A Novel Approach to Functionalised Polycyclic Systems; Intramolecular Diels–Alder Reactions of 2-Acylated Derivatives of 4*H*,6*H*-Thieno[3,4-*c*]furan 5,5-Dioxide

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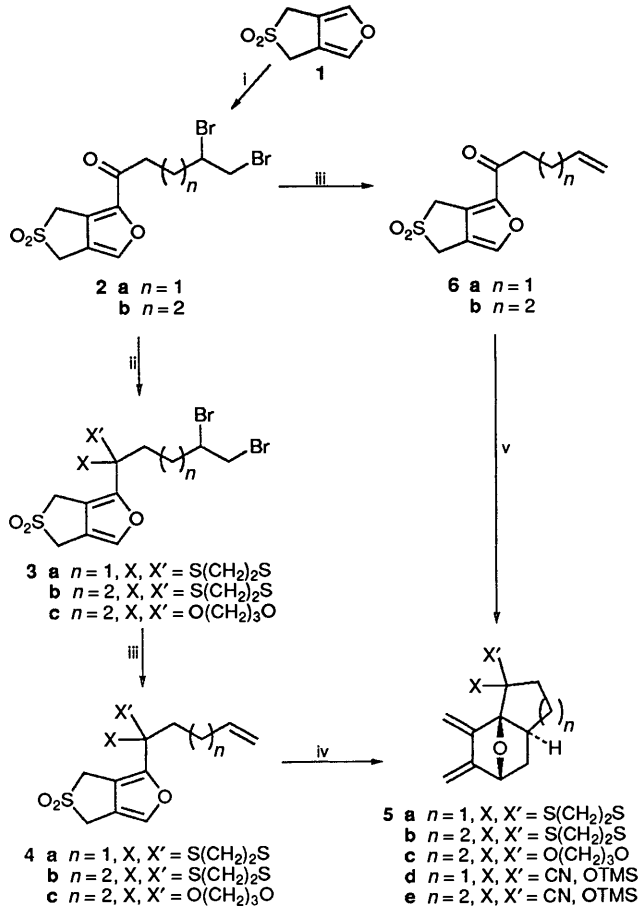
4-*H*, 6*H*-Thieno[3,4-*c*]furan 5,5-dioxide **1** was converted into compounds **4** and **6**, which readily cyclised to give stereoselectively the functionalised tricyclic compound **5** in good yield.

The novel building block, 4*H*,6*H*-thieno[3,4-*c*]furan 5,5-dioxide **1**, is potentially useful for the construction of polycyclic ring systems. If a Diels–Alder reaction on the furan ring of **1** takes place, the 3-sulfolene thus formed could extrude SO_2 by cheletropic reaction to afford a 1,3-diene, which could further undergo cycloaddition. Moreover, incorporation of substituents both on the furan and the sulfolene moieties would be feasible. Accordingly, sequential Diels–Alder reactions, coupled with chemical modification on both moieties, should produce various types of polycyclic ring systems. Thus, we have shown that **1** readily reacts with a variety of dienophiles to yield four types of cycloadducts,[1,2] and, upon alkylation, gives 4-alkylated compounds which lead to fused furan compounds in good yield.[3] Described here is the synthesis of tricyclic compound **5** starting with **1** through acylation of the furan moiety and subsequent intramolecular Diels–Alder reaction.

Treatment of **1** with 4,5-dibromopentanoyl chloride, prepared from pent-4-enoic acid by successive treatment of bromine and thionyl chloride in 85% yield, in the presence of aluminium chloride ($AlCl_3$) at room temperature for 1 h gave the 2-acylated derivative **2a** in 87% yield. Although we previously reported facile acylation on the furan moiety of **1** by means of the mixed anhydride method,[4] the procedure described here, using normal Friedel–Crafts' reaction conditions, was found to be superior in terms of general applicability. The carbonyl group was protected next since it decreases the reactivity of furan as a diene.[5,6] Treatment of **2a** with ethane-1,2-dithiol–toluene-*p*-sulfonic acid (*p*-TsOH) in benzene under reflux for 24 h yielded **3a** in 87% yield, which followed by reduction with zinc in tetrahydrofuran (THF)–phosphate buffer[7] at room temperature for 1.5 h afforded olefin **4a**, a precursor for the intramolecular Diels–Alder reaction in 80% yield. In the same way, **4b** was obtained from **1** with 5,6-dibromohexanoyl chloride through **2b** and **3b** in a similar yield. The use of a ketal protective group instead of a thioketal gave the same results. Successive treatment of **2b** with propane-1,3-diol–*p*-TsOH (**3c**, 96% yield) and Zn as described above afforded the precursor **4c** (94% yield).

The cyclisation proceeded best in refluxing xylene: heating **4** in xylene under reflux for 2 h stereoselectively gave the *exo*-adducts **5** in good yield (**5a**, 74%; **5b**, 70%; **5c**, 74% yield). The stereochemistry of the ring junction was determined by ^1H NMR analysis according to the data reported by Nelson and Allen.[8] The adducts were also obtained in refluxing toluene or benzene in almost the same yield, but in these cases the reaction took a much longer time to complete (8 h in toluene and 6 days in benzene).

The cycloadduct **5** was also produced from the keto olefin **6**, obtained from **2** by Zn treatment (**6a**, 80%; **6b**, 76% yield), in one-pot through sequential protection and cyclisation. Thus, **6** was heated under reflux in benzene with trimethylsilyl cyanide (TMSCN) in the presence of a catalytic amount of potassium



Scheme 1 *Reagents and conditions:* i, 4,5-dibromopentanoyl chloride or 5,6-dibromohexanoyl chloride, $AlCl_3$ in CH_2Cl_2, room temp., 1 h; ii, ethane-1,2-dithiol or propane-1,3-diol–*p*-TsOH, reflux in benzene, 24 h; iii, Zn in THF-phosphate buffer, room temp., 1 h; iv, reflux in xylene, 2 h; v, TMSCN, KCN, 18-crown-6, reflux in benzene, 24 h

cyanide (KCN) and 18-crown-6 for 24 h to afford the adducts **5d** (63%) and **5e** (59% yield). This procedure exclusively gave the *exo*-adducts again, but a mixture of isomers on the cyanohydrin moiety (3 : 1 for **5d** and 3 : 2 for **5e**). The cyclisation must take place after carbonyl protection by TMSCN since heating **6** alone (reflux in xylene for 2 days) gave no adduct. In this case, attempted use of a ketal or a thioketal protective group (propane-1,3-diol or ethane-1,2-dithiol–*p*-TsOH, reflux in benzene for 24 h) resulted in a complex mixture rather than cyanohydrin.

Thus, starting with **1**, the functionalised tricyclic compound **5** was readily synthesised. Usually intramolecular Diels–Alder reactions involving furan do not go to completion, but reach an

equilibrium instead. However, all the cycloadditions described here proceeded smoothly and went to completion. This is due to SO_2 extrusion (the cheletropic reaction) of the initially formed cycloadduct, which is the advantage of using **1** as we noted previously.[1] Interestingly, the cyclisations described here yield not only the decalin systems **5b**, **5c** and **5e** but also the indan systems **5a** and **5d**. This is in marked contrast to the case of the corresponding 2-acylfuran derivatives: Fischer and Hünig reported that the intramolecular cycloadditions of 2-acylfuran derivatives gave only the decalin systems and no formation of the indan systems.[6] Additionally, the stereoselectivity of the cyclisation reactions is much higher than those of the 2-acylfuran cases. Furthermore, the adduct **5** should be of great synthetic utility because it has three asymmetric centres with known relative stereochemistry and a 1,3-diene which could undergo further cycloaddition to form an extra ring. Accordingly, the results shown here demonstrate the versatility of **1** as a building block.

Experimental

Typical Procedure for the Reaction of **4**.—A solution of **4b** (252 mg) in xylene (5 cm^3) was heated at reflux for 2 h. The solvent was evaporated and the residue was purified by silica gel flash chromatography (10 g, 2% AcOEt–hexane) to give the tricyclic adduct **5b** (143 mg, 70%) as a white solid.

5a: δ_H(400 MHz; $CDCl_3$; Me_4Si) 1.32–1.39 (m, 1 H), 1.82 (dt, 1 H, *J** 11.9, 4.6), 2.12–2.24 (m, 2 H), 2.15 (dd, 1 H, *J* 8.5, 11.9), 2.44 (dq, 1 H, *J* 4.6, 8.5), 2.72–2.81 (m, 1 H), 3.34–3.45 (m, 4 H), 4.78 (d, 1 H, *J* 4.6), 4.90 (s, 1 H), 5.21 (s, 1 H), 5.38 (s, 1 H), 5.70 (s, 1 H); *m/z* 252 (M^+) (Found: M^+, 252.0462. $C_{13}H_{16}OS_2$ requires, *M*, 252.0643).

5b: δ_H(400 MHz; $CDCl_3$; Me_4Si) 1.18–1.30 (m, 1 H), 1.60–1.76 (m, 3 H), 1.63 (ddd, 1 H, *J* 2.0, 5.7, 12.1), 1.83 (dd, 1 H, *J* 7.4, 12.1), 2.02 (ddd, 1 H, *J* 2.8, 4.8, 13.1), 2.09 (ddt, 1 H, *J* 2.0, 11.6, 7.4), 2.40 (ddd, 1 H, *J* 4.3, 11.6, 13.1), 3.22–3.42 (m, 4 H), 4.75 (d, 1 H, *J* 5.7), 4.76 (s, 1 H), 5.04 (s, 1 H), 5.53 (s, 1 H), 6.05 (s, 1 H); *m/z* 266 (M^+) (Found: M^+, 266.0801. $C_{14}H_{18}OS_2$ requires, *M*, 266.0799).

5c: δ_H(400 MHz; $CDCl_3$; Me_4Si) 1.14–1.25 (m, 1 H), 1.34–1.41 (m, 1 H), 1.46–1.59 (m, 2 H), 1.53 (ddd, 1 H, *J* 1.8, 5.8, 11.9), 1.69 (ddt, 1 H, *J* 6.7, 10.4, 3.4), 1.76 (dd, 1 H, *J* 7.9, 11.9), 2.12 (ddt, 1 H, *J* 1.8, 11.9, 7.9), 2.14–2.20 (m, 1 H), 2.73–2.82 (m, 2 H), 3.88–3.93 (m, 2 H), 4.00–4.14 (m, 2 H), 4.76 (s, 1 H), 4.77 (d, 1 H, *J* 5.8), 5.05 (s, 1 H), 5.47 (s, 1 H), 5.80 (s, 1 H); *m/z* 248 (M^+) (Found: M^+, 248.1415. $C_{15}H_{20}O_3$ requires, *M*, 248.1412).

Typical Procedure for the Reaction of **6**.—A mixture of **6b** (108 mg, 0.43 mmol), KCN (9 mg, 0.14 mmol), 18-crown-6 (17 mg, 0.06 mmol) and TMSCN (0.51 cm^3, 3.8 mmol) in benzene (30 cm^3) was allowed to reflux for 24 h under argon. The mixture was poured into water and extracted with AcOEt. The combined extracts were washed with brine, dried ($MgSO_4$) and then evaporated. The residue was purified by silica gel flash chromatography (15 g, 1.5% AcOEt–hexane) to give **5e** (73 mg, 59%) as a 3:2 mixture of epimers. The isomers were separated each other by preparative TLC (10% Et_2O–hexane).

5d, *Less polar isomer*: δ_H(400 MHz; $CDCl_3$; Me_4Si) 0.27 (s, 9 H), 1.43 (dddd, 1 H, *J* 1.2, 4.6, 11.0, 14.0), 1.80 (dt, 1 H, *J* 11.9, 4.6), 2.15 (dd, 1 H, *J* 8.6, 11.9), 2.22 (ddt, 1 H, *J* 7.9, 14.0, 11.0), 2.37 (ddd, 1 H, *J* 1.2, 8.2, 12.2), 2.47 (ddt, 1 H, *J* 8.6, 10.4, 4.6), 2.53 (dt, 1 H, *J* 12.2, 9.7), 4.88 (d, 1 H, *J* 4.6), 4.96 (s, 1 H), 5.27 (s, 1 H), 5.40 (s, 1 H), 5.50 (s, 1 H); *m/z* 275 (M^+) (Found: M^+, 275.1344. $C_{15}H_{21}NO_2Si$ requires, *M*, 275.1341).

5d, *More polar isomer*: δ_H(400 MHz; $CDCl_3$; Me_4Si) 0.32 (s, 9 H), 1.42 (ddt, 1 H, *J* 2.0, 15.6, 6.1), 1.81 (dt, 1 H, *J* 11.9, 4.6), 2.11 (dd, 1 H, *J* 8.9, 11.9), 2.16–2.26 (m, 2 H), 2.52–2.58 (m, 1 H), 2.58–2.66 (m, 1 H), 4.86 (d, 1 H, *J* 4.6), 4.93 (s, 1 H), 5.25 (s, 1 H), 5.32 (s, 1 H), 5.41 (s, 1 H); *m/z* 275 (M^+) (Found: M^+, 275.1332. $C_{15}H_{21}NO_2Si$ requires, *M*, 275.1341).

5e, *Less polar isomer*: δ_H(400 MHz; $CDCl_3$; Me_4Si) 0.21 (s, 9 H), 1.14–1.26 (m, 1 H), 1.61 (ddd, 1 H, *J* 2.1, 5.5, 11.9), 1.68–1.78 (m, 1 H), 1.76–1.86 (m, 2 H), 1.81 (dd, 1 H, *J* 7.6, 11.9), 2.05–2.10 (m, 2 H), 2.14–2.22 (m, 1 H), 4.83 (s, 1 H), 4.85 (d, 1 H, *J* 5.5), 5.10 (s, 1 H), 5.30 (s, 1 H), 5.74 (s, 1 H); *m/z* 289 (M^+) (Found: M^+, 289.1489. $C_{16}H_{23}NO_2Si$ requires *M*, 289.1498).

5e, *More polar isomer*: δ_H(400 MHz; $CDCl_3$; Me_4Si) 0.34 (s, 9 H), 1.14–1.26 (m, 1 H), 1.46–1.54 (m, 1 H), 1.60 (ddd, 1 H, *J* 2.1, 5.5, 11.9), 1.62–1.74 (m, 2 H), 1.80 (dd, 1 H, *J* 7.6, 11.9), 2.08–2.20 (m, 3 H), 4.82 (s, 1 H), 4.84 (d, 1 H, *J* 5.5), 5.09 (s, 1 H), 5.47 (s, 1 H), 5.64 (s, 1 H); *m/z* 289 (M^+) (Found: M^+, 289.1501. $C_{16}H_{23}NO_2Si$ requires, *M*, 289.1498).

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* *J* Values are given in Hz.