Unexpected regiocontrol in the Pauson–Khand reaction due to 2-furyl substitution of the alkene component

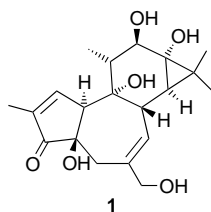Laurence M. Harwood*[a] and Lucía San Andrés Tejera[b]†

[a] Department of Chemistry, University of Reading, Whiteknights, Reading, UK RG6 6AD
[b] Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford, UK OX1 3QY

2-Vinylfuran derivatives undergo regiocontrolled Pauson–Khand reaction, in which the furan exerts the dominant directing influence, to furnish 5-(2-furyl)cyclopent-2-enones, overwhelming the strong directing effects of a homoallylic thioether and appearing to inhibit intramolecular reaction in which bridging constraints are in opposition to the directing influence of the 2-furyl substituent.

For sheer efficiency in construction of cyclopent-2-enones there is surely no match for the Pauson–Khand reaction, which links three components in a single process to furnish products in which the substitution pattern is often highly controlled and predictable.[1] Enantiocontrolled variants have been reported[2] and mild conditions developed in which amine oxides accelerate reaction.[3] The 2-methylcyclopent-2-enone motif is a recurrent sub-unit in many families of terpenoid natural products, such as the tiglianes,[4] and the Pauson–Khand reaction has proven its worth for synthetic approaches to such systems.[1]

In the course of our work towards the total synthesis of phorbol 1 and analogues, via an approach in which the lynch-

pin is the high pressure mediated intramolecular furan Diels–Alder reaction,[5] we required a flexible means of access to a range of 5-substituted 4-(2-furyl)-2-methylcyclopent-2-one intermediates of general structure 2. We envisaged such structures might be accessible via Pauson–Khand reaction of the corresponding (E)-(2-furyl)prop–2–enyl derivatives 3 with μ-propynehexacarbonyldicobalt. Mechanistic considerations and literature precedent[6] made us hopeful of achieving the desired arrangement of the propyne-derived methyl substituent but we recognised the potential for regiochemical ambiguity of alkene incorporation during cyclisation (Scheme 1).

To investigate the outcome, substrates 7a,b were prepared from the corresponding furan-2-carbaldehydes 4 by stereoselective Wittig olefination, reduction of the resultant esters 5 to the alcohols 6 and protection as the tert-butyldimethylsilyl ethers 7.‡ Optimised Pauson–Khand reaction conditions [μ-propynehexacarbonyldicobalt (2 equiv.), CH$_2$Cl$_2$–MeOH (100:1), reflux, 10 days] led to a single cyclopentenone in both cases (8a: 67%, 8b: 41%) uncontaminated by any diene side products (Scheme 2), in marked contrast to previous observations.[7] Attempts to accelerate reaction by addition of amine oxides to the reaction mixture had a detrimental effect. Unfortunately, analysis of NOE difference spectra and couplings in the two-dimensional ¹H NMR spectra of the products
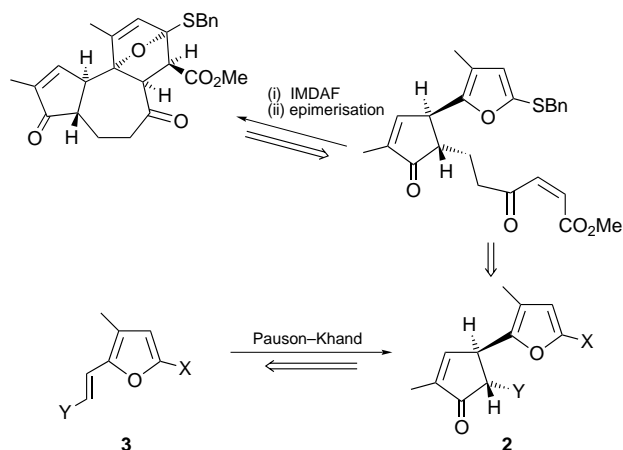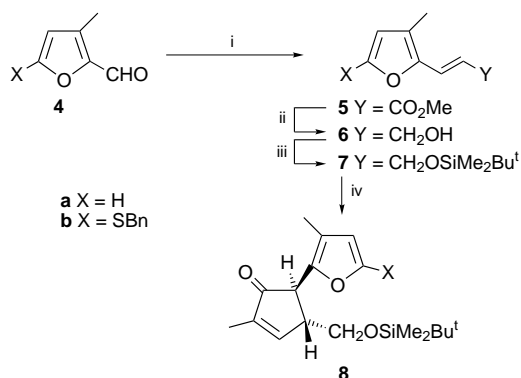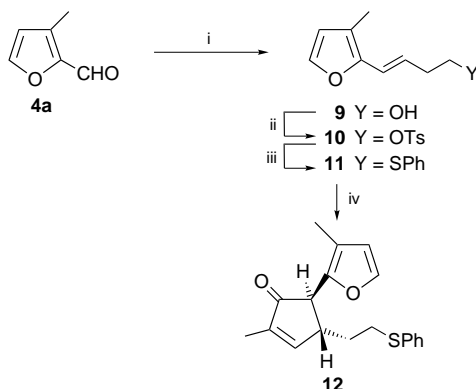

Scheme 1

clearly showed that the undesired C-4/C-5 substitution had been selectively obtained in both cases.§

Reports that a homoallylic thioether on the alkene component accelerates and exerts good regiocontrol on its participation in the Pauson–Khand reaction[8] led us to synthesise 11 in an attempt to obtain the desired substitution pattern. This was achieved via reaction of 4a with the ylide derived from 3-hydroxypropyl(triphenyl)phosphonium bromide to furnish 9, followed by tosylation to form 10 and displacement with sodium phenylthiolate, giving the required substrate 11 (Scheme 3). Pauson–Khand reaction under previously optimised conditions again led to a single cycloadduct 12 (43%)§ in which the furyl group had apparently overwhelmed the directing influence of the homoallylic thioether to furnish the undesired regioisomer once more.

An attempt to force the regiocontrol led us to consider an intramolecular Pauson–Khand cyclisation; tethering the alkene
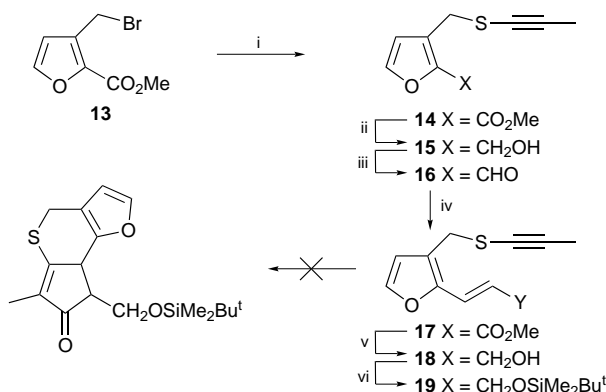

Scheme 2 *Reagents and conditions*: i, Ph$_3$P=CHCO$_2$Me, CH$_2$Cl$_2$, reflux (**a** 74%, **b** 45%); ii, Bu$^i_2$AlH (2 equiv.), toluene, −78 °C (**a** 93%, **b** 78%); iii, Bu^{t}Me$_2$SiCl, Et$_3$N, DMAP (cat.), CH$_2$Cl$_2$, 0 °C → room temp. (**a** 92%, **b** 78%); iv, (HC≡CMe)Co$_2$(CO)$_6$, CH$_2$Cl$_2$–MeOH (100:1), reflux, 10 days (**a** 67%, **b** 41%)

Scheme 3 *Reagents and conditions*: i, Ph₃P=CHCH₂CH₂O⁻ Li⁺, THF, −78 °C → room temp., 58%; ii, TsCl, pyridine, 0 °C → room temp., 88%; iii, PhS⁻ Na⁺, THF, reflux, 57%; iv, (HC≡CMe)Co₂(CO)₆ (2 equiv.), CH₂Cl₂–MeOH (95 : 5), reflux, 10 days, 43%

and alkyne by a thioether which could be hydrogenolysed subsequent to directed cyclopentenylation. Methyl 3-methyl-2-furoate was converted *via* furylic bromination to **13**,[9] halide displacement with lithium propyne-1-thiolate to give **14** and two step conversion to furnish 3-(prop-1-ynylthiomethyl)furan-2-carbaldehyde **16** (Scheme 4). Subsequent elaboration as before gave the intramolecular Pauson–Khand reaction precursor **19** in three steps. However, despite extensive efforts, no conditions could be found which resulted in the isolation of any cyclopentenone, despite the fact that thioether bridges have been used successfully to direct such reactions in prop-2-ynylic systems.[10] From this we conclude that the influence of the 2-furyl substituent attached to the alkene plays a strong role in directing the Pauson–Khand cycloaddition to the extent that, in situations where regiochemical choice is not possible, reaction appears to be disfavoured.

Scheme 4 *Reagents and conditions*: i, Me≡CS⁻Li⁺, Et₂O, −70 °C → room temp., 85%; ii, NaBH₄ (excess), EtOH, room temp., 79%; iii, MnO₂/C, CH₂Cl₂, room temp., 73%; iv, Ph₃P=CHCO₂Me, CH₂Cl₂, reflux, 87%; v, Buⁱ₂AlH (2 equiv.), toluene −70 °C, quant.; vi, ButMe₂SiCl, Et₃N, DMAP (cat.), CH₂Cl₂, room temp., 98%

In conclusion, we present evidence that, for the intermolecular Pauson–Khand reaction, the presence of a 2-furyl substituent on the alkene component substrate exerts a powerful regiodirecting effect causing the furan unit to appear at C-5 of the resultant cyclopent-2-enone. Although rendering this approach inappropriate for our initial specific need, this unexpected regiocontrol has more general synthetic potential.

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Department of Pure and Applied Chemistry, University of Strathclyde, for valuable discussions.

Footnotes and References

§ *Selected data* for **8a**: ν_max(film)/cm⁻¹ 1718, 1255, 1110, 839; δ_H (500 MHz, CDCl₃) 0.46 (s, 6 H), 0.87 (s, 9 H), 1.84 (s, 3 H), 2.01 (s, 3 H), 3.14 (m, 1 H), 3.51 (dd, *J* 3.3, 1 H), 3.70 (dd, *J*₁ 5.2, *J*₂ 10.0, 1 H), 3.79 (dd, *J*₁ 5.2, *J*₂ 10.0, 1 H), 6.20 (d, *J* 1.7, 1 H), 7.20 (d, *J* 1.7, 1 H), 7.31 (br s, 1 H); Selected NOE difference data: **7.31** → 3.65–3.85 (1.5%), 3.14 (4%), 1.84 (3%); *m/z* (CI, NH₃) 321 (MH⁺); Calc. for C₁₈H₂₈O₃Si: C, 67.46, H, 8.80. Found: C, 67.24, H, 8.58%.

For **8b** ν_max(film)/cm⁻¹ 1716, 1254, 1109, 837; δ_H (500 MHz, C₆D₆) 0.07 (s, 6 H), 0.86 (s, 9 H), 1.67 (s, 3 H), 1.79 (s, 3 H), 3.00–3.05 (m, 1 H), 3.33–3.41 (m, 2 H), 3.48 (d, *J* 3.5, 1 H), 3.59 (d, *J* 12.5, 1 H), 6.09 (s, 1 H), 6.74 (br s, 1 H), 7.00–7.12 (m, 5 H); Selected NOE difference data: **6.74** → 3.00–3.05 (6%), 3.33–3.41 (3%), 1.67 (3.5%); *m/z* (CI, NH₃): 443 (MH⁺), 91; Calc. for C₂₅H₃₄O₃SiS: C, 67.83, H, 7.74; S. 7.24. Found: C, 68.03; H, 8.03; S, 7.43%.

For **12**: δ_max(film)/cm⁻¹ 1713, 1481, 1439, 1149, 1088, 740; δ_H (200 MHz, C₆D₆) 1.45 (m, 2 H), 1.61 (s, 3 H), 1.81 (s, 3 H), 2.57 (m, 2 H), 2.93 (m, 1 H), 3.00 (d, *J* 3.3, 1 H), 5.98 (d, *J* 1.7, 1 H), 6.45 (s, 1 H), 6.91–7.23 (m, 6 H); *m/z* (CI, NH₃) 313 (MH⁺); Calc. for C₁₉H₂₁O₂S: 313.12584. Found: 313.12623.

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