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Reactivity of cyclopropanic δ-oxo-α,β-unsaturated esters towards SmI_2: 3-*exo-trig* cyclisation versus cyclopropane ring opening

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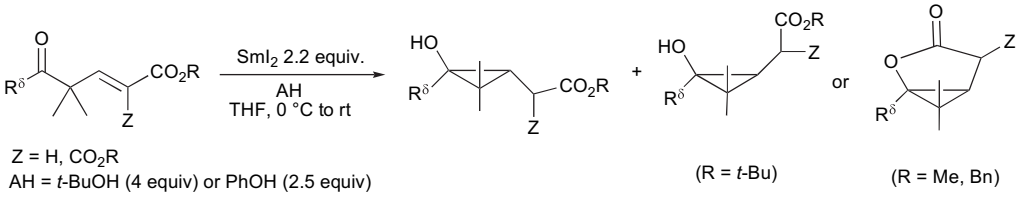
Abstract—*trans*-(2′,2′-Diphenyl-bicyclopropyl-2-yl)-4,4-dimethyl-5-oxo-pent-2-enoic acid methyl ester **9**, undergoes 3-*exo-trig* cyclisation in the presence of SmI_2 without competitive ring opening of Newcomb's bicyclopropylic probe next to the carbonyl group. From this result, it may be concluded that the absence of ring opening observed earlier in the case of 5-cyclopropyl-4,4-dimethyl-5-oxo-pent-2-enoate **7** is not due to the potentially reversible character of this process. Meanwhile, as deduced from kinetic considerations based on data of the literature, the absence of ring opening does not necessarily mean that formation of ketyl radicals is not involved in the 3-*exo-trig* cyclisations of δ-oxo-α,β-unsaturated esters.
Compounds **7** and **9** cyclise with total *syn* selectivity, leading ultimately to lactones. This *syn* selectivity contrasts with that of other alkylic δ-oxo-α,β-unsaturated esters.

1. Introduction

For several years now, we have been engaged in the study of SmI_2-induced radical 3-*exo-trig* cyclisations. We have thus devised a new access to cyclopropanes and cyclopropanols through cyclisation of, respectively, δ-halogeno[1] and γ-disubstituted-δ-oxo-α,β-unsaturated esters.[2] In the case of oxo-esters, γ-disubstitution is required to avoid migration of the ethylenic bond from α,β- to β,γ-position. When the two substituents at γ-position are identical, the reaction may give two diastereoisomers: the *trans*-cyclopropanol resulting from cyclisation according to the *anti* mode and the *cis*-cyclopropanol resulting from cyclisation according to the *syn* mode (Scheme 1, in which R^{γ}=Me for the sake of clarity). For methyl and benzyl esters, the cis adducts spontaneously lactonise in the conditions of the reaction. Lactonisation does not take place with *tert*-butyl esters. The diastereoselectivity (sometimes excellent) was shown to be highly dependent on the structure of the molecule, that is, inter alia, the nature of the R^{δ} group at δ-position and the presence or not of a second carbalkoxy group attached to the double bond (alkylidenemalonates vs monoesters).[2,3]

As already published,[2a] two possible mechanisms were considered for these reactions (Scheme 2). According to the first one, the ketonic substrate **1** is first reduced by SmI_2 to ketyl radical **2**. Intramolecular condensation of the ketyl anion onto the activated double bond of the enoate moiety then leads (potentially in a reversible way) to the cyclised radical intermediate **3**. Whatever the position of the equilibrium, the electrophilic α-carbalkoxy radical is rapidly and irreversibly reduced to carbanion **4** by a second molecule of SmI_2 and the whole reaction is therefore displaced towards cyclisation. Protonation of the carbanion completes the reaction. This



Scheme 1.

Keywords: 3-*exo-trig* Cyclisations; Radical cyclisations; Ketyl radicals.
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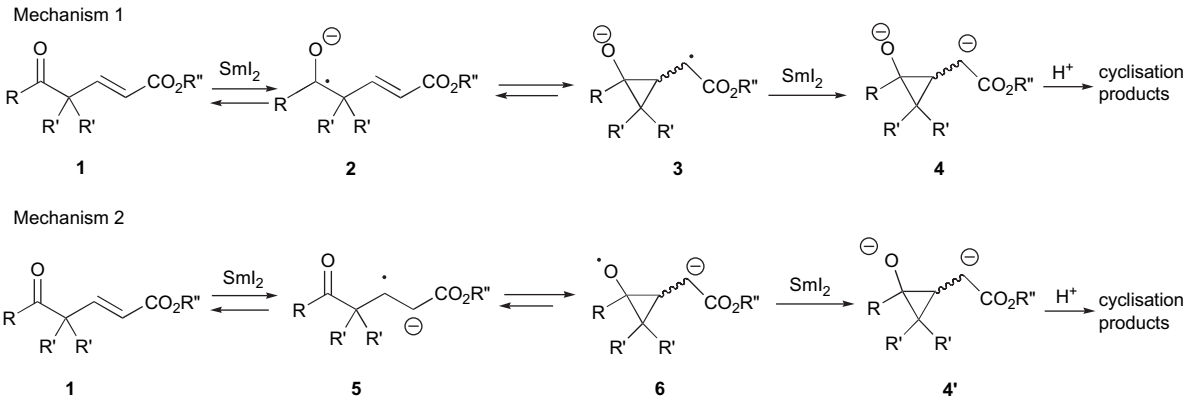


Scheme 2.

mechanism is akin to the one we previously proposed[1] for cyclisation of δ-halogeno-α,β-unsaturated esters.

According to the second mechanism, the reaction starts with reduction of the enoate moiety to radical anion **5**. Reversible intramolecular condensation of this radical anion onto the carbonyl group gives the cyclised cyclopropanoxy radical **6**. Radical **6** is further reduced, in a fast and irreversible process, to cyclopropanoate **4′** already encountered (but not necessarily with the same diastereoisomeric composition) in mechanism 1.

In our previous work we also used the ring opening of cyclopropyl ketyl radical as a probe to try to have further insight into the mechanism of the reactions. There are several examples, in the literature, of reductive ring opening of cyclopropyl ketones in the presence of SmI_2.[5] The rate of ring opening of methyl cyclopropyl ketyl radical has not yet been accurately determined. It has nevertheless been shown to be fast,[4] with a k_o constant at least equal to (and probably greater than) 10^7 s^{-1} at 25 °C. We therefore investigated the reaction of benzyl 5-cyclopropyl-4,4-dimethyl-5-oxo-pent-2-enoate **7** to see if radical ring opening of the cyclopropyl group at δ-position would interfere with the cyclisation process. If so, mechanism 1 would have been validated. In the event, no product of ring opening of the cyclopropyl group was detected and the cyclisation reaction was found to give selectively lactone **8** in virtually quantitative yield (Fig. 1).[2a]

The absence of ring opening with substrate **7** does not necessarily validate mechanism 2. At least three explanations may be proposed:

(i) the reaction effectively goes according to mechanism 2;
(ii) the reaction goes through mechanism 1 but the intramolecular condensation of the ketyl radical onto the activated double bond is rapid enough to exclude any competitive ring opening of the cyclopropyl group at δ-position;

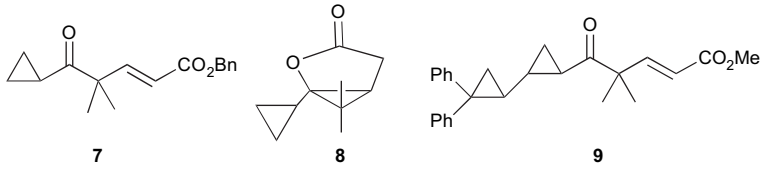
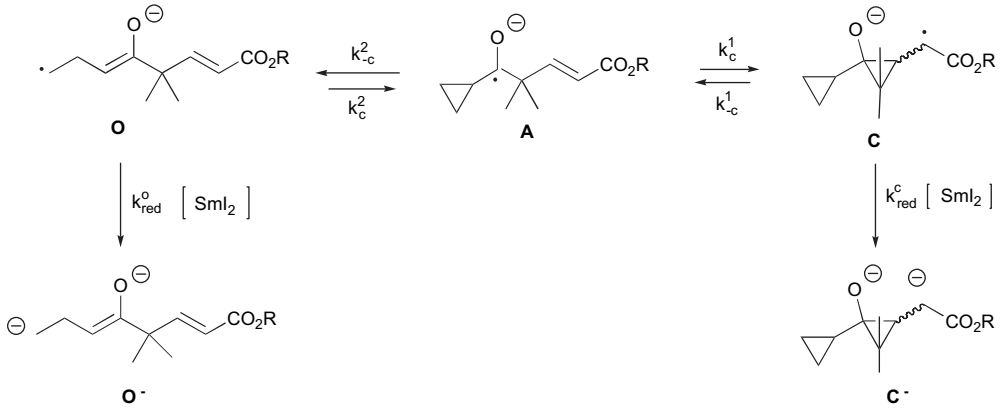
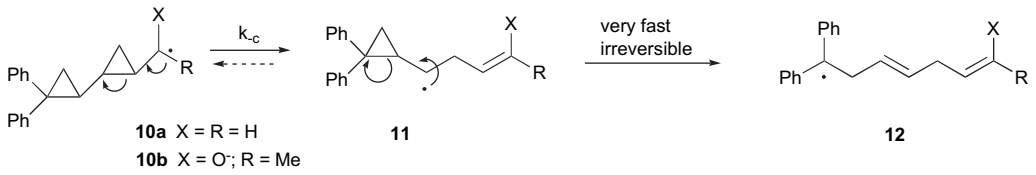


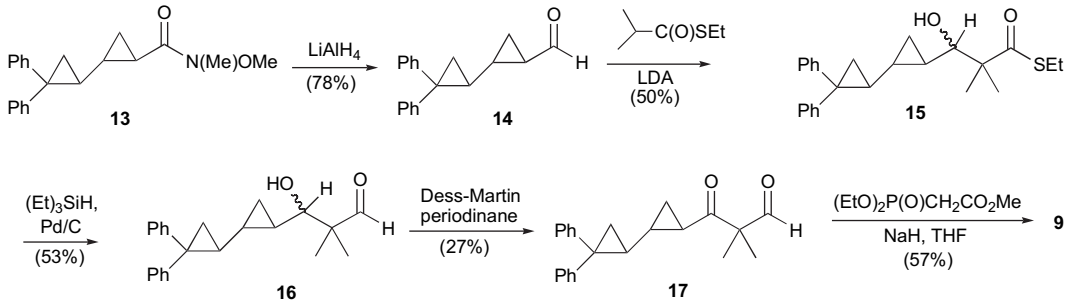
Figure 1.



Scheme 3.



Scheme 4.



Scheme 5.

(iii) the ketyl radical **A** (Scheme 3) does form and may open to homoallylic distonic radical **O**. However, this reaction is potentially reversible; if further reduction of the homoallylic radical **O** by a second molecule of SmI_2 is slow enough compared to ring reformation, then it may be conceived that the whole reaction is shifted towards formation, through **A** and **C**, of ring closed product $\mathbf{C}^-$.

The relative paucity of kinetic values concerning the reactions involving ketyl radicals,[6] especially as compared to those involving carbinyl radical for which much more data are available, makes it difficult to choose among the three above alternatives. Nevertheless, a simple consideration of (even roughly) estimated values for kinetic constants implied in the whole process is in disfavour of proposal (iii) (see Section 3). But it should be noted that all these estimations refer to *free* radical reactions and may very well be, as already convincingly pointed out,[5a] unsuitable for samarium-induced reactions, especially if, as it is the case here, charged radical species are involved. Furthermore many puzzling results have in the past been obtained in connection with the use of ring opening of cyclopropyl ketyl radicals as mechanistic probes in samarium promoted reactions.[5a] We therefore wanted to get additional experimental convincing evidence to decide whether the potentially reversible nature of ring opening of ketyl radical **A** could affect or not the SmI_2-induced reaction of **7**.

To do so, we decided to carry out the SmI_2-induced cyclisation process on compound **9** (4,4-dimethyl-5-(*trans*-2-(2,2-diphenyl-1*R**-cyclopropyl)-1*S**,2*R**-cyclopropyl)-5-oxo-prop-2-enoic acid methyl ester) that incorporates Newcomb's 2′,2′-diphenyl-bicyclopropyl group[7] at δ-position. Rearrangement of the 2′,2′-diphenyl-bicyclopropyl-2-carbinyl radical **10a** to diphenylcarbinyl radical **12** involves two consecutive ring openings (Scheme 4). Due to the fastness (and irreversibility) of ring opening of the intermediate diphenylcyclopropylcarbinyl radical **11a**, the first ring opening may also be considered as irreversible. Its rate has been estimated to be about 4–5 times that of the parent cyclopropylcarbinyl radical.[7] To the best of our knowledge, there is no data concerning the reactivity of the corresponding ketyl radical **10b**.

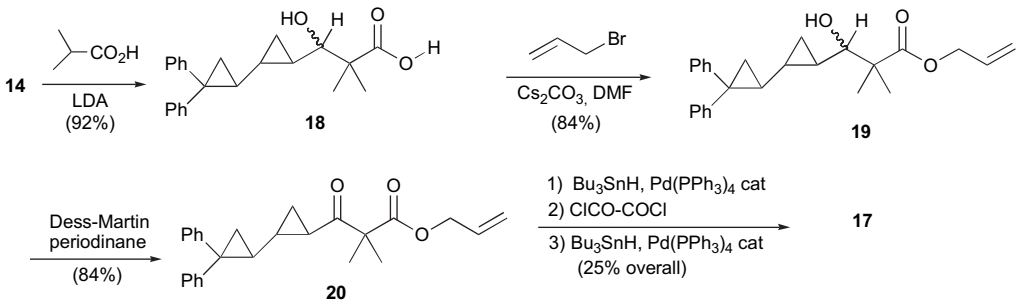
2. Results

2.1. Preparation of δ-oxo-α,β-unsaturated ester 9

Diastereoisomerically pure 4,4-dimethyl-5-(*trans*-2-(2,2-diphenyl-1*R**-cyclopropyl)-1*S**,2*R**-cyclopropyl)-5-oxo-prop-2-enoic acid methyl ester **9** was synthesised from diastereoisomerically pure Weinreb amide **13** (Scheme 5) whose synthesis[†] and thorough characterisation had already been published by Newcomb and co-workers.[7] Reduction of **13** with lithium aluminium hydride gave aldehyde **14**. Compound **14** was converted by aldol condensation with the lithium salt of ethyl thioisobutyrate to β-hydroxythioester **15** as a mixture of diastereoisomers in 50% overall yield. Compound **15** was hydrogenolysed to β-hydroxyaldehyde **16** by Et_3SiH in the presence of Pd/C[8] in 53% yield. Oxidation of **16** with Dess–Martin periodinane gave β-ketoaldehyde **17** in 27% yield. Compound **17** was finally converted to **9** in 57% yield through Wadsworth–Emmons olefination as already published for similar substrates.[2a]

Given the rather low yield of most steps involved, homologation of aldehyde **14** to β-ketoaldehyde **17** was achieved only in 7% overall yield. We therefore investigated another approach, as summarised in Scheme 6. Aldehyde **14** was condensed with the dilithio salt of isobutyric acid to give in 92% yield β-hydroxyacid **18**, which was converted to allyl

[†] Weinreb amide was prepared from 2,2-diphenyl-cyclopropane carboxaldehyde. In our work, this aldehyde was itself not prepared by CrO_3–pyridine oxidation of 2,2-diphenylcyclopropylcarbinol, which gives poor yields[17] but by palladium catalysed hydrostannolysis[11] of 2,2-diphenylcyclopropanecarbonyl chloride.



Scheme 6.

ester **19** in 84% yield by treatment with caesium carbonate and allyl bromide in DMF.[9] β-Hydroxyester **19** was oxidised to allyl β-ketoester **20** with Dess–Martin periodinane in 84% yield. Compound **20** was finally converted to β-ketoaldehyde **17** through three consecutive treaments according to a one-pot protocol, namely, hydrostannolysis to tributyltin carboxylate by the Bu_3SnH/cat $Pd(PPh_3)_4$ system,[10] conversion to acyl chloride with oxalyl chloride and hydrostannolysis to aldehyde, again by the Bu_3SnH/cat $Pd(PPh_3)_4$ system.[11] The overall yield for this three step transformation was only 25% but could in our opinion be optimised.

2.2. SmI_2-induced cyclisation of δ-oxo-α,β-unsaturated ester 9

The reaction of **9** with SmI_2/*t*-BuOH was conducted in the following way: to δ-oxo-α,β-unsaturated ester **9** in solution in THF at 0 °C was added dropwise over a period of a few minutes 2.2 equiv of a 0.1 M solution of SmI_2 in THF. Complete discharge of the typical blue colouration of SmI_2 in THF was observed after 2 h at room temperature. After conventional work-up and purification by flash chromatography on silica, lactone **21** was isolated in 80% yield as a mixture of two diastereoisomers (Scheme 7). No other product could be characterised. The lactone is clearly identified by high resolution mass spectrometry, infra-red spectroscopy (ν(CO)=1772 cm^{-1}, identical with the one observed for lactone **8**) and the characteristic *ABX* system with J_{AB}=ca. 19 Hz, J_{AX}=6–7 Hz and J_{BX}=0 Hz formed by the protons α and β to carbonyl and which, in the case of lactone **21**, is split into two due to the presence of the two diastereoisomeric forms in comparable amounts (Fig. 2).

3. Discussion

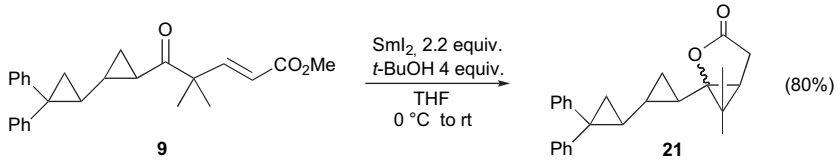
The absence of products from ring opening in the reaction of **9** with SmI_2 clearly invalidates proposal (iii).

According to Scheme 3, the rates of formation at a given instant *t* of ring opened $\mathbf{O}^-$ and ring closed $\mathbf{C}^-$ products is given by:

$$\left(\frac{d[\mathbf{O}^-]}{dt}\right)_t = k^o_{red}[\mathbf{O}]_t[SmI_2]_t \quad (1)$$

$$\left(\frac{d[\mathbf{C}^-]}{dt}\right)_t = k^c_{red}[\mathbf{C}]_t[SmI_2]_t \quad (2)$$

If we assume an ideal case in which the substrate is put in reaction with a large excess of SmI_2 and if we use a steady



Scheme 7.

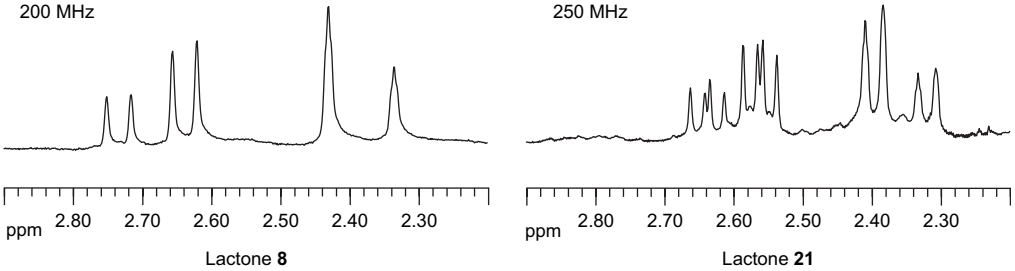


Figure 2. ^{1}H NMR ABX splitting patterns displayed by protons α to the carbonyl group of lactones **8** and **21**.

state approximation for intermediates **O** and **C**, the ratio F of opened to cyclised products is given by Eq. 3:[‡]

$$F = \frac{k^{o}_{red}[\mathbf{O}]}{k^{c}_{red}[\mathbf{C}]} = \frac{k^{o}_{red}}{k^{c}_{red}} \times \frac{k^{2}_{-c}\left(k^{1}_{-c} + k^{c}_{red}[SmI_2]\right)}{k^{1}_{c}\left(k^{2}_{c} + k^{o}_{red}[SmI_2]\right)} \quad (3)$$

For the reversible character of ring opening of ketyl radical to become of consequence on the partitioning between ring closed and ring opened products, the value of k^2_c must be at least of the same order of magnitude as the product $k^o_{red}[SmI_2]$. The value of k^o_{red} may be approximated to about 7×10^6 s^{-1} at 25 °C.[12] The value of k^2_c is not known but, in the carbinyl series, a value of 0.8×10^4 s^{-1} has been found for cyclisation of the free 2-butenyl radical.[13] Even if, in our reaction conditions, the actual value of SmI_2 concentration, which is not constant, is on an average much lower than 0.1 M, reduction of the opened radical appears favoured compared to cyclisation back to **A**. Thus both kinetic considerations and experimental observations are concordant to exclude any influence of the reversibility of ring opening of ketyl radical on the course of the SmI_2-induced cyclisation of δ-oxo-α,β-unsaturated esters bearing a cyclopropyl group at δ-position.

Concerning mechanisms 1 and 2, we have already amply discussed the argument in favour of or against each of them.[2a] Some more considerations can nevertheless be made.

As suggested by one of the referees, a comparison of the reduction potentials of ketones on one hand and of α,β-unsaturated esters on the other hand could help to determine which part of δ-oxo-α,β-unsaturated esters **1** is more likely to accept the first electron transfer. Cyclic voltammetry was thus performed on some representative molecules, in collaboration with Dr Anny Jutand's group (UMR CNRS-ENS-UMPC 8640, Ecole Normale Supérieure, Paris). The cyclic voltammogram of aliphatic ketones *t*-BuCOMe and cyclopropylCOMe performed in THF (containing *n*-Bu_4NBF_4, 0.3 M, as supporting electrolyte), at a gold electrode and a scan rate of 0.5 V s^{-1}, exhibited a badly resolved reduction wave, appearing as a shoulder close to the reduction of the solvent at ca. −2.7 V versus SCE for both compounds. Thus, as observed by Tanko and co-workers,[4] the cyclopropyl group does not appear to substantially stabilise the ketyl radical. The cyclic voltammogram of $CH_3CH{=}CH{-}CO_2Et$, performed under the same conditions, exhibited a well-defined irreversible reduction peak located at a less negative potential: E^p=−2.48 V versus SCE. When comparing the reduction peak potentials of each compound, one sees that the ethyl crotonate is more easily reduced than the aliphatic ketones. The cyclic voltammogram performed on the aromatic ketone $PhCOCH(CH_3)_2$ exhibited a reversible reduction peak at E^p=−2.16 V (E^0=−2.07 V). In a first approach, when comparing peak potentials E^p, one sees that only aromatic ketones are more easily reduced than the α,β-unsaturated ester. However, this assumption would be totally true if standard potentials were compared. Indeed, the aliphatic ketones and ester investigated above exhibited irreversible reduction peaks whose peak potentials cannot be compared because they depend on the rate of the chemical reaction which follows the electron transfer. In other words, only standard potentials E^0 can be compared.

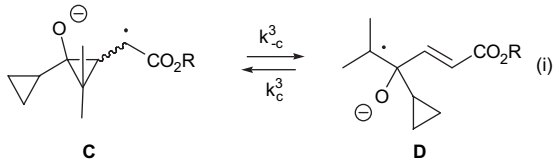
This is why the cyclic voltammetry of two related compounds $PhCH{=}CH{-}CO_2Et$ and $PhCOCH(CH_3)_2$ has been performed in DMF. Both compounds exhibited a reversible reduction peak at E^0=−1.77 V and −2.01 V, respectively.[14] These standard potentials can now be compared. It is thus established that the cinnamic ester is more easily reduced than the aromatic ketone, itself of course more easily reduced than aliphatic ketones.

Therefore, one can assume that the part of the molecules **1**, which preferentially accepts the first electron transfer is the α,β-unsaturated ester group. Meanwhile, caution should be exercised when extrapolating such conclusion based on electrochemistry to reduction by SmI_2 since it has been shown that samarium diiodide behaves not as an outer-sphere but as an inner-sphere electron donating agent towards ketones.[15] Besides, cyclisation according to mechanism 2 leads to a supposedly high in energy cyclopropanoxy radical **C** and could be on that ground disfavoured.

Examination of the values of the different kinetic constants involved in mechanism 1 (Scheme 3), when they are available or may be reasonably estimated, is also instructive.

The k^1_c may be evaluated as follows. The k_c constant for cyclisation of 4-carbalkoxy-but-2-enyl radical is known,[16] with $k_c=2\times10^6$ s^{-1} at 25 °C (from Arrhenius plot, $k_c=1.6\times10^7$ s^{-1} at 80 °C), a 200-fold increase if compared to the cyclisation[13,17] of the parent 3-butenyl radical (similarly, the 5-*exo* cyclisation of the 6-cyano-5-hexenyl radical is 1000 times faster than the cyclisation of 5-hexenyl radical at room temperature[18]). Ketyl radicals are likely to be more nucleophilic and therefore to cyclise more rapidly. We have also (in our case) to take into account the *gem*-dimethyl effect. In the case of 3-butenyl radicals, Newcomb was able to evaluate that *gem*-disubstitution by methyl groups at the 2-position results in a 500-fold increase in the rate of cyclisation.[17] The cyclisation constant k^1_c of Scheme 3 should therefore be at least as high as $2\times10^6\times500$ s$^{-1}=10^9$ s^{-1} (25 °C). This value is to be compared with that of ring opening of cyclopropyl ketyl radical of which we unfortunately know only the lower limit[4] ($k^2_{-c}=10^7$ s^{-1} at 25 °C). Nevertheless, it is clear that the absence of ring opened products

[‡] The cycloreversion of radical intermediate **C** to homoallylic dimethylcarbinyl radical **D** must also be considered. However, in all SmI_2-induced reactions of δ-oxo-α,β-unsaturated esters we investigated, we never detected any

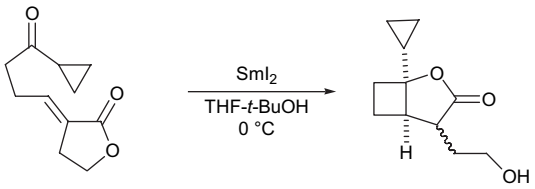


C **D**

product derived from radical intermediates such as **D**. It may be recalled that tertiary carbinyl radicals are hardly reduced to organosamarium in the presence of SmI_2.[23,24] It should be noted that the simple inclusion of equilibrium *i* in Scheme 3 does not affect the above kinetic equations. Meanwhile, equilibrium *i* should be taken into consideration when dealing with the diastereoisomeric issue of the reaction, a fact that we overlooked in our previous publication.[2a]

does not necessarily exclude mechanism 1 (i.e., proposal (ii)). The lack of values for most kinetic constants involved in mechanism 1 (to say nothing about mechanism 2) makes it unfortunately delicate to draw more precise conclusions.[§]

The absence of ring opening in the 4-*exo-trig* cyclisation of compound **22**, reported by Procter and co-workers[19] is more intriguing. 4-*exo-trig* Cyclisations involving carbinyl radicals are notoriously much slower than 3-*exo-trig* ones (k_c=0.1–1 s^{-1} at 60 °C for ring closing of 4-pentenyl radical against 0.8×10^4 s^{-1} at 25 °C for ring closing of 3-butenyl radical[13]). It suggests that whatever the mechanism (mechanism 1 or as proposed by the authors mechanism 2), the cyclisations either of the radical anion onto the carbonyl group or of the ketyl radical onto the activated double bond are fast 4-*exo-trig* processes (Scheme 8).



22

Scheme 8.

Finally, the total diastereoselectivity observed in favour of the formation of lactone with compound **9** incorporating Newcomb's diphenyl-bicyclopropyl group deserves some comment. This diastereoselectivity is intriguing since approximately equimolecular amounts of *trans*-cyclopropanol and of lactone are found in the cyclisation of δ-oxo-α,β-unsaturated esters bearing indifferently an H, Me or *i*-Pr group at δ-position.[2a] The present result thus confirms our earlier observation concerning cyclopropanic compound **7**. But it also invalidates our tentative explanation based on a reversible concerted ring opening of the cyclopropane group during electron transfer from SmI_2 to the carbonyl group.[2a]

[§] If the k_c^2 term is neglected against the product $k_{red}^o[SmI_2]$, the opened to cyclised products ratio F is now given by:

$$F=\frac{k_{-c}^2}{k_c^1}+\frac{k_{-c}^2k_{-c}^1}{k_c^1k_{red}^c[SmI_2]}=\frac{k_{-c}^2}{k_c^1}+\left(\frac{k_{red}^o}{k_{red}^c}\times\frac{k_{-c}^2k_{-c}^1}{k_c^1k_{red}^o[SmI_2]}\right) \quad (4)$$

If the following values are entered (25 °C): $k_{red}^o=7\times10^6$ s^{-1} M^{-1}, $k_c^2=10^4$ s^{-1} (the rate constant value for cyclisation of the 3-butenyl radical),[13,17] $k_{-c}^2=5\times10^7$ s^{-1} (the lower limit value for ring opening of cyclopropyl ketyl radical[4] multiplied by 5 due to the presence of the diphenylcyclopropyl reporter group[7]), $k_c^1=10^9$ s^{-1} (see the text), $k_{-c}^1=1.6\times10^7$ s^{-1} (k value for ring opening of α-carbalkoxy substituted carbinyl radical as determined by Bowry and Beckwith:[16] $k=0.8\times10^6$ s^{-1} from Arrhenius plot, and re-evaluated (×20) according to Newcomb[7]), Eq. 4 becomes:

$$F=5\times10^{-2}+\frac{10^{-1}}{\left(k_{red}^c/k_{red}^o\right)[SmI_2]} \quad (5)$$

It may be safely assumed that the reduction constant of the electrophilic α-carbalkoxy radical **C** is higher than that for the opened primary alkyl radical **O** ($k_{red}^c>k_{red}^o=7\times10^6$ s^{-1} M^{-1}) even if it is difficult to define to which extent. If enough confidence may be put in k values incorporated in Eq. 4 to give Eq. 5, ring opening of cyclopropyl groups at δ-position should not interfere with ring closing of the ketyl radical according to mechanism 1 if [SmI_2] is not too low.

4. Conclusion

trans-(2′,2′-Diphenyl-bicyclopropyl-2-yl)-4,4-dimethyl-5-oxo-pent-2-enoic acid methyl ester **9**, alike 5-cyclopropyl-4,4-dimethyl-5-oxo-pent-2-enoate **7**, cyclises in the presence of SmI_2 to lactone **21** without competitive ring opening of the bicyclopropylic probe at δ-position. This absence of ring opening rules out a possible effect of the reversibility of ring opening of cyclopropyl ketyl radical on the issue of these reactions. It shows that the cyclisation process is, whatever the mechanism (condensation of the ketyl radical onto the activated ethylenic bond or condensation of the radical anion derived from the enoate moiety to the carbonyl group), a very fast process. However, it does not allow to choose between the two mechanisms. Indeed, based on kinetic considerations, ketyl radicals if they form are more likely to evolve through 3-*exo-trig* cyclisation onto the activated double bond than through ring opening of the cyclopropyl group at δ-position.

Finally, the *syn* selectivity of cyclisation of δ-cyclopropylic δ-oxo-α,β-unsaturated esters (as compared to other δ-alkylic substrates) remains unexplained.

5. Experimental

5.1. General information

^{1}H NMR spectra were recorded at 200, 250, 360 or 400 MHz and ^{13}C spectra at 63 or 100 MHz. Chemical shifts are quoted in parts per million relative to TMS. High resolution mass spectra (HRMS) were obtained on a Finnigan-MAT-95-S spectrometer. Infra-red spectra were taken on a Perkin–Elmer 'Spectrum One' model and in $CHCl_3$ solution.

As a rule, reactions were carried out under argon atmosphere, using Schlenk tube, septum and syringe technics.

5.2. Preparation of starting compound 9 (4,4-dimethyl-5-(*trans*-2-(2,2-diphenyl-1*R**-cyclopropyl)-1*S**,2*R**-cyclopropyl)-5-oxo-prop-2-enoic acid methyl ester)

5.2.1. 2,2-Diphenylcyclopropanecarbaldehyde. To a stirred solution of crude 2,2-diphenylcyclopropanecarbonyl chloride (obtained by reaction of 3 g (12.8 mmol) of 2,2-diphenylcyclopropanecarboxylic acid[20] and oxalyl chloride) and $Pd(PPh_3)_4$ (296 mg, 0.26 mmol) in benzene (40 mL) was slowly added with a syringe pump tributyltin hydride (4.32 mL, 16 mmol). The reaction was further stirred at room temperature for 1 h. After evaporation of benzene, the residue was taken up in acetonitrile and partitioned between hexane and acetonitrile using four separatory funnels. The acetonitrile extracts were joined and evaporated to give 4.3 g of crude product. This residue was purified by column chromatography on 150 g of silica mixed with 15 g of potassium fluoride ground in a mortar.[21] White crystals were obtained (2.60 g, 91% yield, from carboxylic acid).

Mp: 72–74 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.67 (d, J=6.9 Hz, 1H), 7.42–7.18 (m, 10H), 2.59–2.50 (m, 1H),

2.26 (t, J=5.1 Hz, 1H), 1.88 (dd, J=8.2 Hz and J'=5.1 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 200.7 (C=O), 144.1 (Cq), 139.6 (Cq), 130.3 (CH_{ar}), 129.1 (CH_{ar}), 128.8 (CH_{ar}), 127.6 (CH_{ar}), 127.1 (CH_{ar}), 41.1 (Cq), 36.9 (CH), 20.5 (CH_2); IR ($CHCl_3$): ν(C=O) 1701 (s).

5.2.2. *trans*-2-(2,2-Diphenyl-1*R-cyclopropyl)-1*S**,2*R**-cyclopropane-carboxaldehyde 14.** $LiAlH_4$ (196 mg, 5.17 mmol) was dissolved in dry diethyl oxide (30 mL). A solution of Weinreb amide **13** (1.33 g, 4.13 mmol) in dry diethyl oxide (10 mL) was added with a cannula. The reaction mixture was further stirred for 2 h at −78 °C and then quenched with aqueous $KHSO_4$ (1.25 g in 26 mL of water). The organic layer was recuperated and the aqueous phase was extracted three more times with 100 mL of diethyl oxide. The organic phases were extracted successively with 1 N aqueous HCl (3×100 mL), aqueous saturated sodium carbonate (2×40 mL) and brine. The organic phases were joined, dried ($MgSO_4$), then evaporated on a Rotovap. The residue was purified by column chromatography on silica (eluent heptane/AcOEt 80:20) to give 850 mg of pure aldehyde (78% yield) as a white solid.

Mp: 50–51 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.77 (d, J=5.9 Hz, 1H), 7.35–7.12 (m, 10H), 1.89–1.80 (m, 1H), 1.49–1.41 (m, 1H), 1.37–1.25 (m, 2H), 1.16–1.08 (m, 1H), 1.03–0.85 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 200.2 (C=O), 146.4 (Cq), 141.3 (Cq), 130.7 (CH_{ar}), 128.6 (CH_{ar}), 128.5 (CH_{ar}), 127.5 (CH_{ar}), 126.9 (CH_{ar}), 126.2 (CH_{ar}), 35.8 (Cq), 31.0 (CH), 28.1 (CH), 23.9 (CH), 19.8 (CH_2), 14.4 (CH_2); HRMS (EI) calcd for $C_{19}H_{18}O$: 262.1358, found: 262.1363; IR ($CHCl_3$): ν(C=O) 1701 (s).

5.2.3. 2,2-Dimethyl-3-(*trans*-2-(2,2-diphenyl-1*R-cyclopropyl)-1*S**,2*R**-cyclopropyl)-3-hydroxy-thiopropionic acid, *S*-ethyl ester 15.** *n*-BuLi 2.48 M in hexanes (1.49 mL, 3.70 mmol) was added to a solution of DIEA (0.55 mL, 3.9 mmol) in dry THF (15 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, then cooled to −78 °C. A solution of thioisobutyric acic *S*-ethyl ester (510 mg, 3.9 mmol) in THF (5 mL) was added and the reaction mixture was further stirred for 1.5 h at −78 °C. A solution of aldehyde **14** (850 mg, 3.2 mmol) in THF (9 mL) was added via a cannula. The reaction mixture was further stirred at −78 °C. After ca. 1 h at −78 °C (the reaction was monitored by TLC), the reaction mixture was quenched with aqueous saturated NH_4Cl (22 mL) followed by ethyl acetate (70 mL). After decantation, the aqueous layer was extracted with ethyl acetate (3×25 mL). The organic extracts were joined, washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by flash column chromatography on silica (eluent heptane/AcOEt 90:10) to give 642 mg of pure **15** as an oil (51% yield).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.28–7.11 (m, 10H), 3.19 (d, J=7.1 Hz, 1H), 2.86 (q, J=7.5 Hz, 2H), 2.1 (s, 1H), 1.72–1.64 (m, 1H), 1.38–1.13 (m, 10H), 0.87–0.66 (m, 3H), 0.19–0.05 (m, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 207.6 (C=O), 147.4 (Cq), 142.0 (Cq), 130.9 (CH_{ar}), 128.5 (CH_{ar}), 128.4 (CH_{ar}), 127.6 (CH_{ar}), 126.6 (CH_{ar}), 125.9 (CH_{ar}), 79.2, 54.9 (Cq), 35.7 (Cq), 31.2, 28.6, 23.4, 23.1 (CH_2), 21.1 (CH_2), 18.7, 17.2, 14.7, 8.34 (CH_2); IR ($CHCl_3$): ν(C=O) 1663 (s).

5.2.4. 2,2-Dimethyl-3-(*trans*-2-(2,2-diphenyl-1*R-cyclopropyl)-1*S**,2*R**-cyclopropyl)-3-hydroxy-propionaldehyde 16.** Thioester **15** (600 mg, 1.52 mmol) was dissolved in dry degassed dichloromethane (8 mL). 208 mg, (0.2 mmol) of 10% palladium on charcoal was rapidly introduced, followed by triethylsilane (1.56 mL) with a syringe. The reaction was monitored by TLC. After 2 h stirring at room temperature, the reaction mixture was filtered through a pad of Celite. After evaporation of solvent, the residue was purified by flash column chromatography on silica gel (eluent heptane/AcOEt 80:20). The aldehyde was obtained as white crystals (271 mg, 53% yield).

Mp: 44–45 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 9.57 (s, 1H), 7.35–7.13 (m, 10H), 3.12 (d, J=7.5 Hz, 1H), 1.73–1.61 (m, 3H), 1.25–1.12 (m, 7H), 1.08–0.69 (m, 2H), 0.18–0.07 (m, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 206.7 (C=O), 130.8 (CH_{ar}), 128.6 (CH_{ar}), 128.5 (CH_{ar}), 127.7 (CH_{ar}), 126.6 (CH_{ar}), 126.0 (CH_{ar}), 78.1, 51.4 (Cq), 35.8 (Cq), 31.3, 28.4, 21.3, 19.6 (CH_2), 18.6, 17.5, 8.41 (CH_2); HRMS (EI) calcd for $C_{23}H_{26}O_2$: 334.1933, found: 334. 1938; IR ($CHCl_3$): ν(C=O) 1721 (s).

5.2.5. 2,2-Dimethyl-3-(*trans*-2-(2,2-diphenyl-1*R-cyclopropyl)-1*S**,2*R**-cyclopropyl)-3-hydroxy-propionic acid 18.** A 2.5 M solution of *n*-BuLi (8.85 mL, 22.1 mmol) was added to a solution of DIEA (2.25 g, 22.3 mmol) in THF (50 mL) at −40 °C. The reaction mixture was brought to 0 °C, stirred for 25 min at this temperature and cooled again at −40 °C. Isobutyric acid (980 mg, 11.1 mmol) was then syringed into the reaction mixture. After heating at 50 °C for 2 h, the reaction mixture was once more cooled at −40 °C. Aldehyde **14** (2.43 g, 9.28 mmol) in solution in THF (50 mL) was added dropwise and the reaction mixture was maintained at −40 °C for 2 h. Quenching with water (50 mL) was followed by extraction with diethyl oxide (3×70 mL). The aqueous phase was recuperated and cooled in an ice/water bath. The acid was precipitated by acidification with dilute aqueous HCl. The heterogeneous mixture was extracted with diethyl oxide (3×70 mL). The ethereal extracts were joined, dried ($MgSO_4$) and evaporated to give 3.0 g of acid **18** as a white solid. NMR showed the presence of the two diastereoisomeric forms in a close to 1:1 ratio (2.99 g, 92% yield).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.36–7.14 (m, 20H), 3.81–3.68 (m, 2H), 3.10 (d, 1H, dia 1, J=7.5 Hz), 2.68 (d, 1H, dia 2, J=10 Hz), 1.85–1.69 (m, 2H), 1.52–1.38 (m, 2H), 1.35 (s, 6H), 1.22 (s, 6H), 1.23–1.12 (m, 2H), 0.96–0.74 (m, 2H), 0.61–0.39 (m, 2H), 0.20–0.10 (m, 4H); IR ($CHCl_3$): ν(C=O) 1748 (s).

5.2.6. 2,2-Dimethyl-3-(*trans*-2-(2,2-diphenyl-1*R-cyclopropyl)-1*S**,2*R**-cyclopropyl)-3-hydroxy-propionic acid allyl ester 19.** Acid **18** (2.96 g, 8.45 mmol) was dissolved in dry DMF (22 mL). Caesium carbonate (2.0 g, 6.1 mmol) was rapidly introduced. The reaction mixture was stirred for 10 min before adding allyl bromide (1.05 g, 8.65 mmol). Stirring was continued for 20 h at room temperature. The reaction mixture was evaporated under vacuum (0.5 Torr) and the residue was taken up in chloroform. To the heterogeneous mixture was added aqueous sodium bicarbonate. The organic phase was decanted

and dried over $MgSO_4$. After evaporation of chloroform, the residue was purified by flash column chromatography on silica (eluent heptane/AcOEt 80:20). A ca. 1:1 mixture of the two diastereoisomers was collected (2.77 g, 84% yield).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.30–7.10 (m, 20H), 5.96–5.82 (m, 2H), 5.27–5.17 (m, 4H), 4.61–4.54 (m, 4H), 3.16 (d, 1H, dia 1, J=7 Hz), 2.83 (d, 1H, dia 2, J=9.5 Hz), 1.71–1.64 (m, 2H), 1.32–1.13 (m, 18H), 0.97–0.68 (m, 4H), 0.38–0.24 (m, 4H), 0.17–0.03 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 177.1 (C=O), 147.2 (Cq), 141.9 (Cq), 132.4 (CH), 130.7 (CH_{ar}), 128.4 (CH_{ar}), 127.7 (CH_{ar}), 126.6 (CH_{ar}), 125.9 (CH_{ar}), 118.2 (CH_2), 80.7, 78.9, 65.4 (CH_2), 53.7 (Cq), 47.9 (Cq), 35.7 (Cq), 28.9, 22.4, 21.8, 20.9 (CH_2), 19.0, 16.7, 11.8 (CH_2), 8.19 (CH_2); IR ($CHCl_3$): ν(C=O) 1725 (s), ν(C=C) 1648 (w).

5.2.7. 2,2-Dimethyl-3-(*trans*-2-(2,2-diphenyl-1*R-cyclopropyl)-1*S**,2*R**-cyclopropyl)-3-oxo-propionic acid allyl ester 20.** A solution of Dess–Martin periodinane (4.63 g, 9.97 mmol) in dry dichloromethane (50 mL) was added through a cannula to a solution of β-hydroxyester **19** in dry dichloromethane (50 mL). The reaction mixture, which became progressively cloudy, was stirred for 2 h at room temperature. After dilution in diethyl oxide, the organic phase was washed with a 1:1 mixture of aqueous 10% $Na_2S_3O_3$ and aqueous 5% $NaHCO_3$ and with brine. The organic phase was dried ($MgSO_4$) and evaporated. The residue was purified by flash column chromatography on silica (eluent heptane/AcOEt 80:20) to give 2.25 g (84% yield) of a white solid.

Mp: 45–48 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.30–7.10 (m, 10H), 5.94–5.83 (m, 1H), 5.33–5.17 (m, 2H), 4.71–4.57 (m, 2H), 1.92–1.86 (m, 1H), 1.59–1.54 (m, 1H), 1.43 (s, 3H), 1.37 (s, 3H), 1.23–1.20 (m, 2H), 0.96–0.85 (m, 2H), 0.65–0.58 (m, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 206.6 (C=O), 173.8 (C=O), 146.8 (Cq), 141.4 (Cq), 131.9 (CH), 130.7 (CH_{ar}), 128.6 (CH_{ar}), 128.5 (CH_{ar}), 127.5 (CH_{ar}), 126.8 (CH_{ar}), 126.1 (CH_{ar}), 118.8 (CH_2), 66.1 (CH_2), 55.9 (Cq), 36.1 (Cq), 28.4, 26.5, 25.7, 22.2, 18.6 (CH_2), 18.2 (CH_2); HRMS (EI) calcd for $C_{26}H_{28}O_3$: 388.2038, found: 388. 2042; IR ($CHCl_3$): ν(C=O) 1735 (s), 1697 (s), ν(C=C) 1648 (w).

5.2.8. 2,2-Dimethyl-3-(*trans*-2-(2,2-diphenyl-1*R-cyclopropyl)-1*S**,2*R**-cyclopropyl)-3-oxo-propionaldehyde 17.**

5.2.8.1. By oxidation of 2,2-dimethyl-3-(*trans*-2-(2,2-diphenyl-1*R-cyclopropyl)-1*S**,2*R**-cyclopropyl)-3-hydroxy-propionaldehyde 16.** A solution of β-hydroxyaldehyde **16** (270 mg, 0.81 mmol) in dried dichloromethane (1 mL) was added, through a cannula, to a solution of Dess–Martin periodinane (540 mg, 1.28 mmol) in dichloromethane (2 mL). The reaction mixture was stirred at room temperature for 45 min, diluted with diethyl oxide (5 mL) and washed with a 1: 1 mixture of aqueous 10% $Na_2S_3O_3$ and aqueous 5% $NaHCO_3$ and with brine. The aqueous washings were re-extracted once with diethyl ether. The organic phases were joined, dried over $MgSO_4$, evaporated and the residue was purified by flash column chromatography on silica (eluent heptane/AcOEt 90:10). A white solid was obtained (72 mg, 27% yield).

5.2.8.2. From 2,2-dimethyl-3-(*trans*-2-(2,2-diphenyl-1*R-cyclopropyl)-1*S**,2*R**-cyclopropyl)-3-oxo-propionic acid allyl ester 20.** In a first Schlenk tube and under argon atmosphere, tributyltin hydride (0.86 mL, 3.2 mmol) diluted in degassed benzene (1.2 mL) was added with a syringe pump over 1 h to a solution of β-ketoester **20** (1.00 g, 2.57 mmol) and $Pd(PPh_3)_4$ (74 mg, 0.065 mmol) in degassed benzene (8 mL). At the end of addition, complete conversion of allyl ester to tributyltin carboxylate was checked by IR spectroscopy on an aliquot ($\nu(CO_2All)$=1735 cm^{-1}, $\nu(CO_2SnBu_3)$=1646 cm^{-1} in $CHCl_3$). The reaction mixture was then transferred via a cannula and over a period of 10 min into a second Schlenk tube containing a solution of oxalyl chloride in degassed benzene (8 mL). A vigorous gas evolution was observed. After completion of addition, the reaction was stirred for 15 min and concentrated under vacuum (0.5 Torr). Benzene (8 mL) was then added and the reaction mixture was reloaded with $Pd(PPh_3)_4$ (74 mg). Tributyltin hydride (0.86 mL, 3.2 mmol) diluted in degassed benzene (2 mL) was added with a syringe pump over 2 h. The solvent was removed under vacuum and the residue was partitioned between hexane and acetonitrile using four separatory funnels. The acetonitrile extracts were joined and evaporated. The residue was purified by column chromatography on silica/KF[21] 10:1 (eluent heptane/AcOEt 95:5) to give 213 mg of aldehyde **17** as a white solid.

Mp: 74–75 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 9.57 (s, 1H), 7.27–7.10 (m, 10H), 1.99–1.94 (m, 1H), 1.53–1.48 (m, 1H), 1.30–1.19 (m, 8H), 1.05–0.98 (m, 1H), 0.94–0.85 (m, 1H), 0.76–0.70 (m, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 207.4 (C=O), 201.2 (C=O), 146.5 (Cq), 141.2 (Cq), 130.4 (CH_{ar}), 128.5 (CH_{ar}), 127.7 (CH_{ar}), 126.7 (CH_{ar}), 126.1 (CH_{ar}), 60.4 (CH_2), 35.9 (CH_2), 28.4, 27.3, 25.9, 19.4, 19.3, 18.6, 17.7; HRMS (EI) calcd for $C_{23}H_{24}O_2$: 332.1776, found: 332. 1781; IR ($CHCl_3$): ν(C=O) 1729 (s), 1698 (s).

5.2.9. 4,4-Dimethyl-5-(*trans*-2-(2,2-diphenyl-1*R-cyclopropyl)-1*S**,2*R**-cyclopropyl)-5-oxo-prop-2-enoic acid methyl ester 9.** Compound **9** was prepared by Wadsworth–Emmons olefination of β-keto-aldehyde **17** with methyl diethoxyphosphonoacetate. The experimental procedure was the same as that used by Nicolaou and co-workers[22] for Wadsworth–Emmons olefination of 2,2-dimethyl-3-oxo-pentanal with *tert*-butyl diethoxyphosphonoacetate. The residue was purified by flash column chromatography on silica (eluent heptane/AcOEt 90:10). Starting from 120 mg of aldehyde, 80 mg of **9** was obtained as an oily compound (57% yield).

^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.28–7.10 (m, 10H), 5.96 (d, 1H, J=14.4 Hz), 5.28 (d, 1H, J=1 Hz), 3.74 (s, 3H), 2.04–1.95 (m, 1H), 1.69–1.44 (m, 1H), 1.30–1.25 (m, 8H), 1.01–0.84 (m, 2H), 0.73–0.64 (m, 1H); HRMS (EI) calcd for $C_{26}H_{28}O_3$: 388.2038, found: 388.2044; IR ($CHCl_3$): ν(C=O) 1719 (s), 1694 (s), ν(C=C) 1647 (m).

5.3. Reaction of 5-(2′,2′-diphenyl-bicyclopropyl-2-yl)-4,4-dimethyl-5-oxo-prop-2-enoic acid methyl ester 9 with SmI_2

In a Schlenk tube and under argon atmosphere, *tert*-butanol (80 mL, 0.82 mmol) was added with a syringe to a solution

of **9** (80 mg, 0.205 mmol) in anhydrous degassed THF (1 mL). The reaction mixture was cooled to 0 °C and a 0.1 M THF solution of SmI_2 (4.5 mL) was added dropwise over a period of a few minutes. The reaction mixture was stirred at room temperature. After ca. 2 h discharge of the blue colour of SmI_2 in THF was observed. The reaction mixture was diluted with diethyl oxide and quenched with 1 N aqueous HCl. The organic phase was recuperated while the aqueous phase was extracted twice with diethyl oxide. Each ethereal phase was in turn washed with aqueous $Na_2S_2O_3$ and brine. The organic phases were joined, dried and evaporated. Purification was achieved by flash column chromatography on silica gel (eluent heptane/AcOEt) to give 60 mg of an oily product, which was identified as lactone **21** (yield 81%).

The reaction was repeated twice with virtually identical results.

Mixture of two diastereoisomeric forms in comparable amounts: ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.41–7.09 (m, 10H+10H), 2.67–2.53 (two overlapping dd, $^2J\sim$20 Hz, $^3J\sim$7 Hz, 1H+1H), 2.40–2.32 (two overlapping d, $^2J\sim$ 20 Hz, 1H+1H), 1.52–1.36 (m, 1H+1H), 1.25–0.68 (m, 11H+11H), 0.67–0.65 (m, 1H+1H), 0.43–0.38 (m, 1H+1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: CO: 177.6, 117.5, Cq ar: 147.3, 147.1, 141.9, 141.8, CH ar: 131.2, 130.6, 128.7, 128.5, 128.4, 127.9, 127.7, 126.7, 126.6, 126.1, 125.9, Cq: 75.4, 74.3, 36.2, 35.8, 26.1, 25.5, CH_2: 30.82, 30.80, 18.80, 18.60, 11.49, 10.01, CH and CH_3: 29.4, 29.0, 23.7, 22.4, 22.3, 22.1, 18.1, 17.8, 17.3, 17.2, 13.9, 13.6; HRMS calcd for $C_{25}H_{26}O_2$: 358.1927, found: 358.1915; IR ($CHCl_3$): ν(C=O) 1772.

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