125.7 MHz): 139.5, 129.0, 128.7, 127.1, 80.5 (C-2), 78.4 (C-5), 77.9 (C-3), 64.2 (C-2′), 51.7 (C-1′), 37.5 (C-4), 25.9 ($SiC(CH_3)_3$), 18.4 (CH_3), 18.2 ($SiC(CH_3)_3$), −4.5 ($Si(CH_3)_2$), −4.7 ($Si(CH_3)_2$). *m/z* (ES^+): 359.2 (M+Na, 100%). HRMS (ES^+) found: 359.2024 ($C_{19}H_{32}O_3SiNa$ requires 359.2018).