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Titanium mediated alkylidenation of substituted cycloalkenones: scope and limitations

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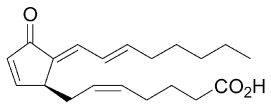
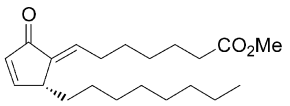
Abstract—The conversion of the cyclopent-2-enone **5** and cyclohex-2-enones **11a**, **c**-**e** into corresponding α'-*exo*-alkylidene compounds using Ti(IV) catalysis, with PPh_3 and an aldehyde, is described.

1. Introduction

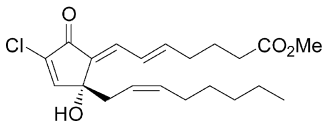
The cross-conjugated dienone unit is present in many natural products of significant biological interest.[1] The unsaturated prostaglandin $\delta^{12,14}$-15-deoxy-PG-J_2 **1**,[2] has been implicated in the control of various medical conditions,[3] and TEI-9826 **2**, a related analogue of PG-A_2, is currently in pre-clinical trials as an anti-tumour agent.[4] Also, 12-oxy-prostaglandins, the clavulones[5] and the chlorovulones[6] such as chlorovulone II **3**, have been isolated from the marine environment. Unnatural 12-amino prostaglandins, such as **4**, have been synthesised and have shown high cytotoxicity.[7]



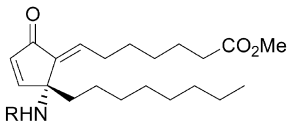
$\Delta^{12,14}$-15-deoxy-PG-J_2 (**1**)



TEI-9826 (**2**)



Chlorovulone II (**3**)



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There are a number of strategies for converting 4-alkylcyclopentenones into the corresponding cross-conjugated dienones. One tactic is to perform an aldol reaction on the cyclopentenone, followed by activation of the alcohol (usually as a sulfonate ester) and elimination.[8] Often preparing the enolate of cyclopentenones can prove problematic and in any case a 3-step protocol for this transformation is not ideal, although a good overall yield can be obtained. Other strategies involve masking the cyclic enone in some manner. Noyori et al. has utilised this approach in a three-component coupling reaction using 4-silyloxycyclopentenones, followed by elimination of the silyloxy group to reveal the cyclic enone.[9] A more recent example involves protecting the *endo*-cyclic carbon–carbon double bond as a norbornene unit, from which cyclopentadiene can be removed in a *retro*-Diels–Alder reaction.[10]

However, we were intrigued by the communication of Suda et al.[11] which reported a one-pot sequence to convert cyclopentenone to a cross-conjugated dienone. A number of examples were reported, but the only substrates investigated were cyclopentenone and cyclohexenone and no further reports have alluded to any extension in this methodology. We wanted to investigate whether this protocol could be extended to substituted cyclopentenones and cyclohexenones.

2. Results and discussion

Initially, we studied the reaction of the 4-aza-cyclopentenone **5**,[12] under similar conditions to those reported. The enone **5** and an equivalent of triphenylphosphine were dissolved in dichloromethane and cooled to −50 °C, whereupon 0.5 equiv. of titanium (IV) isopropoxide, then titanium (IV) chloride were added. At this stage an intense red colour indicated the formation of the enolate, which could be quenched with a variety of aldehydes. Finally, stirring with aqueous potassium carbonate solution released the desired dienones **6a**-**e** (Table 1).

Unlike the reaction with cyclopentenone, these reactions did

Keywords: 5-Alkylidene-cyclopent-2-enones; 6-Alkylidene-cyclohex-2-enones; Titanium enolate chemistry; 4-Aza cycloalk-2-enones.
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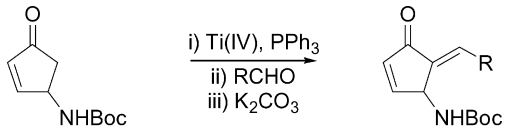
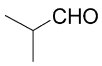
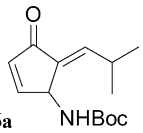
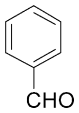
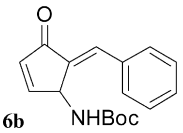
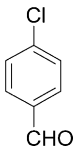
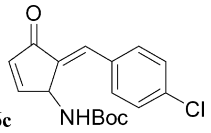
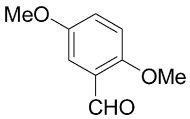
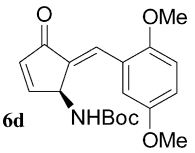
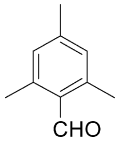
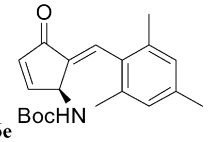
Table 1. Reaction of enone **5** with Ti(IV), PPh_3 and an aldehyde



5 **6a-e**

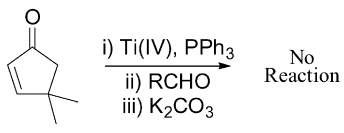
Entry	Aldehyde	Product	Yield (%)[a] [*E*:*Z*][b]	Recovered **5**[a] (%)	Yield based on recovered SM (%)
1[c]		 **6a**	39 [7.3:1]	48	74
2[c]		 **6b**	48[d]	45	87
3[c]		 **6c**	52[d]	37	82
4[e]		 **6d**	60[d]	25	80
5[e]		 **6e**	24[d]	67	73

[a] Yields following purification by flash chromatography.
[b] Ratio determined by amounts of isolated product.
[c] Racemic enone **5** used.
[d] Only (*E*)-isomer detected.
[e] (*R*) enantiomer of **5** used.[12]

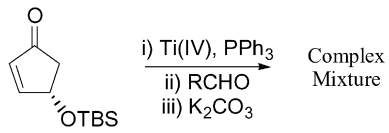
not go to completion, with only moderate yields of dienone being isolated. However, as there was a significant recovery of **5**, the yield based on starting material consumed was good and compares well with the other methods for this transformation, especially as the Suda protocol involves a one-pot operation.

Also, this reaction gives a single geometric isomer when aromatic aldehydes are used, and the small *Z*-isomer impurity in the preparation of **6a** could well be due to light-induced isomerisation rather than a lack of selectivity.[13] A range of aromatic aldehydes could be tolerated, with the more electron-rich 2,5-dimethoxybenzaldehyde actually resulting in the highest conversion. The sterically crowded product **6e** could also be formed, albeit in lower yield, but attempts to use 2-pyridinecarboxaldehyde as the electrophile resulted in no cross-conjugated dienone being formed.

The more demanding enones **7** and **8** were examined. However, the geminally disubstituted enone **7** did not result in any reaction and subjecting the 4-oxa enone **8** to the reaction conditions only resulted in a complex mixture.[14]

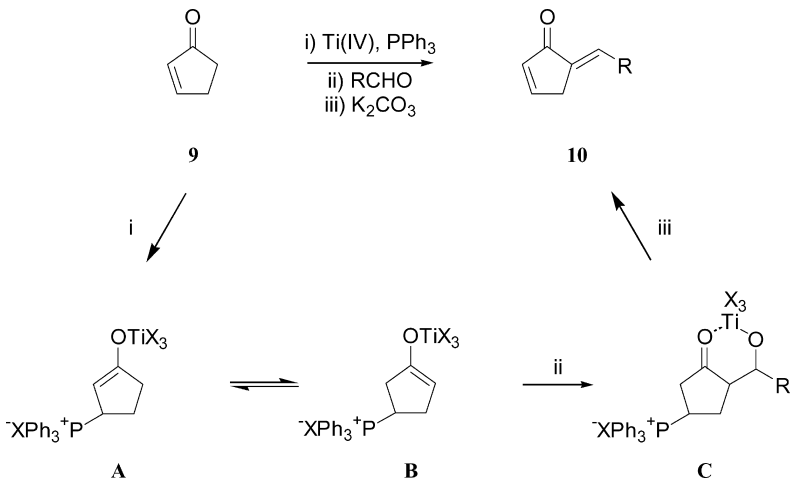


7



8

Suda et al. has proposed a mechanism for this reaction,[11] which is illustrated for cyclopentenone **9** in Scheme 1. Reaction of **9** with triphenylphosphine and the titanium (IV) complex results in the titanium enolate **A**, which isomerises to a regioisomeric enolate **B**. Reacting this equilibrium



Scheme 1.

mixture of enolates **A** and **B** with an aldehyde then gives the aldol product **C** that is transformed into the dienone product **10** by treatment with base.

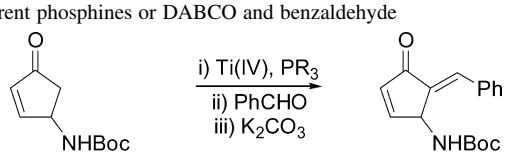
The rates of reaction of the two enolates **A** and **B** are quite different. It is suggested that the steric bulk of the phosphonium substituent in **A** would greatly reduce the reactivity of this enolate, leaving enolate **B** to react and give the product. However, this distinction is partially or completely nullified by adding substituents in the 4-position of the cyclopentenone ring. The addition of a single substituent, such as in **5**, makes it much less clear cut as to which enolate would be the more sterically accessible. Reaction of the aldehyde with **A** would give an aldol product that would regenerate the starting enone on addition of aqueous base on work-up. This material would not be available to proceed along the pathway through **B** to the desired product. Hence, a mixture of starting material and product is obtained in the reactions involving **6a**-**e**.

This mechanistic analysis can also rationalise the results observed for enones **7** and **8**. The decomposition of enone **8** can be explained, as the enolate **B** in this case is likely to be unstable. We believe that the silyloxy-group would be eliminated under these conditions, generating the very reactive cyclopentadienone. The lack of reactivity of **7** can be explained on the grounds of steric arguments. Either the geminal methyl groups inhibit the initial addition of the phosphine, or the two substituents can now shut down the reactivity of enolate **B** completely, allowing only the 'non-productive' enolate **A** to react with aldehyde.

In order to try to increase the level of reactivity in these reactions, other phosphines were investigated (Table 2). The use of tri(*ortho*-tolyl) phosphine did not result in greater productivity. Perhaps, the greater size of the phosphine led to less favourable addition initially, accounting for the lower yield. Disappointingly, reducing the size or altering the electronic properties of the phosphine also led to less favourable results, demonstrating the subtle kinetic effects in this reaction. On the positive side, initial results replacing phosphines with an amine have shown some promise. Using DABCO in this reaction instead of a phosphine gave a 10% yield of the product **6b** along with unreacted enone **5**.

In the course of this work we have made a number of observations that are crucial to obtaining the best results from this reaction. Azeotropic drying of the phosphine prior to use enhances the final yield; adding titanium (IV) isopropoxide, then titanium (IV) chloride allows the maximum tolerance of acid sensitive substrates and, after addition of aqueous potassium carbonate, a extensive period of vigorous stirring (usually over an hour) allows the maximum recovery of both product and starting material.

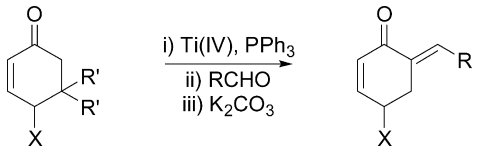
Table 2. Reaction of enone **5** with Ti(IV), different phosphines or DABCO and benzaldehyde



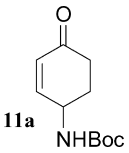
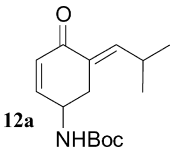
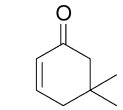
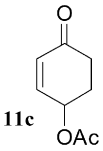
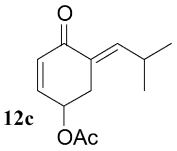
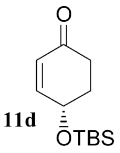
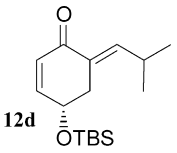
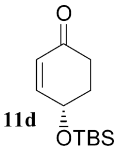
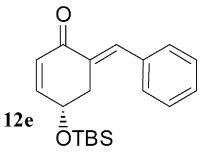
Entry	Phosphine/amine	Yield[a]	Recovered **5**[a] (%)	Yield based on recovered SM
1	PPh_3	48%	45	87%
2	P(*o*-Tol)$_3$	24%	70	80%
3	$P(OPh)_3$	None	71	n/a
4	P(*n*-C_4H_9)$_3$	None	94	n/a
5	P(*t*-C_4H_9)$_3$	None	91	n/a
6	DABCO	10%	55	22%

[a] Yields following purification by flash chromatography.

Table 3. Reaction of substituted cyclohexenones **11a-d** with Ti(IV), PPh_3 and an aldehyde



11a-d **12a-e**

Entry	Substrate	Product	Yield (%)[a,b]	Recovered **11**[a]	Yield based on recovered SM (%)
1	 **11a**	 **12a**	49	33%	73
2	 **11b**	No product	—	—	—
3	 **11c**	 **12c**	87	—	87
4	 **11d**	 **12d**	40	None	40
5	 **11d**	 **12e**	62	None	62

[a] Yields following purification by flash chromatography.
[b] Only isomer shown isolated.

Finally, aqueous extraction can be accompanied with troublesome emulsions, which can be greatly minimised by the filtering of the reaction mixture through a short pad of Celite®, while noting that care needs to be taken to wash the Celite® thoroughly, especially on a larger scale.

This methodology can also be extended to substituted cyclohexenones. For example, the 4-aza substituted enone **11a**,[15] gave a similar yield to that obtained for the corresponding cyclopentenone (Table 3).

As expected the geminally substituted enone **11b** gave no product. In this case, after addition of the phosphine, the aldol reaction can take place at C-2, but not at C-6 due to steric hindrance. This C-2 adduct then regenerates starting material on work-up. Finally, 4-oxacyclohexenones are suitable substrates for the reaction, as these cannot undergo elimination-type processes that plagued the cyclopentenone **8**. The acetate **11c**,[16] performs particularly well and the stability of silyl protecting groups under these conditions is demonstrated by the formation of **12d** and **12e**.

In conclusion, we have successfully applied the Suda reaction to more demanding substrates. Some limitations of this approach have been identified, a mechanistic rational for these observations has been proposed and improvements to the method have been outlined. The method compares well with other methods for this transformation, allowing the conversion of cycloalkenones to cross-conjugated dienones to be performed in a single operation.

3. Experimental

3.1. General

Starting materials were purchased from commercial sources and were used without further purification, except for the phosphines that were azeotropically dried with toluene. Dichloromethane was distilled from CaH_2. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded using a Bruker AMX400 spectrometer. Optical rotation measurements were recorded using an Optical Activity,

Polaar 2001 polarimeter at 589 nm and quoted in units of 10^{-1} deg cm^2 g^{-1}. Flash column chromatography was performed under moderate pressure using silica gel—ICN 32-63, 60 Å. Analytical HPLC measurements were performed on a Gilson HPLC machine using a Synergi Max RP column (Phenomenex).

3.1.1. (5-*iso*-Butylidene-4-oxocyclopent-2-enyl)-carbamic acid *tert*-butyl ester (6a). Triphenylphosphine (1.33 g, 5.07 mmol) was added to a stirred solution of the enone **5** (1.00 g, 5.07 mmol) in dichloromethane (25 cm^3) at room temperature, under an atmosphere of argon. The resulting mixture was then cooled to 50 °C and titanium (IV) *iso*-propoxide (0.75 cm^3, 2.54 mmol) and then titanium (IV) chloride (0.28 cm^3, 2.55 mmol) were added dropwise over 3 min each. The mixture was stirred at −50 °C for a further 15 min, then *iso*-butyraldehyde (1.38 cm^3, 15.2 mmol) was added over 3 min. The mixture was then allowed to warm to room temperature over 15 h. An aqueous solution of potassium carbonate (10% aq., 25 cm^3) was added, the biphasic mixture was stirred for 90 min, then filtered through a short pad of Celite® washing with dichloromethane (50 cm^3) and diethyl ether (50 cm^3). The organic phase of the filtrate was separated and the aqueous phase was extracted with diethyl ether (4×25 cm^3). The combined organics were dried over anhydrous magnesium sulfate and evaporated in vacuo. Flash chromatography (SiO_2, 15%, then 20% ethyl acetate in hexane) gave the starting enone **5** (475 mg, 2.41 mmol, 48% recovery) as a white solid, after giving the less polar (*Z*)-dienone (60 mg, 0.24 mmol, 4.7% (9.0% based on recovery)) and the (*E*)-dienone **6a** (435 mg, 1.73 mmol, 34% (65% based on recovery)) also as white solid; mp 141–142 °C (Et_2O); δ_H (400 MHz, $CDCl_3$) 7.40 (1H, ddd, *J*=6.0, 2.5, 0.8 Hz, C*H*=CHC=O), 6.49 (1H, d, *J*=10.7 Hz, C=C*H*), 6.38 (1H, dd, *J*=6.0, 1.7 Hz, CH=C*H*C=O), 5.47 (1H, br. d, *J*=8.7 Hz, N*H*), 4.56 (1H, br. d, *J*=8.7 Hz, C*H*NH), 2.75 (1H, dsept, *J*=10.7, 6.7 Hz, C*H*$(CH_3)_2$), 1.48 (9H, s, $CO_2C(CH_3)_3$), 1.09 (3H, d, *J*=6.7 Hz, CHC*H*$_3$), 1.07 (3H, d, *J*=6.7 Hz, CHC*H*$_3$); δ_C (100 MHz, $CDCl_3$) 195.2 (s), 156.9 (d), 154.9 (s), 145.2 (d), 136.2 (d), 132.9 (s), 80.3 (s), 51.5 (d), 28.5 (d), 28.3 (q), 22.0 (q), 21.9 (q); *m*/*z* (CI). Found $[MH]^+$ 252.1596 ($[MH]^+$ $C_{14}H_{22}NO_3$ requires 252.1600).

3.1.2. ((*E*)-5-Benzylidene-4-oxo-cyclopent-2-enyl)-carbamic acid *tert*-butyl ester (6b). Triphenylphosphine (333 mg, 1.27 mmol) and the enone **5** (250 mg, 1.27 mmol) in dichloromethane (6 cm^3) was treated, in an analogous manner to that for the preparation of **6a**, with titanium (IV) *iso*-propoxide (0.19 cm^3, 0.64 mmol), titanium (IV) chloride (70 μl, 0.64 mmol) and benzaldehyde (0.39 cm^3, 3.84 mmol). After work-up, flash chromatography (SiO_2, 20%, then 35% ethyl acetate in hexane) gave the starting enone **5** (98 mg, 0.50 mmol, 39% recovery) as a white solid, after giving the less polar dienone **6b** (180 mg, 0.63 mmol, 50% (82% based on recovery)) also as a white solid; mp 148–149 °C (Et_2O); δ_H (400 MHz, $CDCl_3$) 7.62–7.56 (3H, m, C*H*=CHC=O+Ar*H*), 7.49 (1H, br. s, C=C*H*Ar), 7.44–7.39 (3H, m, Ar*H*), 6.50 (1H, dd, *J*=5.9, 1.6 Hz, CH=C*H*C=O), 5.81 (1H, br. d, *J*=7.2 Hz, N*H*), 4.42 (1H, br. d, *J*=7.2 Hz, C*H*NH), 1.44 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 195.5 (s), 157.7 (d), 155.3 (s), 135.4 (d), 134.3 (d), 133.1 (s), 132.2 (s), 131.4 (d), 130.1 (d), 128.7 (d), 80.4 (s), 52.1 (d), 28.3 (q); *m*/*z* (ES) 309 ($[MHNa]^+$, 17%), 308 ($[MNa]^+$, 100). Found $[MNa]^+$ 308.1267 ($[MNa]^+$ $C_{17}H_{19}NO_3Na$ requires 308.1263).

3.1.3. [(*E*)-5-(4-Chlorobenzylidene)-4-oxo-cyclopent-2-enyl]-carbamic acid *tert*-butyl ester (6c). Triphenylphosphine (333 mg, 1.27 mmol) and the enone **5** (250 mg, 1.27 mmol) in dichloromethane (6 cm^3) was treated, in an analogous manner to that for the preparation of **6a**, with titanium (IV) *iso*-propoxide (0.19 cm^3, 0.64 mmol), titanium (IV) chloride (70 μl, 0.64 mmol) and chlorobenzaldehyde (535 mg, 3.81 mmol). After work-up, flash chromatography (SiO_2, 20%, then 35% ethyl acetate in hexane) gave the starting enone **5** (93 mg, 0.47 mmol, 37% recovery) as a white solid, after giving the less polar dienone **6c** (210 mg, 0.66 mmol, 52% (82% based on recovery)) also as a white solid; mp 187–188 °C (Et_2O); δ_H (400 MHz, $CDCl_3$) 7.58 (1H, ddd, *J*=5.9, 2.4, 0.7 Hz, C*H*=CHC=O), 7.51 (2H, dt, *J*=8.6, 1.9 Hz, Ar*H*), 7.43 (1H, br. s, C=C*H*Ar), 7.38 (2H, dt, *J*=8.6, 1.9 Hz, Ar*H*), 6.51 (1H, dd, *J*=5.9, 1.7 Hz, CH=C*H*C=O), 5.79 (1H, br. d, *J*=8.0 Hz, N*H*), 4.41 (1H, br. d, *J*=8.0 Hz, C*H*NH), 1.45 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 195.2 (s), 157.7 (d), 155.3 (s), 136.3 (s), 135.6 (s), 135.5 (d), 132.8 (d), 132.5 (d), 131.6 (s), 129.0 (d), 80.6 (s), 52.0 (d), 28.3 (q); *m*/*z* (ES) 344 ($[M(^{37}Cl)Na]^+$, 32%), 342 ($[M(^{35}Cl)Na]^+$, 100). Found $[MNa]^+$ 342.0890 ($[MNa]^+$ $C_{17}H_{18}NO_3NaCl$ requires 342.0873).

3.1.4. (1*S*)-[(*E*)-5-(2,5-Dimethoxybenzylidene)-4-oxo-cyclopent-2-enyl]-carbamic acid *tert*-butyl ester (6d). Triphenylphosphine (267 mg, 1.02 mmol) and the (*R*)-enantiomer of the enone **5** (201 mg, 1.02 mmol) in dichloromethane (5 cm^3) was treated, in an analogous manner to that for the preparation of **6a**, with titanium (IV) *iso*-propoxide (0.15 cm^3, 0.51 mmol), titanium (IV) chloride (56 μl, 0.51 mmol) and 2,5-dimethoxybenzaldehyde (508 mg, 3.06 mmol). After work-up, flash chromatography (SiO_2, 20%, then 35% ethyl acetate in hexane) gave the starting enone **5** (51 mg, 0.26 mmol, 25% recovery) as a white solid, after giving the less polar dienone **6d** (210 mg, 0.61 mmol, 60% (80% based on recovery)) as a yellow solid; mp 122–124 °C (Et_2O); $[\alpha]_D$=+18.8 (*c* 2.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.87 (1H, s, C=C*H*Ar), 7.57 (1H, dd, *J*=5.9, 2.0 Hz, C*H*=CHC=O), 7.09 (1H, d, *J*=2.9 Hz, *o*-Ar*H*), 6.93 (1H, dd, *J*=9.1, 2.9 Hz, *p*-Ar*H*), 6.86 (1H, d, *J*=9.1 Hz, *m*-Ar*H*), 6.49 (1H, dd, *J*=5.9, 1.6 Hz, CH=C*H*C=O), 5.77 (1H, br. d, *J*=7.0 Hz, N*H*), 4.41 (1H, br. d, *J*=7.0 Hz, C*H*NH), 3.85 (3H, s, OC*H*$_3$), 3.80 (3H, s, OC*H*$_3$), 1.38 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 195.4 (s), 157.5 (d), 153.4 (s), 138.5 (s), 135.5 (d), 132.6 (s), 129.1 (d), 122.7 (d), 118.1 (s), 115.8 (s), 114.6 (d), 112.0 (d), 80.2 (s), 56.1 (q), 55.6 (q), 52.3 (d), 28.2 (q); *m*/*z* (ES) 369 ($[MHNa]^+$, 22%), 368 ($[MNa]^+$, 100). Found $[MNa]^+$ 368.1463 ($[MNa]^+$ $C_{19}H_{23}NO_5Na$ requires 368.1474).

3.1.5. (1*S*)-[4-Oxo-(*E*)-5-(2,4,6-trimethylbenzylidene)-cyclopent-2-enyl]-carbamic acid *tert*-butyl ester (6e). Triphenylphosphine (267 mg, 1.02 mmol) and the (*R*)-enantiomer of the enone **5** (201 mg, 1.02 mmol) in dichloromethane (6 cm^3) was treated, in an analogous manner to that for the preparation of **6a**, with titanium

(IV) *iso*-propoxide (0.15 cm^3, 0.51 mmol), titanium (IV) chloride (56 μl, 0.51 mmol) and mesitaldehyde (0.45 cm^3, 3.05 mmol). After work-up, flash chromatography (SiO_2, 20%, then 35% ethyl acetate in hexane) gave the starting enone **5** (135 mg, 0.68 mmol, 67% recovery) as a white solid, after giving the less polar dienone **6e** (80 mg, 0.24 mmol, 24% (73% based on recovery)) also as a white solid; mp 147–149 °C (Et_2O); $[\alpha]_D=-62.4$ (*c* 2.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.57 (1H, s, C═C*H*Ar), 7.44 (1H, dd, *J*=6.2, 2.2 Hz, C*H*═CHC═O), 6.87 (2H, s, Ar*H*), 6.48 (1H, dd, *J*=6.2, 1.9 Hz, CH═C*H*C═O), 5.33 (1H, br. d, *J*=5.6 Hz, N*H*), 4.10 (1H, br. d, *J*=5.6 Hz, C*H*NH), 2.26 (3H, s, *p*-ArCH_3), 2.20 (6H, s, *o*-Ar(CH_3)$_2$), 1.22 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 194.4 (s), 158.1 (d), 154.3 (s), 137.6 (s), 137.5 (s), 135.9 (d), 135.1 (s), 134.3 (d), 130.4 (s), 128.4 (d), 79.7 (s), 52.6 (d), 28.1 (q), 20.9 (q), 20.2 (q); *m/z* (ES) 351 ([MHNa]$^+$, 22%), 350 ([MNa]$^+$, 100). Found [MNa]$^+$ 350.1719 ([MNa]$^+$ $C_{20}H_{25}NO_3Na$ requires 350.1732).

3.1.6. (*E*)-(5-*iso*-Butylidene-4-oxocyclohex-2-enyl)-carbamic acid *tert*-butyl ester (12a). Triphenylphosphine (525 mg, 2.00 mmol) and the enone **11a** (422 mg, 2.00 mmol) in dichloromethane (12 cm^3) was treated, in an analogous manner to that for the preparation of **6a**, with titanium (IV) *iso*-propoxide (0.30 cm^3, 1.02 mmol), titanium (IV) chloride (110 μl, 1.00 mmol) and *iso*-butyraldehyde (0.55 cm^3, 6.06 mmol). After work-up, flash chromatography (SiO_2, 20% ethyl acetate in petrol) gave the starting enone **11a** (140 mg, 0.66 mmol, 33% recovery) as a white solid, after giving the less polar dienone **12a** (260 mg, 0.98 mmol, 49% (73% based on recovery)) also as a white solid; mp 93–94 °C (Et_2O); δ_H (400 MHz, $CDCl_3$) 6.85 (1H, dd, *J*=10.0, 3.3 Hz, C*H*═CHC═O), 6.59 (1H, d, *J*=9.9 Hz, C═C*H*), 6.15 (1H, dd, *J*=10.0, 1.8 Hz, CH═C*H*C═O), 4.67 (1H, br. s, N*H*), 4.50 (1H, br. s, C*H*NH), 3.01 (1H, dd, *J*=14.3, 5.2 Hz, C*H*H), 2.65 (1H, dsept, *J*=9.9, 6.6 Hz, C*H*(CH_3)$_2$), 2.60 (1H, dd, *J*=14.3, 7.8 Hz, CH*H*), 1.47 (9H, s, $CO_2C(CH_3)_3$), 1.06 (3H, d, *J*=6.6 Hz, CHCH_3), 1.04 (3H, d, *J*=6.6 Hz, CHCH_3); δ_C (100 MHz, $CDCl_3$) 187.9 (s), 154.9 (s), 148.8 (d), 147.3 (d), 131.4 (s), 129.0 (d), 80.1 (s), 46.5 (d), 32.4 (t), 28.3 (q), 27.0 (d), 22.3 (q), 22.1 (q); *m/z* (ES) 289 ([MHNa]$^+$, 20%), 288 ([MNa]$^+$, 100). Found [MNa]$^+$ 288.1573 ([MNa]$^+$ $C_{15}H_{23}NO_3Na$ requires 288.1576).

3.1.7. (*E*)-Acetic acid 5-*iso*-butylidene-4-oxocyclohex-2-enyl ester (12c). Triphenylphosphine (672 mg, 2.53 mmol) and the enone **11c** (390 mg, 2.53 mmol) in dichloromethane (12 cm^3) was treated, in an analogous manner to that for the preparation of **6a**, with titanium (IV) *iso*-propoxide (0.38 cm^3, 1.29 mmol), titanium (IV) chloride (0.14 cm^3, 1.28 mmol) and *iso*-butyraldehyde (0.92 cm^3, 10.1 mmol). After work-up, flash chromatography (SiO_2, 20% ethyl acetate in hexane) gave the dienone **12c** (460 mg, 2.21 mmol, 87%) as a colourless oil; δ_H (400 MHz, $CDCl_3$) 6.85 (1H, ddd, *J*=10.2, 3.0, 1.2 Hz, C*H*═CHC═O), 6.55 (1H, br. d, *J*=10.0 Hz, C═C*H*), 6.11 (1H, dd, *J*=10.2, 1.6 Hz, CH═C*H*C═O), 5.45 (1H, m, C*H*OAc), 3.05 (1H, ddt, *J*=14.0, 5.5, 1.2 Hz, C*H*HCHOAc), 2.68 (1H, ddd, *J*=14.0, 8.5, 2.2 Hz, CH*H*CHOAc), 2.62–2.56 (1H, m, C*H*(CH_3)$_2$), 2.03 (3H, s, O_2CCH_3), 1.00 (3H, d, *J*=6.6 Hz, CHCH_3), 0.97 (3H, d, *J*=6.6 Hz, CHCH_3); δ_C (100 MHz, $CDCl_3$) 186.4 (s), 169.3 (s), 146.7 (d), 145.2 (d), 131.0 (d), 126.9 (s), 66.8 (d), 30.2 (t), 26.1 (d), 21.3 (q), 21.0 (q), 20.0 (q); *m/z* (CI) 209 ([MH]$^+$, 100%), 149 ([MH−AcOH]$^+$, 21), 148 ([M−AcOH]$^+$, 56). Found [MH]$^+$ 209.1183 ([MH]$^+$ $C_{12}H_{17}O_3$ requires 209.1178).

3.1.8. (4*S*)-(*E*)-4-(*tert*-Butyldimethylsilanyloxy)-6-*iso*-butylidenecyclohex-2-enone (12d). Triphenylphosphine (217 mg, 0.83 mmol) and the enone **11d** (187 mg, 0.83 mmol) in dichloromethane (5 cm^3) was treated, in an analogous manner to that for the preparation of **6a**, with titanium (IV) *iso*-propoxide (0.12 cm^3, 0.41 mmol), titanium (IV) chloride (45 μl, 0.41 mmol) and *iso*-butyraldehyde (0.23 cm^3, 2.53 mmol). After work-up, flash chromatography (SiO_2) gave the dienone **12d** (93 mg, 0.33 mmol, 40%) as a colourless oil; $[\alpha]_D=-95.0$ (*c* 2.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 6.84 (1H, dt, *J*=10.3, 1.8 Hz, C*H*═CHC═O), 6.55 (1H, dd, *J*=9.7, 2.3 Hz, C═C*H*), 6.06 (1H, dd, *J*=10.3, 1.8 Hz, CH═C*H*C═O), 4.52 (1H, ddt, *J*=9.4, 5.4, 2.0 Hz, C*H*OTBS), 3.00 (1H, dd, *J*=14.0, 5.4 Hz, C*H*HCHOTBS), 2.70–2.59 (1H, m, C*H*(CH_3)$_2$), 2.55 (1H, ddd, *J*=14.0, 9.4, 2.4 Hz, CH*H*CHOTBS), 1.07 (3H, d, *J*=5.7 Hz, CHCH_3), 1.05 (3H, d, *J*=5.7 Hz, CHCH_3), 0.94 (9H, s, $SiC(CH_3)_3$), 0.14 (6H, s, Si(CH_3)$_2$); δ_C (100 MHz, $CDCl_3$) 188.2 (s), 153.1 (d), 146.2 (d), 129.5 (d), 129.4 (s), 67.2 (d), 35.8 (t), 27.1 (d), 25.8 (q), 22.6 (q), 22.0 (q), 18.1 (s), −4.6 (q), −4.8 (q); *m/z* (CI) 281.1941 ([MH]$^+$ $C_{16}H_{29}O_2Si$ requires 281.1937).

3.1.9. (4*S*)-(*E*)-6-Benzylidene-4-(*tert*-butyldimethylsilanyloxy)-cyclohex-2-enone (12e). Triphenylphosphine (225 mg, 0.86 mmol) and the enone **11d** (194 mg, 0.86 mmol) in dichloromethane (5 cm^3) was treated, in an analogous manner to that for the preparation of **6a**, with titanium (IV) *iso*-propoxide (0.13 cm^3, 0.44 mmol), titanium (IV) chloride (47 μl, 0.43 mmol) and benzaldehyde (0.26 cm^3, 2.56 mmol). After work-up, flash chromatography (SiO_2) gave the dienone **12e** (166 mg, 0.53 mmol, 62%) as a white solid; mp 40–42 °C (Et_2O); $[\alpha]_D=-179.1$ (*c* 1.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.65 (1H, d, *J*=2.6 Hz, C═C*H*Ar), 7.49–7.28 (5H, m, Ar*H*), 6.89 (1H, dt, *J*=10.2, 1.9 Hz, C*H*═CHC═O), 6.16 (1H, dd, *J*=10.2, 1.9 Hz, CH═C*H*C═O), 4.56 (1H, ddt, *J*=9.1, 5.4, 1.9 Hz, C*H*OTBS), 3.39 (1H, dd, *J*=14.4, 5.4 Hz, C*H*HCHOTBS), 2.83 (1H, ddd, *J*=14.4, 9.1, 2.6 Hz, CH*H*CHOTBS), 0.90 (9H, s, $SiC(CH_3)_3$), 0.10 (3H, s, SiCH_3), 0.07 (3H, s, SiCH_3); δ_C (100 MHz, $CDCl_3$) 188.1 (s), 152.9 (d), 136.5 (d), 129.6 (d), 129.5 (s), 129.4 (d), 128.6 (d), 128.5 (d), 127.9 (s), 66.8 (d), 36.9 (t), 25.7 (q), 18.1 (s), −4.6 (q), −4.8 (q); *m/z* (CI) 315.1788 ([MH]$^+$ $C_{19}H_{27}O_2Si$ requires 315.1780).

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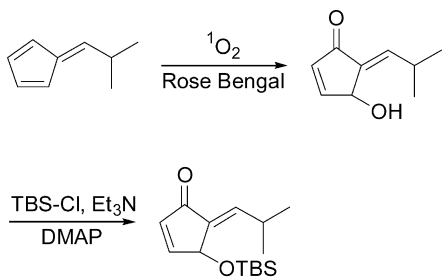
References and notes

1. Straus, D. S.; Glass, C. K. *Med. Res. Rev.,* **2001**, *21*, 185.
2. Fitzpatrick, F. A.; Wynalda, M. A. *J. Biol. Chem.,* **1983**, *258*, 11713.
3. Roberts, S. M.; Santoro, M. G.; Sickle, E. S. *J. Chem. Soc., Perkin Trans.* **2002**, *1*, 1735.
4. Fukushima, S.; Takeuchi, Y.; Kishimoto, S.; Yamashita, S.; Uetsuki, K.; Shirakawa, S.; Suzuki, M.; Furuta, K.; Noyori, R.; Sasaki, H.; Kikuchi, Y.; Kita, T.; Yamori, T.; Sawada, J.; Kojima, M.; Hazato, A.; Kurozumi, S.; Fukushima, M. *Anti-Cancer Drugs* **2001**, *12*, 221.
5. Kikuchi, H.; Tsukitani, Y.; Iguchi, K.; Yamada, Y. *Tetrahedron Lett.* **1983**, *24*, 1549.
6. Iguchi, K.; Kaneta, S.; Mori, K.; Yamada, Y.; Honda, A.; Mori, Y. *Tetrahedron Lett.* **1985**, *26*, 5787.
7. Roulland, E.; Monneret, C.; Florent, J-C.; Bennejean, C.; Renard, P.; Léonce, S. *J. Org. Chem.,* **2002**, *67*, 4399.
8. (a) Weaving, R.; Roulland, E.; Monneret, C.; Florent, J-C. *Tetrahedron Lett.* **2003**, *44*, 2579. (b) Kobayashi, Y.; Murugesh, M. G.; Nakano, M. *Tetrahedron Lett.* **2001**, *42*, 1703–1707. (c) Kobayashi, Y.; Murugesh, M. G.; Nakano, M.; Takahisa, E.; Usmani, S. B.; Ainai, T. *J. Org. Chem.* **2002**, *67*, 7110.
9. Suzuki, M.; Morita, Y.; Koyano, H.; Koga, M.; Noyori, R. *Tetrahedron* **1990**, *46*, 4809.
10. (a) Iqbal, M.; Evans, P. *Tetrahedron Lett.* **2003**, *44*, 5741. (b) Eddolls, J. P.; Iqbal, M.; Roberts, S. M.; Santoro, M. G. *Tetrahedron* **2004**, *60*, 2539–2550.
11. Takanami, T.; Suda, K.; Ohmori, H. *Tetrahedron Lett.* **1990**, *31*, 677.
12. Synthesis of chiral 4-azacyclopentenone building blocks is discussed in: Dauvergne, J.; Happe, A. M.; Jadhav, V.; Justice, D.; Matos, M-C.; McCormack, P. J.; Pitts, M. R.; Roberts, S. M.; Singh, S. K.; Snape, T. J.; Whittall, J. *Tetrahedron* **2004**, *60*, 2559–2567.
13. HPLC analysis of samples of **6a** stored in solution kept in sunlight showed double bond isomerisation, whereas **6b** was shown to be photolytically stable.
14. 4-Oxy-5-alkylidene cyclopentenones can be prepared utilising the procedures described in (a) Kawamoto, A.; Kosugi, H.; Uda, H. *Chem. Lett.* **1972**, 807. (b) Roberts, S. M.; Santoro, M. G.; Änggård, E. E. PCT Pat. Appl. WO 01 44254. (c) Snape, T. J. PhD Thesis, University of Liverpool, 2003; as follows:



($\pm$)-4-[*tert*-Butyldimethylsilanyloxy]-5-[2-methylprop-(*E*)-ylidene]-cyclopent-2-enone. A solution of 6-*iso*-propylfulvene (1.00 g, 8.32 mmol) and a catalytic amount of Rose Bengal in methanol (200 cm^3) was stirred at room temperature with a steady stream of oxygen bubbling through it for 20 min. The solution was irradiated (500W IR lamp), with continuation of the stream of oxygen, for 13 h. The irradiation and oxygen flow were ceased and the methanol removed in vacuo. Flash chromatography (SiO_2, 40% ethyl acetate in hexane) gave an inseparable mixture of the (*E*) and (*Z*)-isomers of the alcohol (320 mg, 2.10 mmol, 25%) as an orange oil. This mixture of alcohols (2.48 g, 16.3 mmol) in dry dichloromethane (24 cm^3) was added dropwise to a stirred solution of *tert*-butyldimethylsilylchloride (3.19 g, 21.2 mmol), triethylamine (8.0 cm^3, 57.0 mmol) and a catalytic amount of dimethylaminopyridine (0.26 g, 2.13 mmol) in dichloromethane (24 cm^3) at 0 °C, under an atmosphere of nitrogen. The reaction mixture was allowed to warm to room temperature over 16 h. Water (60 cm^3) was added, the phases separated and the aqueous phase was extracted with dichloromethane (3×50 cm^3). The combined organics were dried over anhydrous magnesium sulfate and evaporated in vacuo. Flash chromatography (SiO_2, 10% ethyl acetate in petrol) gave the (*Z*)-isomer of the title compound (392 mg, 1.47 mmol, 9.0%) as a yellow oil, followed by the (*E*)-isomer (1.27 g, 4.77 mmol, 29%) also as a yellow oil; δ_H (400 MHz, $CDCl_3$) 7.36 (1H, dd, *J*=6.0, 2.3 Hz, C*H*=CHC=O), 6.45 (1H, d, *J*=10.4 Hz, C=C*H*), 6.37 (1H, d, *J*=6.0 Hz, CH=C*H*C=O), 5.36 (1H, m, C*H*OTBS), 2.94–2.78 (1H, m, C*H*$(CH_3)_2$), 1.08 (3H, d, *J*=6.7 Hz, CHCH_3), 1.07 (3H, d, *J*=6.7 Hz, CHCH_3), 0.91 (9H, s, SiC$(CH_3)_3$), 0.17 (3H, s, SiCH_3), 0.15 (3H, s, SiCH_3); δ_C (100 MHz, $CDCl_3$) 195.4 (s), 158.1 (d), 144.9 (d), 136.5 (d), 134.8 (s), 71.1 (d), 28.6 (d), 26.1 (q), 22.4 (q), 22.3 (q), 18.3 (s), −3.3 (q), −4.0 (q); *m/z* (EI) 266 ($[M]^+$, 1%), 209 ($[M-C_4H_9]^+$, 100). Found $[M]^+$ 266.1701 ($[M]^+$ $C_{15}H_{26}O_2Si$ requires 266.1702). Found: C, 67.7; H, 9.9, $C_{15}H_{26}O_2Si$ requires C, 67.6; H, 9.8%.

15. Sirisoma, N. S.; Johnson, C. R. *Tetrahedron Lett.* **1998**, *39*, 2059.
16. Audia, J. E.; Boisvert, L.; Patten, A. D.; Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 3738.