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Furanyl spiroketals as stereochemical relays in the synthesis of 1,9-*anti* diols: synthesis of insect pheromones

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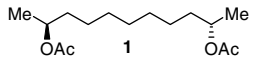
Abstract—A suite of spiroketal insect pheromones (**15** and **17a**–**d**) has been synthesised in good yield and with very high levels of diastereoselectivity via furanyl spiroketals. Remote asymmetric induction is achieved under thermodynamic control. The use of furanyl spiroketals as temporary scaffolds in the synthesis of 1,9-*anti* diols has been demonstrated with the synthesis of the swede midge pheromone (2*S*,10*S*)-2,10-diacetoxyundecane **1**. The enzymatic resolution of a C_2 symmetric 1,9-*anti* diol was used as a confirmation of diastereomeric purity.

Many natural products of biological and pharmacological importance contain two or more stereogenic centres. When the two stereogenic centres are close to each other it is often possible to use one existing stereogenic centre to control the stereoselective synthesis of the other, that is, asymmetric induction. Many examples of 1,2 and 1,3 asymmetric induction exist where the observed stereoselectivity is very high.[1] However, numerous examples of very remote asymmetry can be seen in Nature, a recently reported example being the swede midge pheromone (2*S*,10*S*)-2,10-diacetoxyundecane **1**.[2]

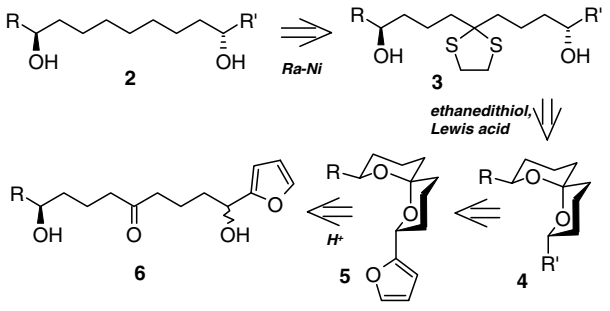


swede midge pheromone

In such cases it becomes thermodynamically more difficult to form a conformationally well-defined intermediate or transition state by which the existing stereogenic centre can exert any stereochemical influence. As such, examples of 1,*n* asymmetric induction where *n* is much greater than three are relatively scarce and the vast majority of syntheses of molecules with such remote asymmetry generate each stereocentre independently. Those examples which do employ asymmetric induction generally involve a stereochemical relay of some kind, where successive asymmetric inductions are combined.[3]

As part of our ongoing research in the area of remote asymmetry we turned our attention to the diastereoselective synthesis of 1,9-*anti* diols and their derivatives. Our approach is outlined retrosynthetically in Scheme 1.

We envisaged that the 1,9-*anti* diol **2** could arise from Raney-nickel desulfuration of thiolane **3**. This in turn could be formed from the Lewis acid mediated transketalisation of the 6,6-spiroketal **4** with ethanedithiol. This spiroketal could arise from functional group manipulation of furanyl spiroketal **5**. As we have previously reported, such spiroketals can be formed diastereoselectively from the acid catalysed spiroketalisation of 5-keto-1,9-diols **6** containing one stereorandom furanyl



Scheme 1. Conceptual outline.

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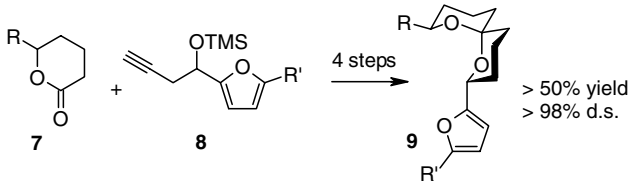
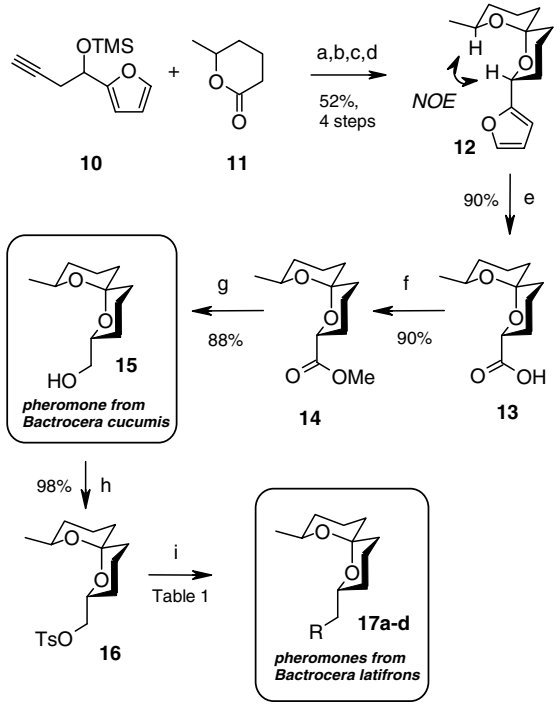
alcohol centre, which can epimerise under the acidic reaction conditions to afford a single thermodynamically favoured 6,6-spiroketal diastereomer with two anomeric effects and two equatorial substituents.[4,5] Thus, the spiroketal acts as a transient, conformationally well-defined scaffold in a stereochemical relay whereby a single configured stereogenic centre (in **7**) controls the configuration of the remote stereogenic centre. These spiroketalisation precursors can be accessed in short order from the coupling of chiral δ-lactones **7** with propargylfuranyl alcohols **8** (Scheme 2).

Spiroketals are an important class of natural product in their own right with many examples exhibiting profound levels of biological activity.[6] They have emerged as an important and abundant class of insect pheromone, particularly within fruit flies,[6c] and we sought to exploit our methodology in a diastereoselective synthesis of the Australasian fruit fly pheromones **15** and **17a–d** (Scheme 3).



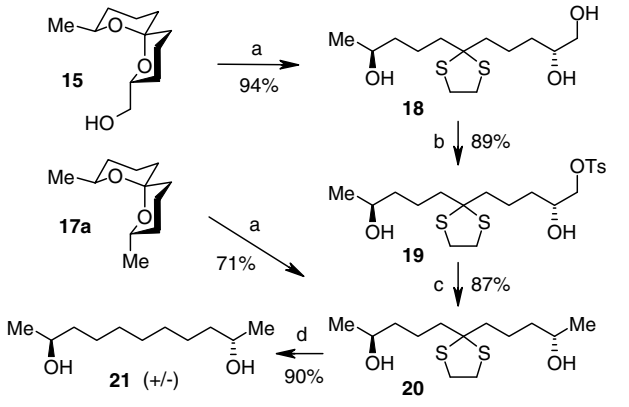
Scheme 2. Diastereoselective spiroketalisation.



Scheme 3. Reagents and conditions: (a) *n*BuLi, THF, −78 °C, lactone **11** −78 to 0 °C; (b) H_2, Pd–C, EtOAc, rt; (c) TBAF, DCM, rt; (d) $TsOH{\cdot}H_2O$, DCM, rt.; (e) $RuCl_3$, $NaIO_4$, H_2O–MeCN–DCM; (f) MeI, K_2CO_3, DMF, 70 °C; (g) $NaBH_4$, *t*BuOH, MeOH, reflux; (h) TsCl, Et_3N, DCM, rt.; (i) see Table 1.

The protected propargylfuranyl alcohol **10** was treated with *n*-butyllithium at −78 °C, followed by the addition of lactone **11** and warming to 0 °C for 1 h. After aqueous workup, the crude material was hydrogenated under an atmosphere of hydrogen in the presence of 5% palladium on carbon. The crude hydrogenation product was desilylated with tetrabutylammonium fluoride and, following aqueous work up, the crude product was exposed to a catalytic amount of toluenesulfonic acid in dichloromethane to effect spiroketalisation and equilibration of the furanyl ether stereocentre into the thermodynamically favoured equatorial position, affording spiroketal **12** as a single diastereomer. Full characterisation at this stage confirmed the structure shown. The spectra for previous intermediates in this sequence were ill-defined, possibly due to equilibration between hydroxyketone and hemiacetal forms. The relative stereochemistry in **12** was established by the observation of an NOE between the axial protons shown in Scheme 3. With the desired furanyl spiroketal in hand, the stage was set for a further elaboration to access the natural products **15** and **17a–d**. The furan group in **12**, whose electron donating nature had contributed pivotally to the equilibration of the adjacent stereogenic centre in the stereochemical relay, now revealed its synthetic utility. Oxidative cleavage to carboxylic acid **13** was carried out efficiently and in high yield with a catalytic amount of ruthenium trichloride using sodium periodate as the stoichiometrical reoxidant in a Sharpless' solvent system of water–dichloromethane–acetonitrile[7] (Scheme 4).

Attempts at reducing carboxylic acid directly to alcohol using lithium aluminium hydride proved unsuccessful. Instead, the carboxylic acid **13** was converted in good yield to methyl ester **14** using methyl iodide and potassium carbonate in DMF. This step could also be achieved using a catalytic toluenesulfonic acid in methanol. Methyl ester **14** was smoothly reduced to the pheromone from *Bactrocera cucumis* **15** using sodium borohydride in a mixture of methanol and *tert*-butanol. The spectroscopic data for this compound were identical with those previously reported for this compound.[8]



Scheme 4. Reagents and conditions: (a) ethanedithiol, $BF_3{\cdot}Et_2O$, DCM, rt; (b) TsCl, Et_3N, DCM, 0 °C; (c) $NaBH_4$, DMSO, 80 °C; (d) Raney-nickel, EtOH, reflux.

Table 1. Conditions for the conversion of **16** to **17a–d**

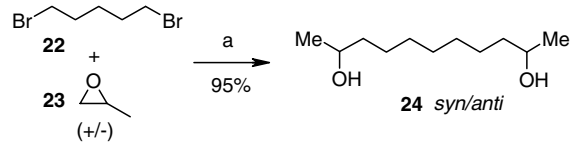
Entry	Conditions	Product (R)	Yield (%)
1	$LiAlH_4$, THF, rt	**17a** (H)	56
2	MeMgBr, CuI, THF, rt	**17b** (Me)	52
3	EtMgBr, CuI, THF, rt	**17c** (Et)	51
4	PrMgBr, CuI, THF, rt	**17d** (Pr)	50

With this natural product made, attention was then turned to elaboration to the other members of the family.

Alcohol **15** was cleanly converted to tosylate **16** in a very high yield using toluenesulfonyl chloride and triethylamine in dichloromethane. Dimethyl spiroketal pheromone **17a** was obtained by treating **16** with lithium aluminium hydride in THF at room temperature. It should be noted that care has to be taken in the isolation of **17a** due to its volatile nature. The pheromones from *Bactrocera latifrons* **17b–d** were synthesised by displacing the tosylate in **16** with the corresponding Grignard reagent in the presence of copper(I) iodide in THF. Again, the spectroscopic data for **17b–d** were in agreement with those previously reported for these compounds[9] (see Table 1).

Having demonstrated the synthetic utility of the methodology towards spiroketal targets we continued with our proposed 1,9-*anti* diol synthesis. Hydroxyspiroketal **15** was treated with an excess of ethanedithiol and boronitrifluoride etherate in dichloromethane at room temperature to afford triol **18** in high yield.[10] Triol **18** was selectively converted to the corresponding mono-tosylate **19** by reaction with toluenesulfonyl chloride and triethylamine at 0 °C. At higher temperatures, significant amounts of bis-tosylated products were obtained. Initial attempts at reductive desulfonylation using lithium aluminium hydride only led to a low yield of product. Pleasingly, when we switched to sodium borohydride in DMSO at 80 °C the C_2 symmetrical diol **20** was afforded in high yield. Diol **20** could also be obtained in good yield by transketalisation of dimethyl spiroketal **17a**. For practical purposes, however, synthesis from **19** was more convenient due to the high volatility of **17a**.

The reductive desulfuration of **20** was achieved with the use of Raney-nickel in refluxing ethanol to afford 1,9-*anti* diol **21** as a single diastereomer in racemic form. The spectroscopic data for **21** matched those previously reported for this compound.[2] As the two stereogenic centres are so remote, however, we recognised the possibility of both *syn* and *anti* diols giving rise to very similar or identical spectroscopic data. As the compound was a racemate, we could not compare the optical rotation with that previously reported for the homochiral compound. Although there appears to be no reasonable mechanism by which either stereogenic centre could have epimerised under the conditions used to manipulate hydroxyspiroketal **15**, we sought to establish further confirmation of the diastereomeric purity. We initially hoped that we could compare the spectroscopic data for **21** with that of the 1:1 reference mixture of *syn*:*anti* diols **24**, which we prepared from the Grignard addition of 1,5-dibromopentane **22** to racemic propene oxide **23** (Scheme 5).[2]



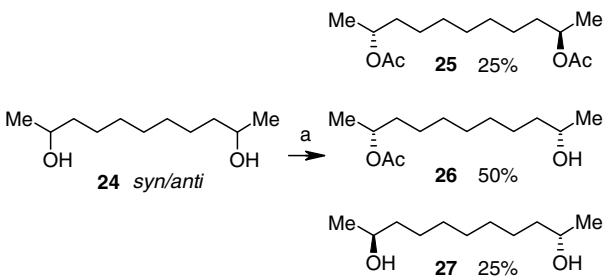
Scheme 5. Reagents and conditions: (a) (i) Mg, THF, reflux; (ii) **23**, CuI, THF, −78 °C to rt.

Unfortunately, however, the *syn*:*anti* mixture **24** appeared as a single compound by all spectroscopic means available, including ^{13}C NMR at 600 MHz. It seems that the two stereogenic centres are simply too far away from each other to have any interaction, as we had anticipated. Although others have managed to distinguish these diastereomers by chromatographic/spectroscopic means, the associated techniques used were unavailable to us.[2,11] We decided to exploit the inherent symmetry of the diol by adopting an enzymatic resolution approach to determine the diastereomeric purity. It has been shown that *Candida antarctica lipase* B (CALB, Novozym 435®) is an extremely selective catalyst for the acylation of (*R*) configured methylalkylcarbinols.[12] Upon treatment with the resin-bound enzyme and a tenfold excess of vinyl acetate in toluene, the reference mixture of *syn*:*anti* diols **24** was converted to a mixture of three compounds at 50% total acylation: 25% diacetyl compound **25** resulting from acylation of the (*R*,*R*) diol, 50% of the monoacetyl compound **26** resulting from acylation of the *meso* (*R*,*S*) diol and 25% of the unreacted (*S*,*S*) diol **27** (Scheme 6).

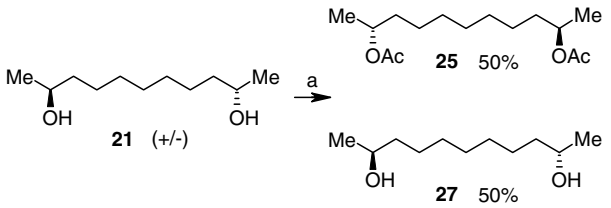
Pleasingly, the reaction seemed to completely halt after 50% total acylation (as monitored by periodic ^1H NMR of small aliquots), indicating that the enzyme system was very selective in this case. Using a greater excess of vinyl acetate made no difference.

Having carried out the control reaction on the *syn*/*anti* reference mixture, we then exposed the racemic *anti* diol **21** to the same conditions. In this case, after 50% total acylation, only two products were observed: 50% of **25** and 50% of **27** (Scheme 7).

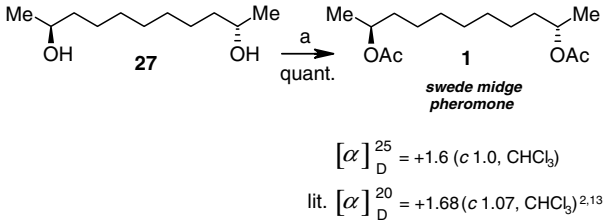
Gratifyingly, no singly-acylated product (which would arise from the presence of the *meso*/*syn* diol) was



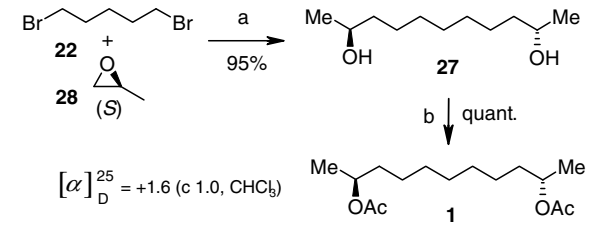
Scheme 6. Reagents and conditions: (a) polyacrylamide-bound Novozyme 435®, 10 equiv vinyl acetate, toluene, rt, 18 h.



Scheme 7. Reagents and conditions: (a) polyacrylamide-bound Novozym 435®, 10 equiv vinyl acetate, toluene, rt, 18 h.



Scheme 8. Reagents and conditions: (a) 3 equiv Ac_2O, 5 equiv DMAP, DCM, rt.



Scheme 9. Reagents and conditions: (a) (i) Mg, THF, reflux; (ii) **28**, CuI, THF, −78 °C to rt; (b) 3 equiv Ac_2O, 5 equiv DMAP, DCM, rt.

observed, indicating very high levels of diastereomeric purity in the starting diol **21**. To complete the synthesis of the swede midge pheromone **1**, we treated the resolved (*S*,*S*) diol **27** with excess acetic anhydride and DMAP in DCM at room temperature to afford diacetate **1** in quantitative yield (Scheme 8).

The optical rotation for **1** was close to that previously reported for this compound.[2,13] We carried out a synthesis of the same molecule using the procedure reported in the isolation paper from 1,5-dibromopropane and (*S*)-propene oxide **28**.[2] The resulting diol was acylated to afford a diacetate, which had exactly the same optical rotation as **1** reported herein confirming that we had indeed synthesised the (*S*,*S*) stereoisomer (Scheme 9).

In conclusion, we have developed a highly diastereoselective synthesis of (*E*,*E*)-6,6-spiroketals. This was applied to the synthesis of several spiroketal-containing insect pheromones. We have demonstrated that these spiroketals can serve as temporary scaffolds in a stereochemical relay synthesis of 1,9-*anti* diols, in particular the swede midge pheromone (2*S*,10*S*)-2,10-diacetoxyundecane **1**. Work is underway to investigate the scope of this methodology and apply it to further natural product syntheses.

Acknowledgements

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References and notes

1. For a recent review see: Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191–1223.
2. Hillbur, Y.; Celander, M.; Baur, R.; Rauscher, S.; Haftmann, J.; Franke, S.; Francke, W. *J. Chem. Ecol.* **2005**, *31*, 1807–1828.
3. For reviews see: (a) Thomas, E. J. *Chem. Rec.* **2007**, *7*, 115–124; (b) Booth, M.; Brain, C.; Castreno, P.; Donnelly, S.; Dorling, E. K.; Germay, O.; Hobson, L.; Kumar, N.; Martin, N.; Moore, C.; Negi, D.; Thomas, E. J.; Weston, A. *Pure App. Chem.* **2006**, *78*, 2015–2028; (c) Mikami, K.; Shimizu, M.; Zhang, H.-C.; Maryanoff, B. E. *Tetrahedron* **2001**, *57*, 2917–2951.
4. Cahill, S.; O'Brien, M. *Tetrahedron Lett.* **2006**, *47*, 3665–3668.
5. Deslongchamps, P.; Pothier, N.; Goldstein, S. *Helv. Chim. Acta* **1992**, *75*, 604–620.
6. For reviews see: (a) Mead, K. T.; Brewer, B. N. *Curr. Org. Chem.* **2003**, *7*, 227–256; (b) Perron, P.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617–1661; (c) Fletcher, M. T.; Kitching, W. *Chem. Rev.* **1995**, *95*, 789–828; (d) Francke, W.; Kitching, W. *Curr. Org. Chem.* **2001**, *5*, 233–251.
7. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938.
8. (a) Perkins, M. V.; Jacobs, M. F.; Kitching, W.; Cassidy, P. J.; Lewis, J. A.; Drew, R. A. I. *J. Org. Chem.* **1992**, *57*, 3365–3380; (b) Mori, K.; Watanabe, H. *Tetrahedron* **1986**, *42*, 295.
9. (a) Perkins, M. V.; Kitching, W.; König, W. A.; Drew, R. A. I. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2501–2506; (b) Cohen, H.; Tong, S. *Tetrahedron* **1997**, *53*, 9487–9496; (c) Solladié, G.; Huser, N. *Tetrahedron: Asymmetry* **1994**, *5*, 255; (d) Brown, H. C.; Kulkarni, S. V.; Racherla, U. S.; Dhokte, U. P. *J. Org. Chem.* **1998**, *63*, 7030–7036; (e) Kitayama, T. *Tetrahedron* **1996**, *52*, 6139–6148; (f) Kitching, W.; O'Shea, M. G. *Tetrahedron Lett.* **1989**, *45*, 1177–1186.
10. (a) Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1983**, *48*, 1303–1312; (b) Schreiber, S. L.; Wang, Z. Y. *J. Am. Chem. Soc.* **1985**, *107*, 5303.
11. For an interesting use of circular dichroism to determine the diastereochemistry of a very similar compound see: MacMillan, J. B.; Linington, R. G.; Andersen, R. J.; Molinski, T. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 5946–5951.
12. (a) Orrenius, C.; Öhrner, N.; Rotticci, D.; Mattson, A.; Hult, K.; Norin, T. *Tetrahedron: Asymmetry* **1995**, *6*, 1217–1220; (b) Ohtani, T.; Nakatsukasa, H.; Kamezawa, M.; Tachibana, H.; Naoshima, Y. *J. Mol. Catal. B* **1998**, *4*, 53–60.
13. The value of −1.68 previously reported in Ref. 2 was a misprint. The actual recorded value was +1.68. Personal communication, W. Francke.