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Synthesis of Bicyclo[4.*n*.1]alkanones

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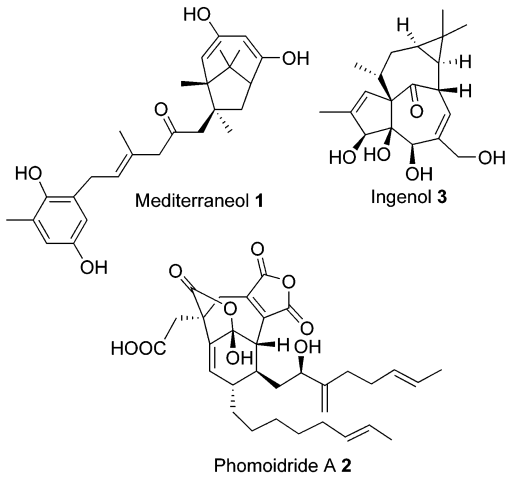
Cyclic β-keto ester *mono*anions react with 1,4-dihalobutenes to give C-alkylated products which subsequently undergo a stereoselective S_N2' O-alkylation reaction to yield functionalized enol ethers. When the starting material was ethyl cyclopentanone carboxylate, the C-alkylated product, treated with a base, directly afforded the functionalized bicyclo[4.2.1]nonanone. The enol ethers were submitted to a flash vacuum thermolysis (FVT) reaction to readily afford functionalized bicyclo-[4.*n*.1]alkanones ($n = 3, 4$). This reaction sequence was applied to the synthesis of a functionalized tricyclo[7.4.1.0^{1,5}]tetradecanone, which represents an analogue to the tricyclic core of ingenol.

Introduction

Functionalized bicyclo[4.*n*.1]alkanes are important substructures present in numerous natural bioactive compounds. For example, the bicyclo[4.2.1]nonane, bicyclo-[4.3.1]decane, and bicyclo[4.4.1]undecane skeletons are respectively present in mediterraneol **1**,[1] phomoidride B **2**,[2] and ingenol **3**[3] (Scheme 1). We have previously reported that the Michaël adducts, resulting from the addition of cyclic β-keto ester *mono*anions to ethyl propynoate led, after acidic treatment, to bicyclic bridgehead ketones and not to the corresponding Robinson annulation products.[4] In this context, the reactivity of (di)anions derived from (a)cyclic mono(or di)-activated ketones was extensively studied by Zhao et al.,[5] Rodriguez et al.,[6] and Langer et al.[7] However, to the best of our knowledge, the reactivity of β-keto ester *mono*anions toward 1,4-dihalobutene has not yet been reported in the literature. Hereafter, we report our results concerning the synthesis of bicyclo[4.*n*.1]alkanone skeletons, starting from cyclic β-keto ester and from 1,4-dihalobutenes. This study allowed us to develop a new approach to an analogue of the tricyclic core present in ingenol.

SCHEME 1



Results and Discussion

We ran our first reaction starting from ethyl cyclopentanone carboxylate **4**. The treatment of the later in refluxing acetone with potassium carbonate, followed by addition of *Z*-1,4-dichlorobutene, afforded the C-alkylated product **5** in 80% yield.[8] Subsequently, compound **5** was treated with a suspension of potassium hydride in THF at −78 °C in the presence of a catalytic amount of *t*-BuOH, to afford the desired bicyclo[4.2.1]nonanone **6** in 90% yield (Scheme 2).[9a]

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(9) (a) The ^{1}H NMR and ^{13}C NMR analysis of the crude reaction mixture did not show any significant difference with the analysis of product **6** obtained after being purified on a silica gel column; however, we noticed an important loss of material when the crude reaction mixture was subjected to a silica gel column (see Experimental Section); (b) Same remarks as for compound **6**.

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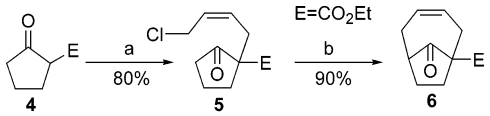
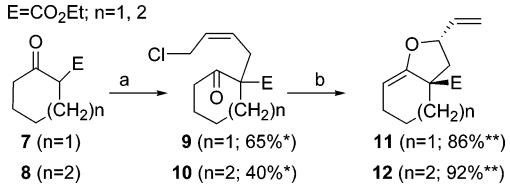
SCHEME 2. Synthesis of Bicyclo[4.2.1]nonanone 6[a]



[a] Reagents and conditions: (a) K_2CO_3, *Z*-1,4-dichlorobutene, acteone, 56 °C; (b) KH, *t*-BuOH cat., THF, −78 °C to rt.

SCHEME 3. Synthesis of Enol Ethers 11 and 12[a]



[a] Reagents and conditions: (a) K_2CO_3, *Z*-1,4-dichlorobutene, acetone, reflux; (b) for **11**: *t*-BuOK, Et_2O, 25 °C; for **12**: KH, *t*-BuOH cat., THF, −78 to 25 °C; (*) NaH/DMF, 25 °C; (**) crude yields.

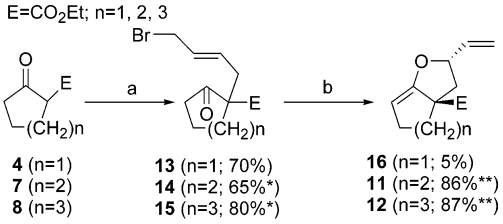
The same reaction conditions were utilized starting from the *β*-keto esters **7** and **8** respectively derived from cyclohexanone and cycloheptanone, to give the C-alkylated products **9** and **10** in good yields. When the latter were treated as above (KH/*t*-BuOH cat./THF), no functionalized bridged bicycloalkanones were formed. Indeed, this reaction led stereospecifically to the enol ethers **11** and **12** by an S_N2' O-alkylation reaction (Scheme 3).[9b] The relative configurations indicated for compounds **11** and **12** deduced from NMR studies were in agreement with those reported for analogous compounds.[5−7]

Our preliminary results were quite different from those described by Rodriguez et al.[6] Indeed, these authors always observed the formation of functionalized bridged bicycloalkanones when dianions, derived from α,α′ activated cycloalkanones, reacted with *Z*-1,4-dichlorobutene. However, Zhao et al. reported that the enol ether of type **11** could be prepared stereospecifically by alkylation of 2-phenylcyclohexanone with *Z*-1,4-dichlorobutene, and subsequent intramolecular O-alkylation.[5]

Next, we turned our attention toward the C-alkylation reaction between *β*-keto esters **4**, **7**, and **8** and *E*-1,4-dibromobutene. The corresponding adducts **13**, **14**, and **15** were easily obtained. The C-alkylation products **13**, **14**, and **15** were not formed when DBU was used as a base. In this case, only the starting material was recovered. Compounds **13**−**15** underwent a S_N2' O-alkylation reaction as above when treated with KH/*t*-BuOH cat. in THF to give the enol ethers **11** and **12** in good yields. However, the C-alkylated product **13**, treated under the same reaction conditions, led to a "sluggish" reaction mixture from which the enol ether **16** was identified. This compound could not be isolated pure, probably because of the inherent strain of the compound. We also observed that the same yields were obtained when the base system KH/*t*-BuOH was advantageously replaced by *t*-BuOK, which is much more convenient (Scheme 4). Our results were in accord with those reported by Zhao et al. and Rodriguez et al.[5,6]

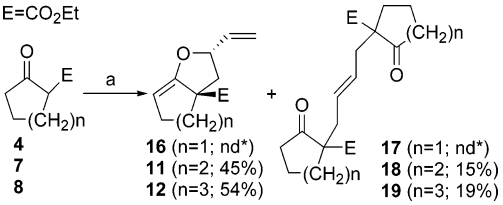
It was also possible to run these two-step reactions as a "one-pot " reaction (Scheme 5). The desired products **11** and **12** were obtained starting from the *β*-keto esters

SCHEME 4. Synthesis of Enol Ethers 11, 12, and 16[a]



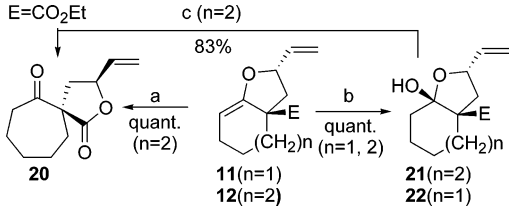
[a] Reagents and conditions: (a) K_2CO_3, *E*-1,4-dichlorobutene, acetone, reflux; (b) *t*-BuOK, THF or Et2O, 25 °C; (*) NaH/DMF, 25 °C; (**) crude yields.

SCHEME 5. "One-Pot" Reaction[a]



[a] Reagents and conditions: (a) *t*-BuOK (3 equiv), *E*-1,4-dibromobutene, THF, 25 °C; (*) not detected.

SCHEME 6. Reactivity of the Enol Ethers 11 and 12[a]

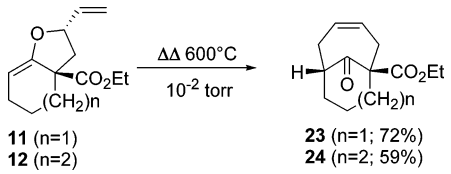


[a] Reagents and conditions: (a) HCl 10%, THF, 20 °C, 10 h; (b) HCl 10%, Et_2O, 20 °C, 2 h; (c) HCl 10%, THF, 20 °C, 4 h or HCl 10%, Et_2O, 20 °C, 40 h.

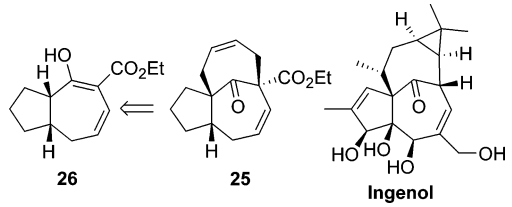
7 and **8**. The dimers **18** and **19** were also generated as the result of a double addition of the *β*-keto ester anions to *E*-1,4-dibromobutene. However, we were unable to obtain the corresponding compounds **16** and **17** when ethyl cyclopentanone carboxylate was used as starting material. So, in our hands, the "one-pot" method was not advantageous compared to the two-step reaction. Moreover, the scale-up of the "one-pot" reaction was not very efficient when amounts greater than 1 mmol were used, and the yields dropped dramatically (approximatively 20%). This is not the case for the two-step reaction.

We also noticed that the enol ether **12**, treated with dilute hydrochloric acid in THF at room temperature for 10 h, led quantitatively to the spirolactone **20**. When the reaction was carried out in ether for 2 h at room temperature, the hydroxy derivative **21** was quantitatively recovered. Compound **21** can be readily transformed into the spiro lactone **20** under acidic conditions (Scheme 6). However, when the enol ether **11** was submitted to the same conditions, only the hydroxy derivative **22** (supported by X-ray crystallographic structure) was quantitatively obtained. When more drastic conditions (THF, reflux) were used, decomposition oc-

SCHEME 7. Flash Vacuum Thermolysis



SCHEME 8

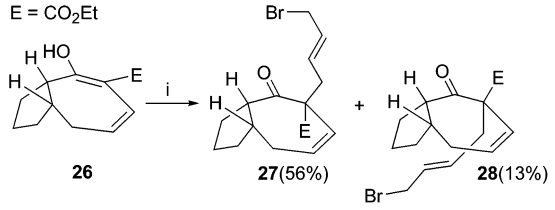


curred and the corresponding spirolactone derivative was not isolated.[10]

To obtain the desired bicyclo[4.*n*.1]alkanones, the enol ethers **11** and **12** were heated at 190 °C in 1,2,4-trichlorobenzene for 14 h to promote a Claisen rearrangement. Under these conditions, the bicyclo[4.3.1]-decanone **23** and the bicyclo[4.4.1]undecanone **24** were formed. Unfortunately, we were unable to separate these compounds from side products; the yield was estimated to be approximatively 50%. To avoid these problems, compounds **11** and **12** were treated under flash-vacuum thermolysis (FVT) conditions (600 °C, 10^{-2} Torr). Thus, the desired bridgehead ketones **23** and **24** were isolated in 72% and 60% yields, respectively (Scheme 7). It should be noted that bicyclo[4.2.1]decanone **6** and bicyclo[4.3.1]-undecanone **23** were also obtained by Snider et al. using a Mn(III)-based oxidative free radical cyclization of unsaturated ketones.[11] However, our reaction sequence led to these functionalized bridged bicycloalkanones in higher yields and as pure compounds. Finally, to the best of our knowledge, compound **24** has not yet been described in the literature.

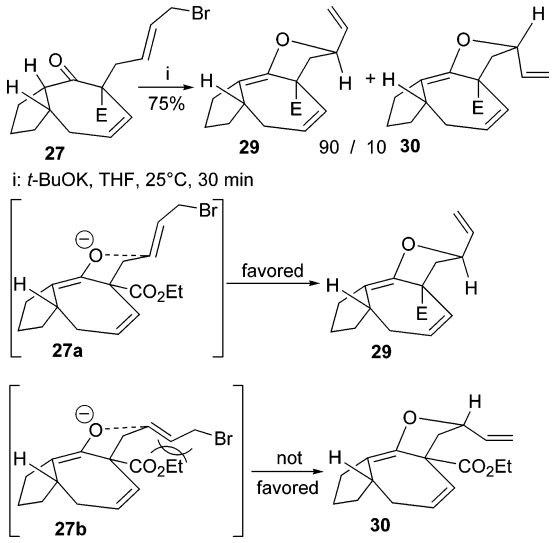
In summary, we were able to develop a general method for the preparation of bicyclo[4.*n*.1]alkanones (n = 2, 3, 4) in good overall yields, starting from the corresponding β-keto esters, thanks to the use of the FVT technique. These results prompted us to use this reaction sequence to develop an original approach to an analogue of the tricyclic substructure found in ingenol, i.e. the tricyclic derivative **25** (Scheme 8).[12] The starting material, i.e. the hydroazulene derivative **26**, is a readily available compound with use of our photochemical ring enlargement reaction of condensed electrophilic cyclobutenes.[13]

SCHEME 9. Alkylation of Compound 26[a]



[a] Reagents and conditions: (i) K_2CO_3, *E*-1,4-dibromobutene, acetone, reflux 2 h.

SCHEME 10. Synthesis of Enol Ethers 29 and 30



The C-alkylation reaction was carried out with *E*-1,4-dibromobutene in the presence of potassium carbonate as a base (Scheme 9). Two separable compounds, **27** and **28**, were formed in a 4/1 ratio in 69% overall yield. It is reasonable to postulate that the major compound **27** results from a favorable approach of the alkylating reagent on the less hindered face (β-face) of the hydroazulene derivative **26**.

Following our model studies, the major compound **27** was treated with *t*-BuOK to afford the two enol ethers **29** and **30** (ratio 90/10; overall yield 75%). The observed 1,3-diasteroselectivity is explained by the destabilization of the transition state **27b** (Scheme 10) as suggested in previous work by Zhao et al.[5]

We were unable to separate the two enol ethers **29** and **30**, and a one-pot reaction led to a complex mixture of products. Therefore, the later mixture was subjected to a FVT reaction at various temperatures. The results were disappointing compared to those obtained during our model studies. Indeed, in all cases, the yields were low and a complex mixture was obtained. We were unable to obtain the desired tricyclic derivative **25** as a pure compound. Compound **25**, which would have resulted from a Claisen rearrangement, was always contaminated with unseparable side products. A second product was isolated as a pure compound, i.e., compound **31** resulting from a tandem Claisen−Cope rearrangement. When the

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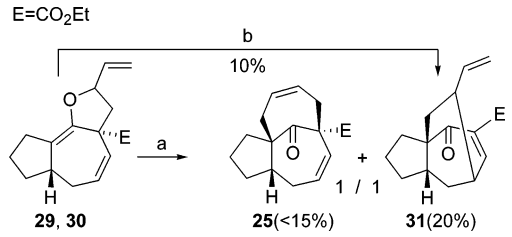
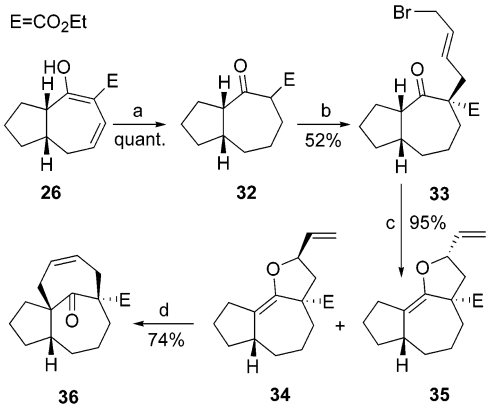
(13) Mislin, G. L.; Miesch, M. *J. Org. Chem.* **2003**, *68*, 433.

SCHEME 11. Flash Vacuum Thermolysis[a]



[a] Conditions: (a) ΔΔ, 520 °C, 10^{-2} mmHg; (b) ΔΔ, 600 °C, 10^{-2} mmHg.

SCHEME 12. Synthesis of Tricyclo[7.4.1.0^{1,5}]tetradecanone 36[a]



[a] Reagents and conditions: (a) H_2, Pd/C, EtOAc, 25 °C; (b) K_2CO_3, acetone, reflux, *E*-1,4-dibromobutene; (c) *t*-BuOK, THF, 25 °C; (d) ΔΔ, 520 °C.

temperature was increased to 600 °C, only the Claisen−Cope rearrangement product **31** was isolated in low yield from a complex mixture. Below 500 °C, the starting material was recovered.

To avoid the formation of compound **31**, and to favor the formation of the desired tricyclic derivative, the same reaction sequence was run starting from the hyroazulene derivative **32** (Scheme 12). Compound **32** results from the catalytic hydrogenation of compound **26**. Hydroazulene **32** was first submitted to the C-alkylation reaction, leading to product **33** along with unreacted starting material. The former was added to a suspension of *t*-BuOK in THF at room temperature to afford the enol ethers **34** and **35** that we were unable to separate (ratio 9/1; overall yield 95%). The mixture of these compounds was submitted to a FVT reaction to readily afford the tricyclic derivative **36** in 74% yield. Compund **36** represents an analogue of the tricyclic substructure found in ingenol (Scheme 12).

Conclusion

In conclusion, we have shown that β-keto ester *mono*anions reacted with 1,4-dihalobutenes to give, in good yields, functionalized enol ethers that undergo a Claisen rearrangement under FVT reaction conditions. By using this reaction sequence, we were able to isolate tricyclic ring systems which are analogous to those found in natural products belonging to the ingenane family. These strategies might be a promising tool for developing new routes to natural compounds bearing a functionalized bridged bicycloalkanone skeleton as their main substructure. In this context, new approaches to ingenol analogues are currently under investigation in our group.

Experimental Section

General Considerations. Reactions were carried out under argon with magnetic stirring and degassed solvents. Et_2O and THF were distilled from Na/benzophenone. Dioxane, benzene, and toluene were dried and distilled over CaH_2, and CH_2Cl_2 over P_2O_5. Thin-layer chromatography (TLC) was carried out on silica gel plates and the spots were visualized under UV lamp (254 or 365 nm) and/or sprayed with a solution of vanillin (25 g) in EtOH/H_2SO_4 (98/2; 1 L) followed by heating on a hot plate. For column chromatography, silica gel (40−60 μm) was used. Melting points (mp) were measured on a hot stage. IR spectra were recorded as CCl_4 solutions. ^{1}H NMR spectra were recorded at 200 or 300 MHz and ^{13}C NMR spectra at 50 or 75 MHz, using the signal of the residual nondeuterated solvent as internal reference. Significant ^{1}H NMR data are tabulated in the following order: chemical shift (δ) expressed in ppm, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constants in hertz, number of protons. The ratio of compounds indicated below was calculated according to the NMR integrations.

General Procedure for the S$_N$′2 O-Alkylation Reaction. (a) Method A: KH/*t*-BuOH cat./THF. To a suspension of KH (1.2 equiv; washed 3× with hexane) in THF (2 mL/1 mmol of KH) was added *t*-BuOH (2 drops) and the suspension was cooled to −78 °C. A solution of the C-alkylated product (1 equiv) in THF (1 mL/1 mmol of starting material) was added dropwise to the suspension and the resulting mixture was stirred 10 min at −78 °C. The cooling bath was removed, and the mixture became orange and was stirred 1 h 30 min at room temperature and cooled at −78 °C. Water was added (2 mL/1 mmol of KH) and the mixture was extrated with ether (3 × 5 mL for 1 mmol of starting material). The organic layers were washed with a saturated aqueous NaCl solution, dried over $MgSO_4$, and filtered and the solvents were removed under reduced pressure (10 mmHg/25 °C). In general, it is unnecessary to purify the crude reaction mixture. There are no significant differences when the crude ^{1}H NMR spectra were compared to those of the chromatographed material. Moreover, we noticed that the yield dropped significantly (10−15%) after running a chromatography. An analytical sample was obtained by chromatography on a silica gel column, using a mixture of EtOAc/hexane as eluent. Compounds **11** and **12** were prepared according to this experimental procedure.

(b) Method B: *t*-BuOK/THF or Et$_2$O. A solution of the C-alkylated product (1 equiv) in THF or Et_2O (1 mL for 1 mmol) was added dropwise at room temperature to a suspension of *t*-BuOK (1.7−1.8 equiv) in THF (3 mL for 1 mmol). After 5 min of stirring, the mixture became orange and was hydrolyzed with 50% aqueous NH_4Cl solution (1 mL for 1 mmol of starting material) and then with water (2 mL for 1 mmol of starting material). After 15 to 30 min of gentle stirring, the mixture was extracted with Et_2O (3 × 5 mL for 1 mmol of starting material), the organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure (10 mmHg/25 °C). In general, it is unnecessary to purify the crude reaction mixture (there are no significant differences when the crude ^{1}H NMR spectra were compared to those of the chromatographed material). Moreover, we noticed that the yield dropped down significantly (10−15%) after running a chromatography. An analytical sample was obtained by chromatography on a silica gel column, using a mixture of EtOAc/hexane as eluent. Compounds **11**, **12**, **16**, **29**, **30**, **34**, and **35** were prepared according to this experimental procedure.

Enol Ether (11). Method B: starting material **9** (1.00 g, 3.86 mmol), KH (780 mg, 6.95 mmol), *t* BuOH (2 drops), enol ether **11** (740 mg, 3.32 mmol, yield 86%). **Method B:** starting

material **14** (452 mg, 1.49 mmol), *t*-BuOK (287 mg, 2.56 mmol); enol ether **11** (285 mg, 1.28 mmol, yield 86%); colorless oil; IR (CCl_4) 1730, 1446 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.20 (t, J = 7.2 Hz, 3H), 1.25−1.75 (m, 4H), 1.90−2.10 (m, 2H), 2.30−2.50 (m, 2H), 4.13 (qd, J = 7.2, 2.2 Hz, 2H), 4.45−4.60 (m, 1H), 4.81 (t, J = 3.6 Hz, 2H), 5.08 (dt, J = 10.2, 1.0 Hz, 1H), 5.23 (dt, J = 17.0, 1.0 Hz, 1H), 5.75 (ddd, J = 17.0, 10.2, 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 19.4, 22.4, 32.1, 43.0, 51.9, 61.0, 79.3, 94.5, 117.1, 136.9, 154.3, 173.9. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.97; H, 8.30.

Enol Ether (12). Method A: starting material **10** (1.335 g, 4.89 mmol), KH (236 mg, 5.87 mmol), *t*-BuOH (2 drops), enol ether **12** (1.070 g, 4.53 mmol, yield 92%); **Method B:** starting material **15** (825 mg, 2.60 mmol), *t*-BuOK (501 mg, 4.46 mmol); enol ether **12** (538 mg, 2.27 mmol, yield 87%); colorless oil; IR (CCl_4) 1712, 1689, 1445 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.30 (t, J = 7.1 Hz, 3H), 1.53−1.61 (m, 3H), 1.70−1.94 (m, 3H), 1.95−2.11 (m, 2H), 2.11−2.42 (m, 1H), 2.51 (dd, J = 5.2, 13.0 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 4.40−4.60 (m, 1H), 5.18 (d, J = 10.1 Hz, 1H), 5.20 (t, J = 6.5 Hz, 1H), 5.30 (dt, J = 17.2, 1.0 Hz, 1H), 5.82 (ddd, J = 17.2, 10.1, 6.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.2, 24.5, 27.1, 27.4, 35.9, 46.4, 56.5, 61.0, 79.2, 98.7, 117.2, 136.6, 159.0, 173.4. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.08; H, 8.46.

Enol Ether (16). Method B: starting material **13** (288 mg, 0.99 mmol), *t*-BuOK (192 mg, 1.75 mmol), enol ether **16** not pure (10 mg, yield 5%); colorless oil; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.29 (t, J = 7.1 Hz, 3H), 1.50−1.70 (m, 2H), 1.85 (ddd, J = 8.3, 9.7, 11.0 Hz, 1H), 2.25−2.50 (m, 2H), 2.63 (dd, J = 5.3, 12.0 Hz, 1H), 2.88 (dddd, J = 1.4, 5.9, 9.7, 14.3 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 4.60 (dd, J = 1.1, 3.4 Hz, 1H), 5.19 (dt, J = 1.1, 10.4 Hz, 1H), 5.31 (dt, J = 1.1, 16.9 Hz, 1H), 5.90 (ddd, J = 7.3, 10.1, 17.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.2, 33.9, 36.3, 41.6, 61.2, 61.9, 90.6, 93.2, 117.4, 137.8, 162.4, 174.2.

Product 29. Method B: starting material **27** (108 mg, 0.30 mmol), *t*-BuOK (59 mg, 0.52 mmol), enol ether **29** (62 mg; 0.22 mmol; yield 75% crude, mixture of isomers **29**/**30** 90/10); colorless oil; IR (mixture of isomers, CCl_4) 1728, 1685, 1446, 1426 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 0.99 (t, J = 7.1 Hz, 3H), 1.30−1.50 (m, 2H), 1.60−1.80 (m, 2H), 1.85 (dd, J = 11.8, 10.9 Hz, 1H), 2.00−2.20 (m, 1H), 2.30−2.45 (m, 1H), 2.50−2.80 (m, 3H), 2.91 (ddt, J = 16.9, 8.6, 2.2 Hz, 1H), 4.02 (ABX_3, J_{AB} = 10.8 Hz, J_{AX} = 7.1 Hz, 2H), 4.74 (dddt, J = 10.9, 6.5, 5.1, 09 Hz, 1H), 5.01 (ddd, J = 10.3, 1.65, 1.1 Hz, 1H), 5.24 (ddd, J = 17.01, 1.65, 1.1 Hz, 1H), 5.78 (ddd, J = 8.5, 2.4, 1.1 Hz, 1H), 5.81 (ddd, J = 17.0, 10.4, 5.5 Hz, 1H), 5.95 (ddd, J = 10.2, 8.5, 5.5 Hz, 1H); ^{13}C NMR (C_6D_6, 75 MHz) δ 13.7, 23.4, 28.8, 29.9, 35.6, 42.2, 44.5, 55.8, 60.9, 78.2, 116.0, 116.7, 129.7, 133.1, 138.0, 144.3, 172.5. Minor isomer (**30**): 4.59 (ddq, J = 9.4, 4.8, 1.5 Hz, 1H), 5.39 (dt, J = 17.1, 1.8 Hz, 1H). Anal. (mixture of isomers) Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.19; H, 7.92.

Product 34. Method B: starting material **33**, **32** (ratio **32**/**33** 1/1, 168 mg, 0.29 mmol of **33** and 0.29 mmol of **32**), *t*-BuOK (90 mg, 0.80 mmol), enol ether **34**/**35** (ratio 90/10) (76 mg, 0.27 mmol, yield 95%); colorless oil; IR (mixture of isomers, CCl_4) 1728, 1556, 1448 cm^{-1}. Major isomer **34**: ^1H NMR (C_6D_6, 300 MHz) δ 1.02 (t, J = 7.1 Hz, 3H), 1.10−1.40 (m, 1H), 1.70−1.90 (m, 6H), 1.90−2.10 (m, 1H), 2.20−2.40 (m, 3H), 2.60−2.90 (m, 2H), 4.06 (ABX_3, J_{AB} = 10.8 Hz, J_{AX} = 7.1 Hz, 2H), 4.79 (dddt, J = 11.3, 6.3, 4.9, 1.1 Hz, 1H), 5.04 (ddd, J = 10.2, 1.6, 1.1 Hz, 1H), 5.27 (ddd, J = 17.0, 1.6, 1.1 Hz, 1H), 5.84 (ddd, J = 17.0, 10.2, 6.4 Hz, 1H); ^{13}C NMR (C_6D_6, 75 MHz) δ 13.9, 23.7, 24.4, 29.2, 30.6, 33.0, 36.4, 41.4, 46.3, 54.4, 60.4, 78.4, 115.7, 115.8, 138.0, 148.5, 174.2. Minor isomer **35**: ^1H NMR (C_6D_6, 300 MHz) δ 1.00 (t, J = 7.1 Hz, 3H), 1.15−2.0 (m, 4H), 2.30−3.10 (m, 5H), 4.05 (q, J = 7.1 Hz, 2H), 4.74 (dddt, J = 11.3, 6.3, 5.2, 1.1 Hz, 1H), 5.04 (ddd, J = 10.2, 1.6, 1.1 Hz, 1H), 5.25 (ddd, J = 17.0, 1.5, 1.2 1H), 5.85 (ddd, J = 17.0, 10.4, 6.6 Hz, 1H). Anal. Calcd for $C_{17}H_{24}O_3$ (mixture of isomers): C, 73.88; H, 8.75. Found: C, 74.091; H, 8.74.

"One-Pot" Reaction: Dimer 18. A solution of the β-keto ester **7** (162 mg, 0.95 mmol) in THF (10 mL) was added dropwise at room temperature to a suspension of *t*-BuOK (275 mg, 2.45 mmol) in THF (85 mL) with stirring for 30 min. *E*-1,4-Dibromobutene (306 mg, 1.43 mmol) in THF (5 mL) was then added rapidly and the mixture was stirred 1 h 40 min at room temperature and hydrolyzed with a saturated aqueous NH_4Cl solution (5 mL). The mixture was extracted with Et_2O (3 × 15 mL), the organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure (10 mmHg/30 °C). The crude product (166 mg) was purified on a silica gel column (15 g SiO_2, EtOAc/hexane 1/99) leading to enol ether **11** (95 mg, 0.43 mmol, 45% yield) and to the dimer **18** (29 mg, 0.08 mmol, 15% yield): colorless oil; IR (CCl_4) 1716 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.15 (t, J = 7.1 Hz, 6H), 1.20−1.70 (m, 8H), 1.75−2.00 (m, 2H), 2.10−2.50 (m, 10H), 4.08 (q, J = 7.1 Hz, 4H), 5.28 (t, J = 4.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) 14.1, 22.4, 27.4, 35.5, 35.6, 37.9, 41.1, 60.9, 61.1, 128.6, 171.4, 207.5. Anal. Calcd for $C_{22}H_{32}O_6$: C, 67.32; H, 8.22. Found: C, 67.15; H, 8.31.

Dimer 19. To a suspension of *t*-BuOK (290 mg, 2.58 mmol) in THF (85 mL) was added at room temperature the β-keto ester **8** (189 mg, 1.02 mmol) in THF (10 mL). The mixture became yellow and was stirred 1 h 30 min at room temperature. Two drops of *t*-BuOH was added followed by a fast addition of *E*-1,4-dibromobutene (330 mg, 1.54 mmol) in THF (5 mL). The mixture was stirred for 2 h 30 min and hydrolyzed with a saturated aqueous NH_4Cl solution (15 mL). The mixture was extracted with Et_2O (3 × 15 mL), the organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure (10 mmHg/30 °C). The crude product (187 mg) was purified on a silica gel column (15 g SiO_2, EtOAc/hexane 1/99) leading to enol ether **12** (72 mg, 0.30 mmol, 30% yield) and to the dimer **19** (103 mg, 0.24 mmol, 48% yield): colorless oil; IR (CCl_4) 1712, 1455 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.21 (t, J = 7.1 Hz, 6H), 1.43−1.90 (m, 7H), 1.91−2.74 (m, 5H), 4.13 (q, J = 7.1 Hz, 4H); 5.35 (t, J = 4.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 24.5, 24.6, 25.5, 29.8, 32.0, 38.3, 41.0, 61.0, 62.8, 129.2, 171.9, 209.1. Anal. Calcd for $C_{24}H_{36}O_6$: C, 68.54; H, 8.63. Found: C, 68.27; H, 8.55.

Acetal 21. To a solution of enol ether **11** (160 mg, 0.72 mmol) in ether (40 mL) was added at room temperature HCl 10% (9 mL). After 2.5 h of stirring at room temperature, a saturated aqueous $NaHCO_3$ solution (10 mL) was added and the mixture was extracted with Et_2O (3 × 5 mL). The organic layers were collected, dried over $MgSO_4$, and filtered and the solvents were removed under reduced pressure (25 °C, 10 mmHg) affording pure acetal **21** (183 mg, 0.72 mmol, quantitative yield): colorless oil; IR (CCl_4) 3602, 3480, 1733, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.27 (t, J = 7.1 Hz, 3H), 1.45−1.82 (m, 7H), 1.82−2.30 (m, 4H), 2.87 (dd, J = 13.0, 7.6 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 4.68 (ddt, J = 15.0, 7.1, 1.0 Hz, 1H), 5.14 (dt, J = 17.0, 1.4 Hz, 1H), 5.91 (ddd, J = 17.0, 10.1, 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 22.3, 23.5, 30.0, 36.3, 38.7, 42.0, 60.8, 60.9, 76.3, 107.6, 115.9, 137.9, 175.1. Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.08; H, 8.57.

Acetal 22: same procedure as above; starting material: enol ether **12** (198 mg, 0.84 mmol), HCl 10% (12 mL), Et_2O (50 mL), acetal **22** (201 mg, quant. yield): colorless oil; IR (CCl_4): 3602, 3300, 1732 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.30 (t, J = 7.0 Hz, 3H), 1.40−2.20 (m, 9H), 2.81 (dd, J = 10.0, 12.5 Hz, 1H), 3.51 (s, 1H), 4.22 (q, J = 7.0 Hz, 2H), 4.70−4.85 (m, 1H), 5.13 (dt, J = 10.3, 1.0 Hz, 1H), 5.31 (dt, J = 17.0, 1.0 Hz, 1H), 5.989 (ddd, J = 6.6, 10.3, 17.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 22.4, 22.9, 33.8, 34.7, 40.2, 55.0, 60.9, 76.4, 104.0, 115.12, 139.4, 174.7. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.12; H, 8.51

Lactone 20. From acetal **21**: same procedure as above, but THF was used instead of ether: acetal **21** (270 mg, 1.06

mmol), HCl 10% (5 mL), THF (5 mL), lactone **20** (182 mg, 087 mmol, 82% yield). From enol ether **12**: same procedure as above: enol ether **12** (120 mg, 0.51 mmol), HCl 10% (1 mL), THF (2 mL), lactone **20** (105 mg, 0.51 mmol, quantitative yield): colorless oil; IR (CCl_4) 1771, 1712, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.07−1.68 (m, 3H), 1.68−2.30 (m, 6H), 2.41−2.62 (m, 1H), 2.83 (ddd, J = 13.3, 8.6, 1.0 Hz, 1H), 3.10 (dt, J = 2.7, 11.8 Hz, 1H), 4.87 (ddt, J = 7.0, 15.8, 1.0 Hz, 1H), 5.28 (dt, J = 10.1, 1.0 Hz, 1H), 5.37 (dt, J = 17.2, 1.0 Hz, 1H), 5.94 (ddd, J = 17.2, 10.1, 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.7, 24.8, 29.5, 33.1, 36.1, 40.9, 60.3, 77.7, 117.9, 134.7, 174.7, 207.2. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.98; H, 7.82.

Bicyclo[4.2.1]nonanone (6). To a suspension of KH (54 mg, 1.34 mmol) in THF (5 mL) was added *t*-BuOH (1 drop). The mixture was cooled to −78 °C and a solution of compound **5** (298 mg, 1.20 mmol) in THF (5 mL) was added dropwise. The cooling bath was removed and the mixture was stirred for 30 min at room temperature. The mixture was hydrolyzed with water (5 mL) and extracted with Et_2O (3 × 5 mL). The organic layer was washed with a saturated aqueous NaCl solution, dried over $MgSO_4$, and filtered and the solvents were removed under reduced pressure (20 °C, 10 mmHg) leading to a crude reaction mixture (225 mg, yield 90%) that was subjected to a silica gel column (15 g SiO_2, hexane) leading to compound **6** (113 mg, 45% yield):[9a] colorless oil; IR (CCl_4) 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.22 (t, J = 7.2 Hz, 3H), 1.60−1.75 (m, 1H), 1.85−2.05 (m, 1H), 2.10−2.60 (m, 6H), 2.65−2.75 (m, 1H), 4.17 (q, J = 7.2 Hz, 2H), 5.50−5.75 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 25.4, 30.8, 31.4, 32.6, 34.6, 45.9, 59.1, 61.3, 125.7, 126.5, 172.2, 217.5. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.42; H, 8.01

General Procedure for the FVT Reaction. The starting material was placed into a round-bottom flask fixed to the FVT apparatus and warmed so that the product flushed through the quartz tube heated at the indicated temperature. The reaction products were collected on a finger cooled with liquid nitrogen. The finger was rinced with ether and the organic layer was dried over $MgSO_4$, filtered, and evaporated under reduced pressure (25 °C, 10 mmHg). The crude reaction mixture was purified by chromatography on a silica gel column eluting with a EtOAc/hexane mixture.

Bicyclo[4.3.1]decanone (23): starting material **11** (208 mg, 0.93 mmol), temperature 600 °C, vacuum 10^{-2} Torr, compound **23** (150 mg, 0.67 mmol, 72% yield); colorless oil; IR (CCl_4) 1712, 1559 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.27 (t, J = 7.2 Hz, 3H), 1.50−1.65 (m, 2H), 1.85−2.50 (m, 6H), 2.55−2.65 (m, 2H), 2.75−2.90 (m, 1H), 4.17 (q, J = 7.2 Hz, 2H), 5.75−5.95 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 18.7, 30.7, 32.4, 33.0, 35.9, 47.3, 61.1, 61.2, 128.9, 129.4, 173.2, 212.0. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.05; H, 8.13.

Bicyclo[4.4.1]undecanone (24): starting material **12** (200 mg, 0.84 mmol), temperature 600 °C, vacuum: 10^{-2} Torr, compound **24** (118 mg, 0.50 mmol, 59% yield); colorless oil; IR (CCl_4) 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.24 (t, J = 7.2 Hz, 3H), 1.30−2.15 (m, 9H), 2.30−2.45 (m, 2H), 2.70−3.00 (m, 2H), 4.15 (qd, J = 7.2, 1.0 Hz, 2H), 5.05−5.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 25.2, 25.5, 29.5, 30.5, 30.6, 33.5, 54.0, 60.9, 65.2, 126.8, 127.3, 173.4, 212.0. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.32; H, 8.43.

Product 27. To a suspension of K_2CO_3 (718 mg, 5.20 mmol) in acetone (20 mL) was added *E*-1,4-dibromobutene (2.78 g, 12.99 mmol) and the β-keto ester **26** (289 mg, 1.30 mmol). The mixture was heated under reflux for 2 h. After being cooled to room temperature, the reaction mixture was filtered and the solvents were evaporated. The crude product was filtered on a silica gel column to eliminate the excess *E*-1,4-dibromobutene leading to a mixture of C-alkylated products. The latter (373 mg) was purified on a silica gel column (15 g SiO_2, EtOAc/hexane: 1/99) leading to the C-alkylated product **28** (62 mg, 0.17 mmol, yield 13%) and to the C-alkylated product **27** (259 mg, 0.73 mmol, yield 56%).

Data for **27**: colorless oil; IR (CCl_4) 1746, 1709, 1685 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.24 (t, J = 7.1 Hz, 3H), 1.40−1.60 (m, 3H), 1.65−1.80 (m, 1H), 1.80−2.00 (m, 1H), 2.05−2.15 (m, 2H), 2.23 (dddt, J = 14.2, 9.4, 6.2, 2.2 Hz, 1H), 2.40−2.70 (m, 3H), 3.24 (ddd, J = 10.1, 8.1, 5.3 Hz, 1H), 3.86 (d, J = 6.8 Hz, 2H), 4.16 (ABX_3, J_{AB} = 10.8 Hz, J_{AX} = 7.1 Hz, 2H), 5.52 (dd, J = 10.6, 2.2 Hz, 1H), 5.72 (m, 2H), 6.07 (ddd, J = 10.6, 8.3, 6.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9, 25.4, 25.7, 29.4, 32.2, 32.6, 38.8, 47.1, 50.9, 61.3, 66.2, 128.3, 130.3, 132.6, 170.6, 210.4. Anal. Calcd for $C_{17}H_{23}Br\ O_3$: C, 57.47; H, 6.53. Found: C, 57.72; H, 6.46.

Data for **28**: colorless oil; IR (CCl_4) 1746, 1709, 1685 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.22 (t, J = 7.1 Hz, 3H), 1.35−1.55 (m, 1H), 1.60−1.95 (m, 5H), 2.00−2.30 (m, 2H), 2.30−2.50 (m, 1H), 3.30 (ddd, J = 10.0, 8.2, 5.5 Hz, 1H), 3.87 (dd, J = 4.0, 2.4 Hz, 2H), 4.16 (ABX_3, J_{AB} = 10.6 Hz, J_{AX} = 7.1 HZ, 2H), 5.73 (m, 2H), 5.83 (dd, J = 10.8, 2.4 Hz, 1H), 5.95 (ddd, J = 10.8, 8.6, 5.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 25.9, 26.2, 29.3, 32.6, 32.7, 37.4, 45.7, 51.87, 61.7, 66.0, 128.3, 129.8, 130.2, 130.7, 170.6, 208.0. Anal. Calcd for $C_{17}H_{23}Br\ O_3$: C, 57.47; H, 6.53. Found: C, 57.29; H, 6.61.

Products 25 and 31: starting material **29**, **30** (130 mg, 0.47 mmol), temperature: 520 °C, vacuum 10^{-2} Torr. The crude reaction mixture (72 mg) was purified on a silica gel column (5 g SiO_2, hexane) affording compound **25** (not pure, 18 mg, 0.065 mmol, 14% yield) and pure compound **31** (25 mg, 0.09 mmol, 19% yield).

Data for **25**: colorless oil; IR 1737, 1446 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, J = 7.1 Hz, 3H), 1.30−1.60 (m, 3H), 1.65−2.15 (m, 5H), 2.20−2.30 (m, 2H), 2.50 (dt, J = 15.6, 6.3 Hz, 2H), 2.68 (dd, J = 14.9, 6.4 Hz, 1H), 2.85 (dd, J = 15.6, 6.3 Hz, 1H), 4.20 (ABX_3, J_{AB} = 10.8, J_{AX} = 7.1 Hz, 2H), 5.48 (dd, J = 10.6, 2.5 Hz, 1H), 5.70−5.90 (m, 2H), 5.90−6.00 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9, 23.5, 31.1, 34.4, 35.4, 35.5, 37.0, 18.3, 61.4, 64.7, 66.5, 129.1, 129.6, 130.3, 131.0, 171.9, 210.9.

Data for **31**: colorless oil; IR 1732, 1680, 1447 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.10−1.20 (m, 3H), 1.31 (t, J = 7.1 Hz, 3H), 1.70−1.90 (m, 4H), 1.90−2.10 (m, 2H), 2.26 (dt, J = 13.5, 8.4 Hz, 1H), 2.42 (ddd, J = 12.3, 9.3, 2.8 Hz, 1H), 2.78 (q, J = 8.2 Hz, 1H), 2.92 (dt, J = 9.3, 2.6 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 4.96 (dt, J = 10.2, 1.1 Hz, 1H), 5.04 (dt, J = 17.0, 1.3 Hz, 1H), 5.64 (ddd, J = 17.0, 10.2, 7.7 Hz, 1H), 7.70 (d, J = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) d 14.1, 23.3, 29.7, 34.6, 34.8, 35.6, 39.5, 41.1, 41.4, 61.1, 61.3, 114.6, 137.4, 141.1, 156.6, 166.1, 202.0. Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.35; H, 8.12.

Product 32. To a solution of β-keto ester **26** (420 mg, 1.89 mmol) in EtOAc (40 mL) was added 10% Pd/C (5 mg) and the reaction mixture was stirred under a hydrogen atmosphere for 5 h at room temperature. The crude reaction mixture was filtered on a Celite pad, and the solvent was removed under reduced pressure (10 mmHg, 25 °C) to give compound **32** as a mixture of isomers (422 mg, 1.89 mmol, quantitative yield); colorless oil; IR (mixture of isomers, CCl_4) 1746, 1709 cm^{-1}. Major isomer: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.22 (t, J = 7.1 Hz, 3H), 0.95−1.15 (m, 1H), 1.15−1.30 (m, 1H), 1.30−1.50 (m, 2H), 1.55−1.80 (m, 5H), 1.85−2.00 (m, 2H), 2.05−2.15 (m, 1H), 2.20−2.40 (m, 1H), 3.15 (q, J = 9.2 Hz, 1H), 3.60 (dd, J = 11.6, 3.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.1, 24.2, 25.2, 26.4, 27.8, 32.5, 34.3, 39.3, 55.8, 57.8, 59.9, 169.1, 207.2. Minor isomer: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.23 (t, J = 7.1 Hz, 3H), 3.28 (dd, J = 11.5, 3.5 Hz, 1H), 3.40 (dt, J = 11.1, 8.1 Hz, 1H), the other signals overlapped with those of the major isomer; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.1, 23.5, 24.6, 25.4, 25.7, 29.3, 33.8, 39.7−8, 50.9, 57.1, 60.2, 169.5, 207.2. Anal. (mixture of isomers) Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 70.00; H, 8.78.

Product 33. To a solution of β-keto ester **32** (189 mg, 0.84 mmol) in acetone (15 mL) was added K_2CO_3 (465 mg, 3.37

mmol) and *E*-1,4-dibromobutene (1.80 g, 8.41 mmol). The mixture was heated under reflux during 3 h. The mixture was filtered through a pad of Celite and the sovent was evaporated under reduced pressure (25 °C, 10 mmHg). The crude reaction mixture was chromatographed on a silica gel column (15 g SiO_2, hexane) affording the excess 1,4-*trans*-dibromobutene and an unseparable 1/1 mixture of starting material **32** and of compound **33** [168 mg, yield for **33** 52% based on consumed starting material]; colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, J = 7.1 Hz, 3H), 1.00−2.40 (m, 9H), 2.63 (d, J = 6.9 Hz, 2H), 3.90 (d, J = 7.2 Hz, 2H), 4.18 (q, J = 7.1 Hz, 2H), 5.55−5.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 22.8, 24.7, 26.0, 30.3, 30.4, 31.4, 34.2, 36.3, 39.7, 49.7, 60.0, 61.8, 129.0, 129.4, 171.1, 209.0.

Product 36: starting material **34** + **35** (85 mg, 0.30 mmol), temperature 520 °C, vacuum 10^{-2} Torr, product **36** (63 mg, 0.023 mmol, 74% yield), colorless oil; IR (CCl_4) 1737, 1694, 1454 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, J = 7.1 Hz, 3H), 1.30−2.20 (m, 12H), 2.20−2.40 (m, 2H), 2.50 (dd, J = 15.7, 6.0 Hz, 1H), 2.77 (ddt, J = 15.7, 5.5, 1.3 Hz, 1H), 4.17 (ABX_3, J_{AB} = 10.8 Hz, J_{AX} = 7.1 Hz, 2H), 5.80 (ddt, J = 11.0, 6.0, 1.6 Hz, 1H), 5.93 (ddd, J = 11.0, 6.8, 5.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 22.3, 22.7, 31.3, 33.2, 34.1, 34.7, 36.3, 40.3, 46.5, 60.8, 62.7, 64.8, 128.9, 129.4, 173.8, 211.8. Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.67; H, 8.81.

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Supporting Information Available: Crystallographic data in CIF format for compound **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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