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Furanyl spiroketals: thermodynamic control of remote asymmetry

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Abstract—(*E*,*E*)-2-Alkyl-8-furanyl-1,7-dioxa-spiro[5.5]undecanes (**1a**–**i**) have been prepared in good yield and with very high diastereoselectivity from lactones (**2a**–**e**) and alkynes (**3a**,**b**) using lithium acetylide coupling, hydrogenation, desilylation and acid catalysed cyclisation/equilibration.

Molecules containing the spiroketal moiety are abundant as natural products, many of which have important biological properties.[1] Due to the stereoelectronic requirements of these molecules, they often have strong conformational preferences.[2] This property has been cleverly exploited in synthesis with diastereoselective formation of spiroketals being achieved under both kinetic and thermodynamic control.[1] Biologically important natural products such as the potent vasoconstrictive algal toxins zooxanthellatoxin A and B[3] and the pheromones of several species of insect,[1c] as well as the synthetic tubulin-depolymerising SPIKET-P,[4] (a reported pharmacophore for spongistatin I) contain (*E*,*E*)-2,8-dialkyl-1,7-dioxa-spiro[5.5]undecanes (Fig. 1). A frequently employed route to this type of spiroketal involves the acid catalysed cyclisation of a 5-keto-1,9-diol. In this approach, the two secondary alcohol chiral centres are required to have the correct *anti*-configuration prior to cyclisation.

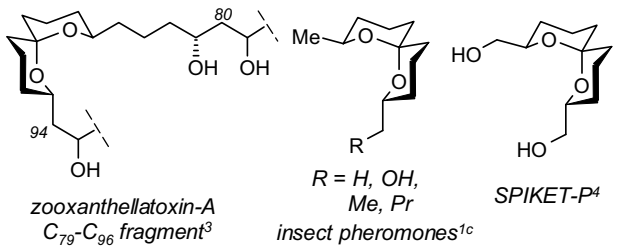

Figure 1. Biologically active molecules containing the (*E*,*E*)-2,8-dialkyl-1,7-dioxa-spiro[5.5]undecane moiety.

Thus, the thermodynamically most stable (*E*,*E*) spiroketal is obtained with two equatorial substituents and a double anomeric effect in operation.

We were interested in the possibility of having a stereorandom secondary alcohol centre, which would epimerise under the conditions of cyclisation. This would allow the other (remote) chiral centre to control the stereochemistry of the spiroketalisation. Thus, a single configured chiral centre would control the formation of the other two chiral centres in the product spiroketal. It has been shown that under acidic conditions, a furanyl ether linkage is unstable with respect to reversible elimination of the alkoxy group to give an intermediate oxonium ion.[5] Bearing in mind the synthetic utility of the furan moiety, we chose to exploit this effect and set out to synthesise 2-alkyl-8-furanyl-1,7-dioxa-spiro-[5.5]-undecanes **1a**–**i** as laid out retrosynthetically in Scheme 1.

The synthesis of the 5-keto-1,9-diol precursor follows a well established sequence[6] and is based on coupling the lithium acetylide of alkynes **3a**,**b** with lactones **2a**–**e** followed by hydrogenation of the triple bond, desilylation and acid catalysed spiroketalisation (Scheme 1).

It is during the spiroketalisation step that remote asymmetric induction takes place, utilising the electron rich nature of the furan ring. The alkyl group R should adopt the sterically favoured equatorial position whilst the spiroketal should favour a conformation where two anomeric effects are operative.[2] Under the acidic, equilibrating conditions the furanyl group should also

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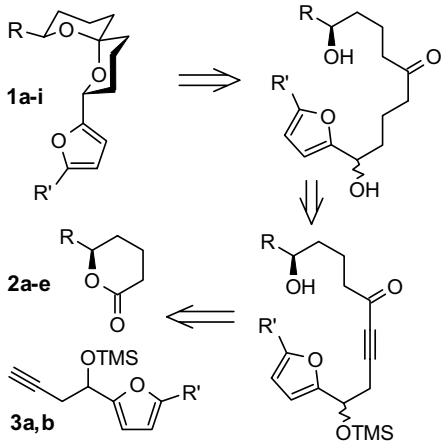
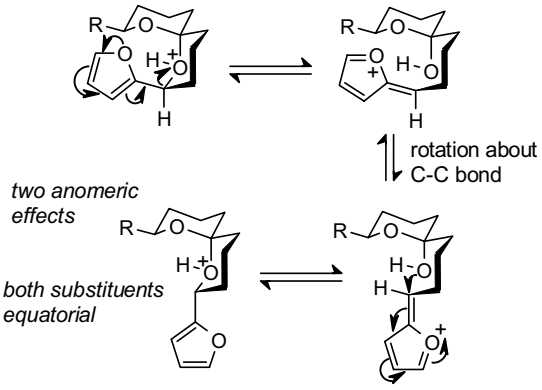


Scheme 1. Retrosynthesis of furanyl spiroketals.



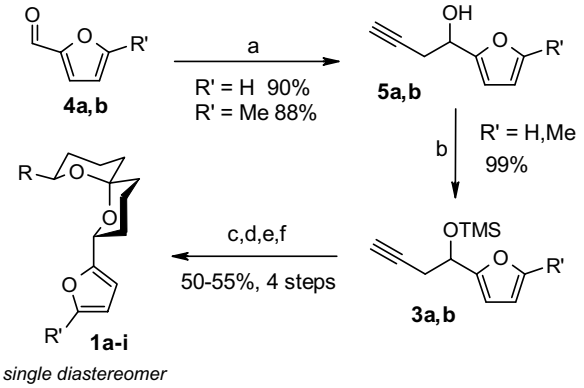
Scheme 2. Proposed mechanism of thermodynamic equilibration.

move into the equatorial position according to the reversible elimination–addition mechanism outlined in Scheme 2.

Thus, the original chiral centre in lactones **2a**–**e** will be used to induce the diastereoselective formation of two new chiral centres: the acetal centre and the remote furanyl substituted centre.

The lactones used were racemic and commercially available. The alkynes **3a**,**b** were synthesised from the inexpensive furaldehydes as shown in Scheme 3. Furaldehyde **4a** and methylfuraldehyde **4b** were coupled with propargyl bromide in tetrahydrofuran using zinc activated by aqueous ammonium chloride[7] to afford the alcohols **5a**[8] and **5b**, which were purified by distillation in 90% and 88% yields, respectively.

These alcohols were protected as the trimethylsilyl ethers **3a**,**b** in practically quantitative yield using chlorotrimethylsilane and imidazole in dichloromethane at room temperature. The alkynes **3a**,**b** were deprotonated at −78 °C with *n*-butyllithium in tetrahydrofuran. This was followed by addition of the lactones **2a**–**e** and the reaction mixture was warmed to 0 °C for 1 h before aqueous work-up.



Scheme 3. Reagents and conditions: (a) propargyl bromide, Zn, NH_4Cl, THF/H_2O, −10 °C to rt, 2 h; (b) TMSCl, imid., DCM, rt, 10 min; (c) *n*-BuLi, THF, −78 °C, lactone **2a**–**e** −78 to 0 °C; (d) H_2, Pd–C, EtOAc, rt; (e) TBAF, DCM, rt; (f) $TsOH.H_2O$, DCM, rt.

The crude coupled product was then subjected to hydrogenation using palladium on carbon in ethyl acetate, followed by desilylation with tetrabutylammonium fluoride in dichloromethane. Finally, the crude material was exposed to catalytic amounts of toluenesulfonic acid in dichloromethane to afford the spiroketals **1a**–**i**.[9]

Gratifyingly, the spiroketal products were formed as a single diastereomer in all cases (Table 1). The stereochemical assignment was based on the observation of NOE enhancements (shown in Fig. 2) in the ^1H NMR spectra of all the spiroketal products.

We believe that the reaction is under thermodynamic control, as outlined in Scheme 2. An alternative explanation, although unlikely, for the high degree of diastereoselectivity is that the alkyne coupling step is diastereoselective and the spiroketalisation is under

Table 1. Results of spiroketal syntheses

Entry	Lactone (R)	Alkyne (R′)	Product	Yield[a] (%)	dr[b]
1	**2a** (n-C_5H_{11})	**3a** (H)	**1a**	52	>98:2
2	**2b** (n-C_6H_{13})	**3a** (H)	**1b**	52	>98:2
3	**2c** (n-C_7H_{15})	**3a** (H)	**1c**	54	>98:2
4	**2d** (n-C_9H_{19})	**3a** (H)	**1d**	51	>98:2
5	**2e** (Me)	**3b** (Me)	**1e**	55	>98:2
6	**2a** (n-C_5H_{11})	**3b** (Me)	**1f**	52	>98:2
7	**2b** (n-C_6H_{13})	**3b** (Me)	**1g**	55	>98:2
8	**2c** (n-C_7H_{15})	**3b** (Me)	**1h**	53	>98:2
9	**2d** (n-C_9H_{19})	**3b** (Me)	**1i**	51	>98:2

[a] Over four steps, isolated after column chromatography.
[b] Single diastereoisomers within the limits of experimental observation.

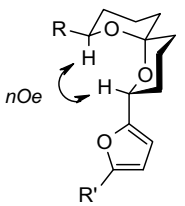


Figure 2. Observed NOE in the ^1H NMR spectra of spiroketals **1a**–**i**.

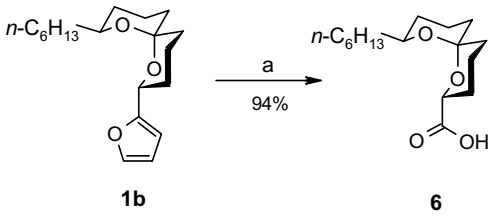
kinetic control. As yet, we have been unable to obtain well resolved spectral data for the coupling products (possibly due to hydroxyketone–hemiacetal equilibration) in order to establish that this step is non-stereoselective. At the end of the reaction sequence, only the diastereomerically pure spiroketals and unreacted lactone starting materials are observed in the NMR spectra of the crude products. Work is under way to synthesise homochiral coupling partners so that both diastereomers of the dihydroxyketones can be subjected (independently) to the spiroketalisation conditions. If our hypothesis is correct then both diastereomers should lead to the same diastereomer of the spiroketal product.

There are many synthetically useful reactions in which furan groups partake. Perhaps the most generally useful transformation is the oxidative cleavage to a carboxylic acid. This is exemplified by the high yielding oxidation of **1b** to the carboxylic acid **6** using ruthenium chloride in a water–acetonitrile–dichloromethane solvent system and sodium periodate as the stoichiometric reoxidant[10] (Scheme 4). From the carboxylic acid **6**, several strategies for chain elongation by carbon–carbon bond formation are possible. As such, the methodology represents a very general synthesis of this class of spiroketal.

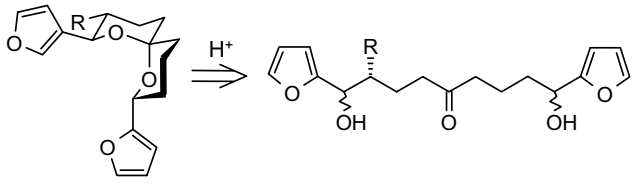
Other useful manipulations of the furan group include lithiation at the 2-position followed by alkylation,[11] Achmatowicz oxidation[12] to the unsaturated 1,4-dicarbonyl moiety (using peroxyacid or *N*-bromosuccinimide for instance) and Diels–Alder chemistry.[13]

We envisage that the underlying concept of the methodology could be applied to other systems, for example, by placing the initial chiral centre at alternative positions on the carbon backbone.

Indeed, from a single correctly configured chiral centre and two stereorandom furanyl alcohols, it should be possible to control the stereochemistry at three new chiral centres (Scheme 5).



Scheme 4. Reagents and conditions: (a) $RuCl_3$ (cat.), $NaIO_4$, MeCN–H_2O–DCM (1:1:1).



Scheme 5. Possible further extension of the methodology.

In conclusion, we have developed a high yielding spiroketal synthesis, which proceeds with very high levels of remote diastereoselectivity. The method is simple, practical, economic and efficient. We believe this methodology will be very useful in the synthesis of the important spiroketal units and we are currently working on the synthesis of several natural products containing this moiety.

Acknowledgement

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.03.135.

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9. Representative experimental procedure for (*E*,*E*)-(2*RS*, 8*RS*)-2-furan-2-yl-8-pentyl-1,7-dioxa-spiro[5.5]undecane

(**1a**): A solution of *n*-butyllithium (2.5 M in hexanes, 1.44 mL, 3.6 mmol) was added dropwise to a solution of the alkyne **3a** (500 mg, 2.4 mmol) in THF (10 mL) at −78 °C under N_2. The mixture was stirred at this temperature for 1 h after which time δ-decalactone **2a** (636 μL, 3.6 mmol) was added in one portion. The mixture was allowed to warm to room temperature and was stirred at this temperature for 1 h. A solution of saturated aqueous ammonium chloride (20 mL) was added. The mixture was extracted with ethyl acetate (2 × 20 mL). The combined organics were washed with brine (20 mL) and dried over magnesium sulfate. The solvent was removed by evaporation under reduced pressure to afford a yellow oil, which was dissolved in ethyl acetate (20 mL). Palladium on carbon (5% Pd, 51 mg, 0.024 mmol) was added. The mixture was stirred and the flask was evacuated under reduced pressure until the solvent was seen to boil. The flask was then filled with hydrogen (balloon). The flask was again evacuated and refilled with hydrogen. The mixture was stirred under hydrogen for 45 min then filtered through Celite. The filter cake was washed with ethyl acetate (2 × 10 mL). The solvent from the combined filtrates was then evaporated under reduced pressure to afford a pale yellow oil, which was dissolved in dichloromethane (10 mL) and a solution of TBAF (1 M, THF, 4.8 mL, 4.8 mmol) was added. The mixture was stirred at room temperature for 30 min. Water (20 mL) was added and the mixture was extracted with ethyl acetate (2 × 20 mL). The combined organics were washed with brine (20 mL) and dried over magnesium sulfate. The solvent was removed under reduced pressure to afford a pale yellow oil, which was dissolved in dichloromethane (25 mL). To this was added *p*-toluenesulfonic acid monohydrate (46 mg, 0.24 mmol) and the mixture was stirred at room temperature for 1 h. Saturated sodium bicarbonate solution (25 mL) was added and the mixture was extracted with diethyl ether (2 × 40 mL). The combined organics were washed with water (40 mL), brine (40 mL) and dried over magnesium sulfate. The solvent was removed under reduced pressure to afford a yellow oil. The crude product was purified by column chromatography on silica gel eluting with a solvent gradient from hexane to 1:1 hexane–ethyl acetate to give a clear colourless oil (365 mg, 52%). R_f 0.63 (hexane–EtOAc 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38 (1H, d, $J = 1.5$ Hz, 5′-H), 6.33 (1H, m, 4′-H), 6.24 (1H, d, $J = 2.9$ Hz, 3′-H), 4.67 (1H, dd, $J = 10.8$ Hz, 2.5 Hz, 2-H), 3.71 (1H, m, 8-H), 1.13–2.10 (20H, m, $10 \times CH_2$), 0.90 (3H, m, 5″-H_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.8 (2′), 141.9 (5′), 110.0 (4′), 106.0 (3′), 96.6 (6), 69.3 (2), 64.8 (8), 36.4 (CH_2), 35.20 (CH_2), 35.15 (CH_2), 32.0 (CH_2), 31.3 (CH_2), 28.8 (CH_2), 25.6 (CH_2), 22.7 (CH_2), 18.9 (CH_2), 18.8 (CH_2), 14.1 (5″). IR (neat): 2932 (s), 2869 (m), 1459 (m), 1439 (m), 1377 (m), 1280 (m), 1256 (w), 1227 (m), 1153 (m), 1100 (m), 1066 (m), 1036 (s), 1010 (s), 977 (s), 915 (s), 896 (m), 884 (m), 868 (m), 805 (m), 733 (m). HRMS (ES^+) found *m/z* 293.2126 [$(M+H)^+$; calcd for $C_{18}H_{29}O_3$: 293.2117].

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