Tetrahedron Letters 50 (2009) 3503–3508

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Reactivity of dearomatised furans synthesised via the decarboxylative Claisen rearrangement

Jason E. Camp, Donald Craig *

Department of Chemistry, Imperial College London, South Kensington Campus, London SW7 2AZ, UK

ARTICLE INFO

Article history:
Received 15 January 2009
Revised 19 February 2009
Accepted 5 March 2009
Available online 18 March 2009

Keywords:
Claisen rearrangement
Microwave-assisted synthesis
Heteroaromatic
Polysubstituted furan
Aldol

ABSTRACT

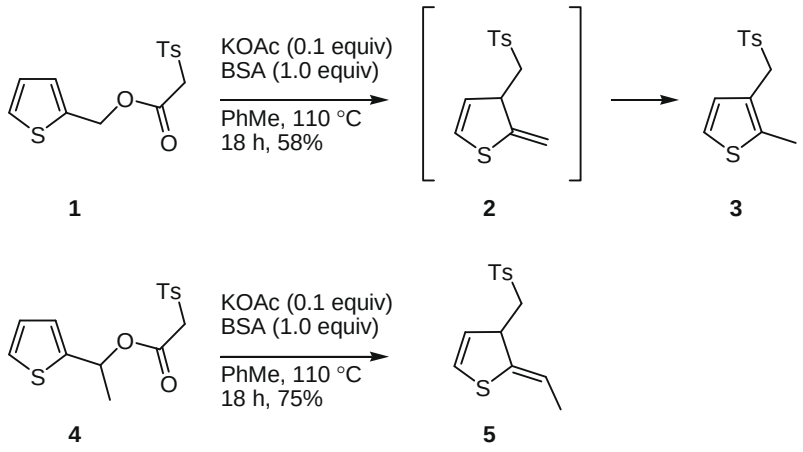
The decarboxylative Claisen rearrangement (dCr) reaction of 1-(furan-2-yl)ethyl 2-tosylacetate afforded 2-ethylidene-3-(tosylmethyl)-2,3-dihydrofuran. Reaction of the dearomatised heterocycle with a variety of electrophiles gave addition products with excellent *syn*-diastereoselectivity. The furanol adducts were then utilised as functionalised scaffolds for a series of subsequent transformations.

Polysubstituted furans are an important structural motif found in many natural products[1] and important pharmaceuticals.[2] The synthetic utility of furans stems from their ready conversion into non-aromatic oxygen heterocycles and the ease with which they may be elaborated to give other oxygen-containing compounds.[3,4] Recently we developed a variant of the Ireland–Claisen rearrangement, the decarboxylative Claisen rearrangement (dCr) reaction, which provides homoallylic sulfones by exposure of allylic tosylacetates to *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and potassium acetate under relatively mild thermal conditions.[5] During the course of our studies on the heteroaromatic variant of this reaction, it was found that substituted thiophene-, pyrrole- and indole-containing substrates gave dCr reaction products in good yields.[6] For example, reaction of thiophene-2-methyl ester **1** with BSA and KOAc under thermal conditions gave thiophene **3**, presumably via non-aromatic intermediate **2** (Scheme 1). In contrast, subjection of tosyl ester **4**, derived from a secondary alcohol, to the same conditions gave rearranged thiophene **5** without rearomatisation. These results can be explained in terms of (i) increased steric buttressing between the furan 2-substituent and the 3-tosylmethyl group in **5**, and (ii) enhanced stabilisation of the more highly substituted exocyclic olefin in the non-aromatic rearrangement product **5**. The synthesis of other dearomatised heterocycles has been reported using Claisen rearrangements,[7] 2,3-Wittig rearrangements,[8] intramolecular organometallic-mediated cyclisations,[9] annulation,[10] Kishner reduction or thermally.[11] Many of the methods for the generation of these compounds rely on forcing conditions, use of toxic metals, or relatively unstable reagents and intermediates. The most important studies on the synthesis and reactivity of dearomatised furans were conducted by Miles et al., who developed the synthesis of 2- and 3-methylene-2,3-dihydrofurans and investigated their use as highly reactive enes in the carbonyl-ene reaction.[12] Herein, we report the use of the dCr reaction for the synthesis of 2-ethylidene-3-(tosylmethyl)-2,3-dihydrofuran, and its use as a potent nucleophile in diastereoselective addition reactions to give highly functionalised furans.

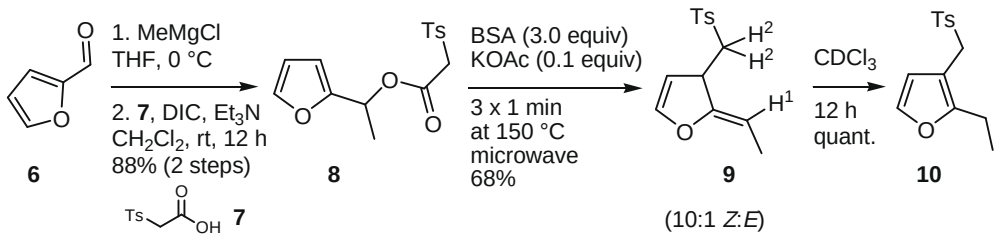
To investigate this intriguing dearomatisation process further we examined the analogous furan system, hoping to take advantage of its lower resonance energy relative to other heteroaromatics.[13] Addition of methylmagnesium chloride to furfural (**6**), followed by diisopropylcarbodiimide (DIC)-mediated coupling of the resultant alcohol with commercially available tosyl acetic acid (**7**) gave furan ester **8** (Scheme 2). Reaction of **8** with BSA and KOAc under microwave irradiation,[14] using a pulse sequence previously optimised for dCr reactions of non-aromatic substrates,[15] provided 2-ethylidene-3-(tosylmethyl)-2,3-dihydrofuran (**9**) in good yield as a 10:1 *Z*/*E* mixture of stereoisomers, as determined by NOE analysis.[16] Upon standing in untreated commercial $CDCl_3$ overnight, **9** aromatised to give exclusively 2-ethyl-3-(tosylmethyl)furan (**10**). In contrast, **9** was found to be stable for over two weeks in CD_2Cl_2, and it was thought that the acid impurities present in untreated $CDCl_3$ were the cause of the rearomatisation. Complete rearrangement from **9** to **10** was achieved in a 10% TFA solution in CD_2Cl_2 in less than 7 min as determined by ^1H NMR.

* Corresponding author.
E-mail address: d.craig@imperial.ac.uk (D. Craig).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.03.091



Scheme 1.



Scheme 2.

Table 1
Reactions of **9** with electrophiles

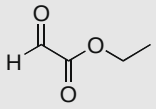
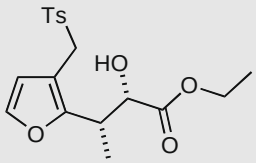
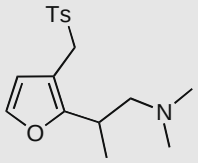
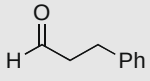
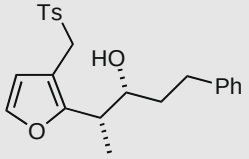
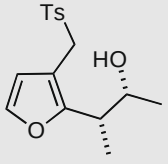
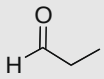
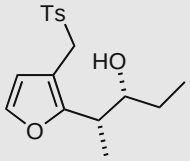
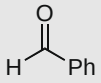
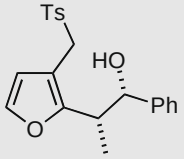
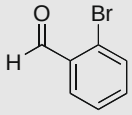
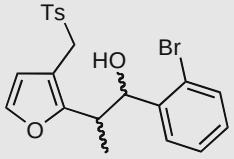
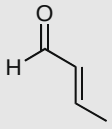
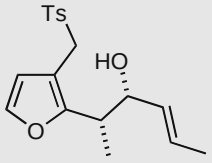
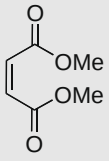
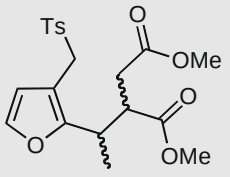
Entry	Electrophile	Conditions temp, solvent, additive, time	Product	Yield (%) (*syn*:*anti*)
1		rt, CH_2Cl_2, none, 2 h	 **11**	91 (10:1)[a]
2		rt, CH_2Cl_2, none, 3 h	 **12**	66
3		0 °C, CH_2Cl_2, $ZnCl_2$, 1 h	 **13**	59 (10:1)
4		0 °C, CH_2Cl_2, $ZnCl_2$, 1 h	 **14**	60 (10:1)

Table 1(*continued*)

Entry	Electrophile	Conditions temp, solvent, additive, time	Product	Yield (%) (*syn*:*anti*)
5		0 °C, CH_2Cl_2, $ZnCl_2$, 1 h	 **15**	62 (10:1)
6		0 °C, CH_2Cl_2, $ZnCl_2$, 1 h	 **16**	75 (10:1)
7		0 °C, CH_2Cl_2, $ZnCl_2$, 1 h	 **17**	82 (5:3)
8		0 °C, CH_2Cl_2, $ZnCl_2$, 1 h	 **18**	58 (5:1)
9		150 °C *m*-xylene, KOAc, 16 h	 **19**	73 (5:3)

[a] Lower *syn*-selectivity was observed at increased temperatures.

Next, reaction of the 10:1 *Z*/*E* mixture of **9** with various electrophiles was investigated. Combination of **9** with the electron-deficient substrates ethyl glyoxalate (entry 1) and Eschenmoser's salt (entry 2) in the absence of Lewis acid gave addition products **11** and **12,** respectively, in good yields (Table 1). Aliphatic aldehydes (entries 3–5) reacted with enol ether **9** at 0 °C in the presence of zinc(II) chloride to give the corresponding furan-containing adducts. The use of other Lewis acids ($TiCl_4$, $BF_3{\cdot}OEt$ and BBr_3) at 0 °C or at rt resulted in either decomposition or rearomatisation of **9** to give **10**. Benzaldehyde (entry 6) and 2-bromobenzaldehyde (entry 7) also reacted with enol ether **9** under the zinc(II) chloride conditions to give the secondary alcohol products in good yields. In contrast, 2-cyanobenzaldehyde was a poor substrate for this reaction, giving only trace amounts of the addition product. Reaction of enol ether **9** with crotonaldehyde in the presence of $ZnCl_2$ gave exclusively the 1,2-addition product **18** as a 5:1 diastereoisomeric mixture. The *syn*-configuration of the products was anticipated on the basis of the analogous *Z*-enol ether additions to aldehydes,[17] and was confirmed by X-ray crystallographic analysis of the dinitrobenzoate ester **14A** of alcohol **14** (Fig. 1).[18] A decrease in dr was observed with increasing steric hindrance of the aldehyde, as observed when 2-bromobenzaldehyde was used as the electro-

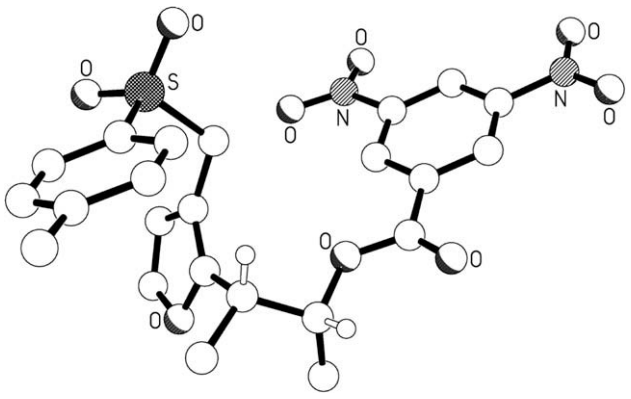
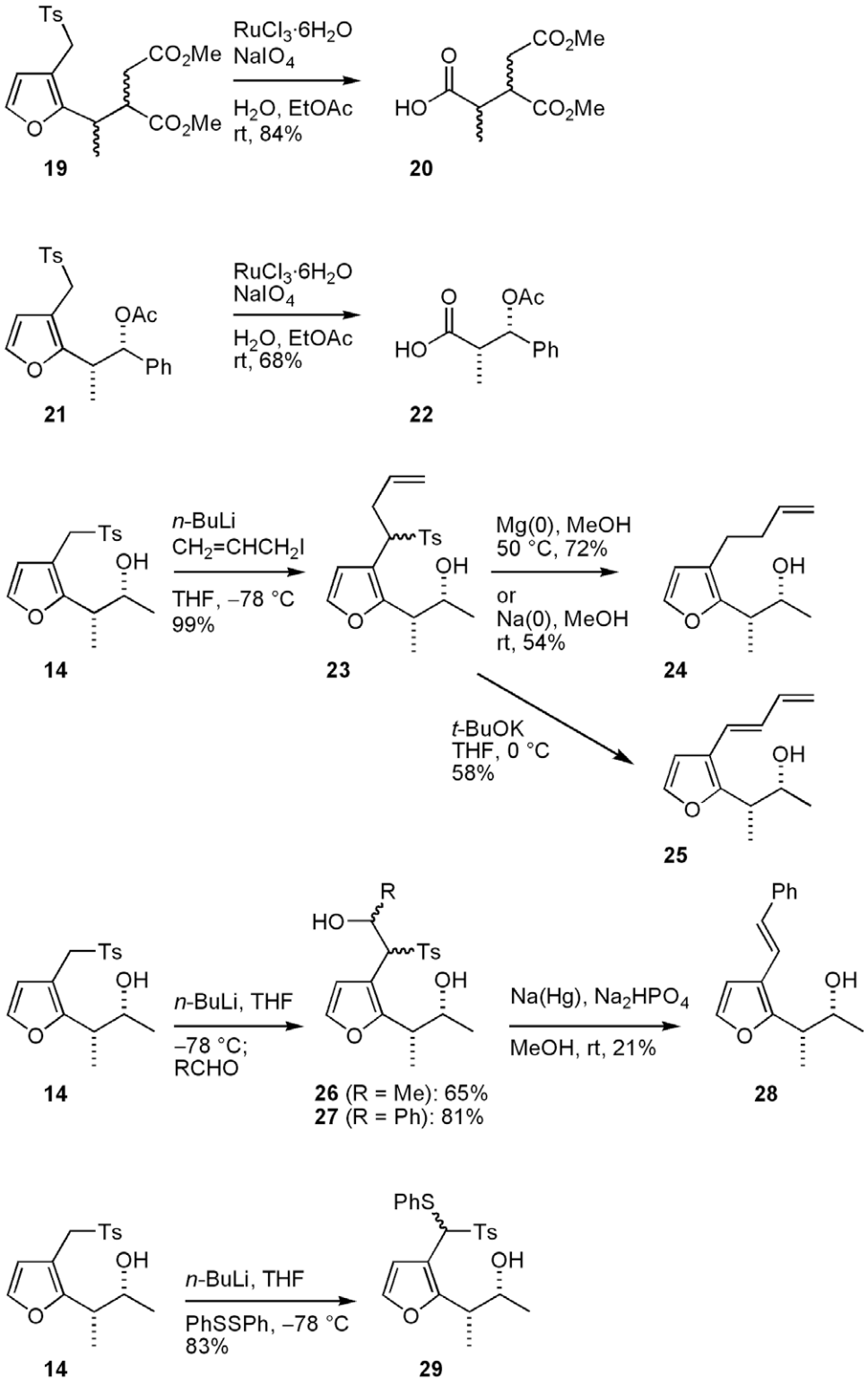


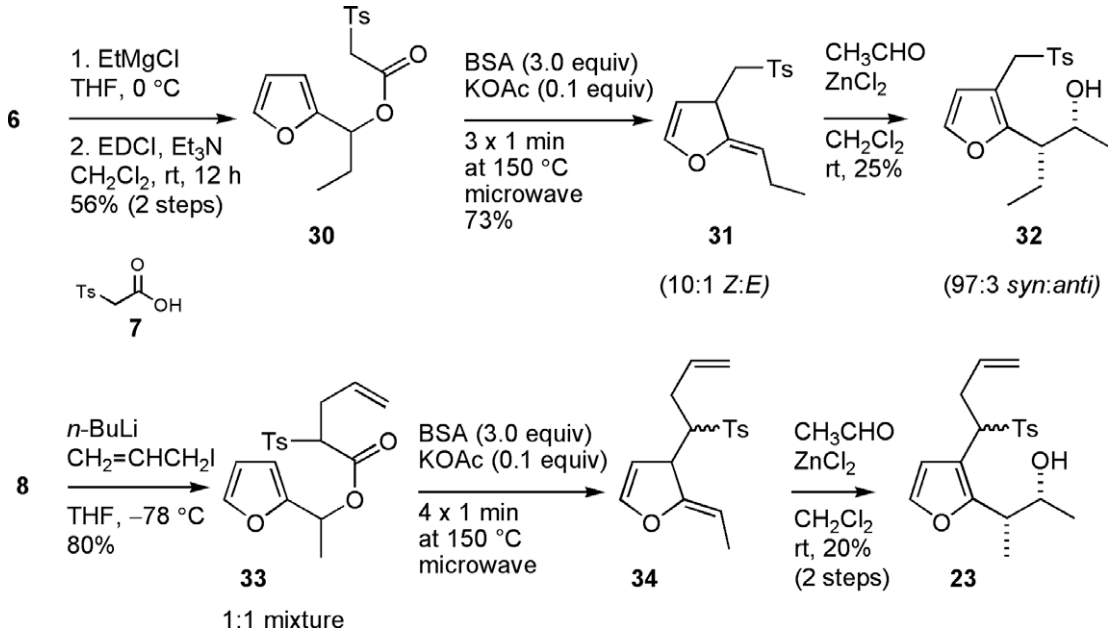
Figure 1. The molecular structure of 14A,[18] majority of hydrogens omitted for clarity.

phile (entry 7). Additionally, the ene-reaction of dimethyl maleate with **9** in the presence of KOAc (entry 9) gave addition product **19** in good yield, but as a 5:3 mixture of diastereomers.

We have explored a number of transformations in order to demonstrate the utility of the furan addition products. For example, treatment of maleate derivative **19** or furanol **21** with ruthenium trichloride-sodium periodate[19] gave acids **20** and **22**, respectively (Scheme 3).[20] Tosyl furan **14** could be alkylated,[21] hydroxy-alkylated[22] and sulfenylated[23] to give the desired substitution products as mixtures of diastereomers at the benzylic position. The tosyl moiety was removed from furan **23** by treatment with either magnesium[24] or sodium[25] to give butenyl-substituted furan **24** in good yields. Treatment of tosyl furan **23** with *t*-BuOK resulted in elimination of the tosyl moiety to yield diene **25**.[26] Additionally, reaction of furanol **27** with sodium amalgam resulted in a Julia–Lythgoe[27] olefination to afford substituted styrene derivative **28**.



Scheme 3.



Scheme 4.

Preliminary investigations into prefunctionalisation at the C2′ and ester methylene positions to introduce mutually reactive functionality were also undertaken. Ethyl ester **30** was synthesised from furfural (**6**) and subjected to the standard heterocyclic dCr conditions to afford enol ether **31** as a 10:1 mixture of *E*/*Z* isomers. Reaction of enol ether **31** with acetaldehyde gave alcohol **32**, indicating that this overall transformation works on homologous substrates. Additionally, allylation of tosyl ester **8** yielded **33** as a 1:1 mixture of diastereomers. Treatment of **33** with BSA and KOAc under microwave irradiation gave enol ether **34**, which was combined with acetaldehyde in the presence of $ZnCl_2$ to give alcohol **23**. This route provides an alternative synthesis of allyl alcohol **23** to that outlined in Scheme 3, and increases the utility and flexibility of this method. These transformations are depicted in Scheme 4.

In conclusion, we have utilised a heterocyclic dCr reaction for the facile synthesis of novel dearomatised furan **9**, which was found to react diastereoselectively with various electrophiles under relatively mild conditions. These addition products are useful substrates for accessing highly substituted furans. Additionally, the dCr precursors could be prefunctionalised, increasing the flexibility of this method for synthetic applications. Currently we are investigating the enantioselective dCr reactions of (*S*)- and (*R*)-1-(furan-2-yl)ethyl 2-tosylacetate, and the addition reactions of the derived enantiomerically pure dearomatised furans with electrophiles. We are also evaluating the factors that affect the diastereomeric ratio of the heterocyclic dCr reaction. The results of these studies will be reported in due course.

Acknowledgements

This work was supported by the EPSRC (Postdoctoral fellowship to J.E.C. through responsive-mode grant EP/F015356). We thank Dr. Andrew White for determining the X-ray structure and Mr. Pete Haycock for the NOE structural determination of **9**.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.091.

References and notes

1. Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795–819.
2. Nakanishi, K. *Natural Products Chemistry*; Kondansha: Tokyo, 1974.
3. For example, see: (a) Tsubuki, M.; Tarumoto, N.; Honda, T. *Heterocycles* **2001**, *54*, 341–350; (b) Sauers, A. L.; Ho, D. M.; Bernhard, S. *J. Org. Chem.* **2004**, *69*, 8910–8915; (c) Liu, G.; Sieburth, S. M. *Org. Lett.* **2005**, *7*, 665–668.
4. For a review, see: Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1955–2020. and references therein.
5. (a) Bourgeois, D.; Craig, D.; King, N. P.; Mountford, D. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 618–621; (b) Craig, D.; Grellepois, F. *Org. Lett.* **2005**, *7*, 463–465; (c) Craig, D.; Grellepois, F.; White, A. J. P. *J. Org. Chem.* **2005**, *70*, 6827–6832; (d) Bourgeois, D.; Craig, D.; Grellepois, F.; Mountford, D. M.; Stewart, A. J. W. *Tetrahedron* **2006**, *62*, 483–495.
6. Craig, D.; King, N. P.; Kley, J. T.; Mountford, D. M. *Synthesis* **2005**, 3279–3282.
7. (a) Thomas, A. F.; Ozainne, M. *J. Chem. Soc. C* **1970**, 220–224; (b) Raucher, S.; Lui, A. S.-T.; MacDonald, J. E. *J. Org. Chem.* **1979**, *44*, 1885–1887.
8. (a) Caruana, P. A.; Frontier, A. J. *Tetrahedron* **2004**, *60*, 10921–10926; (b) Usami, T.; Shirai, N.; Sato, Y. *J. Org. Chem.* **1992**, *57*, 5419–5425.
9. (a) Tidwell, J. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11797–11810; (b) Elder, A. M.; Rich, D. H. *Org. Lett.* **1999**, *1*, 1443–1446; (c) Sakamato, T.; Kondo, Y.; Uchiyama, H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1941–1942.
10. Ojida, A.; Abe, A.; Kanematsu, K. *Heterocycles* **1994**, *38*, 2585–2588.
11. Padwa, A.; Cohen, L. A. *Tetrahedron* **1982**, *23*, 915–918.
12. (a) Miles, W. H.; Dethoff, E. A.; Tuson, H. H.; Ulas, G. *J. Org. Chem.* **2005**, *70*, 2862–2865; (b) Miles, W. H.; Connell, K. B. *Tetrahedron Lett.* **2003**, *44*, 1161–1163; (c) Miles, W. H.; Berreth, C. L.; Anderton, C. A. *Tetrahedron Lett.* **1996**, *37*, 7893–7896; (d) Miles, W. H.; Berreth, C. L.; Smiley, P. M. *Tetrahedron Lett.* **1993**, *34*, 5221–5222.
13. Joule, J. A.; Mills, K.; Smith, G. E. *Heterocyclic Chemistry*; Chapman & Hall: London, 1995.
14. Microwave irradiation reactions were performed on a biotage initiator microwave reactor, with the temperature determined by IR.
15. Craig, D.; Paina, F.; Smith, S. C. *Chem. Commun.* **2008**, 3408–3410.
16. An NOE was observed between H^1 and H^2. Additionally, a characteristic downfield quartet corresponding to H^1 was detected in the proton NMR.
17. For examples of diastereoselective *Z*-enolate addition, see: Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066–1081.
18. The 3,5-dinitrobenzoate ester of **14** was crystallised as two different polymorphs, **14A** and **14B**, the molecular structures of which are very similar. Polymorph A is reported here, and polymorph B is reported in the Supplementary data. *Crystal data for* **14A**: $C_{23}H_{22}N_2O_9S$, $M = 502.49$, triclinic, $P\bar{1}$ (no. 2), $a = 9.2313(3)$, $b = 11.4829(2)$, $c = 12.2474(4)$ Å, $\alpha = 71.534(3)$, $\beta = 88.253(3)$, $\gamma = 68.460(3)°$, $V = 1139.98(7)$ Å^3, $Z = 2$, $D_c = 1.464$ g cm^{-3}, μ(Mo-Kα) = 0.200 mm^{-1}, $T = 173$ K, pale yellow hexagonal blocks, Oxford Diffraction Xcalibur 3 diffractometer; 7292 independent measured reflections, F^2 refinement, $R_1 = 0.038$, $wR_2 = 0.109$, 6062 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{max} = 64°$], 317 parameters. CCDC 703903.
19. Miles, W. H.; Fialcowitz, E. J.; Halstead, E. S. *Tetrahedron* **1993**, *57*, 9925–9929.

20. Furans have been used extensively as protected ester and 1,4 diketone equivalents in complex organic syntheses. For examples, see: (a) Raczo, J. *Tetrahedron* **2003**, *59*, 10181–10186; (b) Kusakabe, M.; Kitano, Y.; Kobayashi, Y.; Sato, F. *J. Org. Chem.* **1989**, *54*, 2085–2091; (c) Pearlman, B. A.; Padilla, A. G.; Hach, J. T.; Havens, J. L.; Pillai, M. D. *Org. Lett.* **2006**, *8*, 2111–2113.
21. Mori, K.; Komatsu, M. *Tetrahedron* **1987**, *43*, 3409–3412.
22. Roush, W. R.; Russo-Rodriguez, S. *J. Org. Chem.* **1985**, *50*, 5465–5468.
23. Craig, D.; McCague, R.; Potter, G. A.; Williams, M. R. V. *Synlett* **1998**, 55–57.
24. (a) Brown, A. C.; Carpino, L. A. *J. Org. Chem.* **1985**, *50*, 1749–1750; (b) Baker, K. V.; Brown, J. M.; Hughes, N.; Skarnulis, A. J.; Sexton, A. *J. Org. Chem.* **1991**, *56*, 698–703.
25. Taber, D. F.; Jiang, Q. J.; Chen, B.; Zhang, W.; Campbell, C. L. *J. Org. Chem.* **2002**, *67*, 4821–4827.
26. Du Penhoat, C. H.; Julia, M. *Tetrahedron* **1986**, *42*, 4807–4816.
27. Ermolenko, L.; Sasaki, N. A.; Potier, P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2465–2473.