Tetrahedron 66 (2010) 7856–7860

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

An efficient one-pot four-step domino reaction for the synthesis of C2-substituted 3-methylcyclohex-2-enones

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ARTICLE INFO

Article history:
Received 16 June 2010
Received in revised form 13 July 2010
Accepted 13 July 2010
Available online 29 July 2010

Keywords:
Domino reaction
Enone
Cyclization
β-Ketoester

ABSTRACT

An efficient one-pot four-step domino reaction of substituted β-ketoesters has been optimized giving rise to a large panel of C2-substituted 3-methylcyclohex-2-enones, an important scaffold for the preparation of various initiators for cationic or radical cyclizations. The developed methodology is quite general and applicable to a wide range of β-ketoester substrates, allowing the introduction of various functionalities at the C2 position of the 3-methylcyclohex-2-enones, in good to excellent yields.

1. Introduction

C2-substituted 3-methylcyclohex-2-enones **1** are known to be efficient initiators for diastereoselective 6-*endo*-*trig* cyclizations[1] giving rise to decalin systems stereoselectively (Fig. 1), a scaffold present in a wide range of natural products, such as di- and triterpenes.[2] Moreover, **1** is also a key intermediate in the access to several other relevant initiators for cationic or radical cyclizations, such as keto-epoxide **2**,[3] allylic alcohol **3**,[4] dienol acylate **4**,[5] exocyclic olefin **5**[6] or 2-alkenyl-1,3-dithiolane **6**,[7] from which interesting polycyclic compounds could be further generated.

Importantly, C2-substituted 3-methylcyclohex-2-enones **1** have also been used as key synthetic intermediates in numerous total synthesis of natural products, such as (+/−)-dichroanal B,[8] umbrosone,[9] (+/−)-isopisiferin[10] and more recently (+/−)-triptolide[7] (Fig. 2).

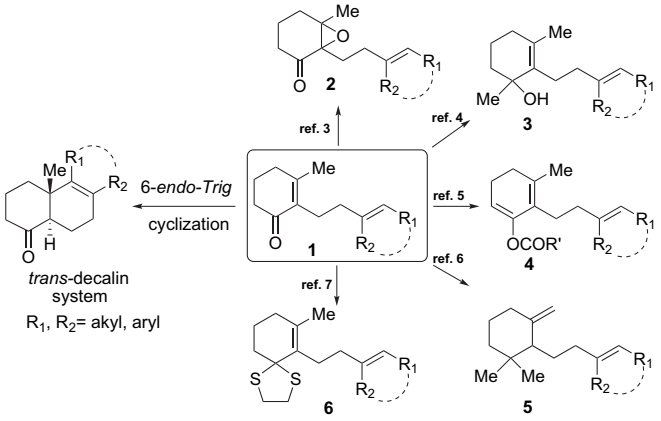

Figure 1. Synthetic relevance of C2-substituted 3-methylcyclohex-2-enones.

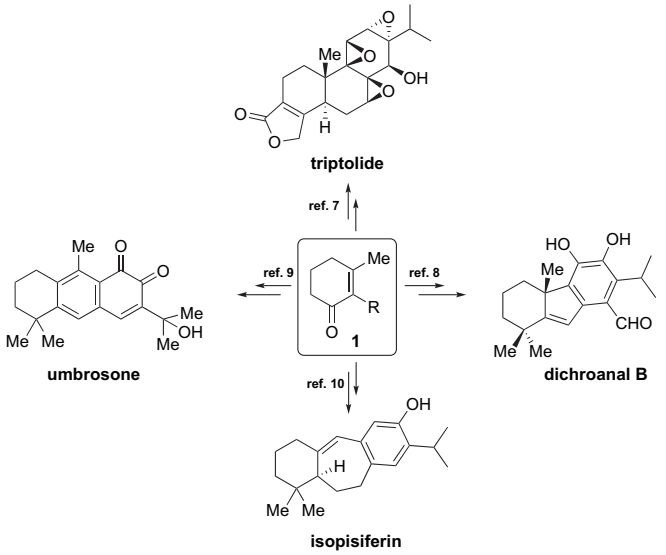

Figure 2. Use of C2-substituted 3-methylcyclohex-2-enones **1** in natural products synthesis.

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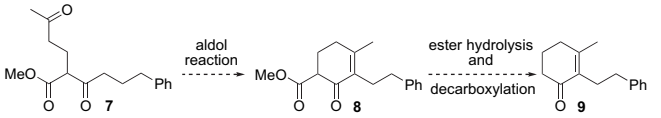
0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.07.029

The important feature of this class of versatile compounds (**1**) is the chemical nature of the nucleophilic functionality introduced at the C2 position that participates to the cyclization event. To date, four methods have been reported in literature for the preparation of C2-susbtituted 3-methylcyclohex-2-enones. The main procedure consists in the alkylation of Hagemann's ester, realized under heating with various bases (sodium or potassium ethoxide, or potassium *tert*-butoxide), followed by a one-pot saponification and decarboxylation.[11] However, this multistep procedure suffers from major drawbacks, such as the formation of C4-susbtituted 3-methylcyclohex-2-enone and/or dialkylated by-products, when highly electrophilic halides are used.[12] The second method consists in the direct alkylation of the C2 position of 3-methylcyclohex-2-enone via the dienolate with alkyl halides. However, only few examples have been reported in the literature, due to the limited scope of application of the methodology.[4b,13] The third route to access C2-substituted 3-methylcyclohex-2-enones is based on a multistep sequence consisting first in the alkylation of 1,5-dimethoxy-1,4-cyclohexadiene with alkyl halides. This protocol described initially by Piers et al.[14] is then followed by the hydrolysis of the adduct to 1,3-cyclohexanedione system, which upon etherification affords the corresponding enol, that is, engaged in the reaction with Grignard reagents giving rise to the C2-substituted 3-methylcyclohex-2-enone.[15] Good overall yields are usually obtained. However, the reaction sequence still remains lengthy (five steps) and requires the synthesis of the starting diene by Birch reaction of suitable substituted aromatic substrates. This multistep protocol has been further optimized by Sutherland et al.[12b,16] allowing the synthesis of various C2-substituted 3-methylcylohex-2-enones in two steps with good overall chemical yields. However, even though the number of steps has been reduced, the reaction requires tedious preparation of sensitive diene reagents, limiting the practicability of the reaction. As a consequence, the development of a straightforward and mild general procedure to access C2-substituted 3-methylcylohex-2-enones **1** in few steps remains a challenge of crucial importance due to the versatility of their chemistry.[17] Recently, we described the formal total synthesis of (+/−)-triptolide by using a novel *6-endo-trig* cationic cyclization of 2-alkenyl-1,3-dithiolanes (Fig. 2).[7] The synthesis of the key C2-substituted 3-methylcylohex-2-enone cyclization precursor relied on an efficient one-pot four-step domino reaction of a substituted β-ketoester. Herein, we described the optimization of this protocol and the result of our studies on the scope and application of this domino process that affords efficiently C2-substituted 3-methylcyclohex-2-enones **1**.

2. Results and discussion

Our strategy for the preparation of C2-substituted 3-methylcyclohex-2-enones consisted in the regioselective intramolecular aldol reaction of the substituted β-ketoester **7** leading to the elimination product **8**, which would give the desired compound **9** after a second decarboxylation step (Table 1). Firstly, the intramolecular aldol reaction was studied with **7** as the model substrate, in order to find suitable conditions for the preparation of **8**. The substituted β-ketoester **7** of interest was synthesized from the corresponding β-ketoester by a Michael addition onto methylvinylketone (MVK) (see Supplementary data). The intramolecular aldol reaction of **7** was first tried in dichloromethane as solvent in the presence of potassium carbonate as base and at room temperature for 16 h. Unfortunately, in these conditions, the aldol reaction was inefficient and **7** was recovered unchanged (Table 1, entry 1). The addition of methanol to better dissolve K_2CO_3 permitted the aldol reaction to proceed and adduct **8** was formed in a reasonable yield of 58% (entry 2). This result might be ascribed to the in situ formation of potassium methoxide and/or to the polarity increase of the reaction medium.

Table 1
Exploring the conditions for the intramolecular aldol reaction



Entry	Base[a]	Solvent	*T*	Product	Yield[b]
1	K_2CO_3	DCM	rt	—	—
2	K_2CO_3	DCM/MeOH	rt	**8**	58%
3	K_2CO_3	MeOH	rt	**8**	50%
4	L-proline	DCM	40 °C	—	—
5	TBD	DCM	40 °C	—	—
6	DBU	DCM	rt	—	—
7	DBU	DCM	40 °C	**9**	53%
8	DBU	MeCN	80 °C	**9**	50%
9	DBU	MeCN	80 °C[c]	**9**	89%

[a] 1.1 equiv of base was used.
[b] Isolated yield.
[c] The reaction was carried out during 3 h.

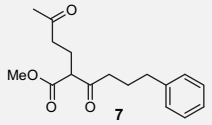
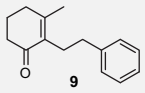
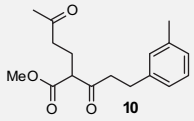
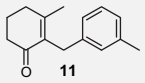
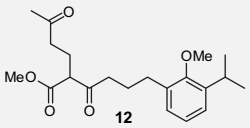
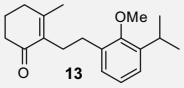
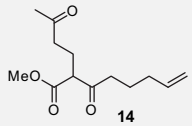
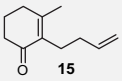
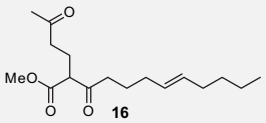
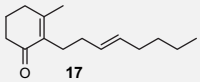
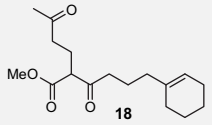
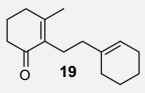
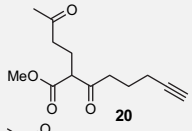
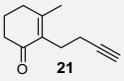
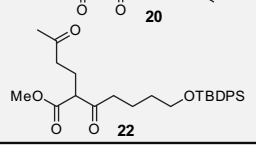
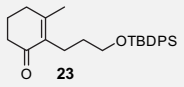
However, performing the aldol reaction in pure methanol with potassium carbonate was less efficient (entry 3). As a consequence, other bases, such as 1,5,7-triazabicyclo[4.4.0]dec-1-ene (TBD),[18] L-proline and diazabicycloundecene (DBU) were tested in DCM. It was noticed that no reaction occurred when L-proline or TBD were used as base even under reflux conditions, and the starting β-ketoester **7** was recovered quantitatively (entries 4 and 5). We next evaluated the reactivity of DBU, known to promote domino reactions for the synthesis of 5-trifluoromethylated cyclohexenone in DCM.[19] Interestingly, only under reflux conditions, these conditions allowed the direct formation of **9** in 53% of yield, arising from a one-pot four-step domino reaction via adduct **8** (entries 6 and 7).

This transformation consisted in the aldol reaction followed by the in situ saponification of the methyl ester and decarboxylation of the corresponding 1,3-ketoacid. Since the conversion of **7** was limited in dichloromethane, a more polar solvent with a higher boiling point, such as acetonitrile was envisioned. The domino reaction was thus performed at 80 °C for 16 h in acetonitrile, however, **9** was isolated in slightly decreased 50% yield (entry 8). It was eventually found that an extended reaction time (16 h) at 80 °C was responsible for the partial degradation of the desired reaction product **9**. Therefore, the reaction time of the domino reaction was finally optimized at 80 °C for 3 h with 1.1 equiv of DBU, allowing an efficient access to **9** in 89% of isolated yield (entry 9). Attempts to reduce the amount of DBU to 0.1 equiv in this reaction failed and only a limited conversion of **7** resulted, most likely due to the formation of the stable amidinium salt by abstraction of the most acidic proton of **7**, scavenging the base for further turnover of the catalyst.

Finally, with the optimized conditions in hand for the preparation of the C2-substituted 3-methylcyclohex-2-enone **9**, we next applied this reaction to a large panel of functionalized β-ketoesters in order to study the scope and limitations of the domino process (Table 2). Accordingly, substituted β-ketoesters **10**–**22** were synthesized from the corresponding β-ketoesters by an improved Michael addition with MVK (see Supplementary data). All the substrates shown in Table 2 were reacted with 1.1 equiv of DBU in acetonitrile at 80 °C for 3 h. The majority of the domino reactions proceeded well, affording the corresponding C2-substituted 3-methylcyclohex-2-enones **11**–**23**, in good to excellent yields.

β-ketoester **10** and **12** bearing di- and trisubstituted arene behaved similarly to **7** and gave the expected C2-substituted 3-methylcyclohex-2-enones **11** and **13** with excellent yields of 85% and 90%, respectively (entries 2 and 3). The reactivity of substrates functionalized with unsaturated functions in their side chain was next examined. Substituted β-ketoesters carrying terminal alkene **14**, disubstituted (*E*)-alkene **16** or cyclohexene moiety **18** reacted

Table 2
One-pot four-step domino reaction of a panel of β-ketoesters

Entry	Starting β-ketoester	Product	Yield (%)
1			89
2			85
3			90
4			78
5			86
6			73
7			84
8			69

satisfactorily under the optimal conditions of the domino reaction, and permitted access to the expected C2-substituted 3-methylcyclohex-2-enones **15**, **17** and **19**, in good yields ranging from 73% to 86% (entries 4, 5 and 6). Moreover, C2-substituted 3-methylcyclohex-2-enone **21**, having a terminal alkyne in the side chain, was efficiently synthesized starting from substituted β-ketoester **20**, with a good isolated yield of 84% (entry 7). The reaction conditions also tolerated functionalized β-ketoester **22** bearing a primary *tert*-butyldiphenylsilyl (TBDPS) protected alcohol, yielding the corresponding 3-methylcyclohex-2-enone **23** in a good chemical isolated yield 69% (entry 8). As a general trend, it is important to note that this one-pot four-step domino reaction allows the introduction of a wide variety of functionalities on the side chain of the C2-substituted 3-methylcyclohex-2-enone, useful for further functionalizations, cyclizations, or functional group transformations.

The mechanism of this one-pot four-step domino reaction is similar to the one described for the preparation of 5-trifluoromethylated cyclohexenones.[19] However, in contrary to precedent report this reaction does not proceed if a catalytic amount of DBU is used. The first step of the domino process consists in the regioselective intramolecular aldol reaction, leading to the addition product **24** (Fig. 3), and then to the dehydration product **25**. In situ ester hydrolysis followed by decarboxylation deliver the desired C2-substituted 3-methylcyclohex-2-enone **9**.

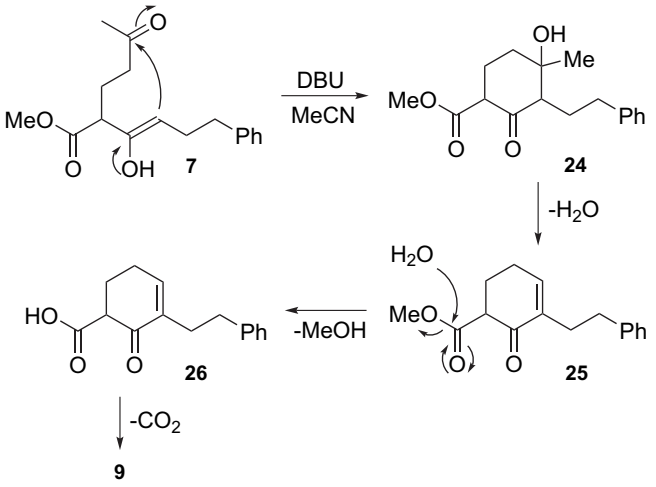


Figure 3. Rational mechanism of the one-pot four-step domino reaction.

3. Conclusion

We have developed a new protocol for the straightforward preparation of C2-substituted 3-methylcyclohex-2-enones, an important scaffold in organic chemistry. The reaction consists in a one-pot four-step domino reaction using DBU in acetonitrile under reflux conditions. Several C2-substituted 3-methylcyclohex-2-enones were successfully synthesized with good to excellent yields, ranging from 69% to 90%. The optimized conditions are compatible with various functionalities on the side chain of the starting substituted β-ketoester, such as alkene, alkyne and TBDPS protected alcohols.

4. Experimental section

4.1. General methods

All reagents were purchased from Sigma–Aldrich, ABCR, Alfa-Aesar and Acros and were used as received. NMR spectra were recorded on a Brücker Advance 400 (300 MHz ^{1}H NMR, 75 MHz ^{13}C NMR) in $CDCl_3$. Chemical shift values (δ) are reported in parts per million (residual chloroform δ=7.26 ppm for ^{1}H; residual chloroform δ=77.16 ppm for ^{13}C). Infra-red spectra were recorded with a Nicolet 380 FT-IR apparatus. High resolution mass spectra were recorded with an Agilent Q-Tof 6520 apparatus equipped with a positive ESI source. Syntheses and analysis of starting β-ketoesters are reported in Supplementary data.

4.2. General procedure for the synthesis of substituted β-ketoesters used in this study

Potassium carbonate (4.00 mmol, 1.0 equiv) followed by a solution of methylvinylketone (MVK) (4.00 mmol, 1.0 equiv) in dichloromethane (2 mL) was added to a solution of the starting β-ketoester (4.00 mmol, 1.0 equiv) in dichloromethane (11 mL). The reaction mixture was stirred for 16 h. After quenching by addition of water (25 mL), the aqueous phase was extracted by diethyl ether (3×20 mL). The combined organic extracts were washed with brine, dried over sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography on a silica gel column (eluent: chloroform) to give the desired substituted β-ketoesters.

*4.2.1. Methyl-3-oxo-2-(3-oxobutyl)-6-phenylhexanoate (**7**).* Obtained as a colourless oil (981 mg, 74%). R_f (98/2 $CHCl_3$/MeOH)=0.61. IR (neat): ν=2950, 1742, 1711, 1497, 1367, 1201, 1159, 748, 701 cm^{-1}. ^1H NMR: δ=7.14 (m, 6H), 3.70 (s, 3H), 3.48 (t, J=7.2 Hz, 1H), 2.44 (m, 6H), 2.02 (m, 5H), 1.84 (quint., J=7.4 Hz, 2H) ppm. ^{13}C NMR: δ=207.6, 204.8, 170.1, 141.5, 128.6, 128.5, 126.1, 57.3, 52.5, 41.3, 40.6, 34.9, 30.0, 24.9, 21.9 ppm. HRMS (ESI, m/z): calcd for $C_{17}H_{22}O_4$ $[M+H]^+$: 291.1596, found: 291.1591.

*4.2.2. Methyl 2-[3-(3-methylphenyl)propanoyl]-5-oxohexanoate (**10**).* Obtained as a yellow oil (3.48 g, 90%). R_f (95/5 $CHCl_3$/MeOH)=0.87. IR (neat): ν=2952, 1743, 1712, 1489, 1435, 1360, 1205, 1161, 782 cm^{-1}. ^1H NMR: δ=7.14 (t, J=7.6 Hz, 1H), 6.96 (m, 3H), 3.67 (s, 3H), 3.49 (t, J=6.8 Hz, 1H), 2.78 (m, 4H), 2.39 (t, J=6.8 Hz, 2H), 2.32 (s, 3H), 2.09 (s, 3H), 2.03 (m, 2H) ppm. ^{13}C NMR: δ=207.5, 204.2, 169.9, 140.6, 138.1, 129.2, 128.5, 127.0, 125.4, 57.5, 52.5, 43.6, 40.4, 30.0, 29.5, 21.8, 21.4 ppm. HRMS (ESI, m/z): calcd for $C_{17}H_{22}O_4$ $[M+H]^+$: 291.1596, found: 291.1600.

*4.2.3. Methyl 6-(3-isopropyl-2-methoxyphenyl)-3-oxo-2-(3oxo-butyl) hexanoate (**12**).* Obtained as a yellow oil (1.42 g, 96%). R_f (95/5 $CHCl_3$/MeOH)=0.55. Data analysis of compound **12** can be found in Ref. 7.

*4.2.4. Methyl-3-oxo-2-(3-oxobutyl)oct-7-enoate (**14**).* Obtained as a yellow oil (1.31 g, 66%). R_f (95/5 $CHCl_3$/MeOH)=0.76. IR (neat): ν=2952, 1743, 1712, 1641, 1436, 1367, 1206, 1159, 998, 914 cm^{-1}. ^1H NMR: δ=5.69 (m, 1H), 4.95 (m, 2H), 3.70 (s, 3H), 3.50 (t, J=7.2 Hz, 1H), 2.44 (m, 4H), 2.11 (s, 3H), 2.03 (m, 4H), 1.63 (quint., J=7.2 Hz, 2H) ppm. ^{13}C NMR: δ=207.5, 204.9, 170.1, 137.8, 115.4, 57.3, 52.5, 41.2, 40.6, 32.9, 30.0, 22.5, 21.9 ppm. HRMS (ESI, m/z): calcd for $C_{13}H_{20}O_4$ $[M+H]^+$: 258.1705, found: 258.1708.

*4.2.5. Methyl (7E)-3-oxo-2-(3-oxobutyl)dodec-7-enoate (**16**).* Obtained as a yellow oil (2.18 g, 65%). R_f (95/5 $CHCl_3$/MeOH)=0.79. IR (neat): ν=2955, 2929, 1744, 1713, 1435, 1409, 1367, 1204, 1159, 1066, 720 cm^{-1}. ^1H NMR: δ=5.35 (m, 1H), 5.24 (m, 1H), 3.70 (s, 3H), 3.50 (t, J=7.2 Hz, 1H), 2.46 (m, 4H), 2.11 (s, 3H), 1.98 (m, 6H), 1.58 (quint., J=7.2 Hz, 2H), 1.28 (m, 4H), 0.86 (m, 3H) ppm. ^{13}C NMR: δ=207.5, 205.1, 170.1, 131.2, 128.5, 57.3, 52.5, 41.5, 40.6, 31.9, 30.0, 27.1, 26.5, 23.5, 22.4, 21.9, 14.0 ppm. HRMS (ESI, m/z): calcd for $C_{17}H_{28}O_4$ $[M+H]^+$: 297.2066, found: 297.2062.

*4.2.6. Methyl 6-cyclohex-1-en-1-yl-3-oxo-2-(3-oxobutyl)hexanoate (**18**).* Obtained as a yellow oil (2.15 g, 85%). R_f (95/5 $CHCl_3$/MeOH)=0.83. IR (neat): ν=2926, 2836, 1743, 1713, 1436, 1366, 1204, 1159, 1108, 1008, 918 cm^{-1}. ^1H NMR: δ=5.35 (m, 1H), 3.71 (s, 3H), 3.50 (t, J=7.2 Hz, 1H), 2.40 (m, 4H), 2.12 (s, 3H), 2.04 (m, 2H), 1.87 (m, 7H), 1.49 (m, 7H) ppm. ^{13}C NMR: δ=207.5, 205.1, 170.1, 136.8, 121.9, 57.4, 52.4, 41.5, 40.6, 37.4, 30.0, 28.1, 25.3, 23.0, 22.6, 21.9, 21.4 ppm. HRMS (ESI, m/z): calcd for $C_{17}H_{26}O_4$ $[M+H]^+$: 295.1909, found: 295.1912.

*4.2.7. Methyl-3-oxo-2-(3-oxobutyl)oct-7-ynoate (**20**).* Obtained as a colourless oil (736 mg, 86%). R_f (95/5 $CHCl_3$/MeOH)=0.82. IR (neat): ν=3281, 2954, 1741, 1710, 1435, 1369, 1207, 1161, 1108, 649 cm^{-1}. ^1H NMR: δ=3.71 (s, 3H), 3.52 (t, J=7.2 Hz, 1H), 2.59 (m, 2H), 2.46 (t, J=7.2 Hz, 2H), 2.19 (m, 2H), 2.11 (s, 3H), 2.05 (m, 2H), 1.94 (t, J=2.8 Hz, 1H), 1.75 (quint., J=7.2 Hz, 2H) ppm. ^{13}C NMR: δ=207.5, 204.5, 170.0, 83.4, 69.3, 57.4, 52.5, 40.5, 40.4, 30.0, 22.0, 21.9, 17.6 ppm. HRMS (ESI, m/z): calcd for $C_{13}H_{18}O_4$ $[M+H]^+$: 239.1283, found: 239.1280.

*4.2.8. Methyl 7-{[tert-butyl(diphenyl)silyl]oxy}-3-oxo-2-(3-oxobutyl) heptanoate (**22**).* Obtained as a yellow oil (2.36 g, 85%). R_f (95/5 $CHCl_3$/MeOH)=0.57. IR (neat): ν=2958, 2901, 1745, 1716, 1428, 1393, 1242, 1160, 1110, 1078, 1066, 823, 743, 703, 314, 505 cm^{-1}. ^1H NMR: δ=7.64 (m, 4H), 7.36 (m, 6H), 3.70 (s, 3H), 3.64 (t, J=6.4 Hz, 2H), 3.50 (t, J=6.8 Hz, 1H), 2.45 (m, 4H), 2.04 (m, 5H), 1.64 (m, 2H), 1.51 (m, 2H), 1.05 (s, 9H) ppm. ^{13}C NMR: δ=207.5, 204.9, 170.1, 135.6, 134.0, 129.7, 127.8, 63.6, 57.3, 52.5, 41.9, 40.6, 31.9, 30.0, 27.0, 21.9, 20.1, 19.3 ppm. HRMS (ESI, m/z): calcd for $C_{28}H_{38}O_5Si$ $[M+H]^+$: 483.2567, found: 483.2562.

4.3. General procedure for the synthesis of C2-substituted 3-methylcyclohex-2-enones

DBU (0.243 mmol, 1.1 equiv) was added to a solution of substituted the β-ketoester (0.221 mmol, 1.0 equiv) in acetonitrile (5 mL, extra dry, water<10 ppm, AcroSeal®) and the reaction mixture was stirred under reflux for 3 h until completion. After cooling the reaction media to room temperature and addition of water (20 mL), the aqueous phase was extracted with diethyl ether (3×10 mL). The combined organic extracts were dried over sodium sulfate and evaporated in vacuo. The residue was purified by flash chromatography on a silica gel column to give the desired C2-susbtituted 3-methylcyclohex-2-enone.

*4.3.1. 3-Methyl-2-(2-phenylethyl)cyclohex-2-enone (**9**).* Obtained from **7** (73 mg, 0.25 mmol) as a yellow oil (48 mg, 89%). R_f (70/30 cyclohexane/EtOAc)=0.61. IR (neat): ν=2930, 1664, 1628, 1496, 1454, 1380, 1180, 1138, 1033, 754, 702 cm^{-1}. ^1H NMR: δ=7.15 (m, 5H), 2.55 (m, 4H), 2.37 (t, J=6.0 Hz, 2H), 2.28 (t, J=6.0 Hz, 2H), 1.89 (quint., J=6.0 Hz, 2H), 1.74 (s, 3H) ppm. ^{13}C NMR: δ=198.8, 156.2, 142.4, 134.8, 128.8, 128.3, 125.9, 38.1, 35.2, 32.9, 27.7, 22.4, 21.2 ppm. HRMS (ESI, m/z): calcd for $C_{15}H_{18}O$ $[M+H]^+$: 215.1436, found: 215.1432.

*4.3.2. 3-Methyl-2-(3-methylbenzyl)cyclohex-2-enone (**11**).* Obtained from **10** (3.44 g, 11.85 mmol) as a yellow oil (2.15 g, 85%). R_f (80/20 cyclohexane/EtOAc)=0.59. IR (neat): ν=2921, 2866, 1659, 1625, 1605, 1429, 1377, 1181, 1136, 958, 749, 693 cm^{-1}. ^1H NMR: δ=7.10 (t, J=7.6 Hz, 1H), 6.93 (m, 3H), 3.65 (s, 2H), 2.42 (t, J=5.6 Hz, 2H), 2.38 (t, J=6.0 Hz, 2H), 2.30 (s, 3H), 1.97 (s, 3H), 1.94 (m, 2H) ppm. ^{13}C NMR: δ=198.6, 157.0, 140.6, 137.8, 134.9, 129.2, 128.2, 126.5, 125.3, 37.9, 33.1, 30.6, 22.3, 21.9, 21.5 ppm. HRMS (ESI, m/z): calcd for $C_{15}H_{18}O$ $[M+H]^+$, 215.1436, found: 215.1439.

*4.3.3. 2-[2-(3-Isopropyl-2-methoxyphenyl)ethyl]-3-methylcyclohex-2-enone (**13**).* Obtained from **12** (1.42 g, 3.92 mmol) as a yellow oil (1.02 g, 90%). R_f (80/20 cyclohexane/EtOAc)=0.59. Data analysis of compound **13** can be found in Ref. 7.

*4.3.4. 2-But-3-enyl-3-methylcyclohex-2-enone (**15**).* Obtained from **14** (1.28 g, 5.34 mmol) as a yellow oil (685 mg, 78%). R_f (70/30 cyclohexane/EtOAc)=0.64. Data analysis of compound **15** can be found in Ref. 4a.

*4.3.5. 3-Methyl-2-[(3E)-oct-3-en-1-yl]cyclohex-2-enone (**17**).* Obtained from **16** (2.15 g, 7.25 mmol) as a colourless oil (1.37 g, 86%). R_f (80/20 cyclohexane/EtOAc)=0.66. IR (neat): ν=2926, 2860, 1662, 1628, 1455, 1430, 1378, 1325, 1179, 1138, 1118, 1051, 725 cm^{-1}. ^1H NMR: δ=5.30 (m, 2H), 2.30 (m, 6H), 1.96 (m, 4H), 1.88 (m, 5H), 1.27 (m, 4H), 0.86 (m, 3H) ppm. ^{13}C NMR: δ=198.8, 155.4, 135.4, 130.4, 129.2, 38.0, 33.0, 32.1, 27.0, 26.8, 25.4, 22.5, 22.4, 21.4, 14.1 ppm. HRMS (ESI, m/z): calcd for $C_{15}H_{24}O$ $[M+H]^+$: 221.1905, found: 221.1902.

*4.3.6. 2-(2-Cyclohex-1-enylethyl)-3-methylcyclohex-2-enone (**19**).* Obtained from **18** (2.07 g, 7.04 mmol) as a yellow liquid (1.12 g, 73%). R_f (80/20 cyclohexane/EtOAc)=0.68. IR (neat): ν=2926, 2836, 1743, 1713, 1436, 1366, 1204, 1159, 1108, 1008, 918 cm^{-1}. ^1H NMR: δ=5.35 (m, 1H), 2.29 (m, 6H), 1.80 (m, 12H), 1.55 (m, 2H), 1.50 (m, 2H) ppm. ^{13}C NMR: δ=198.7, 155.1, 137.8, 135.6,

121.0, 38.0, 37.2, 32.9, 28.4, 25.3, 23.9, 23.1, 22.6, 22.4, 21.2 ppm. HRMS (ESI, *m*/*z*): calcd for $C_{15}H_{22}O$ $[M+K]^+$: 257.1308, found: 257.1304.

*4.3.7. 2-But-3-ynyl-3-methylcyclohex-2-enone (**21**).* Obtained from **20** (706 mg, 2.96 mmol) as a colourless oil (403 mg, 84%). R_f (80/20 cyclohexane/EtOAc)=0.39. IR (neat): ν=2939, 1656, 1627, 1430, 1380, 1327, 1181, 1138, 1122, 1048, 633 cm^{-1}. ^1H NMR: δ=2.51 (t, *J*=7.2 Hz, 1H), 2.33 (m, 4H), 2.22 (td, *J*=2.8 , 7.2 Hz, 2H), 1.99 (s, 3H), 1.90 (m, 2H), 1.88 (t, *J*=2.8 Hz, 1H) ppm. ^{13}C NMR: δ=198.6, 157.2, 133.9, 84.4, 68.4, 37.8, 33.0, 24.5, 22.3, 21.7, 18.0 ppm. HRMS (ESI, *m*/*z*): calcd for $C_{11}H_{14}O$ $[M+H]^+$: 163.1123, found: 163.1121.

*4.3.8. 2-(3-{[tert-Butyl(diphenyl)silyl]oxy}propyl)-3-methylcyclohex-2-enone (**23**).* Obtained from **22** (2.33 g, 4.83 mmol) as a yellow oil (1.36 g, 69%). R_f (80/20 cyclohexane/EtOAc)=0.65. IR (neat): ν=2931, 2858, 1664, 1428, 1380, 1110, 1088, 823, 742, 702, 613, 505 cm^{-1}. ^1H NMR: δ=7.66 (m, 4H), 7.35 (m, 6H), 3.64 (t, *J*=6.4 Hz, 2H), 2.29 (m, 6H), 1.87 (m, 5H), 1.54 (m, 2H), 1.06 (s, 9H) ppm. ^{13}C NMR: δ=198.7, 155.3, 135.5, 135.4, 134.1, 129.5, 127.6, 63.8, 37.8, 32.8, 32.0, 26.9, 22.3, 21.6, 21.1, 19.2 ppm. HRMS (ESI, *m*/*z*): calcd for $C_{26}H_{34}O_2Si$ $[M+H]^+$: 407.2406, found: 407.2402.

Acknowledgements

We acknowledge the Laboratoire Pierre Fabre (Plantes et Industries) and the CNRS for financial support to S.G.

Supplementary data

Supplementary data associated with this article can be found in online version at, doi:10.1016/j.tet.2010.07.029. These data include MOL files and InChIKeys of the most important compounds described in this article.

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