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Tandem retro-aldol/Wittig/Michael and related cascade processes

Sandra Beltrán-Rodil [a], James R. Donald [a], Michael G. Edwards [a], Steven A. Raw [b], Richard J. K. Taylor [a,*]

[a] Department of Chemistry, University of York, Heslington, York YO10 5DD, UK
[b] AstraZeneca, Process Research and Development, Silk Road Business Park, Charter Way, Macclesfield, Cheshire SK10 2NA, UK

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ABSTRACT

A number of novel tandem sequences initiated by a retro-aldol process are described along with preliminary scope and limitation studies. These include (i) retro-aldol/Wittig trapping/intramolecular Michael addition, (ii) retro-aldol/aza-Wittig/intramolecular imine addition, (iii) retro-aldol/Henry/intramolecular Michael addition and (iv) retro-aldol/Knoevenagel/intramolecular Michael addition sequences. A range of novel functionalised cyclopentanes, and related systems, are described which should prove to be useful synthetic building blocks.

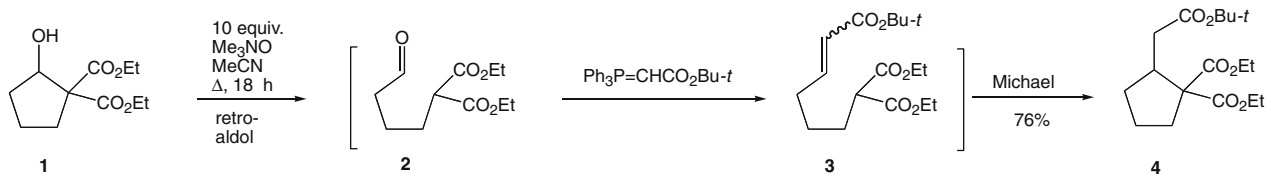
There is great current interest in the development of new tandem and telescoped processes.[1] We have been active in this area[2,3] and herein report a series of novel cascade sequences initiated by a retro-aldol process. The retro-aldol reaction is well known[4–8] but, to our knowledge, has been little exploited in preparative chemistry.[5,6] The process can be effected enzymatically[8] but a base-mediated process[4–7] seemed to be better suited to our intended purposes. The research by Rodriguez and Zweifel[7] describing the use of commercially available trimethylamine N-oxide (TMAO) to effect the retro-aldol reaction seemed to provide a useful initial protocol.

In order to assess the viability of a retro-aldol-initiated tandem sequence we investigated the process outlined in Scheme 1. The readily available 2,2-di(carboethoxy)cyclopentanol **1**[9] was chosen as the first substrate to investigate; it was felt that the double activation of the resulting retro-aldol enolate would facilitate the process. On treatment of cyclopentanol **1** with TMAO in acetonitrile at reflux,[7] in the presence of *t*-butoxycarbonylmethylene(triphenylphosphorane), we were delighted to isolate the novel trisubstituted cyclopentane **4** in 76% yield.[10] In this one-pot process we had effected a retro-aldol reaction followed by Wittig trapping and then intramolecular Michael addition. It should be noted that the overall transformation corresponds to the formal displacement of an unactivated secondary alcohol of the neopentyl structural type by an ester enolate.

Having demonstrated the potential of such a retro-aldol-initiated sequence, we went on to optimise the reaction conditions (Table 1). As can be seen, reducing the recommended[6] large excess of TMAO from ten equivalents to two resulted in incomplete conversion (NMR analysis) with a small amount of the intermediate alkene **3** being identified (entry ii).

The use of other bases was also investigated. We were pleased to discover that a range of amine bases could be employed successfully in acetonitrile as solvent. These included tetramethylpiperidine (TMP), tetramethylguanidine (TMG), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as well as triethylamine and 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD). With stoichiometric triethylamine in acetonitrile, the only product observed was alkene **3** (entry iii) whereas, under the same conditions, the more basic MTBD gave only cyclopentane **4** (entry iv).

However, further optimisation produced two sets of conditions, each utilising only 5 mol % MTBD, which efficiently produced *E*-alkene **3** or cyclopentane **4** depending on the choice of reaction solvent. Thus, cyclopentane **4** is best prepared using catalytic MTBD in MeCN at reflux (80%, entry v).[11] On changing to dichloromethane



Scheme 1.

* Corresponding author. Tel.: +44 (0)1904 432606; fax: +44 (0)1904 434523.
E-mail address: rjkt1@york.ac.uk (R.J.K. Taylor).

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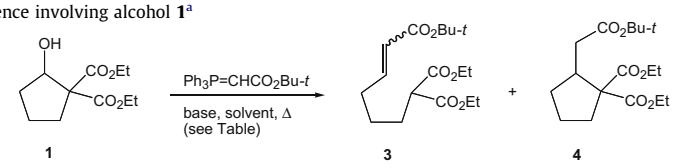
at reflux, the use of catalytic MTBD gave only *E*-alkene **3** (80%, entry vi).

We next examined the scope of the retro-aldol/Wittig/intramolecular Michael addition sequence in terms of the phosphorane component (Scheme 2). Thus, 2,2-di(carboethoxy)cyclopentanol **1**, on treatment with 5 mol % MTBD and ethoxycarbonylmethylene(triphenylphosphorane), *N*-methoxy-*N*-methylamino(triphenylphosphoranylidene)acetamide, 1-triphenylphosphoranylidene-2-propanone and cyanomethylene(triphenylphosphorane) generated the corresponding substituted cyclopentanes **5–8** in 71–83% yield.

This success encouraged us to investigate other sequences initiated by a retro-aldol reaction that would give products displaying diverse substitution patterns (Scheme 3). We first explored the use of the commercially available Staudinger imino phosphorane, *N*-(triphenylphosphoranylidene)aniline **9**. Treatment of 2,2-di(carboethoxy)cyclopentanol **1** with 5 mol % MTBD and imi-

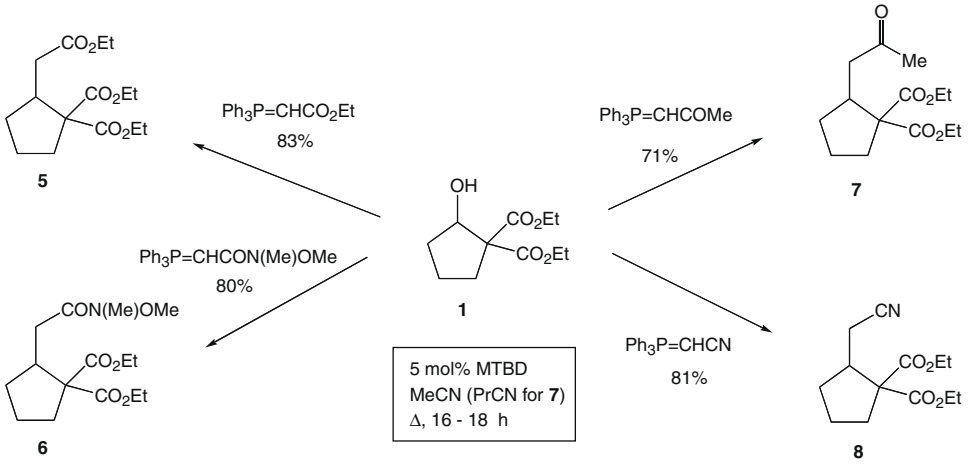
Table 1
Preliminary studies on the retro-aldol sequence involving alcohol **1**[a]



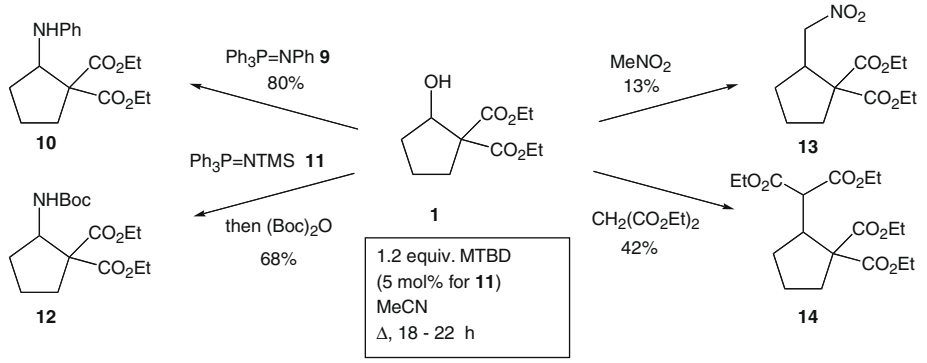
1 3 4

Entry	Base (equiv)	Solvent /conditions	Yield **3**(%)	Yield **4** (%)
i	TMAO (10 equiv)	MeCN Δ, 18 h	—	76
ii	TMAO (2 equiv)	MeCN Δ, 16 h	17[b]	83[b]
iii	Et_3N[c] (1.2 equiv)	MeCN Δ, 19 h	78(*E*:*Z* = 97:3)	—
iv	MTBD (1.2 equiv)	MeCN Δ, 15 h	—	56
v[11]	MTBD[d] (0.05 equiv)	MeCN Δ, 16 h	—	80
vi	MTBD (0.05 equiv)	CH_2Cl_2 Δ, 18 h	80%(*E* only)	—

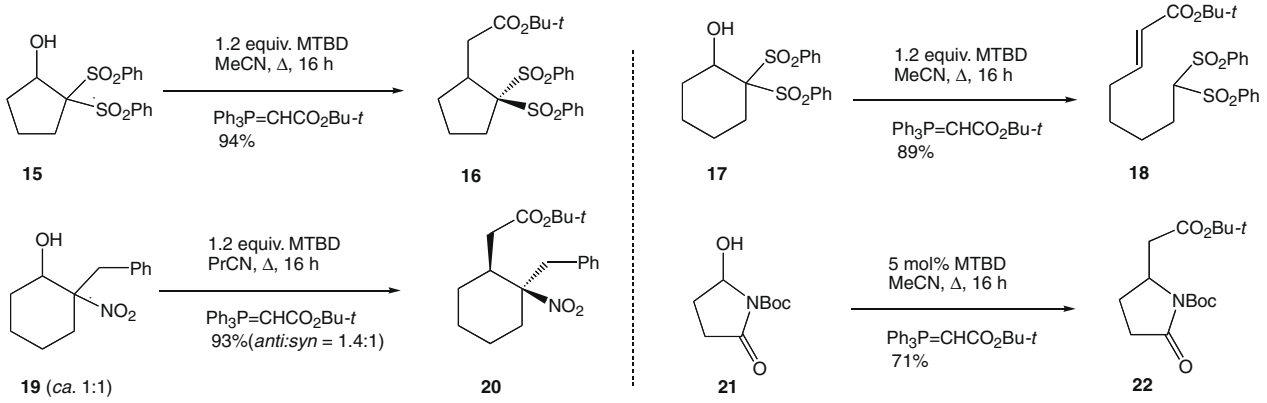
[a] Reaction conditions: **1** (0.26 mmol), ylide (0.31 mmol), solvent (5 mL).
[b] Ratio obtained by NMR analysis of unpurified reaction mixture.
[c] Similar results obtained with TMP, TMG and DBU.
[d] With 0.01 equiv of MTBD, **4** (55%) and **3** (10%) were obtained.



Scheme 2.



Scheme 3.



Scheme 4.

nophosphorane **9** gave cyclopentylamine derivative **10** in excellent yield via a retro-aldol/aza-Wittig/intramolecular imine addition sequence. The use of *N*-trimethylsilyl(triphenylphosphoranylidene)amine **11** produced the rather unstable parent cyclopentylamine after work-up; for characterisation purposes the amine was trapped with $(Boc)_2O$ giving carbamate **12**. Again, these tandem transformations correspond to Mitsunobu-type displacements of an unactivated secondary alcohol, in this case by the formal use of benzylamine or *t*-butylcarbamate; of course, such amine nucleophiles are insufficiently acidic to participate in Mitsunobu processes, thus emphasising the value of these tandem sequences.

Nitromethane could also be used, with the resulting retro-aldol/Henry/intramolecular Michael addition sequence giving (nitromethyl)cyclopentane **13**, albeit in low yield. Finally, a retro-aldol/Knoevenagel/intramolecular Michael addition sequence produced adduct **14** in 42% yield.

At this point, we moved on to look at other substrates (Scheme 4). The readily available[12] bis-sulfones **15** and **17** were investigated first. The cyclopentanol example **15** underwent the expected retro-aldol reaction/Wittig trapping/intramolecular Michael addition giving cyclopentane **16** in 94% yield. In contrast, and under the same conditions, the corresponding bis-sulfonyl cyclohexanol **17** gave alkene **18** (containing a small amount of the isomeric deconjugated alkene) and cyclisation was not observed, even under forcing conditions.

Next, nitro-substituted cyclohexanols were investigated. No reaction was observed on treatment of 2-nitrocyclohexanol with *t*-butoxycarbonylmethylene(triphenylphosphorane) and base but the corresponding benzylated nitrocyclohexanol analogue **19** reacted to produce cyclohexane **20** in excellent yield (the reaction was incomplete using acetonitrile as solvent and butyronitrile was required for efficient conversion). This is the first example of a retro-aldol sequence using a monoactivated substrate[13] and the first cascade sequence resulting in a cyclohexane system. Finally, a heterocyclic example was studied. Pyrrolidone derivative **21**[14] underwent a retro-aldol-like ring-opening/Wittig trapping/intramolecular Michael addition sequence producing adduct **22** in 71% yield.[15]

In summary, we have established the synthetic viability of a number of cascade sequences initiated by a retro-aldol reaction. These comprise (i) retro-aldol/Wittig trapping/intramolecular Michael addition, (ii) retro-aldol/aza-Wittig/intramolecular imine addition, (iii) retro-aldol/Henry/intramolecular Michael addition and (iv) retro-aldol/Knoevenagel/intramolecular Michael addition sequences. These tandem processes have been used to prepare a range of novel functionalised cyclopentanes, and related systems, which should prove to be useful synthetic building blocks. We are currently optimising and extending these processes and investigating applications in target synthesis.

Acknowledgements

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10. All novel compounds were fully characterised spectroscopically and by HRMS.
11. Preparation of 2-*tert*-butoxycarbonylmethyl-cyclopentane-1,1-dicarboxylic acid diethyl ester **4**: A round-bottomed flask equipped with a reflux condenser and a stir bar was charged with 2-hydroxycyclopentane-1,1-dicarboxylic acid diethyl ester **1** (61.5 mg, 0.267 mmol), *tert*-butoxycarbonylmethylene(triphenylphosphorane) (122 mg, 0.320 mmol) and dry CH_3CN (5 mL) and the reaction maintained under an Ar atmosphere. MTBD in CH_3CN was added via microsyringe (0.14 M , 96.5 μL, 0.0135 mmol, 0.05 equiv). The reaction mixture was then allowed to stir at reflux for 16 h. After cooling to rt, CH_2Cl_2 (25 mL) and water (25 mL) were added to partition the reaction mixture. The organic layer was then washed with HCl (1 M, 25 mL) and brine (25 mL) and dried over Na_2SO_4. The solvent was removed in vacuo and the product purified by flash column chromatography (silica gel, eluting with Et_2O/pet. ether, 1:9) to afford *tert*-butoxy ester **4** (70.5 mg, 80%) as a colourless oil, R_f 0.6 (Et_2O/pet. ether, 1:1); IR (neat) 3451 (w), 2978 (m), 2875 (s), 1725 (s), 1452 (m), 1388 (m), 1367 (m), 1259 (s), 1149 (s), 1099 (m), 1030 (m), 945 (w), 918 (w), 855 (m), 762 (w), 731 (m) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.25–4.08 (4H, m), 2.73 (1H, dddd, *J* 11.0, 11.0, 7.5, 3.5 Hz), 2.65 (1H, dd, *J* 15.5, 3.5 Hz), 2.36 (1H, ddd, *J* 13.5, 9.0, 7.0 Hz), 2.11–2.00 (3H, m), 1.88–1.78 (1H, m), 1.68–1.56 (1H, m), 1.49–1.46 (1H, m), 1.43 (9H, s), 1.25 (3H, t, *J* 7.0 Hz), 1.24 (3H, t, *J* 7.0 Hz); δ_C (100 MHz, $CDCl_3$) 171.9, 171.8, 171.1, 80.1, 62.5, 60.9 (×2), 42.4, 37.3 , 33.9, 30.6, 27.8, 22.4, 13.9, 13.8; *m/z* (ESI) 351 $[MNa]^+$; [HRMS (ESI): calcd for $C_{17}H_{28}O_6Na$: 351.1778, found: $[MNa]^+$, 351.1783 (–1.3 ppm error)].
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