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The synthesis and development of 2,5-disubstituted tetrahydrofurans as potential scaffolds for diversity-oriented synthesis

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ABSTRACT

The synthesis of 2,5-disubstituted tetrahydrofurans from donor silylmethylcyclopropanes (without bearing an acceptor function) is described. Their further elaboration via a wide range of synthetic transformations is presented to highlight the potential of this method and the resulting THFs as potential scaffolds for diversity-oriented synthesis.

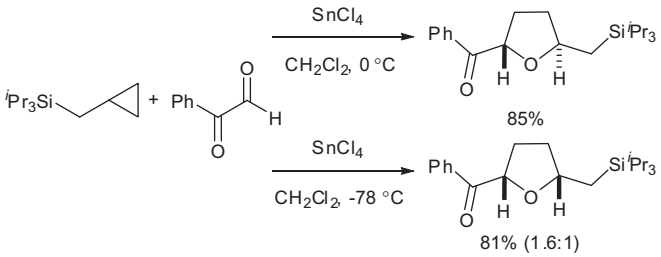
The 2,5-disubstituted tetrahydrofuran (THF) motif is found widely throughout nature, notably appearing in highly topical and active Annonaceous acetogenins and many polyether-containing compounds and antibiotics. Robust routes to access this structural motif, and particularly ones which also incorporate functionality for additional elaboration are currently of great interest. Herein we report one such route, and several subsequent transformations of the resultant 2,5-disubstituted THF, illustrating its potential as a novel scaffold for diversity-orientated synthesis.

We have had a long standing interest in organosilicon chemistry, and particularly utilising the β-effect of silicon to stabilise adjacent carbocations during a reaction.[1–5] As part of this, we reported the reaction of silylmethylcyclopropanes with glyoxals in the presence of a Lewis acid, to give 2,5-disubstituted tetrahydrofurans (Scheme 1).[6] Depending upon the exact nature of the reaction conditions, it was possible to obtain either the *cis* or *trans*-substitution pattern. It was envisaged that the presence of the α-ketone and the silicon moiety would render this a useful scaffold for diversity-oriented synthesis. Therefore, we have investigated the potential of this scaffold for further elaboration and our findings are reported herein.

First we investigated transformations involving the keto functionality; all are novel transformations of this particular scaffold.

(i) Horner–Wadsworth–Emmons reactions

It was envisaged that the α-ketone could be converted into the trisubstituted alkene using a Wittig or related reaction, presenting the opportunity for the introduction of a variety of functional groups and also the means to couple the THF to another molecule. It is generally accepted that ketones are slow to react under standard Wittig reaction conditions, but far more reactive in the Horner–Wadsworth–Emmons reaction, which also has the practical advantage that the phosphorus by-products are relatively water soluble. Deprotonation of triethyl phosphonoacetate with sodium hydride in diethyl ether followed by addition of the *trans*-diastereoisomer of THF **1** gave the alkene in an excellent 96% yield as a 1:1.2 mixture of alkene geometric isomers **2** (Scheme 2). Separation of the isomers was achieved by column chromatography. NOE studies confirmed that no epimerisation of the C-5 proton had occurred and the relative stereochemistry of the THF ring remained *trans* but identification of the different alkene geometries was inconclusive, and thus it was impossible to state whether the *E*/*Z* isomer was the major one.



Scheme 1. Synthesis of 2,5-disubstituted tetrahydrofurans.

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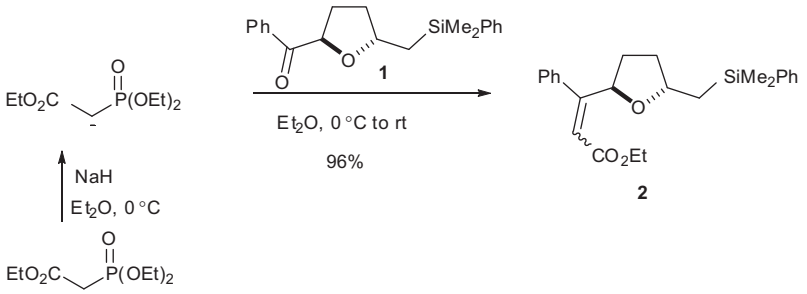
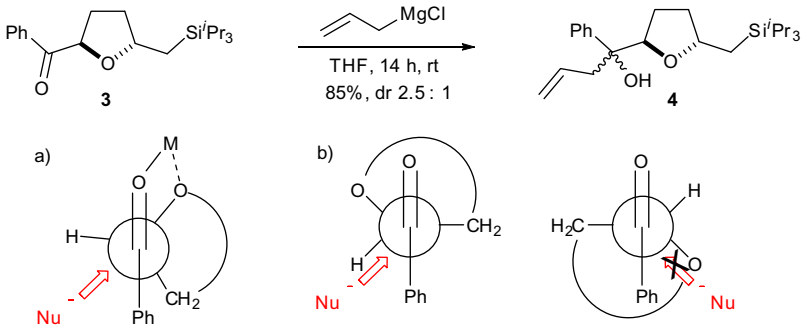


Scheme 2. The Horner–Wadsworth–Emmons reaction employing α-ketotetrahydrofurans.



Scheme 3. Grignard addition to α-ketotetrahydrofurans under possible (a) chelation or (b) Felkin–Anh control.

(ii) Nucleophilic addition

Nucleophilic addition of an organometallic reagent to the ketone was next investigated. Addition of allylmagnesium chloride to the *trans* THF diastereoisomer **3** gave the desired tertiary alcohol **4** in 85% yield (Scheme 3) as a mixture of diastereoisomers (2.5:1). The higher proportion of one diastereoisomer over the other is believed to be the result of chelation control of the addition[7] through the THF oxygen, favouring the *anti* arrangement of the C-5 proton and hydroxy group in the product.

(iii) Enolate formation

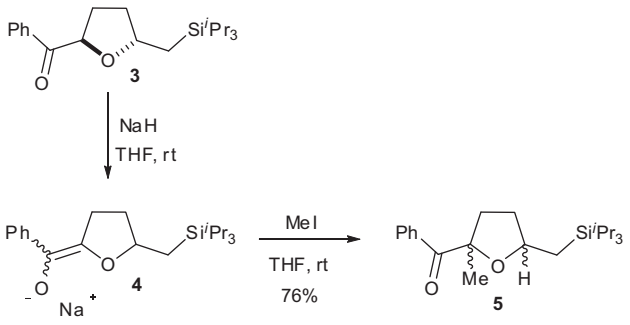
In addition to forming a new C–C bond at the carbonyl carbon atom, it should also be possible to form a new C–C bond at the α-position to the carbonyl group via the corresponding enolate. The presence of only one enolisable proton would remove any chemo- or regioselectivity issues, and would generate a quaternary centre in the product. When reacting **3** with LDA in THF at −78 °C and quenching with MeI, only decomposition of the starting material was observed. However, employing sodium hydride as the base with **3** at room temperature and again quenching with MeI resulted in formation of the methyl substituted THF **5** in 76% yield (Scheme 4). Given that it would be possible to form both *E*- and *Z*-enolates **4**, it was unsurprising that the product **5** was obtained as two (inseparable) diastereoisomers (1.5:1).

(iv) Reduction of the carbonyl group

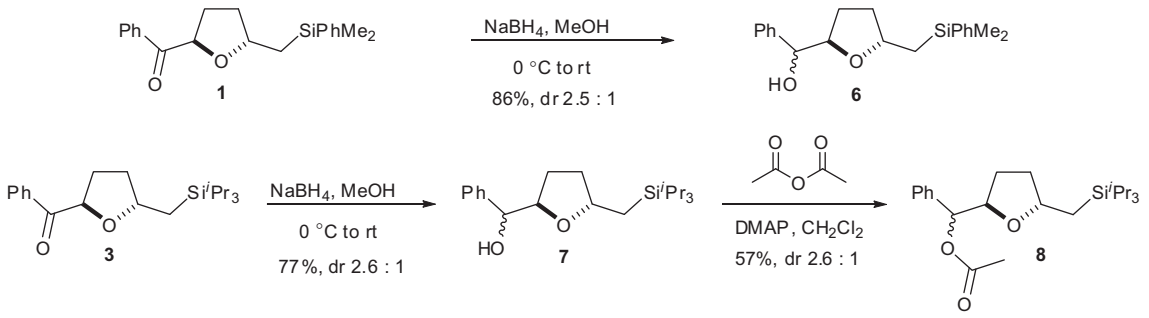
Reduction of the ketone occurred readily using sodium borohydride with both the dimethylphenyl **1** and triisopropyl **3** containing THFs, giving the 2-hydroxymethyl THFs **6** and **7** in excellent yields. The secondary alcohol **7** could be converted into the ester **8** in moderate yield using acetic anhydride (Scheme 5). It is interesting to note that the products obtained both from the reduction with sodium borohydride and from the nucleophilic addition with allylmagnesium chloride were obtained in the same diastereomeric ratio (2.5:1), even though sodium borohydride is considered to be a far weaker chelating agent.[8]

The direct reduction of the ketone to the methylene moiety was also attempted. The one-step Clemmensen reduction using amalgamated zinc (prepared by stirring a 5% mercuric chloride solution with metallic zinc for 1 h) resulted in the decomposition of the starting material. The Salvador-modified ultrasound-assisted Clemmensen reduction[9] using zinc in acetic acid also led to degradation of the starting THF (Scheme 6).

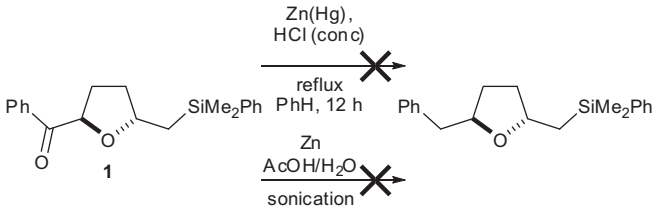
It was considered possible that the THF was incompatible with the strongly acid reaction conditions. As an alternative, non-acidic route, it was proposed to reduce the ketone to the alcohol and follow this with a Barton-McCombie radical deoxygenation. Conversion of the diastereomeric mixture of alcohols derived from the $NaBH_4$ reduction into the methyl xanthate **9** was achieved with carbon disulfide, methyl iodide and sodium hydride in tetrahydrofuran at 0 °C. Treatment of the methyl xanthate with tri-*n*-butyltin hydride and AIBN in toluene at reflux gave the 2,5-disubstituted THF **10** in an overall yield of 50% from the ketone (Scheme 7). NOE results confirmed the THF was still the single *trans*-diastereoisomer across the ring. Thus, even though the initial cyclisation is currently limited to the use of highly reactive glyoxalates as the aldehyde component, this sequence permits access to the cyclisation products of simpler, less reactive aldehydes.



Scheme 4. Enolate formation and subsequent C–C bond formation in α-ketotetrahydrofurans.



Scheme 5. Reduction of a ketone moiety to the corresponding alcohol, and subsequent esterification.

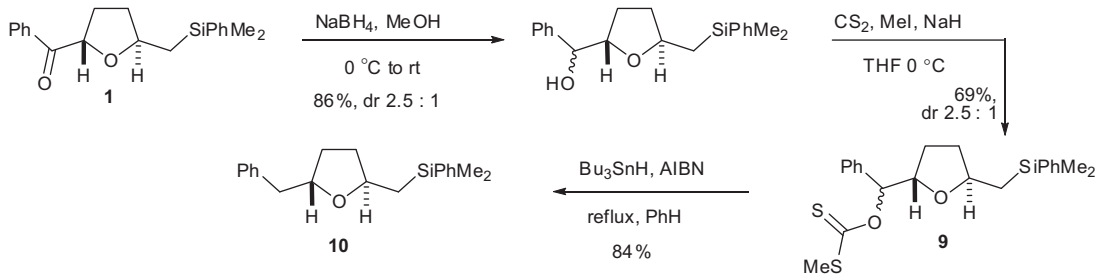


Scheme 6. Attempted Clemmensen reductions.

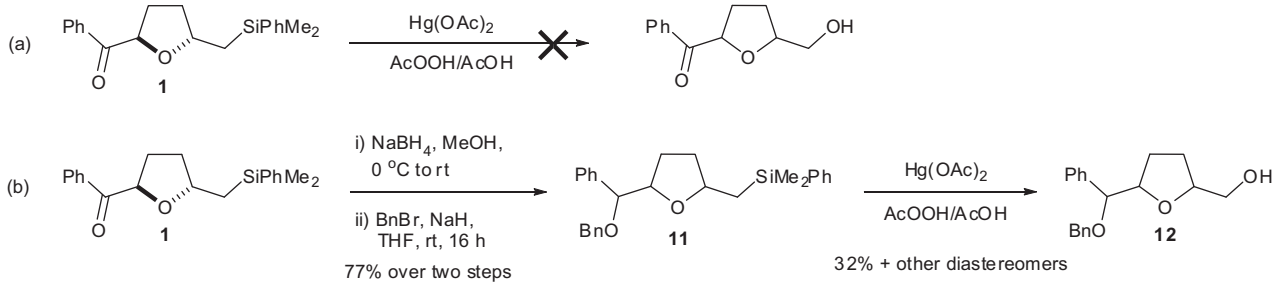
In addition to the many transformations available via the ketone, it is also entirely feasible to modify the THF adducts via the silicon moiety. Indeed, when devising our route to THFs, the incorporation of the silicon moiety was always to fulfil a dual role: to stabilise any build of positive charge at the β-carbon during the cyclisation step (via the β-effect) and to act as a masked alcohol in the THF product,[10] while remaining chemically inert throughout a range of other transformations, as already demonstrated.

Fleming reported several methods for the conversion of the phenyldimethylsilyl group using Br^+, Hg^{2+} and H^+ as electrophiles; the advantages of mercuridesilylation or bromodesilylation being that the entire procedure could be carried out in one pot with peracetic acid as the oxidant, although the authors have noted that the bromine-based method should be avoided if a ketone functionality was present.[11] No product was isolated from the reaction of the α-keto THF with mercuric acetate and peracetic acid (Scheme 8a), although the reaction mixture showed the presence of several phenylmercury species indicating that the electrophilic aromatic substitution had occurred. Suspecting that the presence of the ketone was the problem, removal by reduction followed by benzyl protection of the resulting alcohol gave THF **11** as a mixture of diastereoisomers. Desilylation of the protected α-hydroxy-THF now proceeded well (Scheme 8b) and in high yield, to give a mixture of diastereoisomers **12**.[12] Fortunately, purification by column chromatography gave a pure sample of one diastereoisomer, in 32% yield; the remaining mass balance comprised the other inseparable diastereomers. We are currently examining further uses for the alcohol moiety in these compounds.

In summary, we have demonstrated that 2-keto-5-silylmethyl substituted tetrahydrofurans are versatile building blocks for a variety of transformations and offer a unique opportunity for the rapid generation of molecular complexity. These are currently under investigation for a variety of applications, including in natural product synthesis and will be reported in due course.



Scheme 7. Reduction and subsequent radical deoxygenation.



Scheme 8. Oxidative removal of the silicon moiety.

Acknowledgments

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12. Representative procedures for the preparation of the 2,5-disubstituted THFs and the sodium borohydride mediated reduction have already been published.[6]

(±)-(5-(Benzyloxy(phenyl)methyl)tetrahydrofuran-2-yl)methanol **12**.[11]
To a stirred solution of ((5-(benzyloxy(phenyl)methyl)tetrahydrofuran-2-yl)methyl)dimethyl(phenyl)silane (0.12 g, 0.31 mmol) in peracetic acid (30% wt sol. in acetic acid, 3 mL) was added in one portion mercury(II) acetate (0.11 g, 0.35 mmol). The reaction was stirred for 2 h then washed with water (10 mL), sat. NaS_2O_3 (10 mL) and sat. $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the organic fractions were combined, washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to yield the impure product as a white solid (0.19 g). Purification by flash column chromatography [silica gel, gradient elution 50% hexane/diethyl ether – 100% diethyl ether] isolated a single diastereoisomer of the title compound (0.03 g, 0.10 mmol, 32%) as a colourless viscous oil; R_f 0.14 [80% diethyl ether/hexane]; ν_{max}(film)/cm^{-1} 3439 (O–H), 3062, 3030, 2870, 1495, 1454, 1062 (C–O); δ_H (400 MHz; $CDCl_3$) 1.55–1.67 (3H, m, overlapping signals CH_2 C-4 and CH_aH$_b$ C-3 THF), 1.73–1.82 (1H, m, CH$_a$H$_b$ C-3 THF), 2.16 (1H, br s, OH), 3.43 (1H, app dd, J = 11.1 and 5.1, CH_aH$_b$OH), 3.66 (1H, app br d, J = 11.7, CH$_a$H$_b$OH), 4.04–4.10 (1H, m, CH C-2 THF), 4.24–4.31 (2H, m, overlapping signals CH C-5 THF and *H*COBn), 4.34 (1H, d, J = 12.1 PhCH$_a$H$_b$O), 4.56 (1H, d, J = 12.1, PhCH$_a$H$_b$O), 7.24–7.39 (10H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) 27.3 (CH_2, C-3 THF), 28.9 (CH_2, C-4 THF), 65.0 (CH_2, CH_2OH), 70.6 (CH_2, PhCH_2O), 80.1 (CH, C-2 THF), 82.5 (CH, C-5 THF), 84.0 (CH, *H*COBn), 127.6 (*p*-CH Ar), 127.9 (2 × o-CH Ar), 128.0 (2 × *o*-CH Ar), 128.2 (*p*-CH Ar), 128.4 (2 × *m*-CH Ar), 128.5 (2 × *m*-CH Ar), 138.5 (*ipso*-C Ph), 139.0 (*ipso*-C Ph); LRMS (EI$^+$, *m*/*z*): 298 ([M]$^+$, 1%), 197 (26), 101 (23), 91 (100), 57 (28); HRMS (ESP, *m*/*z*) 316.1902 [M+NH$_4$]$^+$, $C_{19}H_{26}O_3N$ requires 316.1907.