Regio- and Diastereoselective Conjugate Addition to 4,4-Dimethylcyclohexadienones

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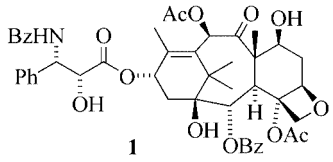
Conjugate addition of vinyl cuprate and dimethyl malonate to 4,4-dimethylcyclohexa-2,5-dienones has allowed facile access to mono- and bis-adducts in satisfactory yields. While the high diastereoselectivity of such processes to afford *trans*-bis-adducts was predictable, an unprecedented regioselectivity was observed with 2,4,4-trimethylcyclohexa-2,5-dienone, with the first addition occurring exclusively at the C-5 carbon atom (distal from the methyl group) and with the second addition of a bulky nucleophile such as dimethyl malonate even prevented.

Introduction

The enormous social and economic interest in Taxol (**1**) and its analogues[1] suggests and justifies the efforts made to discover new strategies for the construction of its peculiar ring system. Even though several total syntheses of Taxol have recently been reported,[1] work towards the synthesis of taxane skeletons is still in progress in many research groups as they search for simpler structures offering similar bioactivity.



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In this context, and in the light of previous applications of cyclohexadienone derivatives in the synthesis of taxanes,[2] we wanted to test the possibility of introducing suitable functionalizations onto 4,4-dimethylcyclohexa-2,5-dienone systems for the synthesis of proper precursors of the A/B rings of the taxane nucleus.

On the other hand, the conjugate addition of carbon nucleophiles to α,β-unsaturated esters or ketones is one of the most widely exploited carbon–carbon bond-forming reactions,[3] as clearly evidenced by the innumerable synthetic applications of the Michael addition of malonates[4] and organocopper reagents[5] to enones.

On this basis, we decided to study the application of the above methodology to dienones **2a**,**b** as Michael acceptors. Surprisingly, as previously observed,[2d] these readily accessible compounds have been until now scarcely exploited in this context, presumably as a result of the severe steric crowding at the β-carbon atoms.

Results and Discussion

When 4,4-dimethylcyclohexa-2,5-dienone (**2a**)[2d] was allowed to react with vinylmagnesium bromide (2 equiv.) in dry THF at –50 °C in the presence of copper bromide·dimethyl sulfide (10 mol %)[6] for 30 min, vinylcyclohexenone **3a** was successfully isolated in 83% yield by rapid chromatographic work-up. Following this same procedure, compound **3a** was exclusively converted into the *trans*-divinyl derivative **4a** in 77% yield (Scheme 1). Attempts to improve the formation of **4a** by direct treatment of **2a** with an excess of the Grignard reagent were unsuccessful.

Analogously, 2,4,4-trimethylcyclohexa-2,5-dienone (**2b**)[7] reacted with vinylmagnesium bromide under these conditions to give the 5-vinyl-substituted product **3b** in 65% yield as a unique regioisomer. Treatment of **3b** under the same conditions afforded, however, a more complex reaction mixture from which it was possible to isolate, by careful chromatographic separation, the two diastereomeric ketones **4b** and **5b** in a 2:1 ratio (^{1}H NMR) and the alcohol **6b** in 50 and 20% yields, respectively. While **4b** and **5b** are the expected *trans*-divinyl conjugate addition products, **6b** is the fruit of a competitive 1,2-attack by the organometallic reagent on the carbonyl group. The formation of **6b** could be related to the enhanced difficulties associated with 1,4-addition to **3b** compared with **3a**.

These difficulties account for the complete regioselectivity observed in the addition to **2b**. In fact, the methyl group on C-2 is able to discriminate between the two possible ad-

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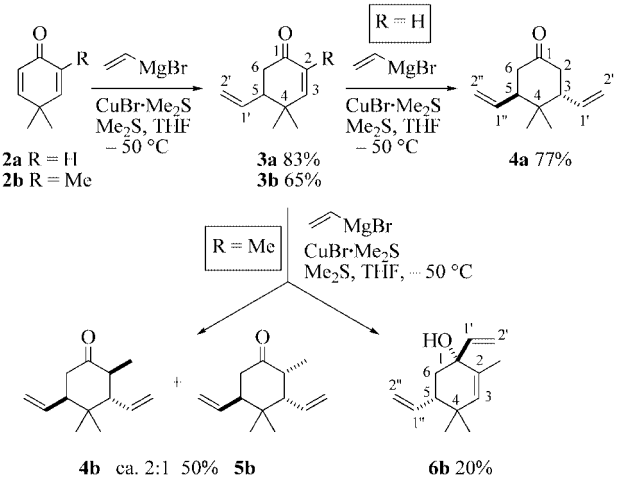


Scheme 1.

dition pathways. On the basis of the trihapto d(Cu)–π_3*(enone) complex transition states invoked to explain the high diastereoselectivity observed for such processes,[8] analogous transition states can be used to rationalize the regioselective behaviour of **2b**. The steric hindrance experienced by the metal and its ligands vicinal to the methyl group in the formation of transition state **A,** which leads to C-3 carbon attack, associated with the electron-releasing effect of the methyl group, is likely to determine the exclusive preference for the alternative assembly **B** involving C-5 carbon approach (distal from the methyl group), leading to **3b** (Figure 1).

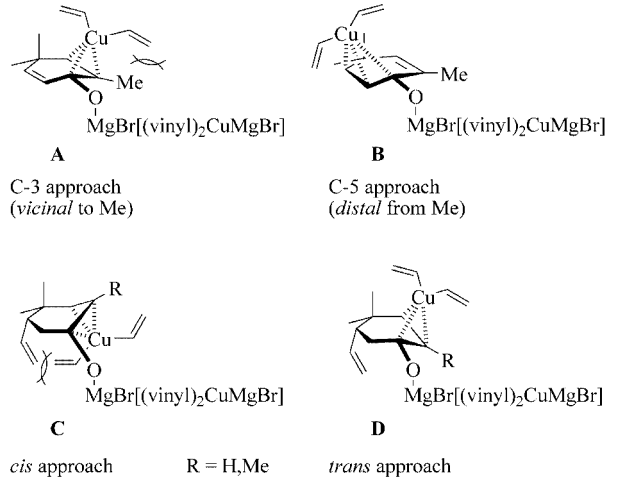
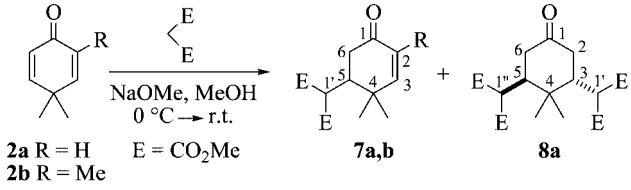


Figure 1. Transition states for vinyl cuprate addition to **2a,b**.

The *trans* stereochemistry observed for the double-addition compounds **4a, 4b** and **5b** is in agreement with the literature data concerning the conjugate addition of organocuprates to 5-substituted 2-cyclohexenones in which, in general, the *trans* products are formed almost exclusively even if they are less stable than the corresponding *cis* (all-equatorial) compounds.[8] Therefore, the addition of vinyl cuprate to **3a** or **3b** by the *cis* approach **C** is definitely disfavoured on the basis of the steric interactions between the two vinyl groups, validating the observed preference for the *trans* geometry **D** (Figure 1).

The reactions of **2a**,**b** with dimethyl malonate were also investigated. When cyclohexadienone **2a** was added to an ice-cold solution of dimethyl malonate (1.2 equiv.) in dry methanol containing a catalytic amount of sodium methoxide (0.2 equiv.), partial conversion (65%) into the mono- and dimalonyl derivatives **7a** and **8a**, isolated in 41 and 10% yields, respectively, was observed after 48 h at room temperature (Scheme 2, entry 1). Attempts to improve the conversion of the starting material by employing greater amounts of dimethyl malonate or longer reaction times only increased the amount of **8a** formed; dimalonyl derivative **8a** was obtained as the exclusive product and isolated in 70% yield with a large excess (5 equiv.) of dimethyl malonate and a reaction time of 96 h (Scheme 2, entry 2).[9]



Entry	CH_2E_2	NaOMe	Time	Yield	
1	1.2 equiv.	0.2 equiv.	48 h	**7a** 41%	**8a** 10%
2	5.0 equiv.	1.0 equiv.	96 h	**7a** –	**8a** 70%
3	2.0 equiv.	0.2 equiv.	24 h	**7b** 79%	

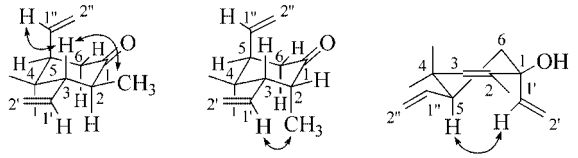
Scheme 2.

Analogously to vinyl cuprate addition, the trimethyl derivative **2b** easily reacted with dimethyl malonate (2 equiv.) under the above conditions for 24 h to give exclusively, through an absolutely regioselective reaction, the 5-alkyl derivative **7b** in 79% yield (Scheme 2, entry 3). Every effort to perform a second alkylation reaction with dimethyl malonate at the C-3 carbon atom of **7b** was unsuccessful. This result can be attributed again to both the steric and electron-donor effects exerted by the methyl group at the 2-position, which disfavour nucleophilic attack on the C-3 carbon, and is in agreement with previously reported results concerning the inertness of 2,6-disubstituted quinone monoacetals as Michael acceptors towards the sodium enolate of ethyl acetoacetate.[10]

The structures of the new products **3a**,**b**, **4a**,**b**, **5b**, **6b**, **7a**,**b** and **8a** followed from analytical and spectroscopic data (see Expt. Sect.). Whereas the ^{1}H NMR spectra of **3a** and **7a** are characterized by two doublets at δ = 6.55 and 5.73 ppm, and 6.58 and 5.87 ppm, respectively, for H-3 and H-2, the spectra of **3b** and **7b** present a quartet at δ = 6.41 (^4J = 1.4 Hz) and 6.31 ppm (^4J = 1.3 Hz), respectively, for H-3 weakly coupled to the protons of the methyl group at the 2-position, in agreement with the assigned regiochemistry.

In accord with the C_2 symmetry of the *trans* diastereomers **4a** and **8a**, their ^{13}C NMR spectra exhibit seven and ten resonances, respectively, while the corresponding proton spectra exhibit only one singlet at δ = 1.05 and 1.07 ppm, respectively, for the methyl groups at the 4-position.

The stereochemistry of compounds **4b**, **5b** and **6b** was unambiguously determined on the basis of the following considerations. The proton spectrum of the major all-*trans* diastereomer **4b**, which is likely to favour a chair-like conformation with the 2-methyl and the 3-vinyl groups in equatorial positions, presents for H-3 a doublet of doublets ($J_{2,3}$ = 11.8 Hz and $J_{3,1'}$ = 9.7 Hz) at δ = 1.95 ppm, with the major coupling constant highly diagnostic of a *trans* diaxial relationship between H-3 and H-2. A different situation was evidenced for H_{eq}-6 and H_{ax}-6, which give rise to a doublet of doublets of doublets and a doublet of doublets at δ = 2.81 and 2.32 ppm, respectively, with the geminal coupling constant (J = 14.4 Hz) and also vicinal coupling constants ($J_{5,6}$ = 5.8 Hz for the former and 3.0 Hz for the latter) supporting *trans* diequatorial and *cis* axial–equatorial relationships with H-5. Moreover, the proposed stereochemistry was confirmed on the basis of a NOESY 1D experiment: irradiation of the H-3 signal caused positive NOE effects on H-1′′ and 2-CH_3 at δ = 5.72 and 0.95 ppm, respectively (Figure 2). In accord with the different configuration at C-2, the ^{1}H NMR spectrum of compound **5b** exhibits, with respect to the spectrum of **4b**, a significant downfield shift ($\Delta\delta \approx 0.57$ ppm) for H-2 as a consequence of a preferential equatorial arrangement as well as a small upfield shift ($\Delta\delta \approx 0.06$ ppm) for 2-CH_3; moreover, the doublet of triplets of H-1′ is upfield shifted ($\Delta\delta$ = 0.23 ppm) while the H-3 resonance undergoes a downfield shift ($\Delta\delta$ = 0.24 ppm). In particular, the latter signal appears as a doublet of doublets ($J_{3,1'}$ = 10.6 Hz and $J_{2,3}$ = 5.6 Hz) at δ = 2.19 ppm, with the minor coupling constant strongly supporting the *cis* axial–equatorial relationship between H-3 and H-2. The *cis* arrangement of the 2-methyl and 3-vinyl groups was also confirmed by a positive NOE effect detected for 2-CH_3 at δ = 0.89 ppm by irradiation of the clean H-1′ signal at δ = 5.34 ppm (Figure 2). The proton spectrum of the divinyl derivative **6b** clearly exhibits a doublet of doublets of doublets at δ = 2.14 ppm for H-5, with the major coupling constant ($J_{5,6}$ = 12.6 Hz) deposing in favour of a *trans* diaxial relationship with H_{ax}-6. Also, the *trans* stereochemistry was unambiguously established on the basis of a positive NOE effect between H-5 and H-1′.



4b **5b** **6b**

Figure 2. Observed NOE effects for compounds **4b**, **5b** and **6b**.

In conclusion, these results evidenced the possibility of synthesising new 5-substituted 4,4-dimethylcyclohexenones and *trans*-3,5-disubstituted 4,4-dimethylcyclohexanones with high regio- and stereocontrol and in good yields. The steric hindrance associated with the two methyl groups at the 4-position in compounds **2a**,**b** is likely responsible for their low reactivity, especially with bulky nucleophiles, and when combined with the presence of a methyl group at the 2-position, causes complete regioselectivity in the first addition to dienones and even hampers the second addition, as in the case of dimethyl malonate. To the best of our knowledge, analogous regioselectivity has only been observed in the 1,4-addition of amines to 2-alkylquinone monoketals, which involves the exclusive attack of the nitrogen nucleophile on the less-hindered conjugate position.[11]

These findings have certainly established a simple methodology that is likely able to access suitable precursors of taxane skeletons and, in particular, the peculiar regioselectivity observed for **2b** could be very promising in the planning of new synthetic routes.

The potential synthetic applications of these reactions, with particular regard towards enantioselective reactions, are under investigation in our laboratories.

Experimental Section

General Remarks: All reactions were carried out under nitrogen and the solvents were appropriately dried before use (THF was distilled from sodium/benzophenone and MeOH from magnesium activated with iodine). Silica gel plates (Merck F_{254}) and silica gel 60 (Merck, 230–400 mesh) were used for TLC and flash chromatography, respectively; petroleum ether employed in chromatographic work-up refers to fractions with a boiling range of 40–70 °C. IR spectra were recorded with a Perkin–Elmer 881 or a Perkin–Elmer Spectrum BX FT-IR System spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions with Varian–Gemini and Varian Mercuryplus 400 instruments operating at 200 and 50 MHz and 400 and 100 MHz, respectively. Mass spectra were recorded with a QMD 1000 Carlo–Erba instrument linked by GC or with a direct inlet; relative percentages are shown in brackets. Elemental analyses were performed with a Perkin–Elmer 2400 analyzer. Analytical samples of oily products were obtained by dissolution in diethyl ether, filtration, evaporation to dryness and prolonged evacuation at room temperature (10^{-2} Torr).

General Procedure for the Copper-Catalysed Conjugate Addition of Vinylmagnesium Bromide to Cyclohexadienones 2a,b and Cyclohexenones 3a,b: A solution of enone (1 mmol) in dry THF (1 mL) was added through a cannula to a solution of CuBr·Me_2S (0.020 g, 0.1 mmol) and Me_2S (0.5 mL) in the same solvent (2 mL) cooled to –50 °C. Then a 1 M solution of vinylmagnesium bromide in THF (2 mL, 2 mmol) was added dropwise with stirring whilst keeping the reaction temperature below –40 °C. The reaction mixture (which changed from brown to orange during the addition) was stirred at –50 °C for 30 min and then decomposed in ice and aqueous hydrochloride (ca. 1 M, 15 mL), extracted with diethyl ether (3×15 mL) and dried. The crude product left by evaporation to dryness under reduced pressure was subjected to flash column chromatography.

4,4-Dimethyl-5-vinylcyclohex-2-enone (3a): Chromatographic resolution (petroleum ether/ethyl acetate, 13:1 v/v) of the residue derived from 4,4-dimethylcyclohexa-2,5-dienone (**2a**) (0.122 g, 1 mmol) afforded **3a** (R_f = 0.29, 0.125 g, 83%) as a colourless oil. IR (film): $\tilde{\nu}$ = 3078, 2966, 1689, 1465, 1419, 1376, 1268, 922, 791, 731 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.91 (s, 3 H, 4-CH_3), 1.03 (s, 3 H, 4-CH_3), 2.22–2.51 (m, 3 H, H-5 and 6-CH_2), 4.92–5.04 (m, 2 H, 2′-CH_2), 5.67 (ddd, J = 16.8, 10.3, 7.0 Hz, 1 H, H-1′), 5.73 (d, J = 9.9 Hz, 1 H, H-2), 6.55 (d, J = 9.9 Hz, 1 H, H-3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.7 (q, 4-CH_3), 27.4 (q,

4-CH_3), 35.5 (s, C-4), 39.2 (t, C-6), 48.0 (d, C-5), 116.6 (t, C-2′), 126.1 (d, C-2), 136.8 (d, C-1′), 159.95 (d, C-3), 198.7 (s, C-1) ppm. MS (EI): *m*/*z* (%) = 150 (7) $[M]^+$, 135 (3), 108 (10), 96 (71), 83 (100), 58 (69), 53 (26). $C_{10}H_{14}O$ (150.22): calcd. C 79.96, H 9.39; found C 79.89, H 9.38.

2,4,4-Trimethyl-5-vinylcyclohex-2-enone (3b): The crude product obtained from 2,4,4-trimethylcyclohexa-2,5-dienone (**2b**) (0.136 g, 1 mmol) was resolved by chromatographic work-up (petroleum ether/ethyl acetate, 15:1 v/v) to give compound **3b** (R_f = 0.36, 0.107 g, 65%) as a colourless oil. IR (film): $\tilde{\nu}$ = 3078, 2964, 1677, 1465, 1448, 1419, 1364, 1174, 1018, 919 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.99 (s, 3 H, 4-CH_3), 1.12 (s, 3 H, 4-CH_3), 1.75 (d, *J* = 1.4 Hz, 3 H, 2-CH_3), 2.40–2.58 (m, 3 H, H-5 and 6-CH_2), 5.01–5.14 (m, 2 H, 2′-CH_2), 5.78 (ddd, *J* = 16.8, 10.4, 7.5 Hz, 1 H, H-1′), 6.41 (q, *J* = 1.4 Hz, 1 H, H-3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.3 (q, 2-CH_3), 20.8 (q, 4-CH_3), 27.8 (q, 4-CH_3), 35.6 (s, C-4), 39.2 (t, C-6), 48.3 (d, C-5), 116.4 (t, C-2′), 132.0 (s, C-2), 137.0 (d, C-1′), 155.5 (d, C-3), 199.1 (s, C-1) ppm. MS (EI): *m*/*z* (%) = 164 (11) $[M]^+$, 149 (46), 121 (12), 110 (78), 95 (65), 83 (23), 67 (100), 53 (36). $C_{11}H_{16}O$ (164.20): calcd. C 80.44, H 9.82; found C 80.57, H 10.08.

(3*R,5*R**)-4,4-Dimethyl-3,5-divinylcyclohexanone (4a):** Chromatographic work-up (petroleum ether/ethyl acetate, 13:1 v/v) of the residue derived from **3a** (0.150 g, 1 mmol) gave compound **3b** (R_f = 0.32, 0.138 g, 77%) as a colourless oil. IR (film): $\tilde{\nu}$ = 3077, 2968, 1713, 1636, 1419, 1388, 1234, 1002, 917 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.05 (s, 6 H, 2×CH_3), 2.29–2.54 (m, 6 H, 2-CH_2, H-3, H-5 and 6-CH_2), 4.97–5.10 (m, 4 H, 2′-CH_2 and 2′′-CH_2), 5.78 (ddd, *J* = 17.0, 10.2, 7.3 Hz, 2 H, H-1′ and H-1′′) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.3 (q, 2×CH_3), 35.2 (s, C-4), 43.1 (t, C-2 and C-6), 49.3 (d, C-3 and C-5), 116.65 (t, C-2′ and C-2′′), 137.8 (d, C-1′ and C-1′′), 210.8 (s, C-1) ppm. MS (EI): *m*/*z* (%) = 178 (20) $[M]^+$, 163 (16), 149 (37), 133 (11), 120 (29), 85 (37), 81 (77), 57 (56), 55 (100). $C_{12}H_{18}O$ (178.27): calcd. C 80.85, H 10.18; found C 80.50, H 10.39.

Conjugate Addition of Vinylmagnesium Bromide to 2,4,4-Trimethyl-5-vinylcyclohex-2-enone (3b): The residue derived from **3b** (0.164 g, 1 mmol) was resolved into two components by careful chromatographic work-up (petroleum ether/ethyl acetate, 30:1 v/v). The first band gave a 2:1 mixture of (2*S**,3*S**,5*R**)-2,4,4-trimethyl-3,5-divinylcyclohexanone (**4b**) and (2*R**,3*S**,5*R**)-2,4,4-trimethyl-3,5-divinylcyclohexanone (**5b**) (R_f = 0.45, 0.097 g, 50%) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ (the values in square brackets refer to the minor diastereomer) = 0.88 (s, 3 H, 4-CH_3), [0.89 (d, *J* = 5.6 Hz, 3 H, 2-CH_3)], [0.90 (s, 3 H, 4-CH_3)], 0.95 (d, *J* = 6.5 Hz, 3 H, 2-CH_3), [1.17 (s, 3 H, 4-CH_3)], 1.18 (s, 3 H, 4-CH_3), 1.95 (dd, *J* = 11.8, 9.7 Hz, 1 H, H-3), [2.19 (dd, *J* = 10.6, 5.6 Hz, 1 H, H-3)], 2.25–2.36 (m, 3 H, H-2 major, H_{ax}-6 major and H_{ax}-6 minor), 2.38–2.45 (m, 3 H, H-5 major, H-5 minor and H_{eq}-6 minor), 2.81 (ddd, *J* = 14.4, 5.8, 1.0 Hz, 1 H, H_{eq}-6), [2.88 (quintet, *J* = 5.6 Hz, 1 H, H-2)], 4.93–5.15 (m, 8 H, 2′-CH_2 and 2′′-CH_2 major and minor), [5.34 (dt, *J* = 16.6, 10.5 Hz, 1 H, H-1′)], 5.57 (dt, *J* = 16.9, 9.7 Hz, 1 H, H-1′), 5.67–5.78 (m, 2 H, H-1′′ major and minor) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ (the values in square brackets refer to the minor diastereomer) = 12.6 (q, 2-CH_3), [12.7 (q, 2-CH_3)], [22.0 (q, 4-CH_3)], 22.9 (q, 4-CH_3), 27.6 (q, 4-CH_3 major and 4-CH_3 minor), 35.65 (s, C-4), [36.1 (s, C-4)], 43.1 (t, C-6), [43.45 (t, C-6)], [43.5 (d, C-2)], 44.4 (d, C-2), [47.9 (d, C-5)], 52.7 (d, C-5), 55.4 (d, C-3), [61.7 (d, C-3)], [116.1 (t)], 116.9 (t), 117.7 (t), [119.4 (t)], [134.6 (d, C-1′)], 137.4 (d, C-1′), [137.75 (d, C-1′′)], 137.8 (d, C-1′′), 211.65 (s, C-1), [211.8 (s, C-1)] ppm. An analytical sample of **4b** (R_f = 0.35) was obtained as a colourless liquid by further chromatographic resolution (petroleum ether/ethyl acetate, 40:1 v/v) of the above mixture. IR (film): $\tilde{\nu}$ = 3076, 2971, 2932, 2878, 1712, 1677, 1639, 1368, 917 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (s, 3 H, 4-CH_3), 0.95 (d, *J* = 6.5 Hz, 3 H, 2-CH_3), 1.18 (s, 3 H, 4-CH_3), 1.95 (dd, *J* = 11.8, 9.7 Hz, 1 H, H-3), 2.27–2.35 (m, 1 H, H-2), 2.32 (dd, *J* = 14.4, 3.0 Hz, 1 H, H_{ax}-6), 2.39–2.44 (m, 1 H, H-5), 2.81 (ddd, *J* = 14.4, 5.8, 1.0 Hz, 1 H, H_{eq}-6), 4.93–5.11 (m, 4 H, 2′-CH_2 and 2′′-CH_2), 5.57 (dt, *J* = 16.9, 9.7 Hz, 1 H, H-1′), 5.72 (ddd, *J* = 17.0, 10.4, 8.7 Hz, 1 H, H-1′′) ppm. MS (EI): *m*/*z* (%) = 192 (22) $[M]^+$, 177 (16), 165 (3), 149 (9), 137 (12), 123 (14), 109 (28), 95 (57), 81 (84), 67 (100), 54 (75). $C_{13}H_{20}O$ (192.30): calcd. C 81.20, H 10.48; found C 80.94, H 10.81.

The second band afforded (1*R**,5*S**)-2,4,4-trimethyl-1,5-divinylcyclohex-2-en-1-ol (**6b**) (R_f = 0.23, 0.039 g, 20%) as a colourless oil. IR (film): $\tilde{\nu}$ = 3388, 3077, 2959, 2866, 1666, 1638, 1450, 1360, 1000, 916 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.85 (s, 3 H, 4-CH_3), 0.96 (s, 3 H, 4-CH_3), 1.63 (d, *J* = 1.3 Hz, 3 H, 2-CH_3), 1.68 (br. s, 1 H, OH), 1.70 (dd, *J* = 12.6, 3.0 Hz, 1 H, H_{eq}-6), 1.81 (t, *J* = 12.6 Hz, 1 H, H_{ax}-6), 2.14 (ddd, *J* = 12.6, 8.0, 3.0 Hz, 1 H, H-5), 4.96–5.04 (m, 2 H, 2′′-CH_2), 5.09–5.15 (m, 2 H, 2′-CH_2), 5.27 (q, *J* = 1.3 Hz, 1 H, H-3), 5.76 (ddd, *J* = 17.1, 10.3, 8.0 Hz, 1 H, H-1′′), 5.87 (dd, *J* = 17.2, 10.8 Hz, 1 H, H-1′) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.1 (q, 2-CH_3), 23.0 (q, 4-CH_3), 28.8 (q, 4-CH_3), 35.2 (s, C-4), 39.6 (t, C-6), 45.7 (d, C-5), 75.5 (s, C-1), 113.9 (t), 115.2 (t), 132.6 (s, C-2), 137.2 (d), 138.9 (d), 142.2 (d) ppm. MS (EI): *m*/*z* (%) = 192 (3) $[M]^+$, 177 (5), 165 (13), 149 (19), 133 (20), 123 (29), 107 (29), 85 (66), 83 (76), 57 (84), 55 (100). $C_{13}H_{20}O$ (192.30): calcd. C 81.20, H 10.48; found C 80.86, H 10.38.

Conjugate Addition of Dimethyl Malonate to Cyclohexadienone 2a: A solution of **2a** (0.122 g, 1 mmol) in dry methanol (1 mL) was added dropwise at 0 °C to 0.2 equiv. of sodium methoxide (0.4 mL of a 0.5 M solution prepared from 0.046 g of sodium and 4 mL of MeOH) and dimethyl malonate (0.161 g, 0.14 mL, 1.2 mmol) in the same solvent (1 mL). The reaction mixture was stirred at room temperature for 48 h and then decomposed in aqueous hydrochloride (ca. 1 M, 10 mL), extracted with diethyl ether (3×15 mL) and dried. The crude product left by evaporation to dryness under reduced pressure was subjected to flash column chromatography (petroleum ether/ethyl acetate, 6:1 v/v). While the first band allowed unreacted **2a** to be recovered (R_f = 0.52, 0.043 g, 35%), the second one afforded 5-[bis(methoxycarbonyl)methyl]-4,4-dimethylcyclohex-2-enone (**7a**) (R_f = 0.29, 0.105 g, 41%) as a colourless oil. IR (film): $\tilde{\nu}$ = 2958, 1733, 1683, 1436, 1272, 1202, 1154 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.08 (s, 3 H, 4-CH_3), 1.19 (s, 3 H, 4-CH_3), 2.45–2.90 (m, 3 H, H-5 and 6-CH_2), 3.64 (d, *J* = 5.1 Hz, 1 H, H-1′), 3.71 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 5.87 (d, *J* = 10.3 Hz, 1 H, H-2), 6.58 (d, *J* = 10.3 Hz, 1 H, H-3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.4 (q, 4-CH_3), 28.0 (q, 4-CH_3), 36.2 (s, C-4), 37.0 (t, C-6), 43.0 (d, C-5), 51.5 (d, C-1′), 52.3 (q, OCH_3), 52.8 (q, OCH_3), 126.5 (d, C-2), 159.4 (d, C-3), 168.7 (s, CO_2CH_3), 169.0 (s, CO_2CH_3), 198.1 (s, C-1) ppm. MS (EI): *m*/*z* (%) = 254 (4) $[M]^+$, 239 (6), 179 (16), 162 (7), 149 (16), 123 (100), 107 (19), 96 (35), 83 (32), 67 (32), 53 (28). $C_{13}H_{18}O_5$ (254.28): calcd. C 61.40, H 7.14; found C 61.29, H 7.14. The slowest moving fractions gave a small amount of compound **8a** (R_f = 0.14, 0.039 g, 10%).

When the above reaction was carried out with 1 equiv. of NaOMe (2 mL of a 0.5 M solution prepared from 0.046 g of sodium and 4 mL of MeOH) and dimethyl malonate (0.660 g, 0.57 mL, 5 mmol) for 96 h at room temperature, chromatographic work-up (petroleum ether/ethyl acetate, 3:1 v/v) allowed (3*R**,5*R**)-3,5-bis[bis(methoxycarbonyl)methyl]-4,4-dimethylcyclohexanone (**8a**) (R_f = 0.28, 0.271 g, 70%) to be isolated as a colourless liquid. IR

(film): $\tilde{\nu}$ = 2956, 1732, 1434, 1373, 1292, 1242, 1194, 1150 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.07 (s, 6 H, 2 × CH_3), 2.47–2.50 (m, 4 H, 2-CH_2 and 6-CH_2), 2.61–2.71 (m, 2 H, H-3 and H-5), 3.60 (d, J = 4.8 Hz, 2 H, H-1′ and H-1′′), 3.71 (s, 6 H, 2 × OCH_3), 3.72 (s, 6 H, 2 × OCH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.1 (q, 2 × CH_3), 35.9 (s, C-4), 39.5 (t, C-2 and C-6), 43.0 (d, C-3 and C-5), 51.6 (d, C-1′ and C-1′′), 52.5 (q, 2 × OCH_3), 53.0 (q, 2 × OCH_3), 169.1 (s, 2 × CO_2CH_3), 169.2 (s, 2 × CO_2CH_3), 207.4 (s, C-1) ppm. MS (EI): m/z (%) = 355 (1) $[M - OMe]^+$, 326 (4), 254 (10), 239 (14), 123 (100). $C_{18}H_{26}O_9$ (383.39): calcd. C 55.95, H 6.78; found C 56.26, H 6.80.

5-[Bis(methoxycarbonyl)methyl]-2,4,4-trimethylcyclohex-2-enone (7b): The reaction mixture obtained from the addition at 0 °C of a solution of **2b** (0.136 g, 1 mmol) in dry methanol (1 mL) to 0.2 equiv. of sodium methoxide (0.4 mL of a 0.5 M solution prepared from 0.046 g of sodium and 4 mL of MeOH) and dimethyl malonate (0.266 g, 0.23 mL, 2 mmol) in the same solvent (1 mL) was stirred at room temperature for 24 h. The reaction crude was quenched with aqueous hydrochloride (ca. 1 M, 10 mL), extracted with diethyl ether (3 × 15 mL), dried and the solvents evaporated to dryness under reduced pressure. Chromatographic work-up (petroleum ether/ethyl acetate, 4:1 v/v) yielded compound **7b** (R_f = 0.45, 0.212 g, 79%) as a colourless oil. IR (film): $\tilde{\nu}$ = 2957, 1733, 1668, 1437, 1272, 1202, 1150 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.04 (s, 3 H, 4-CH_3), 1.14 (s, 3 H, 4-CH_3), 1.71 (d, J = 1.3 Hz, 3 H, 2-CH_3), 2.43–2.86 (m, 3 H, H-5 and 6-CH_2), 3.60 (d, J = 5.2 Hz, 1 H, H-1′), 3.69 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 6.31 (q, J = 1.3 Hz, 1 H, H-3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.4 (q, 2-CH_3), 21.5 (q, 4-CH_3), 28.3 (q, 4-CH_3), 36.6 (s, C-4), 37.0 (t, C-6), 43.2 (d, C-5), 51.6 (d, C-1′), 52.4 (q, OCH_3), 52.8 (q, OCH_3), 132.5 (s, C-2), 154.8 (d, C-3), 168.7 (s, CO_2CH_3), 169.1 (s, CO_2CH_3), 198.2 (s, C-1) ppm. MS (EI): m/z (%) = 268 (2) $[M]^+$, 253 (2), 237 (2), 209 (1), 195 (15), 137 (68), 136 (100), 121 (24). $C_{14}H_{20}O_5$ (268.31): calcd. C 62.67, H 7.51; found C 63.00, H 7.41.

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