Highly Diastereoselective Anionic [3 + 2] Annulation Strategy for Functionalized Cyclopentenes *via* α-Oxoketene Dithioacetals

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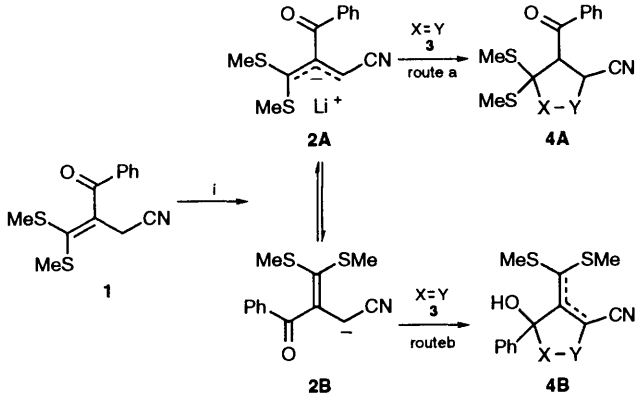
The allyl anion **2** derived from deprotonation of benzoyl(cyanomethyl)ketene dithioacetal **1** with LDA, is shown to undergo anionic [3 + 2] annulation with various activated olefins *via* tandem Michael addition aldol condensation to afford the corresponding functionalized cyclopentenes in a highly diastereoselective manner.

The development of methodology for the construction of the functionalized cyclopentene ring remains a focus of intense synthetic efforts and many ingenious approaches have been described.[1] The [3 + 2] annulation strategy involving condensation of a 3-carbon fragment (including allenylsilane and allylstannanes) and other ambiphilic conjunctive reagents with electron-deficient olefins is still one of the most potent approaches for the construction of these ring systems.[2,3] Similarly, the transition metal-catalysed [3 + 2] cycloaddition of trimethylenemethane (TMM) equivalent conjunctive reagents with various olefins has received considerable attention for five-membered ring formation.[1,2b] Of particular interest are anionic [3 + 2] cycloadditions involving [π_4s + π_2s] cycloaddition of allyl anion and olefins to give the cyclopentane ring.[3] Although several workers[3] have carried out pioneering work in this direction, a process that parallels the Diels–Alder reaction in its scope and effectiveness has yet to be developed.

In continuation of our synthetic programme on oxoketene dithioacetals,[4] we envisioned the utilization of the anion **2** derived from the bifunctional ketene dithioacetal **1**, as 1,3-dipole which would be able to react with various activated olefins *via* a purely anionic process with concurrent formation of two carbon–carbon bonds to afford cyclopentane derivatives (see Scheme 1). One might expect two modes in which the **2** can



Scheme 1 *Reagents and conditions:* i, LDA, THF, −78 °C, 0.5–1 h

participate in a [3 + 2] anionic process. The first reaction (route a) *via* Michael-induced ring closure (MIRC) (Tandem Michael addition) is, however, considered to be sluggish, since the overall reaction is equivalent to 5-*endo-trig* ring closure which has been predicted by Baldwin to be a disfavoured process.[5] Route b in which **1** behaves as functionalized bis(methylthio) TMM equivalent involving a tandem Michael addition aldol condensation appears to be more feasible (see Scheme 1). In our earlier work, we have shown that the anion **2** reacts with aryl isothiocyanates by route a to give substituted thiophenes, whereas with benzaldehyde, route b is followed to afford dihydrofuran derivatives.[6] We have now found that **2** undergoes [3 + 2] annulation with activated olefins *via* route b in a highly regio- and stereoselective manner to afford substituted cyclopentene derivatives in good yields. The results of these studies are reported herein.

In a typical experiment, a solution of **1** (10 mmol) in THF was added to LDA (13 mmol) at −78 °C under a nitrogen atmosphere, followed by addition of benzylideneacetophenone (10 mmol). Subsequent work-up and column chromatography of the reaction mixture afforded a white solid (88%), which was characterized as the cyclopentene adduct **4a** (Table 1) as a single diastereoisomer on the basis of spectral and analytical data and also by X-ray crystallography which further established the intramolecular hydrogen bonding between the 5-carbonyl and the 1-hydroxy group.*

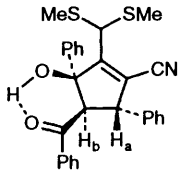
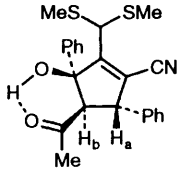
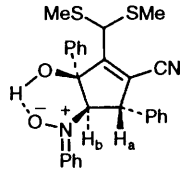
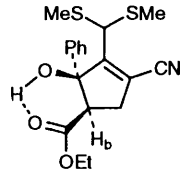
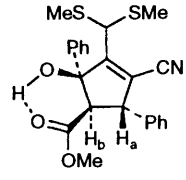
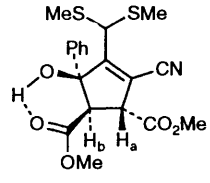
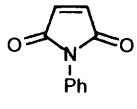
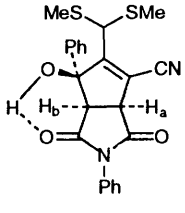
Further cyclization of **2** with other dienophiles, *i.e.* benzylideneacetone, nitrostyrene, ethyl acrylate, ethyl cinnamate, methyl fumarate (entries 2–6) under identical conditions also afforded the stereohomogenous cyclopentene derivatives **4b–f** (Table 1) in high yields as determined by ^{1}H and ^{13}C NMR spectroscopy. Reaction of **2** with *N*-phenylmaleimide similarly, yielded the bicyclic adduct **4g** (entry 8). Attempts to isolate open-chain acyclic Michael adducts from any of these reactions were unsuccessful.

The cyclopentenes **4a–g** are apparently formed *via* route b involving a tandem Michael addition aldol condensation. Addition of HMPA or TMEDA to the reaction mixture (in the reaction of **2** with **3a**) changed neither the course of the reaction nor the stereochemistry of the adduct **4a**. Interestingly, the reaction of **2a** with dimethyl maleate afforded the same cycloadduct **4f** obtained by addition of **2a** with dimethyl fumarate; this indicates the importance of the *trans* arrangement of the ester groups during cyclization. Also, the attempted cycloaddition of **2** with acrylonitrile and stilbene afforded no open-chain or cyclic adducts and the starting material **1** was recovered along with intractable tar.

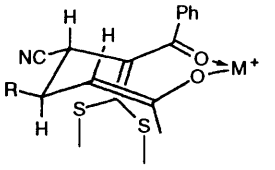
These results can be explained by a stepwise mechanism wherein the bond rotation is competitive with the cyclization

* A *trans* stereochemical assignment for H_a and H_b in **4a** was further supported by its NOE difference spectra showing very weak (< 1%) NOE enhancement. A Dreiding model of **4a** also supports a *trans* correlation between the 4-phenyl and 5-benzoyl groups with a H_a–C(4)–C(5)–H_b dihedral angle > 125°. Attempted acylation of **4a** with acetyl chloride gave initially the acetylated product as a white solid (supported by its ^{1}H NMR spectra) which underwent cleavage to give back **4a** during crystallization with various solvents; this indicates that **4a** is stabilized by intramolecular hydrogen bonding between the 5-benzoyl and 1-hydroxy groups.

Table 1 Synthesis of cyclopentene derivatives

Entry	Dienophile	Product	Yield (%)	M.p. (°C)
1	PhCH=CHCOPh **3a**	 **4a**	88	162–163
2	$PhCH=CHCOCH_3$ **3b**	 **4b**	61	167–168
3	$PhCH=CHNO_2$ **3c**	 **4c**	66	148–150
4	$CH_2=CHCO_2Et$ **3d**	 **4d**	75	93–94
5	$PhCH=CHCO_2Me$ **3e**	 **4e**	71	164–165
6	$MeO_2CCH=CHCO_2Me$	 **4f**	72	146–148
7	**3f**, *E* **3g**, *Z*			
8		 **4g**	65	85–86

of the unobserved acyclic Michael adduct. In most of the cases, it is possible that the acyclic intermediate is chelated (Structure **A**) in such a way that the bond rotation is somewhat hindered, while with dimethyl maleate, a retro-Michael reaction could play a role in directing the stereochemical outcome of the cyclization step because of the conformational requirements of the chelated acyclic adduct. Failure of acrylonitrile and stilbene to afford cyclic adducts with **2** could also be rationalized in terms of inability of the resulting Michael adducts to exist in chelated form and resulting in their retro-Michael cleavage under the experimental conditions.



A

In conclusion, we have demonstrated that the readily available bifunctional α-oxoketene dithioacetals are potentially useful substrates for anionic [3 + 2] cyclopentannulation with a variety of acyclic and cyclic acceptors in a highly diastereoselective manner. The experimental simplicity and the mildness of reaction conditions coupled with the functional group flexibility in oxoketene dithioacetals should allow the application of this methodology to the synthesis of a wide range of functionalized stereohomogenous cyclopentene derivatives. We are now exploring the scope and mechanistic detail of this novel annulation with various functionalized ketene dithioacetals.

Experimental

Melting points were measured on a Thomas Hoover melting point (Capillary Method) apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 297 spectrophotometer. ^{1}H NMR (90 MHz) spectra were recorded on a Varian EM-390 spectrometer. Highfield ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Gemini-300BB spectrometer and are reported as δ values downfield from TMS. The mass spectra were recorded on a JEOL JMS-D 300 Mass spectrometer. Elemental analysis were performed on a Heraeus CHN-O-Rapid Analyzer.

Tetrahydrofuran (THF) was distillised from sodium benzophenone ketyl immediately before use. LDA was prepared by the addition of butyllithium (in ether) to diisopropyl amine (in THF), at 0 °C under nitrogen. The solution was stirred for 0.5 h.

General Procedure for the Preparation of the Adducts **4a–g**.—A solution of compound **1** (10 mmol) in THF was added to LDA (13 mmol) in THF at −78 °C under a nitrogen atmosphere and the reaction mixture was stirred for 45 min and then treated with the dienophile (10 mmol) at −78 °C. After further stirring for 30 min, the reaction mixture was quenched (saturated aq. NH_4Cl; 100 cm^3), extracted with $CHCl_3$ (3 × 25 cm^3) and the combined extracts were evaporated. The residue thus obtained was purified by column chromatography over silica gel using hexane–ethyl acetate (99:1) as eluent.

5-Benzoyl-2-[bis(methylsulfonyl)methyl]-3-cyano-1,4-diphenylcyclopent-2-enol **4a**. Colourless crystals (2.06 g, 88%), m.p. 162–163 °C (chloroform–hexane); ν_{max}(KBr)/cm^{-1} 3425 (OH), 2210 (CN) and 1660 (CO); δ_H(400 MHz, $CDCl_3$), 2.11 (3 H, s, SCH_3), 2.22 (3 H, s, SCH_3), 4.14 [1 H, s, $CH(SCH_3)_2$], 4.18 (1 H, s, OH exchangeable with D_2O), 4.26 (1 H, d, *J* 7.6, H_b), 5.21 (1 H, d, *J* 7.6, H_a) and 7.02–7.36 (15 H, m, ArH); δ_C(75 MHz, $CDCl_3$) 13.79, 16.20 (SCH_3), 49.51, 52.51, 68.11 [$CH(SCH_3)_2$, 4-CH, 5-CH], 88.85 (C-1), 114.70 (C≡N), 118.58 (C-3), 126.02, 127.60, 127.88, 127.94, 128.41, 128.63, 128.65, 129.23, 132.98 (CHAr), 136.89, 139.0, 141.91 (C-1′ Ar), 156.74 (C-2) and 196.5 (CO); *m/z* 471 (M^+, 3%) and 405 (M^+ − 48) (Found: C, 71.5; H, 5.7; N, 3.1. $C_{28}H_{25}NO_2S_2$ requires C, 71.30; H, 5.43; N, 2.97%).

5-Acetyl-2-[bis(methylthio)methyl]-3-cyano-1,4-diphenylcyclopent-2-enol **4b**. Colourless crystals (1.24 g, 61%), m.p. 167–168 °C (chloroform–hexane); ν_{max}(KBr)/cm^{-1} 3445 (OH), 2240 (CN) and 1718 (CO); δ_H(90 MHz, $CDCl_3$) 1.78 (3 H, s, CH_3), 2.08 (3 H, s, SCH_3), 2.21 (3 H, s, SCH_3), 3.52 (1 H, d, *J* 7.5, H_b), 4.11 [1 H, s, $CH(SCH_3)_2$], 4.27 (1 H, s, OH, exchangeable with D_2O), 5.06 (1 H, d, *J* 7.5, H_a) and 6.81–7.72 (10 H, m, ArH) (Found: C, 67.7; H, 5.9; N, 3.65. $C_{23}H_{23}NO_2S_2$ requires C, 67.45; H, 5.66; N, 3.42%).

2-[Bis(methylthio)methyl]-3-cyano-5-nitro-3,5-phenylcyclopent-2-ene **4c**. Light yellow crystals (1.35 g, 66%), m.p. 148–150 °C (chloroform–hexane); ν_{max}(KBr)/cm^{-1} 3352 (OH), 2250 (CN), 1568 (NO_2); δ_H(300 MHz, $CDCl_3$) 2.14 (3 H, s, SCH_3), 2.27 (3 H, s, SCH_3), 4.22 [1 H, s, $CH(SCH_3)_2$], 4.33 (1 H, s, OH, exchangeable with D_2O), 5.08 (1 H, d, *J* 7.1, H_a), 5.28 (1 H, d, *J* 7.1, H_b) and 7.25–7.47 (10 H, m, ArH); δ_C(75 MHz, $CDCl_3$) 13.91, 17.20 (SCH_3), 50.68, 53.48 [4-CH, $CH(SCH_3)_2$], 88.03 (1-C), 100.55 (5-CH), 114.91, 117.16 (C≡N and 3-C), 126.77, 128.87, 130.07, 130.22, 130.34, 130.66 (CH, Ar), 136.74, 140.51 (C-1′, Ar), 155.89 (2-C); *m/z* 365 (M^+ − 47, 50%), 318 [M^+ − 2(SCH_3), 100%] (Found: C, 61.4; H, 4.9; N, 7.0. $C_{21}H_{20}N_2O_3S_2$ requires C, 61.14; H, 4.89; N, 6.79%).

Ethyl 3-[Bis(methylthio)methyl]-4-cyano-2-hydroxy-2-phenylcyclopent-3-enecarboxylate **4d**. Colourless crystals (1.35 g, 75%), m.p. 93–94 °C (chloroform–hexane); ν_{max}(KBr)/cm^{-1} 3450 (OH), 2242 (CN) and 1728 (CO); δ_H(90 MHz, $CDCl_3$) 1.20 (3 H, t, *J* 7, CH_3), 2.03 (3 H, s, SCH_3), 2.21 (3 H, s, SCH_3), 2.70–3.55 (3 H, m, CH_2 and 1-CH), 4.01–4.40 [3 H, distorted q, CH_2 and $CH(SCH_3)_2$] and 7.43 (5 H, br s, ArH); δ_C(75 MHz, $CDCl_3$) 13.3, 13.9 (SCH_3), 16.01 (CH_3), 35.6 (CH_2), 49.0 (1-CH), 55.2 [$CH(SCH_3)_2$], 61.1 (OCH_2), 88.3 (C-2), 112.50 (C-4), 117.3 (C≡N), 125.30, 128.20, 128.50 (CH, Ar), 134.3 (C-1, Ar), 156.9 (C-3) and 170.9 (CO); *m/z* 363 (M^+, 12%) and 316 (M^+ − 47, 50%) (Found: C, 59.7; H, 6.0, N, 4.0. $C_{18}H_{21}NO_3S_2$ requires C, 59.50; H, 5.82; N, 3.85%).

Methyl 3-[Bis(methylthio)methyl]-4-cyano-3,5-diphenyl-2-hydroxycyclopent-3-enecarboxylate **4e**. Light yellow crystals (1.50 g, 71%), m.p. 164–165 °C (chloroform–hexane); ν_{max} (KBr)/cm^{-1} 3430 (OH), 2230 (CN) and 1721 (CO); δ_H(300 MHz, $CDCl_3$) 2.10 (3 H, s, SCH_3), 2.24 (3 H, s, SCH_3), 3.36 (1 H, d, *J* 8, H_b), 3.57 (3 H, s, OCH_3), 4.15 [1 H, s, $CH(SCH_3)_2$], 4.22 (1 H, br s, OH exchangeable with D_2O), 4.91 (1 H, d, *J* 8, H_a) and 7.26–7.50 (10 H, m, ArH); δ_C(75 MHz, $CDCl_3$) 14.28, 17.23 (SCH_3), 50.62, 53.07, 53.55 [1-CH, 5-CH, $CH(SCH_3)_2$], 57.34 (OCH_3), 89.47 (C-2), 115.76, 119.51 (C≡N, C-4), 126.89, 128.85, 129.21, 129.39, 129.69 and 130.29 (CH, Ar); 139.58, 142.91 (C-1′ Ar), 157.66 (C-3) and 170.53 (CO); *m/z* 378 (M^+ − 47, 55%) and 360 (M^+ − 47 − HOH, 100%) (Found: C, 65.2; H, 5.7; N, 3.5. $C_{23}H_{23}NO_3S_2$ requires C, 64.91; H, 5.44; N, 3.29%).

Dimethyl 4-[Bis(methylthio)methyl]-3-cyano-5-hydroxy-5-phenylcyclopent-3-ene-1,2-dicarboxylate **4f**. Colourless crystals (1.46 g, 72%), m.p. 146–148 °C (chloroform–hexane); ν_{max}-(KBr)/cm^{-1} 3371 (OH), 2216 (CN), 1732 and 1706 (CO); δ_H(300 MHz, $CDCl_3$) 2.03 (3 H, s, SCH_3), 2.22 (3 H, s, SCH_3), 3.67 (3 H, s, OCH_3), 3.79 (1 H, d, *J* 7.1, H_b), 3.84 (3 H, s, OCH_3), 4.08 [2 H, br s, $CH(SCH_3)_2$ and OH exchangeable with D_2O], 4.52 (1 H, d, *J* 7.1, H_a) and 7.39–7.43 (5 H, m, ArH); δ_C(75 MHz, $CDCl_3$) 14.79, 17.22 (SCH_3), 50.21, 52.89, 53.43 [1-CH, 2-CH, $CH(SCH_3)_2$], 54.20, 59.99 (OCH_3), 88.92 (C-5), 113.50, 114.95 (C≡N, C-3), 126.79, 129.57, 129.72 (CH Ar), 142.43 (C-1′Ar), 159.62 (C-4), 170.47 and 171.35 (CO); *m/z* 360 (M^+ −

Table 2 Crystal data and details of structural determination

Crystal data	
Mol. formula	$C_{28}H_{25}NO_2S_2$
M	471.44
System and space group	monoclinic, $P2_1/c$
a, b, c (Å)	12.155(1), 20.491(2), 10.933(2)
α, β, γ (°)	90.0, 114.95(1), 90.00
V(Å^3)	2468.93
Z	4
D_c (g cm^{-3})	1.26
F(000) (e$^-$)	992
λ(Cu-Kα)(Å)	1.5418
Crystal size (mm)	0.20 × 0.14 × 0.02
Shape and colour	colourless small platelets
Data collection	
Temp. (K)	Room temp.
Radiation (Å)	1.5418
θ min/max (°)	3.0, 60.0
Scan type	$\omega/2\theta$
Total number of reflections measured	4130
Total number of unique reflections	3654
Total number of reflections used in refinement	1488
Refinement	
Number of parameters	288
Weighting scheme	$W = 1/[\sigma^2(F_o) + g(F_o)^2]$
Parameter g	0.000 52
Final $R = (\varepsilon, \Delta F/(\varepsilon F_o)$	0.067
Final $R_w = \varepsilon(\omega\Delta F)^2/\varepsilon(\omega F_o)^2$	0.061

47, 40%), 342 (M^+ − 47 − HOH, 92%) (Found: C, 56.2; H, 5.4; N, 3.7. $C_{19}H_{21}NO_5S_2$ requires C, 55.99; H, 5.19; N, 3.44%).

5-[*Bis(methylthio)methyl*]-6-*cyano*-2,4-*diphenyl*-4-*hydroxy*-1,2,3,3a,4,6a-*hexahydrocyclopenta*[c]*pyrrole*-1,3-*dione* **4g**. Yellow solid (1.42 g, 65%), m.p. 85–86 °C (dichloromethane–hexane); $\nu_{max}(CHCl_3)$/cm^{-1} 3450 (OH), 2250 (CN) and 1723 (CO); δ_H(300 MHz, $CDCl_3$) 1.89 (3 H, s, SCH_3), 2.16 (3 H, s, SCH_3), 3.74 (1 H, d, J 8, H_b), 4.13 [1 H, s, $CH(SCH_3)_2$], 4.24 (1 H, d, J 8, H_a), 4.49 (1 H, s, OH exchangeable with D_2O) and 7.24–7.48 (10 H, m, ArH); δ_C(75 MHz, $CDCl_3$) 15.43, 17.15 (SCH_3), 49.36, 52.76, 56.72 [$CH(SCH_3)_2$, 3-CH, 4-CH], 88.70 (C-5), 110.69, 114.78 (C≡N, C-2), 126.18, 127.52, 129.99, 133.04, 130.15, 130.31 (CH, Ar), 132.46 (C-1′ Ar), 142.97 (C-1), 162.97 (C-1′ >NPh), 173.31 and 173.60 (CO); m/z 389 (M^+ − 47, 12%) (Found: C, 63.6; H, 4.9; N, 6.7. $C_{23}H_{20}N_2O_3S_2$ requires C, 63.28; H, 4.62; N, 6.42%).

X-Ray Data Measurement and Processing.—The X-ray data were collected using a CAD4 diffractometer and Ni-filtered Cu-Kα radiation (λ = 1.541 78 Å). The structure was solved *via* use of direct methods and refined by full-matrix least squares. In view of the small number of observed data (a result of small size of crystals), phenyl rings were refined as idealized rigid bodies. Otherwise all non-hydrogen atoms were refined anisotropically and non-phenyl hydrogens isotropically. Structural parameters for the X-ray determination have been deposited with the Cambridge Crystallographic Data Centre.* Standard crystallographic results are given in Table 2.

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* See 'Instructions for Authors (1994)', *J. Chem. Soc., Perkin Trans. 1*, 1994, Issue 1.

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