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Conjugate addition–Peterson olefination reactions: expedient routes to cross conjugated dienones

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Abstract—The synthesis of 5-alkylidenecyclopent-2-enones is readily achieved in two steps via a one-pot conjugate addition–Peterson olefination sequence, using *exo*-2-trimethylsilyl-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one, followed by a *retro*-Diels–Alder reaction.

The cross conjugated dienone unit is present in various naturally occurring compounds of biological interest.[1] For example, the clavulone **1** and **2**[2] series of marine natural products, the unsaturated prostaglandin $\Delta^{12,14}$-15-deoxy-PG-J_2 **3**,[3] and the related C-18 chromomoric acids **4**[4] all contain this structural motif. Additionally **5**,[5] an analogue of PG-A_2, is currently in pre-clinical trials as an anticancer agent (Fig. 1).

We were attracted to the possibility of utilising a conjugate addition–Peterson olefination[6] sequence as a novel means of accessing this important structural motif (Fig. 2). Surprisingly, this efficient transformation has been virtually ignored following its disclosure in 1984.[7] A cyclopentene unit was chosen to mask the endocyclic carbon–carbon double bond in the cyclopentenone moiety, since this group may be readily removed by a *retro*-Diels–Alder process.[8]

Crucially, *exo*-2-trimethylsilyl-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one **6** is readily available in high yield and on multi-gram scale via the Pauson–Khand cyclisation between trimethylsilyl acetylene and norbornadiene.[9] This species undergoes facile and chemoselective 1,4-conjugate addition with both organocuprate and organomagnesium reagents in the presence of copper(I) salts, generating the expected α-trimethylsilyl ketone conjugate adducts on protonation. Classical Peterson olefination[6] reactions were effected following treatment of these conjugate adducts with LDA then benzaldehyde. However, the yields for this two-step process were disappointingly low. Pleasingly, it was discovered that addition of benzaldehyde (Table 1, entry 1) to an in situ generated solution of the conjugate adduct **7** (from Me_2CuLi, or MeMgBr and 10 mol% CuI) led to excellent yields of the corresponding exocyclic enone **8a**. In the case of the reaction with Me_2CuLi, ^1H NMR spectroscopic analysis of the crude reaction mixture indicated the formation of only one of the possible four compounds. X-Ray structure analysis demonstrated both the *E*-stereochemistry of the alkene formed and the diastereoselectivity of the conjugate addition from

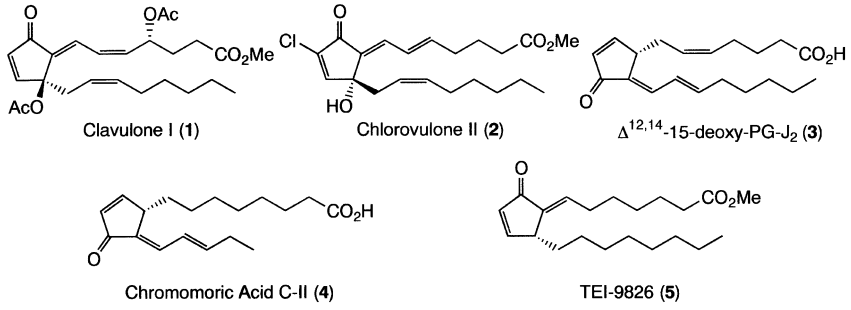

Figure 1. Cross-conjugated cyclopentenones of biological interest.

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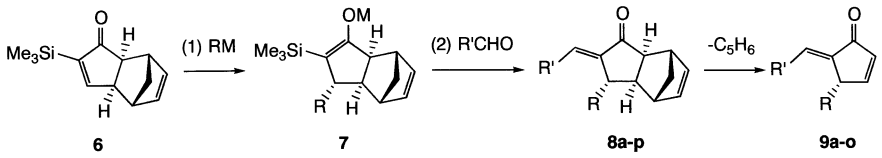
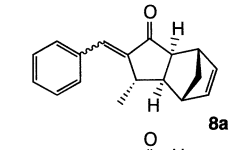
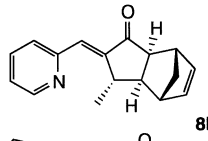
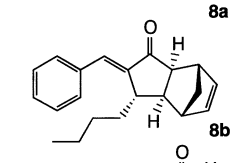
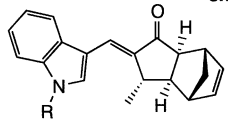
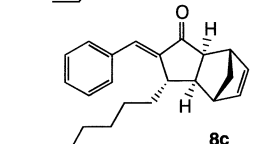
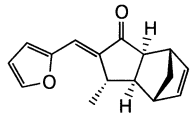
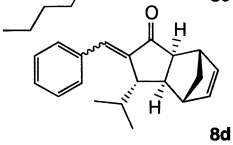
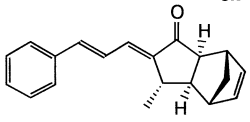
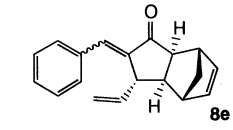
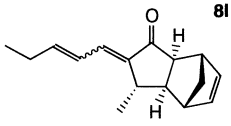
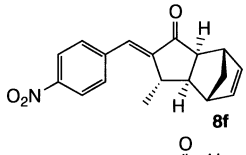
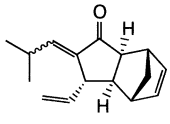
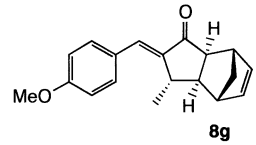
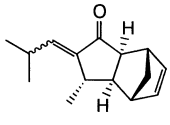
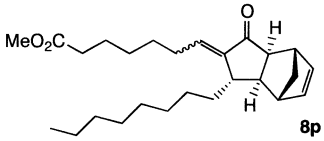


Figure 2. The one-pot conjugate addition–Peterson olefination reaction [M = metal].

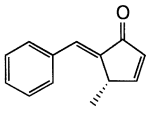
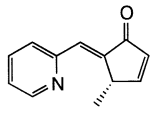
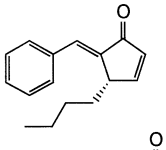
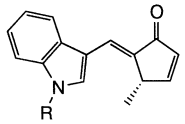
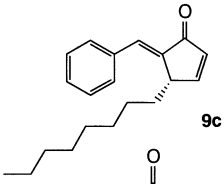
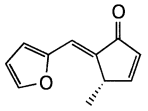
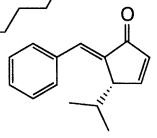
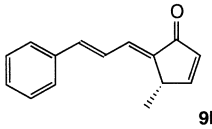
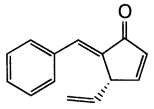
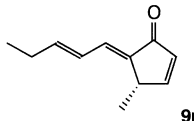
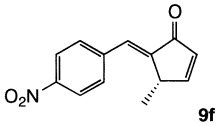
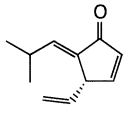
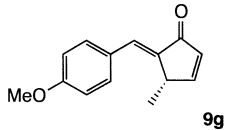
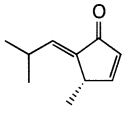
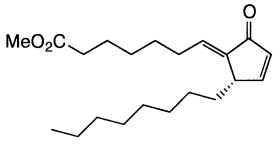
the less hindered face of the enone **6**. When MeMgBr was used a small amount of the *cis*-alkene, separable by flash column chromatography, was also formed (*E:Z*, 75:25). The addition of *n*-butyl- and *n*-octyl-[10] organometallics also successfully generated the analogous Peterson products in good yield, following the addition of benzaldehyde (entries 2 and 3). The 1,4-addition of the more sterically hindered *iso*-propylmagnesium chloride, and vinylmagnesium bromide proceeded smoothly using catalytic CuI (10 mol%) and in both cases the corresponding magnesium enolate reacted efficiently with benzaldehyde, affording enones **8d** and **8e** as separable mixtures of stereoisomers (entries 4 and 5).

Table 1. Conjugate addition–Peterson olefination: synthesis of exocyclic enones **8a**–**8p**[11]

Entry	Product	Yield[a] [*E:Z*][b]	Entry	Product	Yield[a] [*E:Z*][b]
1	 **8a**	93%[c] 86%: *E:Z*, 75:25[d]	8	 **8h**	45%[c]
2	 **8b**	91%[c]	9		**8i**: R = Me:13%[c] **8j**: R = Ts: 83%[c]
3	 **8c**	84%[c]	10	 **8k**	94%[c]
4	 **8d**	81%: *E:Z*, 58:42[d]	11	 **8l**	68%[c]
5	 **8e**	94%: *E:Z*, 93:7[d]	12	 **8m**	88%: *E:Z*, 88:12[c] 97%: *E:Z*, 85:15[d]
6	 **8f**	92%[c]	13	 **8n**	88%: *E:Z*, 52:48[d]
7	 **8g**	45%[c]	14	 **8o**	61%: *E:Z*, 67:33[c] 83%: *E:Z*, 30:70[d]
15	 **8p**	81%; *E:Z*, >95:5[c] 57%; *E:Z*, 35:65[d]			

[a]Total yield following purification by flash column chromatography; [b]Ratio determined by ^{1}H-NMR spectroscopy of the crude reaction mixture; [c]R_2CuLi, Et_2O (see Reference 10); [d]RMgBr, 10 mol% CuI, Et_2O.

Table 2. *retro*-Diels–Alder: synthesis of cross-conjugated cyclopentenones **9a**–**9o** and **5**[11]

Entry	Product	Yield[a]	Entry	Product	Yield[a] [*E*:*Z*][b]
1	 **9a**	84%	8	 **9h**	**NR**
2	 **9b**	83%	9		**9i**: R = Me: **NR**: **9j**: R = Ts: 28%
3	 **9c**	76%	10	 **9k**	64%
4	 **9d**	87%	11	 **9l**	77%: *E*:*Z*, 92:8
5	 **9e**	73%	12	 **9m**	33%: *E*:*Z*, 91:9 (83% based on recovered **8m**)
6	 **9f**	85%	13	 **9n**	73%
7	 **9g**	68%	14	 **9o**	82%: *E*:*Z*, 91:9[c]
15	 **5**	86%; *E*:*Z*, 81:19			

Conditions: $MeAlCl_2$ (1 equiv.), maleic anhydride (5 equiv.), DCM, 40°C, 1 to 24 h; [a]Yield following purification by flash column chromatography, **NR** = no reaction; [b]Ratio from ^{1}H-NMR spectroscopy of the crude reaction mixture; [c]Using *Z*-**8o** : 67%; *E*:*Z*, 88:12 (22% *E*-**8o**).

Additional aromatic and heteroaromatic aldehydes were shown to be successful reaction partners, although it was found that the reaction was sensitive to the electronic nature of the aldehyde. Thus, employment of 4-methoxybenzaldehyde led to a sluggish reaction with low yields of the corresponding alkene **8g** (entry 7). In contrast use of 4-nitrobenzaldehyde led to a rapid reaction and the enone **8f** was isolated in excellent yield (entry 6). 2-Pyridyl carboxaldehyde afforded the enone **8h** in 45% yield (entry 8). This moderate yield may reflect competing complexation of the azo-functional group with the copper species present after the conjugate addition. The electron rich *N*-methyl indole 3-carboxaldehyde, gave a low yield (13%) of the exocyclic enone **8i**; however, the corresponding *N*-tosyl indole carboxaldehyde afforded the adduct **8j** in excellent yield (83%) (entry 9). Similarly 2-furfural gave the enone **8k** in 94% yield (entry 10) stereoselectively. The process described also proceeded efficiently with α,β-unsaturated aldehydes (entries 11 and 12), thereby providing a strategy for the installation of the exocyclic dienone unit present in natural products **1** to **4** (Fig. 1).

At this stage it was of interest to ascertain whether aldehydes possessing acidic α-protons would participate in the process, or if the carbanionic intermediate **7** might prove to be incompatible with such reaction partners. However, this concern proved to be unfounded and freshly distilled isobutyraldehyde gave good yields of the corresponding adducts **8n** and **8o** (entries 13 and 14). Interestingly, the stereochemical integrity of the double bond formed was much less well

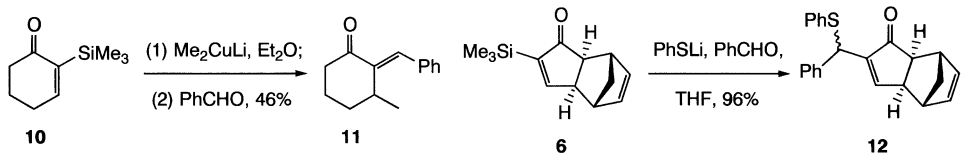


Figure 3.

defined in these instances and significant amounts of the readily separable *Z*-stereoisomers were formed. As before (entries 1, 4 and 5) this lack of stereoselectivity was most marked when organomagnesium reagents were employed in the conjugate addition reaction. It seems reasonable to speculate that this phenomenon is partly due to a change in counterion in the intermediate **7** (Li→MgBr) and that the counterion influences the path of the Peterson reaction.

This reaction sequence described was then applied to a rapid synthesis of (±)-TEI-9826 **5**.[5] Thus, addition of either $(^{n}Oct)_2CuLi$, or $^{n}OctMgBr$ (10 mol% CuI) to **6**, followed by addition of methyl 7-oxoheptanoate[12] afforded the exocyclic enone **8p** in good yield (entry 15).

The *retro*-Diels–Alder reactions of the norbornadiene adducts **8a**–**p** described in Table 2 were performed in DCM at 40°C using $MeAlCl_2$ and an excess of maleic anhydride as a cyclopentadiene trap.[8b] Generally, this method provided good yields of the corresponding cross conjugated cyclopentenones **9a**–**o** (see Table 2). Notable exceptions were compounds containing basic azo-functionality (entries 8 and 9), in these examples none of the cyclopentenone products **9h** and **9i** were detected. It was of interest that following employment of this Lewis acid methodology the purified *Z*-exocyclic enones **8a** and **8o** underwent significant alkene isomerisation, affording predominantly the *E*-cross conjugated cyclopentenone products **9a** and **9o**. For example, treatment of *Z*-**8o** under these conditions gave **9o** in 67% yield (*E*:*Z*, 88:12) and 22% of isomerised starting material *E*-**8o**. Similarly, the functionalised adduct **8p** was smoothly converted to the target dienone **5** in 86% yield.

Preliminary experiments demonstrate that this process may be applied in a more general sense. For example, under the standard conditions indicated in Table 1, cyclohexenone **10**[13] afforded the *trans*-enone **11** stereoselectively in 46% yield. Additionally, it was found that nucleophiles other than carbanions may be used: PhSLi and benzaldehyde generated an undetermined diastereomeric mixture of **12** (60:40) in 96% yield, resulting from an initial conjugate addition–Peterson olefination process followed by nucleophilic attack at the exocyclic double bond and elimination. Optimum yields for this process were achieved following a one-pot reaction protocol in which all the reagents were added simultaneously (Fig. 3).

In conclusion, we have developed an efficient and novel method for the synthesis of cross-conjugated cyclopentadienones in two high yielding steps. Significantly the conjugate addition reaction proceeds with very high diastereoselectivity; consequently in order to generate enantioenriched, or homochiral products the corresponding enantioenriched, or homochiral Pauson–Khand adduct could be employed.[14] Future work will involve the development of the process described for the synthesis of homochiral dienones and the application of this method for the synthesis of **3** and **4**.

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10. Representative procedure: 3-octyl-2-[1-phenyl-meth-(*E*)-ylidene]-2,3,3a,4,7,7a-hexahydro-4,7-methanoinden-1-one **8c**: Under N_2 a 1.7 M solution of *tert*-butyllithium in pentane (4.9 cm^3, 8.33 mmol, 4 equiv.) was added dropwise to a solution of *n*-octyl iodide (0.75 cm^3, 4.15 mmol, 2 equiv.) in a mixture of pentane (17 cm^3) and Et_2O (10 cm^3) at −78°C. Stirring was continued at −78°C for 0.25 h before warming to room temperature over 1 h. The solution of *n*-octyl lithium was re-cooled to −78°C and added to a slurry of CuI (395 mg, 2.07 mmol, 1 equiv.) in Et_2O (10 cm^3) at −78°C via cannula. The mixture was warmed to −20°C over 1 h and the resultant cuprate was cooled to −40°C before a solution of the enone **6** (452 mg, 2.07 mmol, 1 equiv.) in Et_2O (5 cm^3) was added dropwise [washed with Et_2O (2 cm^3)]. After stirring for 1 h (−40°C→−20°C) benzaldehyde (0.42 cm^3, 4.13 mmol, 1 equiv.) was added and the reaction was stirred for 18 h and allowed to warm to room temperature. Saturated NH_4Cl (25 cm^3) and EtOAc (25 cm^3) were added and the resultant aqueous layer was further extracted with EtOAc (2×25 cm^3). The combined organic extracts were then dried over $MgSO_4$. Filtration, followed by solvent removal in vacuo and flash column chromatography (Hex–EtOAc; 19:1) afforded the title compound **8c** (604 mg, 84%) as a viscous yellow liquid. R_f=0.25 (Hex–EtOAc; 19:1); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.5 Hz, CH_3), 1.18–1.52 (15H, m, CH_2), 1.64–1.73 (1H, m, CH_2), 2.05 (1H, d, *J* 7.5 Hz, CH), 2.47 (1H, d, *J* 7.5 Hz, CH), 2.82 (1H, s, CH), 3.01–3.09 (1H, m, CH), 3.12 (1H, s, CH), 6.23 (1H, dd, *J* 2.75, 5.5 Hz, CH), 6.28 (1H, dd, *J* 3.0, 5.5 Hz, CH), 7.30 (1H, d, *J* 2.0 Hz, CH), 7.34–7.44 (3H, m, ArH), 7.56 (2H, d, *J* 7.0 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 14.1, 22.6, 26.9, 29.2, 29.5, 29.6, 31.8, 34.7, 43.3, 44.4, 46.5, 48.4, 49.8, 53.7, 128.7, 129.4, 130.7, 133.4, 135.0, 137.6, 138.9, 144.3, 209.2; *m*/*z* (CI) 349 (MH^+, 10%), 283 ($MH-C_5H_6^+$, 100%); Found 349.25394, $C_{25}H_{33}O$ requires 349.25314 (+2.5 ppm); Found C, 85.9; H, 9.4%, $C_{25}H_{32}O$ requires C, 86.2; H, 9.2%.
11. All new compounds were fully characterised by ^1H and ^{13}C NMR spectroscopic techniques, by microanalysis and/or high resolution mass spectroscopy.
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