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An improved protocol for the Prins desymmetrisation of cyclohexa-1,4-dienes

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ABSTRACT

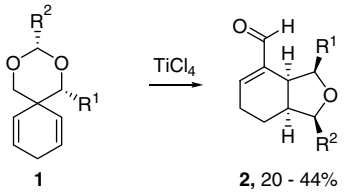
Improved conditions are reported for the Prins-pinacol rearrangement of cyclohexa-1,4-diene-derived acetals. The use of triflic acid gives particularly clean reaction, resulting in a mixture of regioisomers in an approximately 10:1 ratio. A tethered version of this reaction is also reported, giving a tricyclic compound with the same stereochemistry as the core of the cladiellin diterpenes.

The Prins reaction of cyclic acetal derivatives permits an extremely versatile entry into highly functionalised tetrahydropyrans,[1] and has been widely used in total synthesis.[2] Since the initial product of the Prins cyclisation is a carbenium ion, there are a number of possibilities for rearrangement reactions. Notable amongst these is the Prins-pinacol sequence pioneered by the group of Overman.[3] Application of the Prins reaction to distinguish between diastereotopic double bonds in chiral substrates has received limited attention.[4] Due to the considerable potential of cyclohexa-1,4-diene desymmetrisation reactions,[5,6] we have initiated a programme of research in this area,[7] and have recently reported that the Prins-pinacol rearrangement of compounds **1** give the benzo[*c*]furan carboxaldehyde derivatives **2** in modest yields (Scheme 1).[8]

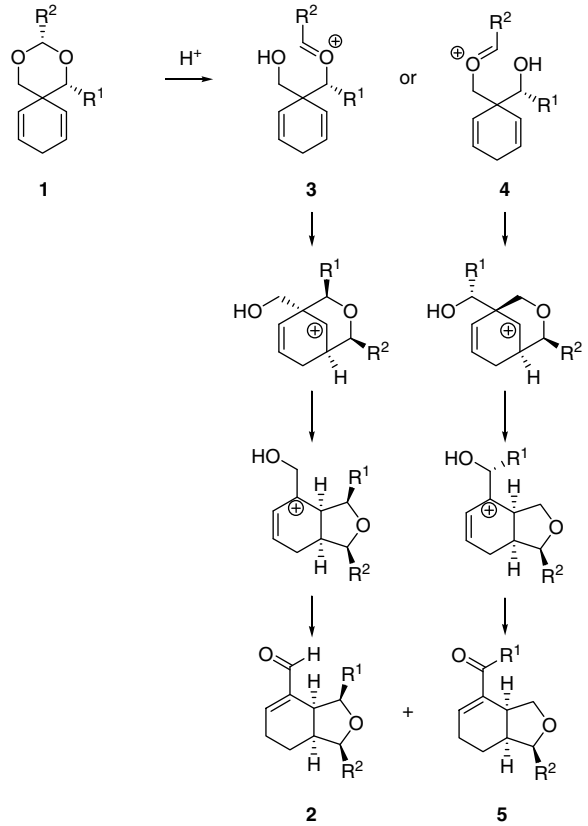
The low yields of the aldehyde products are mainly due to the formation of a number of chlorinated by-products. We therefore sought alternative conditions for this transformation, focusing on the use of strong acid catalysts with non-nucleophilic counter-ions.

The use of both triflic acid and boron trifluoride etherate was found to be effective, with the former generally giving higher yields (1.1–5 equiv). Both gave extremely clean reactions.

Whilst the use of titanium tetrachloride permitted regiospecific acetal opening, triflic acid gave small amounts of ketone products **5** formed from oxocarbenium ion **4** (Scheme 2). In this instance, the chirality present in the starting material is lost upon formation of the ketone product **5**. Since racemic substrates were used in the present study, it is not possible to determine whether any diastereoselection occurs during the cyclisation of oxocarbenium ion **4**.



Scheme 1.



Scheme 2.

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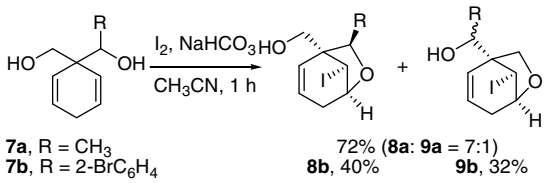


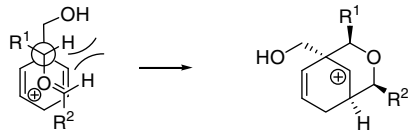
Scheme 3.

The iodocyclisation of compounds **7** gives single (unassigned) stereoisomers of compounds **9** (Scheme 3),[9] so we would certainly not rule out this possibility. Where R^1 = Me, only the cis isomers **2** of the aldehydes were obtained (Table 1). The reaction is reasonably tolerant of steric bulk, although the acetal derived from pivalaldehyde (entry 4) gave slow conversion and low isolated yields of products.

In examples where R^1 = Ph, epimerisation to the *trans* aldehyde **6** occurs if longer reaction times are used, although this is essentially suppressed by using an excess of acid and a short reaction time (Table 2). The example in entry 6 is particularly noteworthy since this compound was not formed when $TiCl_4$ was used.[8] The product stereochemistries were determined by NOESY NMR methods, and by comparison with our previous work.

The stereochemistry of the formation of compounds **2** is determined by the minimisation of $A^{1,3}$ strain in the transition state (Scheme 4).[8]

We therefore reasoned that if the R^1 and R^2 groups were tethered, as in structure **10**, the stereochemical outcome of the reaction

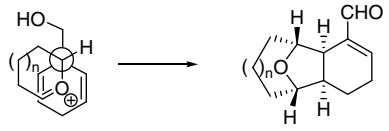


Scheme 4.

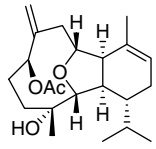
should be reversed, giving **11** (Scheme 5). Significantly, this is the stereochemistry observed in the cladiellin diterpenes such as 7-deacetoxyalcyonin acetate **12**.[10]

The substrate for such a reaction, **13**, was prepared as shown in Scheme 6. Gratifyingly, when this compound was treated with triflic acid in dichloromethane, deprotection of the silyl ether groups occurred followed by formation and Prins-pinacol rearrangement of the oxocarbenium ion, giving compound **14**. The mass balance for this deprotection–cyclisation-rearrangement sequence is low, such that the crude reaction mixture consists almost entirely of the desired product as a single diastereoisomer. Attempts to improve the efficiency of the overall process by initial deprotection of compound **13** gave only complex mixtures of products.

Determination of the stereochemistry of compound **14** was not straightforward, with no diagnostic cross-peaks being observed in



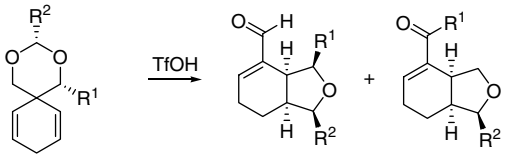
10 **11**



12, 7-deacetoxyalcyonin acetate

Scheme 5.

Table 1
Prins rearrangement of compounds **1** (R′ methyl)

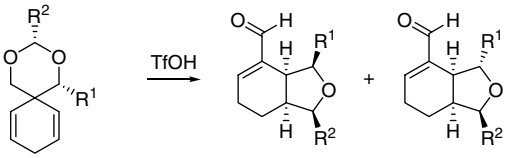


1 **2** **5**

Entry	R^1	R^2	Equiv TfOH	Time	Yield **2** (%)	Yield **5** (%)
1	Me	Me	1.6	15 min	66	6
2	Me	*n*-Bu	1.1	90 min	60	7.5
3	Me	*i*-Bu	1.1	90 min	53	7
4[a]	Me	*t*-Bu	1.1	4 h	11	5
5	Me	Ph	1.1	90 min	48	Trace

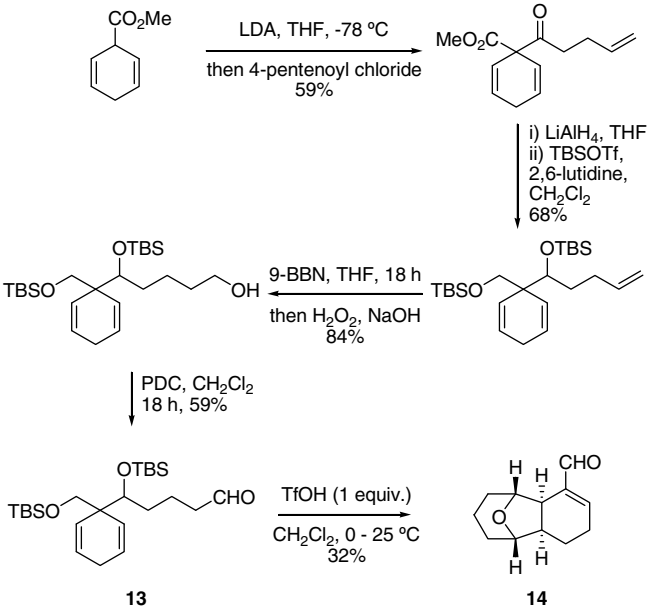
[a] 25% starting material was recovered.

Table 2
Prins rearrangement of compounds **1** (R′ phenyl)



1 **2** **6**

Entry	R^1	R^2	Equiv TfOH	Time	Yield **2** (%)	Yield **6** (%)
1	Ph	Me	5	15 min	64	0
2	Ph	Me	1.1	1 h	50	8
3	Ph	Me	1.5	1.5 h	0	61
4	Ph	*n*-Bu	1.1	1 h	51	4
5	Ph	*i*-Bu	5	15 min	58	0
6	Ph	Ph	5	15 min	61	0



Scheme 6.

the NOESY NMR spectrum. Based on molecular modelling of the two possible diastereoisomers, the observed NMR coupling constants are far more compatible with the diastereoisomer shown. This evidence, coupled with the mechanistic reasoning shown above, leads us to propose the stereochemistry as shown.

In summary, the Prins-pinacol reaction of cyclohexa-1,4-diene-derived acetals is improved significantly by the use of triflic acid. A tethered version of this reaction has been developed which gives the correct stereochemistry for the cladiellin diterpenes. Further studies on this class of compound are underway, and will be reported in due course.

Compound **14**: Trifluoromethanesulfonic acid (0.02 ml, 0.178 mmol) was added dropwise to a solution of aldehyde **13** (78 mg, 0.178 mmol) in CH_2Cl_2 (2 ml) at 0 °C. The resulting brown solution was warmed to room temperature and stirred for 20 min before being quenched with saturated aqueous sodium hydrogen carbonate solution. The crude product was extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 before the solvent was removed in vacuo. Chromatography on silica gel (1:6 EtOAc/petroleum ether) afforded compound **14** (11 mg, 32%) as a colourless oil (Found: M^+, 192.1141. $C_{12}H_{16}O_2$ requires M, 192.1150); ν_{max} (neat) 2933, 2850, 1682, 1643, 1464, 1430, 1177, 1010, 872, 739 and 668 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 9.37 (1H, s, aldehyde), 6.97 (1H, dd, *J* 5.1, 4.1, alkene CH), 3.96 (1H, app. s, CH–O), 3.89 (1H, app. br s, CH–O), 2.95 (1H, d, *J* 8.6, ring junction CH), 2.41 (1H, app. dt, *J* 8.6, 5.5, ring junction CH), 2.33–2.24 (1H, m, one of CH_2 next to double bond), 2.21–2.11 (1H, m, one of CH_2 next to double bond) and 1.72–1.53 (7H, m) and 1.44–1.38 (1H, m); δ_C (100 MHz; $CDCl_3$) 194.5 (CH), 153.3 (CH), 143.8 (C), 82.5 (CH), 82.3 (CH), 39.4 (CH), 38.9 (CH), 30.7 (CH_2), 30.6 (CH_2), 26.5 (CH_2), 23.0 (CH_2) and 16.5 (CH_2); *m/z* (TOF EI^+) 192 (M, 76%), 145 (44) and 91 (100).

Acknowledgements

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References and notes

1. (a) Snider, B. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: New York, 1991; Vol. 2, pp 527–561; (b) Jiménez-Núñez, E.; Claverie, C. K.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5452–5455; (c) Barry, C. S.; Bushby, N.; Harding, J. R.; Hughes, J. R.; Parker, G. D.; Roe, R.; Willis, C. L. *Chem. Commun.* **2005**, 3727–3729; (d) Jasti, R.; Vitale, J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2004**, *126*, 9904–9905; (e) Barry, C. St. J.; Crosby, S. R.; Harding, J. R.; Hughes, R. A.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2003**, *5*, 2429–2432; (f) Patterson, B.; Marumoto, S.; Rychnovsky, S. D. *Org. Lett.* **2003**, *5*, 3163–3166; (g) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679–4686.
2. (a) Tian, X.; Jaber, J. J.; Rychnovsky, S. D. *J. Org. Chem.* **2006**, *71*, 3176–3183; (b) Barry, C. S.; Elsworth, J. D.; Seden, P. T.; Bushby, N.; Harding, J. R.; Alder, R. W.; Willis, C. L. *Org. Lett.* **2006**, *8*, 3319–3322; (c) Bahnk, K. D.; Rychnovsky, S. D. *Chem. Commun.* **2006**, 2388–2390; (d) Lee, C.-H. A.; Loh, T.-P. *Tetrahedron Lett.* **2006**, *47*, 1641–1644; (e) Barry, C. S.; Bushby, N.; Charmant, J. P. H.; Elsworth, J. D.; Harding, J. R.; Willis, C. L. *Chem. Commun.* **2005**, 5097–5099; (f) Aubele, D. L.; Wan, S.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2005**, *44*, 3485–3488; (g) Chan, K.-P.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 4491–4494; (h) Vitale, J. P.; Wolckenhauer, S. A.; Do, N. M.; Rychnovsky, S. D. *Org. Lett.* **2005**, *7*, 3255–3258; (i) Barry, C. S.; Bushby, N.; Harding, J. R.; Willis, C. L. *Org. Lett.* **2005**, *7*, 2683–2686; (j) Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420–8421; (k) Rychnovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217–1219.
3. (a) Overman, L. E.; Velthuisen, E. J. *J. Org. Chem.* **2006**, *71*, 1581–1587; (b) Overman, L. E.; Velthuisen, E. J. *Org. Lett.* **2004**, *6*, 3853–3856; (c) Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143–7157; (d) Hanaki, N.; Link, J. T.; MacMillan, D. W. C.; Overman, L. E.; Trankle, W. G.; Wurster, J. A. *Org. Lett.* **2000**, *2*, 223–226; (e) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352–359; (f) Hopkins, M. H.; Overman, L. E.; Rishton, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 5354–5365.
4. For the use of a Prins reaction to desymmetrise a 1,8-diene see: Rychnovsky, S. D.; Yang, G.; Hu, Y.; Khire, U. R. *J. Org. Chem.* **1997**, *62*, 3022–3023.
5. Studer, A.; Schleth, F. *Synlett* **2005**, 3033–3041.
6. Villar, F.; Kolly-Kovac, T.; Equey, O.; Renaud, P. *Chem. Eur. J.* **2003**, *9*, 1566–1577; Villar, F.; Equey, O.; Renaud, P. *Org. Lett.* **2000**, *2*, 1061–1064; Curran, D. P.; Qi, H. Y.; De Mello, N. C. *J. Am. Chem. Soc.* **1994**, *116*, 8430–8431; Curran, D. P.; Geib, S. J.; Lin, C.-H. *Tetrahedron: Asymmetry* **1994**, *5*, 199–202; Lebeuf, R.; Robert, F.; Schenk, K.; Landais, Y. *Org. Lett.* **2006**, *8*, 4755–4758; Studer, A.; Schleth, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 313–315; Schleth, F.; Vogler, T.; Harms, K.; Studer, A. *Chem. Eur. J.* **2004**, *10*, 4171–4185; Wipf, P.; Rector, S. R.; Takahashi, H. *J. Am. Chem. Soc.* **2002**, *124*, 14848–14849; Nguyen, T. M.; Seifert, R. J.; Mowrey, D. R.; Lee, D. *Org. Lett.* **2002**, *4*, 3959–3962; Bland, D.; Hart, D. J.; Lacoutiere, S. *Tetrahedron* **1997**, *53*, 8871–8880; Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106–11112; Fujioka, H.; Kitagaki, S.; Ono, N.; Kitagawa, H.; Kita, Y.; Matsumoto, K. *Tetrahedron: Asymmetry* **1994**, *5*, 333–336; Wipf, P.; Kim, Y. *Tetrahedron Lett.* **1992**, *33*, 5477–5480; Martin, S. F.; Campbell, C. L. *J. Org. Chem.* **1988**, *53*, 3184–3190; Martin, S. F.; Davidsen, S. K.; Puckette, T. A. *J. Org. Chem.* **1987**, *52*, 1962–1972; Grainger, R. S.; Tisselli, T.; Steed, J. W. *Org. Biomol. Chem.* **2004**, *2*, 151–153; Carreño, M. C.; González, M. P.; Houk, K. N. *J. Org. Chem.* **1997**, *62*, 9128–9137.
7. Elliott, M. C.; El Sayed, N. N. E. *Tetrahedron Lett.* **2005**, *46*, 2957–2959; Elliott, M. C.; El Sayed, N. N. E.; Ooi, L.-l. *Tetrahedron Lett.* **2007**, *48*, 4561–4564.
8. Elliott, M. C.; El Sayed, N. N. E.; Paine, J. S. *Eur. J. Org. Chem.* **2007**, 792–803.
9. Butters, M.; Elliott, M. C.; Hill-Cousins, J.; Paine, J. S.; Walker, J. K. E. *Org. Lett.* **2007**, *9*, 3635–3638.
10. Overman, L. E.; Pennington, L. D. *Org. Lett.* **2000**, *2*, 2683–2686; MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391–10392; MacMillan, D. W. C.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2001**, *123*, 9033–9044; Molander, G. A.; Jeffrey, S. C. *Tetrahedron Lett.* **2002**, *43*, 359–362; Kim, H.; Lee, H.; Kim, J.; Kim, S.; Kim, D. *J. Am. Chem. Soc.* **2006**, *128*, 15851–15855.