Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 63 (2007) 1100–1106
Tetrahedron

Tandem Michael/Michael reactions mediated by phosphines or aryl thiolates

Paul M. Brown,[a] Nina Käppel,[a] Patrick J. Murphy,[a,*] Simon J. Coles[b] and Michael B. Hursthouse[b]

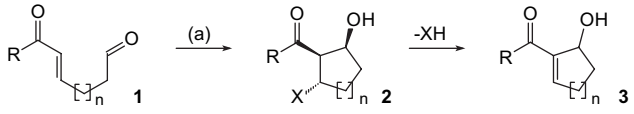
[a]*School of Chemistry, University of Wales, Bangor, Gwynedd LL57 2UW, United Kingdom*
[b]*Department of Chemistry, University of Southampton, Highfield, Southampton SO17 1BJ, United Kingdom*

Received 14 September 2006; revised 9 November 2006; accepted 23 November 2006

Abstract—Tri-*n*-butyl phosphine was found to effect tandem Michael/Michael cyclisations leading to the formation of cyclopentenes and cyclohexenes in good yields, whilst *p*-TolSH in conjunction with a catalytic amount of *p*-TolSNa effected cyclisation to the corresponding cyclopentanes and cyclohexanes.

1. Introduction

We have previously reported the ability of a range of nucleophiles, including secondary amines, thiols and phosphines to effect a tandem intramolecular Michael/aldol cyclisation of enones **1** leading to either the adducts **2** or the eliminated Baylis–Hillman type products **3**[1] (Scheme 1).

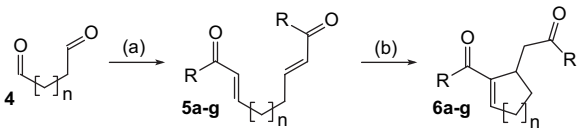


Scheme 1. Reagents and conditions: (a) R_2NH, R_3P, TolSH, n=1, 2; R=Alkyl, Ph, OR; X=R_2N, R_3P^+, TolS.

We also investigated the development of this reaction and envisaged that a similar Michael/Michael sequence might offer a flexible route to cycloalkenes. This observation was also reported by Roush et al.[2] who have reported their studies on this reaction, which they refer to as a '*vinylogous Morita–Baylis–Hillman*' reaction and Krische et al.[3] who refer to the reaction as an intramolecular Rauhut–Currier reaction.[4] Cyclisations of this type have been previously reported using a range of carbanions,[5] metal thiolates[6] and metal amides[7] together with sequences initiated by free radicals.[8]

We began out work in this area by embarking on an investigation of the scope of the reaction with regards to the nature of the electron-withdrawing group on the alkene and the ring size of the product formed. We thus prepared the bis-enones **5a–f** in reasonable yield from the aldehydes **4**, by treatment with a 2-fold excess of the requisite stabilised phosphorane.[1,9]

With the substrates in hand we initially treated them with a catalytic amount of n-Bu_3P (0.2–0.5 equiv) in chloroform at room temperature to effect cyclisation (Scheme 2, Table 1). We were pleased to find that the phenyl enones **5a** and **5b** both underwent cyclisation to give the corresponding cyclopentene **6a** and cyclohexene **6b** in high yield (entries 1 and 2), however the substrate **5c**, which would generate a cycloheptene product, was resistant to cyclisation under these conditions even on prolonged reaction and increased temperature (entry 3). Similarly attempted cyclisation of the enoate substrates **5d** and **5e** was also unsuccessful, possibly reflecting a low reactivity of enoates towards Michael addition[2] (entries 4 and 5). We also investigated the methyl-substituted enones **5f** and **5g** and found that they also underwent cyclisation in good yield (entries 6 and 7) (Scheme 2).



Scheme 2. Reagents and conditions: (a) 2 equiv RCOCH=PPh_3, 44–63% (see Refs. 1 and 7); (b) see Table 1.

We also investigated the enone **8a** and enoate **8b** in which the two Michael acceptors are linked by an aromatic ring and found that these displayed similar reactivity to the previous examples. We found that the enone substrate **8a** cyclised smoothly to give the isomeric indenes **9a** and **9b** in excellent overall yield, whilst enoate **8b** was resistant to cyclisation under these conditions (Scheme 3).

We investigated the lack of reactivity of the enoate substrates in more detail and prepared the mixed substrates **12** and **14** from the aldehyde **11**[1c] via Wittig reaction. On treatment of **12** with n-Bu_3P under standard conditions, we obtained the

Keywords: Tandem reactions; Michael additions; Phosphines.
* Corresponding author. E-mail addresses: paddy@bangor.ac.uk; p.j.murphy@bangor.ac.uk

0040–4020/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.tet.2006.11.064

Table 1

Entry	5	R	*n*	Method[a]	6	Yield (%)
1	**5a**	Ph	1	0.3 equiv, *n*-Bu_3P, 16 h	**6a**	80
2	**5b**	Ph	2	0.3 equiv, *n*-Bu_3P, 4 h	**6b**	68
3	**5c**	Ph	3	0.3 equiv, *n*-Bu_3P, 21 days[b]	**6c**	0
4	**5d**	OMe	1	0.3 equiv, *n*-Bu_3P, 4 days[c]	**6d**	0
5	**5e**	OMe	2	0.3 equiv, *n*-Bu_3P, 4 days[c]	**6e**	0
6	**5f**	Me	1	0.2 equiv, *n*-Bu_3P, 5 h	**6f**	66
7	**5g**	Me	2	0.2 equiv, *n*-Bu_3P, 16 h	**6g**	58

[a] Reactions are performed in chloroform (ca. 1–2 mL per mmol of substrate) at rt.
[b] A further 0.3 equiv of phosphine added after one week and the reaction refluxed for 16 h.
[c] A further 0.3 equiv of phosphine added after 1 day and the reaction was refluxed for 16 h.

cyclohexene **13** as the only product, highlighting the low reactivity of the enoate to phosphine addition, but confirming that the enoate is a suitable acceptor for the cyclisation step of the tandem process. Substrate **14** allowed us to investigate the relative reactivity of the two enones we have investigated and not surprisingly we found that a 76:24 mixture of products **15** and **16** were formed in which the product **15** arising from initial Michael addition to the phenyl substituted enone was preferred. Repetition of the reaction at 0 °C gave a slightly improved selectivity for the formation of **15** (Scheme 4).

Following this work, we investigated the thiol-mediated cyclisation of the substrates **5a**,**b**,**d**,**e** and **11** and were disappointed to find that all these substrates were resistant to cyclisation when treated with *p*-TolSH at room temperature or at reflux and only the products **19**, resulting from a single Michael addition of the thiol to the enone, were observed. We thus employed alternate conditions in which a catalytic amount of TolSNa was added to the reaction, which was then heated at reflux in THF. We were pleased to find that both the enone substrates **5a** and **5b** underwent cyclisation to the corresponding carbocycles **17a** and **17b** in good yield and as essentially single stereoisomers (entries 1 and 2). Structural determination was based on the presence of large trans-diaxial coupling constants for the methine proton at C-2 of the product **17b** (*J* 10.5, 11 Hz) and corroborating NOE measurements. Similar reaction of the enoate substrates **5d** and **5e** were largely unsuccessful and under all conditions employed led primarily to the Michael adducts **19d** and **19e**. However, when we treated the mixed enone/enoate substrate **11** under these conditions, we were pleased to find that two cyclisation products **17f** and **18** were formed in high overall yield (entry 5), the structure of **18** being determined by X-ray crystallography[10] (Fig. 1).

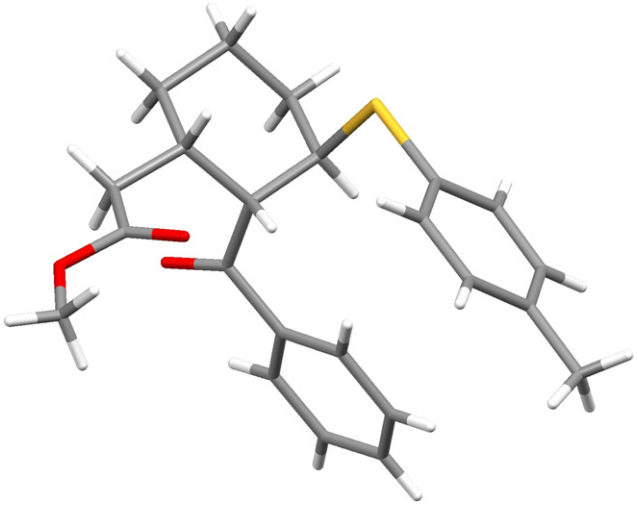
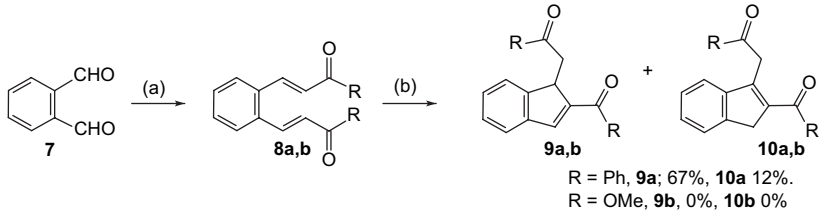
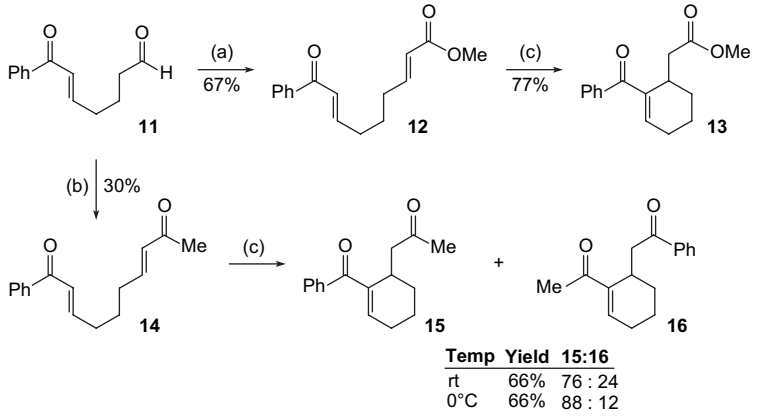


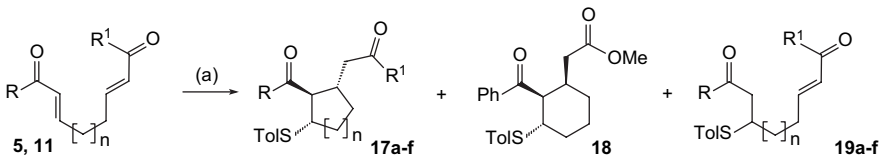
Figure 1. X-ray crystal structure of **18**.



Scheme 3. Reagents and conditions: (a) 2 equiv RCOCH=PPh_3, 42, 85%; (b) 0.3 equiv *n*-Bu_3P, $CHCl_3$, rt, 16 h.



Scheme 4. Reagents and conditions: (a) 1.5 equiv Ph_3PCHCO_2Me, CH_2Cl_2, rt, 48 h; (b) 1.5 equiv $Ph_3PCHCOMe$, CH_2Cl_2, rt, 72 h; (c) 0.3 equiv *n*-Bu_3P, $CHCl_3$, rt, or 0 °C to rt, 16 h.



Scheme 5. Reagents and conditions: (a) 0.9 equiv TolSH, 0.2 TolSNa, Δ, THF, 16 h and see Table 2.

The reason for the formation of a mixture of products in this reaction and the predominance of **18** as the major product is unclear. A strong possibility is that the reaction is a stepwise process in which the addition products **19** are formed rapidly (as appears to be the case from NMR studies) and the cyclisation occurs independently as a result of a base-catalysed enolate formation. It is also possible that the products formed in the case of the enone substrates **5a/b** are equilibrium products from a reversible cyclisation step whilst **17f/18** reflect a non-reversible process due to the lower acidity of the α-protons of the ester function (Scheme 5). These reactions do however demonstrate that an enone is required for an effective cyclisation, a factor that is probably associated with the ability to form an enol/enolate under the conditions employed (Table 2).

Table 2

Entry	**5**	R	R^1	*n*	**17** (%)	**18** (%)	**19** (%)
1	**5a**	Ph	Ph	1	**17a** (58)	—	—
2	**5b**	Ph	Ph	2	**17b** (59)	—	—
3	**5d**	OMe	OMe	1	**17d** (0)[a]	—[a]	67
4	**5e**	OMe	OMe	2	**17e** (0)[a]	—	40
5	**11**	Ph	OMe	2	**17f** (14)	56	—

[a] An inseparable diastereomeric mixture of cyclised products was obtained in 9% yield.

In conclusion, we have reported that the tandem Michael/Michael cyclisation of bis-enones is a viable process for the preparation of five- and six-membered carbocycles, however it does not appear to be applicable to the synthesis of larger ring system, a fact also largely apparent in our studies on tandem Michael/aldol reactions.[1] In addition, the use of bis-enoates in these processes does not appear feasible, however they are suitable acceptor groups in mixed enone/enoate substrates. A general order of reactivity towards addition of phosphines was also established and appears to be Ph>Me>>>OR.

2. Experimental

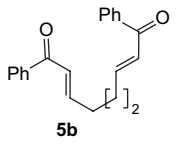
2.1. General

Column chromatography was carried out on Kieselgel (230–400 mesh) with the eluant specified. TLC was conducted on precoated Kieselgel 60 F_{254} (Art. 5554; Merck) glass plates. All reactions were conducted in oven-dried apparatus under an atmosphere of argon. Light petroleum refers to the fraction boiling in the range 35–60 °C. Dichloromethane, diethyl ether and THF were dried and distilled before use. Chemical shifts are reported as δ values relative to TMS as an internal standard. $^1H/^{13}C$ NMR spectra were recorded in deuterochloroform on either a Bruker AC250 or an AVANCE500 spectrometer and referenced to residual $CHCl_3$. IR were recorded as thin films or as chloroform solutions on a Perkin–Elmer 1600 series instrument. Mass spectra were recorded on a VG Masslab Model 12/253 spectrometer using CI (ammonia), EI or ES. All compounds were oils/gums unless otherwise stated.

2.2. Preparation of bis-enones and enoates

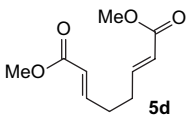
Enones **5a**, **5c** and **5f** were prepared according to the literature procedures,[1,7,11] whilst **5b–e** and **5g** and were prepared as follows.

2.2.1. (2*E*,7*E*)-1,9-Diphenyl-2,7-nonadiene-1,9-dione (5b).[11,12]



Benzoyltriphenylphosphorane (34.58 g, 91 mmol) was dissolved in THF (200 mL) whereupon aqueous glutaric dialdehyde solution (25%, 9.8 mL, 26 mmol) was added together with $MgSO_4$ (ca. 30 g) and the mixture stirred for 2 days. After drying ($MgSO_4$) and filtration, the reaction solvent was evaporated and the solid mass remaining was triturated with ether (4×50 mL). The combined triturates were then dried ($MgSO_4$), filtered and evaporated. Silica gel chromatography (40–60% ether in petrol) gave **5b** (5.37 g) in 68% yield. R_f (40–60% ether in petrol) 0.37; δ_H 1.79 (2H, p, *J* 7.5 Hz, CH_2), 2.41 (4H, dt, *J* 6.3, 7.5 Hz, 2×CH_2), 6.93 (2H, d, *J* 15.3, 2×C*H*), 7.08 (2H, dt, *J* 15.3, 6.3 Hz, 2×C*H*), 7.45–7.95 (10H, m, 2×Ph); δ_C 26.6 (CH_2), 32.1 (CH_2), 126.4 (CH), 128.5 (CH), 132.7 (CH), 137.8 (C), 148.6 (CH), 190.5 (C); ν_{max} 3058, 2933, 1669 (C═O), 1619 (C═C).

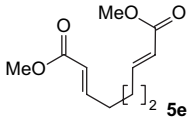
2.2.2. (2*E*,6*E*)-Octa-2,6-dienedioic acid dimethyl ester 5d.



Methoxycarbonylmethylenetriphenylphosphorane (40.00 g, 120 mmol) was added to a solution of succinaldehyde (2.00 g, 23 mmol) dissolved in CH_2Cl_2 (100 mL) and the mixture stirred for 18 h. After this time, the solvent was removed in vacuo and the resulting solid extracted with warm ether (4×50 mL). The extracts were diluted with hexane (100 mL) and cooled to −20 °C overnight. The solution was then filtered to remove precipitated triphenylphosphine

oxide and evaporated to give a crude product, which was purified via column chromatography (30% ether in petrol) to give **5d** (1.42 g) in 31% yield. R_f (30% ether in petrol) 0.18; δ_H 2.38 (4H, m, 2×CH_2), 3.74 (6H, s, 2×OCH_3), 5.85 (2H, d, J 15.6 Hz, 2×CH), 6.95 (2H, dt, J 15.6, 6.5 Hz, 2×CH); δ_C 30.1 (CH_2), 51.3 (OCH_3), 121.8 (CH), 147.1 (CH), 166.5 (C); ν_{max} 2952, 1720 (C═O), 1658 (C═C); m/z (CI, NH_3) 199 (10, MH^+) 167 (100, M^+); HRMS (CI, NH_3) $C_{10}H_{15}O_4$ ([M+H]$^+$) required 199.0970, found 199.0968.

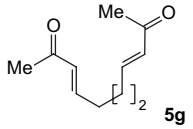
2.2.3. (2*E*,7*E*)-Nona-2,7-dienedioic acid dimethyl ester 5e.



5e

This was prepared in an identical manner to **5b** using methoxycarbonylmethylenetriphenylphosphorane (10.00 g, 29.94 mmol) and glutaric dialdehyde (3.96 mL, 1.00 g, 10 mmol). Silica gel chromatography (30% ether in petrol) gave **5e** (0.73 g) in 35% yield. R_f (30% ether/petrol) 0.22; δ_H 1.65 (2H, m, CH_2), 2.25 (4H, m, 2×CH_2), 3.74 (6H, s, 2×OCH_3), 5.87 (2H, d, J 16.6 Hz, 2×CH), 6.95 (2H, m, 2×CH); δ_C 26.8 (CH_2), 31.6 (CH_2), 51.5 (OCH_3), 121.6 (CH), 148.3 (CH), 166.9 (C); ν_{max} 2994, 2950, 2860, 1726 (C═O), 1658 (C═C); m/z (CI, NH_3) 213 (5, MH^+) 181 (100); HRMS (CI, NH_3) $C_{11}H_{17}O_4$ (MH^+) required 213.1127, found 213.1124.

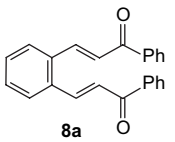
2.2.4. (3*E*,8*E*)-3,8-Undecadiene-2,10-dione 5g.[5b,13]



5g

This was prepared in an identical manner to **5b** using acetylmethylenetriphenylphosphorane (28.9 g, 91 mmol) and aqueous glutaric dialdehyde solution (25%, 9.8 mL, 26 mmol). Silica gel chromatography (30–50% ether in petrol) gave **5g** (2.71 g) in 58% yield. R_f (30% ether/petrol) 0.03; δ_H 1.46 (2H, pentet, J 7.5 Hz, CH_2), 2.01 (6H, s, 2×CH_3), 2.06 (4H, dt, J 4.2, 7.5 Hz, 2×CH_2), 5.85 (2H, d, J 16.2 Hz, 2×CH), 6.56 (2H, dt, J 16.2, 6.7 Hz, 2×CH); δ_C 26.0 (CH_2), 26.4 (CH_3), 31.3 (CH_2), 131.3 (CH), 146.9 (CH), 197.6 (C).

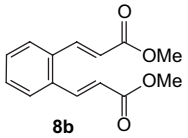
2.2.5. (*E*)-3-{2-[(*E*)-3-Oxo-3-phenyl-1-prophenyl]phenyl}-1-phenyl-2-propen-1-one 8a.[8c]



8a

Benzoylmethylenetriphenylphosphorane (2.84 g, 7.47 mmol) and *o*-phthalicdicarboxaldehyde (0.4 g, 3.0 mmol) were dissolved in CH_2Cl_2 (5 mL) and stirred at rt for 2 days. After evaporation, silica gel chromatography (30–50% ether/petrol) gave **8a** (0.43 g). R_f (50% ether/petrol) 0.52; δ_H 7.42–7.64 (8H, m, 8×ArH), 7.60 (2H, d, J 15.9 Hz, 2×CH), 7.75 (2H, m, 2×ArH), 8.05 (4H, m, 4×ArH), 8.21 (2H, d, J 15.9 Hz, 2×CH); δ_C 126.1 (CH), 128.2 (CH), 128.6 (CH), 130.2 (CH), 133.0 (CH), 135.4 (C), 137.9 (C), 141.7 (CH), 190.1 (C); ν_{max} 3018, 1663 (C═O), 1605, 1447, 928, 754.

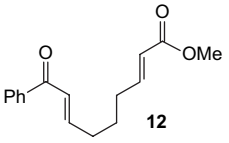
2.2.6. (*E*)-4-[2-((*E*)-3-Oxo-but-1-enyl)-phenyl]-but-3-en-2-one 8b.



8b

o-Phthalicdicarboxaldehyde (0.4 g 3.0 mmol) and methoxycarbonylmethylenetriphenylphosphorane (3.00 g, 9.00 mmol) were dissolved in THF (5 mL) and stirred at rt for 2 days. After evaporation, column chromatography (30% ether/petrol) gave **8b** (0.63 g) as a white solid in 85% yield; mp 46–48 °C, R_f (30% ether/petrol) 0.31; δ_H 3.83 (6H, s, 2×OMe), 6.35 (2H, d, J 15.8 Hz, 2×CH), 7.39 (2H, m, 2×ArH), 7.56 (2H, m, 2×ArH), 8.03 (2H, d, J 15.8 Hz, 2×CH); δ_C 51.7 (OMe), 121.5 (CH), 126.6 (CH), 129.4 (CH), 132.4 (C), 141.5 (CH), 166.8 (C); ν_{max} 3064, 3022, 2951, 1720 (C═O), 1635 (C═C), 1436; m/z (CI, NH_3) 264 (100, M+NH_4^+); HRMS (CI, NH_3) $C_{14}H_{18}NO_4$ (M+NH_4^+) required 264.1236, found 264.1235.

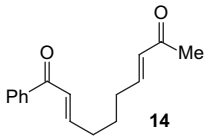
2.2.7. (2*E*,7*E*)-9-Oxo-9-phenyl-nona-2,7-dienoic acid methyl ester 12.



12

(*E*)-7-Phenyl-7-oxohept-5-enal[1c] **11** (1.5 g, 7.4 mmol) and carbomethoxymethylenetriphenylphosphorane (3.7 g, 11.1 mmol) were dissolved in CH_2Cl_2 (5 mL) and stirred at rt for 48 h. After evaporation, column chromatography (30% ether in petrol) gave **12** (1.28 g) in 67% yield. R_f (30% ether/petrol) 0.39; δ_H 1.70 (2H, pentet, J 7.5 Hz, CH_2), 2.33 (2H, dt, J 7.3, 7.0 Hz, CH_2), 2.35 (2H, dt, J 7.3, 7.0 Hz, CH_2), 3.73 (3H, s, OMe), 5.85 (1H, d, J 15.9 Hz, CH), 6.89 (1H, d, J 15.9 Hz, CH), 7.00 (2H, m, 2×CH), 7.43–7.94 (5H, m, Ph); δ_C 26.5 (CH_2), 31.5 (CH_2), 32.0 (CH_2), 51.5 (OMe), 121.6 (CH), 126.4 (CH), 128.5 (CH), 128.5 (CH), 132.7 (CH), 137.8 (C), 148.4 (C), 148.5 (C), 166.9 (C), 190.6 (C); ν_{max} 3062, 2950, 1672 (C═O), 917; m/z (CI, NH_3) 259 (60%, MH^+) 258 (20%, M^+); HRMS (CI, NH_3) $C_{16}H_{19}O_3$ (MH^+) required 259.1329, found 259.1329.

2.2.8. Methyl(2*E*,7*E*)-9-oxo-9-phenyl-2,7-nonadienoate 14.[14]



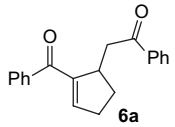
14

(*E*)-7-Phenyl-7-oxohept-5-enal[1c] **11** (337 mg, 1.4 mmol) and acetylmethylenetriphenylphosphorane (668 mg, 2.1 mmol) were dissolved in CH_2Cl_2 (3 mL) and stirred at rt for 3 days. After evaporation, column chromatography (20% ether/petrol) gave **14** (107 mg) in 30% yield. R_f (20% ether/petrol) 0.22; δ_H 1.63 (2H, pentet, *J* 7.5 Hz, CH_2), 2.16 (3H, s, CH_3), 2.26 (4H, m, 2CH_2), 6.01 (1H, d, *J* 15.9 Hz, C*H*), 6.72 (1H, dt, *J* 15.9, 7.0 Hz, C*H*), 6.83 (1H, d, *J* 15.3 Hz, C*H*), 6.96 (1H, dt, *J* 15.3, 6.4 Hz, C*H*), 7.43–7.50 (3H, m, 3×Ar*H*), 7.84–7.86 (2H, m, 2×Ar*H*); δ_C 26.4 (CH_2), 26.8 (CH_3), 31.7 (CH_2), 32.0 (CH_2), 126.2 (CH), 128.4 (CH), 128.5 (CH), 131.6 (CH), 132.6 (CH), 137.6 (C), 147.1 (CH), 148.4 (CH), 190.3 (C), 198.3 (C); ν_{max} 3000, 2949, 1708 (C=O), 1601, 1450, 754.

2.3. Cyclisation of bis-enones 5

General method: The required bis-enones **5a**–**g** (100–200 mg) were dissolved in chloroform (1 mL per mmol of substrate) and neat *n*-Bu_3P (0.3 equiv) was added via syringe and the reaction agitated. Further amounts of *n*-Bu_3P were added if required (see Table 1). After completion of the reaction, typically 4–16 h for successful reactions (monitored via ^1H NMR) the solvent was removed under vacuum and the cyclised product purified by silica gel chromatography using an ether/petrol mixture, see specific examples for R_f values.

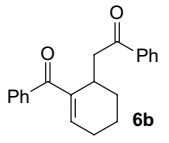
2.3.1. 2-(2-Benzoylcyclopent-2-enyl)-1-phenylethanone 6a.



6a

Yield: 80%; R_f (20% ether/petrol) 0.19; δ_H 1.81 (1H, m, CH*H*), 2.35 (1H, m, CH*H*), 2.58 (1H, m, CH*H*), 2.69 (1H, m, CH*H*), 2.84 (1H, dd, *J* 15.5, 10.4 Hz, CH*H*), 3.76 (1H, m, C*H*), 3.81 (1H, dd, *J* 15.5, 2.8 Hz, CH*H*), 6.61 (1H, dt, *J* 1.6, 2.6 Hz, C*H*), 7.46–8.08 (10H, m, 2×Ph); δ_C 29.5 (CH_2), 32.6 (CH_2), 41.6 (CH), 42.4 (CH_2), 128.3 (CH), 132.0 (CH), 133.0 (CH), 136.9 (C), 139.0 (C), 146.1 (C), 148.0 (CH), 194.2 (C), 199.8 (C); ν_{max} 3059, 2917, 1682 (C=O), 1636 (C=C), 1597, 1447, 719; MS (EI) 290 (55%, M^+); HRMS (EI) $C_{20}H_{18}O_2$ (M^+) required 290.1307, found 290.1308.

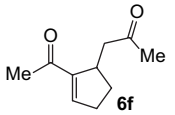
2.3.2. 2-(2-Benzoyl-2-cyclohexen-1-yl)-1-phenyl-1-ethanone 6b.



6b

Yield: 68%; R_f (20% ether/petrol) 0.24; δ_H 1.72 (4H, m, 2×CH_2), 2.30 (2H, m, CH_2), 2.83 (1H, dd, *J* 10.6, 14.6 Hz, CHH), 3.44 (1H, dd, *J* 10.6, 3.1 Hz, CHH), 3.52 (1H, m, CH), 6.66 (1H, t, *J* 3.5 Hz, CH), 7.44–8.11 (10H, m, 2×Ph); δ_C 18.1 (CH_2), 26.1 (CH_2), 26.5 (CH_2), 30.4 (CH), 42.5 (CH_2), 128.1 (CH), 128.5 (CH), 128.6 (CH), 129.2 (CH), 131.6 (CH), 133.0 (CH), 136.7 (C), 138.8 (C), 141.5 (C), 145.0 (CH), 198.1 (C), 199.7 (C); ν_{max} 3000, 2935, 1675 (C=O), 1641, 1597, 1447, 908; MS (EI): 304 $[M]^+$ (75%); HRMS (EI) $C_{21}H_{20}O_2$ ($[M]^+$) required 304.1463, found 304.1462.

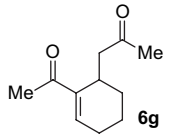
2.3.3. 1-(2-Acetyl-2-cyclopenten-1-yl)-acetone 6f.



6f

Yield: 66%; R_f (40% ether/petrol) 0.16; δ_H 1.54 (1H, m, CH*H*), 2.10 (3H, s, CH_3), 2.20 (1H, m, CH*H*), 2.28 (3H, s, CH_3), 2.50 (2H, m, CH_2), 2.96 (1H, dd, *J* 16.8, 3.4 Hz, CH*H*), 3.33 (1H, m, C*H*), 6.75 (1H, dt, *J* 1.5, 2.8 Hz, C*H*); δ_C 26.9 (CH_2), 29.8 (CH_2), 29.9 (CH_3), 31.9 (CH_3), 39.2 (CH_2), 47.5 (CH), 146.0 (C), 196.6 (C), 208.4 (C); ν_{max} 2949, 1721 (C=O), 1673 (C=O) 1627 (C=C); MS (CI) 184 (100%, M+NH_4^+); HRMS (CI, NH_3) $C_{10}H_{18}NO_2$ (M+NH_4^+) required 184.1338, found 184.1336.

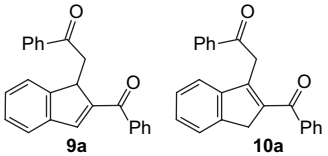
2.3.4. 1-(2-Acetyl-cyclohex-2-enyl)-propan-2-one 6g.



6g

Yield: 58%; R_f (30% ether/petrol) 0.19; δ_H 1.59 (4H, m, 2×CH_2), 2.16 (3H, s, CH_3), 2.23–2.33 (3H, m, CH*H*, CH_2), 2.27 (3H, s, CH_3), 2.60 (1H, dd, *J* 15.7, 3.4 Hz, CH*H*), 3.15 (1H, m, C*H*), 6.95 (1H, t, *J* 4.0 Hz, C*H*); δ_C 16.9 (CH_2), 25.5 (CH_3), 25.9 (CH_2), 26.1 (CH_2), 27.6 (CH_3), 29.7 (CH), 47.4 (CH_2), 141.9 (C), 142.6 (CH), 198.7 (C=O), 208.1 (C=O); ν_{max} 2923, 1715 (C=O), 1664 (C=O) 1616 (C=C) 1380; MS (EI) 180 (40%, M^+); HRMS (EI) $C_{11}H_{16}O_2$ (M^+) required 180.1150, found 180.1147.

2.3.5. 2-(2-Benzoyl-1*H*-inden-1-yl)-1-phenyl-1-ethanone 9a and 2-(2-benzoyl-1*H*-inden-3-yl)-1-phenyl-1-ethanone 10a.



9a **10a**

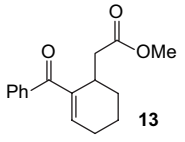
Bis-enone **8a** (84 mg, 0.249 mmol) was dissolved in chloroform (1 mL), treated with *n*-Bu_3P (12.2 μL) and stirred at rt

for 16 h. After evaporation, silica gel chromatography gave the title compounds **9a** and **10a** in a combined yield of 79% and in a 85:15 ratio.

Compound **9a**: R_f (30% ether/petrol) 0.32; δ_H 3.20 (1H, dd, *J* 17.0, 9.5 Hz, CH*H*), 4.08 (1H, dd, *J* 17.0, 3.2 Hz, CH*H*), 4.71 (1H, ddd, *J* 9.5, 3.2, 1.6 Hz, C*H*), 7.33–7.63 (13H, m, CH, 12×Ar*H*), 7.82 (2H, m, 2×Ar*H*), 7.99 (2H, m, 2×Ar*H*); δ_C 39.5 (CH_2), 45.3 (CH), 124.2 (CH), 124.5 (CH), 127.5 (CH), 128.6 (CH), 132.0 (CH), 133.1 (CH), 136.9 (C), 139.2 (C), 141.6 (C), 144.3 (CH), 147.4 (C), 149.5 (C), 193.0 (C), 198.5 (C); ν_{max} 3066, 2923, 1683 (C═O), 1628 (C═C), 1598, 1447, 908; *m/z* (CI, NH_3) 339 (100% $[M+H]^+$); HRMS (CI, NH_3) $C_{24}H_{18}O_2$ ($[M+H]^+$) required 339.1385, found 339.1383.

Compound **10a**: R_f (30% ether/petrol) 0.24; δ_H 3.95 (2H, s, CH_2), 4.49 (2H, s, CH_2), 7.33–7.63 (10H, m, 10×Ar*H*), 7.82 (2H, m, 2×Ar*H*), 7.99 (2H, m, 2×Ar*H*); δ_C 37.5 (CH_2), 40.8 (CH_2), 121.8 (CH), 124.1 (CH), 126.9 (CH), 127.8 (CH), 128.2 (CH), 128.4 (CH), 128.6 (CH), 132.0 (CH), 133.3 (CH), 136.6 (C), 140.1 (C), 141.1 (C), 143.5 (C), 144.4 (C), 146.1 (C), 195.0 (C), 195.8 (C); ν_{max} 3018, 2978, 1684 (C═O), 1634 (C═C), 1521, 1423, 928; *m/z* (CI, NH_3) 339 (100% $[M+H]^+$); HRMS (CI, NH_3) $C_{24}H_{18}O_2$ ($[M+H]^+$) required 339.1385, found 339.1384.

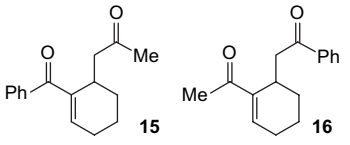
2.3.6. (2-Benzoyl-cyclohex-2-enyl)-acetic acid methyl ester 13.



13

Keto-ester **12** (100 mg, 0.39 mmol) was dissolved in chloroform (1 mL) at 20 °C and tri-*n*-butyl phosphine (51 μL, 0.205 mmol) was added. The reaction was agitated for 1 h, following which the solvent was evaporated and the crude material was purified via column chromatography (30% ether in petrol) to give **13** (77 mg) in 77% yield as an oil. R_f (30% ether/petrol) 0.3; δ_H 1.65 (2H, m, CH_2), 1.73 (2H, m, CH_2), 1.75 (1H, m, C*H*), 2.25 (2H, m, CH_2), 2.40 (2H, m, CH_2), 3.63 (3H, s, OMe), 6.55 (1H, dt, CH, *J* 4.0, 1.2 Hz), 7.41–7.67 (5H, m, Ph); δ_C 18.3 (CH_2), 26.0 (CH_2), 27.2 (CH_2), 30.1 (CH), 37.9 (CH_2), 51.5 (Me), 128.0 (CH), 129.3 (CH), 131.6 (C), 138.6 (C), 141.0 (C), 144.2 (CH), 172.9 (C), 197.6 (C); ν_{max} 3024 (C–H), 2934 (C–H), 2864 (C–H), 1732 (C═O), 1644 (C═C); *m/z* (CI, NH_3) 259 (100%, $[M+H]^+$) 258 (25%, $[M]^+$); HRMS (CI, NH_3) $C_{16}H_{19}O_3$ ($[M+H]^+$) required 259.1329, found 259.1328.

2.3.7. 1-(2-Benzoyl-2-cyclohexen-1-yl)-acetone 15 and 2-(2-acetyl-2-cyclohexen-1-yl)-1-phenyl-1-ethanone 16.



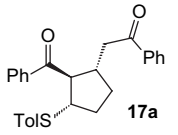
Keto-ester **14** (0.190 g, 0.78 mmol) was dissolved in chloroform (1 mL) at 0 °C and tri-*n*-butyl phosphine (61 μL, 0.245 mmol) was added. The reaction was agitated for 1 h and the solvent was evaporated. The crude material was purified via column chromatography (15% ether in petrol) to give **15** and **16** (0.126 g) as an inseparable mixture (88:12) in 66% yield.

Compound **15** (major): R_f (15% ether/petrol) 0.31; δ_H (2H, m, CH_2), 2.15 (3H, s, CH_3), 2.20 (2H, m, CH_2), 2.26 (2H, m, CH_2), 2.45 (1H, dd, *J* 15.9, 9.5 Hz, CH*H*), 2.69 (1H, dd, *J* 15.9, 3.5 Hz, CH*H*), 3.34 (1H, m, C*H*), 6.55 (1H, m, ═C*H*), 7.38–7.65 (5*H*, m, Ph); δ_C 18.2 (CH_2), 26.0 (CH_2), 26.9 (CH_2), 29.2 (CH_3), 29.9 (CH), 47.4 (CH_2), 128.1 (CH), 129.2 (CH), 131.6 (CH), 138.6 (C), 141.2 (C), 144.4 (CH), 197.9 (C), 208.1 (C). Compound **15** (minor): R_f (15% ether/petrol) 0.31; δ_H (partial data) 3.46 (1H, m, C*H*), 7.00 (1H, m, ═C*H*); δ_C 16.8 (CH_2), 25.6 (CH_3), 26.0 (CH_2), 26.2 (CH), 28.8 (CH), 42.6 (CH_2), 128.5 (CH), 129.2 (CH), 132.9 (CH), 136.7 (C), 142.3 (C), 143.1 (CH), 199.0 (C), 199.9 (C); ν_{max} 3020 (C–H), 2941 (C–H), 2875 (C–H), 1715 (C═O), 1678 (C═O) 1644 (C═C); *m/z* (CI, NH_3) 243 (100%, $[M+H]^+$); HRMS (CI, NH_3) $C_{16}H_{19}O_2$ ($[M+H]^+$) required 243.1385, found 243.1382.

2.4. Thiolate cyclisation

General method: The required enone/enoate (1–5 mmol) was dissolved in THF (4 mL per mmol) and 4-methylbenzenethiol (0.9 equiv) together with sodium-4-methylbenzenethiolate (0.25 equiv) were added. The reaction mixture was then refluxed for 16 h, cooled, evaporated onto silica gel (ca. 0.5 g per mmol substrate) and purifed by column chromatography (ether/petrol, see specific examples).

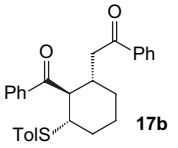
2.4.1. 2-(2-Benzoyl-3-*p*-tolylsulfanyl-cyclopentyl)-1-phenyl-ethanone 17a.



17a

Compound **17a**: 58% yield; R_f (10% ether/petrol) 0.14; δ_H 1.78 (1H, m, CH*H*), 1.89 (1H, m, CH*H*), 2.17 (2H, m, CH_2), 2.29 (3H, s, CH_3), 3.02 (1H, m, C*H*), 3.15 (2H, d, *J* 7.3 Hz, CH_2), 3.65 (1H, t, *J* 6.0 Hz, C*H*), 3.87 (1H, m, C*H*), 7.01–7.92 (14H, m, 2×Ph, 4×ArH); δ_C 21.0 (CH_3), 31.5 (CH_2), 32.8 (CH_2), 39.9 (CH), 44.0 (CH_2), 51.9 (CH), 58.3 (CH), 128.0 (CH), 128.5 (CH), 128.5 (CH), 129.7 (CH), 131.3 (C), 132.4 (CH), 133.0 (CH), 133.5 (CH), 133.6 (CH), 136.7 (C), 137.0 (C), 137.3 (C), 198.9 (C), 201.4 (C); ν_{max} 3058, 2922, 1680 (C═O), 1596, 1447; *m/z* (CI, NH_3): 415 (100%, $[M+H]^+$); HRMS (CI, NH_3) $C_{27}H_{26}O_2S$ ($[M+H]^+$) required 415.1732, found 415.1727.

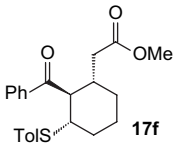
2.4.2. 2-(2-Benzoyl-3-*p*-tolylsulfanyl-cyclohexyl)-1-phenyl-ethanone 17b.



17b

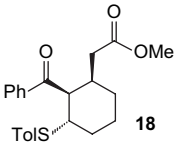
Compound **17b**: 59% yield; R_f (10% ether/petrol) 0.11; δ_H 0.98 (1H, m, CH*H*), 1.12 (1H, m, CHH), 1.37 (1H, m, CHH), 1.43 (1H, m, CHH), 1.76 (1H, m, CHH), 1.91 (3H, s, CH_3), 2.11 (1H, m, C*H*), 2.13 (1H, m, CH*H*), 2.17 (1H, m, CH*H*), 2.51 (1H, m, CH*H*), 2.95 (1H, ddd, *J* 4.0, 10.5, 12.0 Hz, C*H*), 3.14 (1H, dd, *J* 10.5, 10.5 Hz, C*H*), 7.00–7.69 (14H, m, 2×Ph, 4×ArH); δ_C 21.1 (CH_3), 25.4 (CH_2), 30.9 (CH_2), 34.2 (CH_2), 39.5 (CH), 43.6 (CH_2), 50.8 (CH), 53.9 (CH), 128.1 (CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 129.5 (CH), 130.2 (C), 133.1 (CH), 133.3 (CH), 133.4 (CH), 136.6 (C), 137.5 (C), 139.0 (C), 198.7 (C), 203.9 (C); ν_{max} 3061, 2927, 1676, 1596, 811, 703; *m*/*z* (CI, NH_3) 429 (100%, $[M+H]^+$); HRMS (CI, NH_3) $C_{28}H_{29}O_2S$ ($[M+H]^+$) required 429.1888, found 429.1889.

2.4.3. (2-Benzoyl-3-*p*-tolylsulfanyl-cyclohexyl)-acetic acid methyl esters 17f and 18.



17f

Compound **17f** (minor): 14% yield; R_f (30% ether/petrol) 0.3; δ_H 0.75 (1H, m, CH*H*), 1.00 (2H, m, CH_2), 1.37 (2H, m, CH_2), 1.61 (1H, m, CH*H*), 1.70 (1H, m, CH*H*), 1.76 (1H, m, CH*H*), 1.85 (3H, s, CH_3), 1.86 (1H, m, C*H*), 2.87 (1H, ddd, *J* 11.3, 11.3, 3.8 Hz, C*H*), 3.02 (1H, dd, *J* 11.3, 10.4 Hz, C*H*), 3.10 (3H, s, CH_3), 7.00–7.50 (9H, m, Ph, 4×Ar*H*); δ_C 20.5 (CH_2), 24.4 (CH_3), 31.5 (CH_2), 33.8 (CH_2), 38.5 (CH_2), 38.8 (CH_3), 50.4 (CH), 51.0 (CH), 52.6 (CH), 128.3 (CH), 128.6 (CH), 128.8 (CH), 131.2 (C), 132.7 (CH), 134.3 (C), 136.4 (C), 171.0 (C), 203.0 (C); ν_{max} 3022, 2934, 2857, 1726 (C═O), 1674 (C═O); *m*/*z* (ES): 383 (100%, $[M+H]^+$); HRMS (ES) $C_{23}H_{27}O_3S$ ($[M+H]^+$) required 383.1681, found 383.1679.



18

Compound **18** (major): 55% yield; R_f (30% ether/petrol) 0.40; mp 56–58 °C; δ_H 1.18 (2H, m, CH_2), 1.25 (2H, m, CH_2), 1.53 (2H, m, CH_2), 1.95 (3H, s, CH_3), 1.98 (2H, m, CH_2), 2.32 (1H, m, C*H*), 3.04 (1H, m, C*H*), 3.10 (3H, s, CH_3), 3.32 (1H, dd, *J* 6.0, 4.7 Hz, C*H*), (9H, m, Ph, 4×Ar*H*); δ_C 20.8 (CH_2), 21.2 (CH_3), 28.8 (CH_2), 29.3 (CH_2), 32.1 (CH), 35.8 (CH_2), 46.9 (CH), 48.8 (CH), 51.4 (Me), 128.2 (CH), 128.6 (CH), 129.8 (CH), 129.9 (C), 130.3 (C), 133.0 (CH), 133.2 (C), 135.0 (CH), 173.1 (C), 200.8 (C); ν_{max} 3058, 2938, 2870, 1726; *m*/*z* (ES) 383 (100%, $[M+H]^+$); HRMS (CI, NH_3) $C_{23}H_{27}O_3S$ ($[M+H]^+$) required 383.1681, found 383.1683.

Acknowledgements

Thanks are given to the EPSRC for a studentship to PMB (GR/M50584), the Erasmus Scheme (NK) and to the EPSRC Mass Spectrometry Centre at Swansea.

References and notes

1. (a) Black, G. P.; Dinon, F.; Fratucello, S.; Murphy, P. J.; Nielsen, M.; Williams, H. L.; Walshe, N. D. A. *Tetrahedron Lett.* **1997**, *38*, 8561–8564; (b) Dinon, F.; Richards, E. L.; Murphy, P. J.; Hibbs, D. E.; Hursthouse, M. B.; Malik, K. M. A. *Tetrahedron Lett.* **1999**, *40*, 3279–3282; (c) Richards, E. L.; Murphy, P. J.; Dinon, F.; Fratucello, S.; Brown, P. M.; Gelbrich, T.; Hursthouse, M. B. *Tetrahedron* **2001**, *57*, 7771–7784.
2. Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 2404–2405.
3. Wang, L.-C.; Luis, A. L.; Agapiou, K.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 2402–2403.
4. (a) Rauhut, M. M.; Currier, H. U.S. Patent 3074999, 19630122, 1963, American Cyanamid; (b) McClure, J. D. *J. Org. Chem.* **1970**, *35*, 3045–3048.
5. (a) Saito, S.; Hirohara, Y.; Narahara, O.; Moriwake, T. *J. Am. Chem. Soc.* **1989**, *111*, 4533–4535; (b) Klimko, P. G.; Singleton, D. A. *J. Org. Chem.* **1992**, *57*, 1733–1740; (c) Cooke, M. P.; Gopal, D. *Tetrahedron Lett.* **1994**, *35*, 2837–2840; (d) Klimko, P. G.; Singleton, D. A. *Synthesis* **1994**, 979–982; (e) Savchenko, A. V.; Montgomery, J. *J. Org. Chem.* **1996**, *61*, 1562–1563; (f) Montgomery, J.; Oblinger, E.; Savchenko, A. V. *J. Am. Chem. Soc.* **1997**, *49*, 4911–4920.
6. (a) Voigt, K.; Lansky, A.; Noltemeyer, M.; de Meijere, A. *Liebigs Ann.* **1996**, 899–911; (b) Erguden, J.-K.; Moore, H. W. *Org. Lett.* **1999**, *1*, 375–377; (c) Chavan, S. P.; Subbarao, Y. T.; Chittiboyina, A. G.; Sivappa, R.; Suresh, C. G. *Tetrahedron: Asymmetry* **2001**, *12*, 1101–1103.
7. (a) Uyehara, T.; Shida, N.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 753–754; (b) Uyehara, T.; Shida, N.; Yamamoto, Y. *J. Org. Chem.* **1992**, *57*, 3139–3145; (c) Shida, N.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1992**, *57*, 5049–5051; (d) Urones, J. G.; Garrido, N. M.; Diez, D.; Dominguez, S. H.; Davies, S. G. *Tetrahedron: Asymmetry* **1997**, *8*, 2683–2685; (e) Urones, J. G.; Garrido, N. M.; Díez, D.; Dominguez, S. H.; Davies, S. G. *Tetrahedron: Asymmetry* **1999**, *10*, 1637–1641; (f) Bull, S. D.; Davies, S. G.; Smith, A. D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2931–2938.
8. (a) Renaud, R. N.; Stephens, C. J.; Bérubé, D. *Can. J. Chem.* **1982**, *60*, 1687–1691; (b) Boger, D. L.; Mathvink, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 4003–4008; (c) Suwa, T.; Nishino, K.; Miyatake, M.; Shibata, I.; Baba, A. *Tetrahedron Lett.* **2000**, *41*, 3403–3406.
9. (a) Murphy, P. J.; Williams, H. L.; Hibbs, D. E.; Hursthouse, M. B.; Malik, K. M. A. *Tetrahedron* **1996**, *52*, 8315–8332; (b) Black, G. P.; Murphy, P. J.; Walshe, N. D. A. *Tetrahedron* **1998**, *54*, 9481–9488.
10. Cambridge Crystallographic Data Centre deposition number CCDC 615910. Formula: $C_{23}H_{26}O_3S$: Unit cell parameters: *a* 7.22450(10), *b* 24.0470(3), *c* 11.75190(10), *β* 92.2160(10), space group *P*21/*c*.
11. Hon, Y.-S.; Chu, K.-P.; Hong, P.-C.; Lu, L. *Synth. Commun.* **1992**, *22*, 429–443.
12. Montgomery, J.; Savchenko, A. V.; Zhao, Y. *J. Org. Chem.* **1995**, *60*, 5699–5701.
13. Enholm, E. J.; Kinter, K. S. *J. Am. Chem. Soc.* **1991**, *113*, 7784–7785.
14. Felton, G. A. N.; Bauld, N. L. *Tetrahedron* **2004**, *60*, 10999–11010.