Tetrahedron 66 (2010) 7012–7016

Contents lists available at ScienceDirect

Tetrahedron

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

Domino reactions starting from alkynyl esters tethered to 2-methyl-1,3-cycloalkanediones. Efficient access to polyfunctionalized diquinanes, allenoates, and oxetanes

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ARTICLE INFO

Article history:
Received 22 April 2010
Received in revised form 8 June 2010
Accepted 8 June 2010
Available online 12 June 2010

Keywords:
Allenoate
Domino reactions
Oxetane
Diquinane
TBAF
Molecular sieves

ABSTRACT

The reactivity of alkynyl esters tethered to 2-methyl-1,3-cycloalkanediones toward TBAF and TBAF in the presence of 4 Å molecular sieves is reported. Polyfunctionalized diquinanes, allenaotes or oxetanes resulting from anionic domino reactions can be readily available with high to complete diastereoselectivities.

1. Introduction

The elaboration of bicyclic polyfunctionalized ring systems remains a challenge in organic synthesis. Of particular interest are 5-6 and 6-6 fused ring systems that are main building blocks for the synthesis of natural products.[1] In this context, the elaboration of allenoates and oxetanes fused to such bicyclic ring systems represents significant synthetic interest. Indeed, these compounds are not only main substrates for the synthesis of biologically active substances but also can undergo a wide range of transformations to yield original synthetic building blocks.[2,4] Following our recently reported cascade reaction promoted by TBAF[5] or by Lewis acids,[6] the reactivity of alkynyl esters tethered to 2-methyl-1,3-cycloalkanediones caught our attention.[7]

2. Results and discussion

2.1. TBAF addition to alkynyl esters tethered to 2-methyl-1,3-cycloalkanediones

When TBAF was added to the acetylenic ω-ketoester **1**,[8] no reaction occurred except degradation of the starting material. This result was quite surprising considering that allenoates were easily obtained when alkynyl esters tethered to cycloalkanones were treated with TBAF.[5] On the other hand, the addition of ^{t}BuOK to compound **1** led to a complex mixture of compounds from which it was possible to isolate very small quantities of allenoates **2** (<10%) and trace amounts of oxetanes **3**. Once again, this result was in sharp contrast with our previous results (Scheme 1).[5]

To solve this problem, the monoprotected acetylenic ω-ketoesters **4**–**7** were utilized as starting material. When TBAF was added to the latter, the formation of the allenoates **8**–**11** as major compounds took place. Unreacted starting material was also recovered (5–20%) despite the addition of excess TBAF. Allenoates **8**–**10** were obtained with a total diastereoselectivity for the ring junction; however, allenoate **11** was isolated as a mixture of cis and trans isomers (1/1.6). The allenoates were formed mainly as *E* isomers.[9] The structure of allenoates **10** and **11** was unambiguously confirmed by X-ray crystallographic analysis, which

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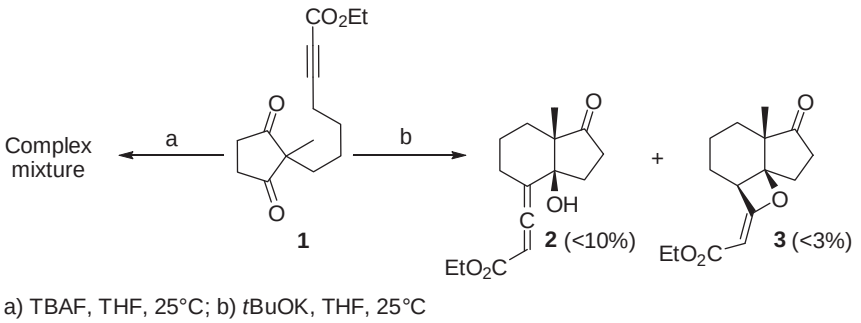
doi:10.1016/j.tet.2010.06.025



Scheme 1. Addition of TBAF or ^{t}BuOK to acetylenic ω-ketoester **1**.

confirmed a cis ring junction for the 5-6 fused ring system and a trans ring junction for the 6-6 fused ring system (Fig. 1).[10] α,β-Unsaturated β-ketoester **12** (15%) or oxetanes **13** (22%), and allenoate **19** was probably favored because the β-acetate group induces less steric hindrance than the α-acetate group and therefore the dioxolane group (Scheme 3).

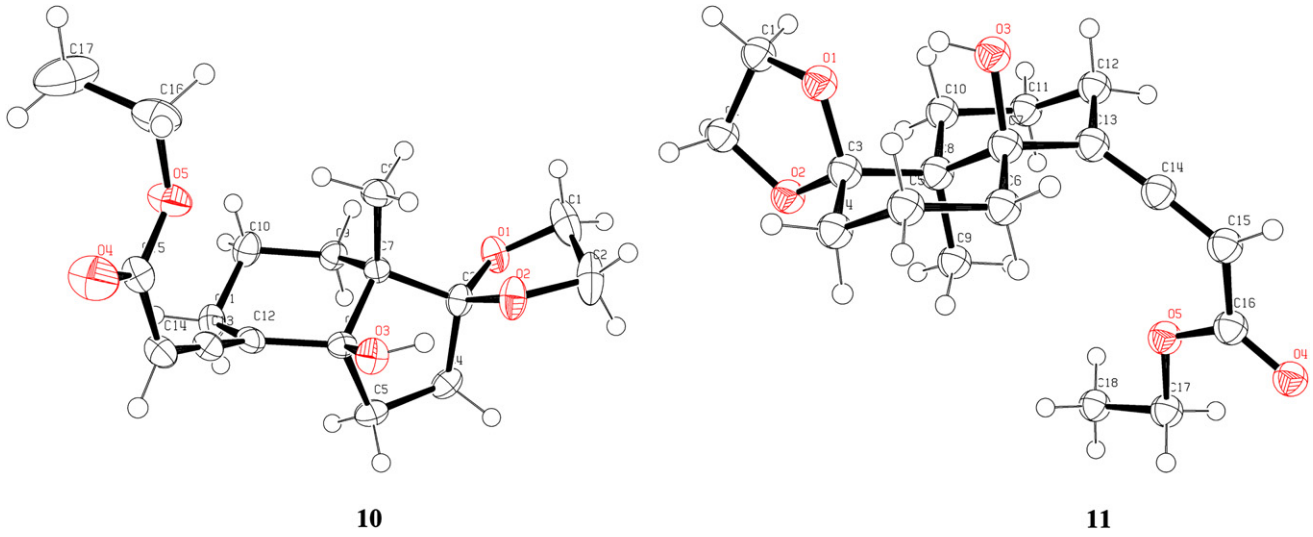


Figure 1. X-ray structures of allenoates **10** and **11**.

14 (23%) were formed as side products (Scheme 2). The oxetanes **13** and **14** were obtained as a unique product bearing an *E*-substituted double bond and, respectively, a cis and trans ring junction (Scheme 2).[11]

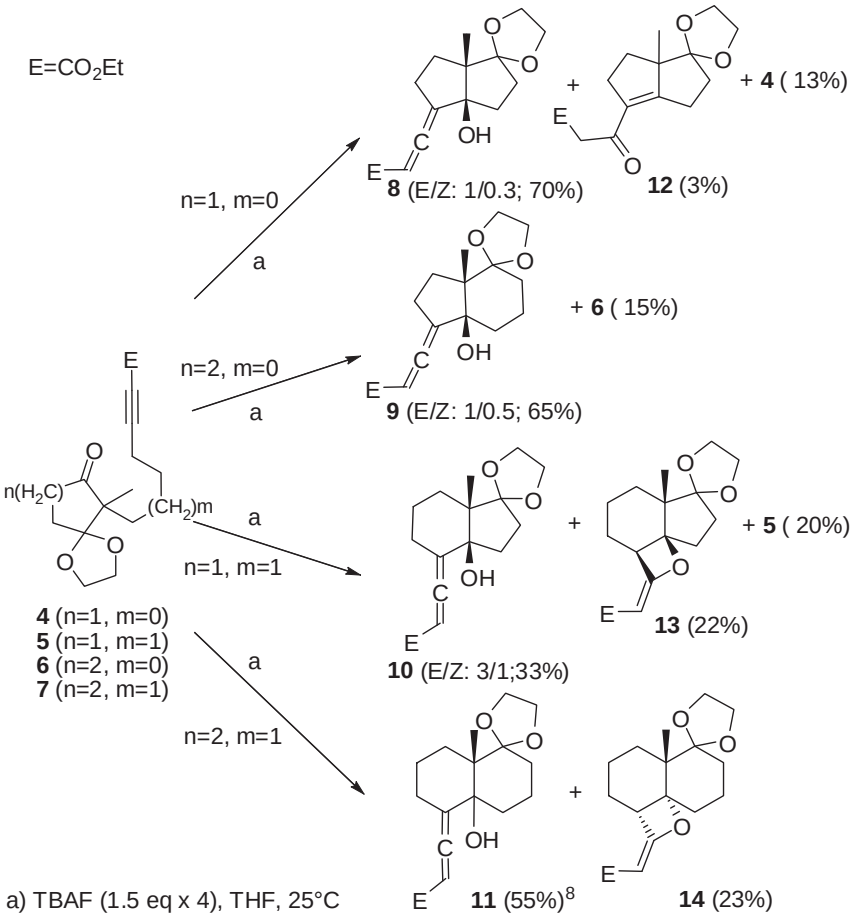
2.2. TBAF addition to alkynyl esters tethered to 2-methyl-3-oxocyclopentyl acetate

Five-membered rings allenoates were obtained in higher yield than the corresponding six-membered rings, the lowest yield being observed for the formation of allenoate **10**. A careful examination of molecular models indicated that the steric hindrance induced by the dioxolane ring might be disadvantageous for the cyclization reaction. To support this hypothesis, the dioxolane group was replaced by an acetate group leading to the *anti* acetate **15**, **16**, and *syn* acetate **21**, which were readily separable.[12] TBAF was added to the *anti* acetate **15** (n=1) leading to the formation of the diquinane **17** (40%) along with the α, β-unsaturated β-ketoester **18** (17%) and unreacted starting material (8%). On the other hand, starting from the *anti* acetate **16** (n=1), the desired allenoate **19** was isolated in good yield (77%) along with the oxetane **20** (3%). When the TBAF reaction was carried out starting from the *syn* acetate **21**, the reaction was sluggish affording allenoate **22** (15%) and oxetane **23** (12%) and recovered starting material (40%). Thus, the formation of

2.3. TBAF addition to alkynyl esters tethered to 2-methyl-1,3-cycloalkanediones in the presence of molecular sieves

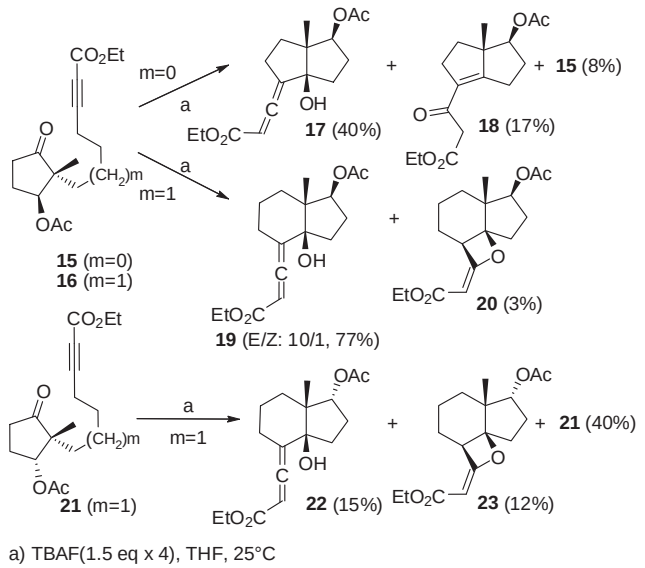
To improve the yield of the anionic domino reaction leading to the allenoates, the TBAF reaction was performed in the presence of 4 Å molecular sieves[13] because the water content of the reaction medium could hamper the progress of this type of reaction. Starting from the acetylenic ω-ketoester **1**, a complete decomposition of the latter was observed. However some unexpected results were obtained when TBAF was added to the acetylenic ω-ketoesters **4**–**7**, **15**, **16**, and **21** in the presence of 4 Å molecular sieves. Indeed, the formation of allenoates only took place starting from compound **6** and, surprisingly, either α,β-unsaturated β-ketoesters **12** and **18** were isolated or the oxetanes **13**, **14** and **20**, **23** resulting from a 4-*exo*-dig cyclization were quantitatively obtained.[14] The quantitative formation of oxetanes **20** and **23** readily took place regardless of the relative configuration of the acetate group. However, when the formation of five-membered rings was involved, the diquinane **18** was obtained in a low yield (Scheme 4).

Thus, a new methodology was set up, affording, with a complete chemoselectivity, either allenoates or oxetanes at least when the formation of a six-membered ring took place. A mechanism was previously proposed for the formation of the allenoates,[2] the key step being the formation of the *anti* intermediate **A** where HF is involved. The latter evolves toward cumulenolate **B** leading finally

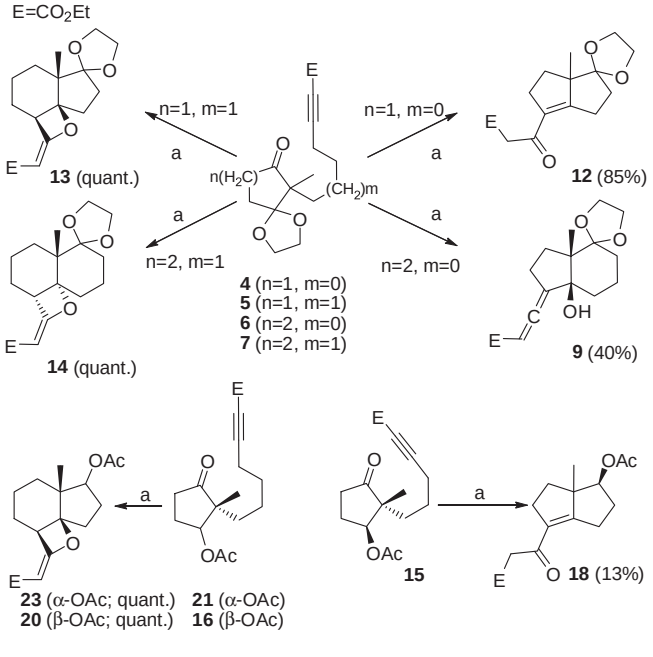


Scheme 2. TBAF addition to acetylenic ω-ketoesters **4**–**7**.

to the allenoates. On the other hand, **B** can be in equilibrium with **C**, which undergoes a nucleophilic attack on the central carbon of the allenoate affording the oxetene derivative **D**. The latter evolves toward carbanion **E** to yield finally the oxetane derivatives after protonation. It is also reasonable to say that the formation of the *syn* intermediate **F** takes place after addition of TBAF to the



Scheme 3. TBAF addition to the acetylenic ω-ketoesters **15**, **16**, and **21**.

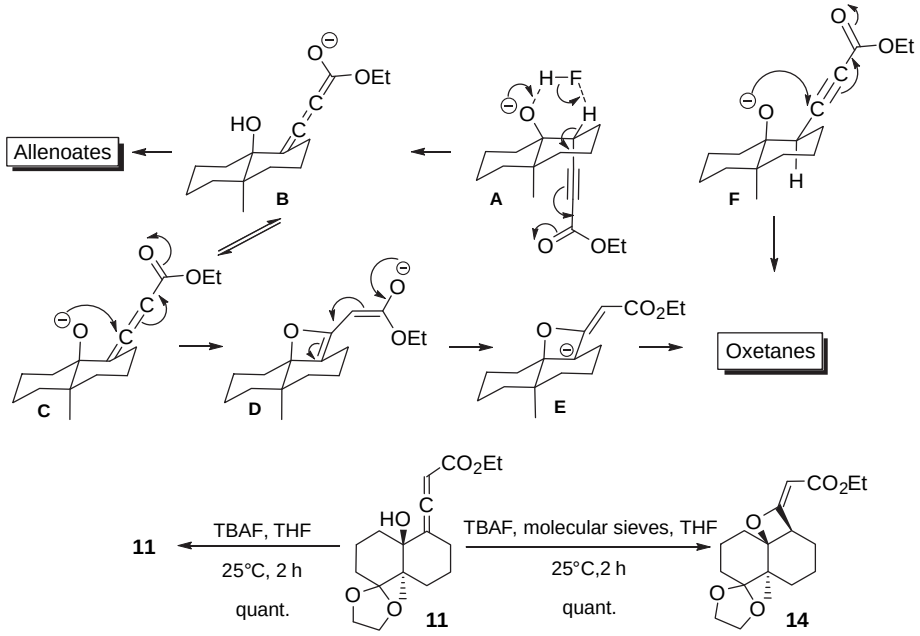


Scheme 4. TBAF addition to the acetylenic ω-ketoesters **13**–**16** and **21** in the presence of 4 Å molecular sieves.

corresponding acetylenic ω-ketoester; the resulting alcoolate undergoes a 4-*exo* dig cyclization to give finally the corresponding oxetanes. However, it remains unclear why TBAF/molecular sieves favored the formation of the *syn* intermediate **F**. One proposal could be that molecular sieves act as acid scavengers.[15] Thus, HF could be 'trapped' by the sieves so that the formation of intermediate **B** was disfavored. Nevertheless this proposal could explain that the addition of TBAF to the acetylenic ω-ketoester **7** afforded a mixture of allenoates and oxetanes. Moreover, we have shown that the addition of TBAF to the allenoate **11** in the presence of molecular sieves yielded quantitatively the corresponding oxetane. However, in the presence of TBAF alone, no reaction took place and the starting material **11** was quantitatively recovered. This result supports our pathway accounting for the formation of allenoates and oxetanes (Scheme 5).

3. Conclusions

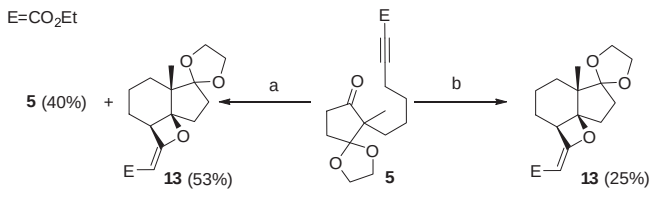
In summary, starting from alkynyl esters tethered to 2-methyl-1,3-cycloalkanediones, TBAF in the presence of 4 Å molecular sieves exclusively promoted a 4-*exo*-dig cyclization to afford polyfunctionalized oxetanes at least when the formation of six-membered rings was involved. In the absence of molecular sieves, TBAF promoted a highly chemoselective reaction leading to polyfunctionalized allenoates; this reaction was not related to the size of the ring to be formed. Thus, an approach to chemical diversity was developed due to the presence (or absence) of molecular sieves: polyfunctionnalized diquinanes, oxetanes, hydrindane, and hydronaphtalene derivatives were readily obtained. Further studies are currently underway to explore the scope and limitations of the TBAF/TBAF-molecular sieves intramolecular anionic cascade reactions.



Scheme 5. Possible pathways accounting for the formation of allenoates/oxetanes.

2.4. Triton B and ^{t}BuOK addition to alkynyl esters tethered to 2-methyl-1,3-cycloalkanediones in the presence of molecular sieves

Furthermore, the addition of Triton B (40% in water) to the acetylenic ω-ketoester **5** yielded exclusively the oxetane **13** along with unreacted starting compound **5**. On the other hand, the addition of ^{t}BuOK to compound **5** gave a sluggish reaction mixture from which oxetane **13** was isolated in 25% yield. These results support the fact that the presence of TBAF was necessary to obtain allenoates (Scheme 6).



Scheme 6. Treatment of acetylenic ω-ketoester **5** with bases.

4. Experimental section

4.1. General

Et_2O and THF were distilled from Na/benzophenone, CH_2Cl_2 over P_2O_5. Thin-layer chromatography (TLC) was carried out on silica gel plates and the spots were visualized under a UV lamp (254 or 365 nm) and/or sprayed with an acidic alcoholic solution of vanillin or with phosphomolybdic acid followed by heating on a hot plate. For column chromatography, silica was used. Melting points (mp) were measured on a hot plate. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at 75 or 125 MHz using the signal of the residual nondeuteriated solvent as the internal reference. Significant ^{1}H NMR spectroscopic data are tabulated in the following order: chemical shift (δ) expressed in parts per million, multiplicity (s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet), coupling constants J in hertz, number of protons. The ratios of compounds indicated below were calculated from the NMR integrations. IR spectra were recorded as CCl_4 solutions. Microanalysis were carried out by the Service Commun d'Analyses du CNRS, Institut de Chimie-Strasbourg. High-resolution mass spectra (HRMS) were performed on a Agilent 6520 Accurate Mass Q-TOF.

4.2. General procedure for the synthesis of allenoates

To a solution of acetylenic ω-ketoesters **4**–**7** (1 equiv) in anhydrous THF (0.08 M) was added at room temperature every 0.5 h a solution of TBAF in THF (1 M, 1.5 equiv). After 2 h the mixture was quenched with a saturated solution of $NaHCO_3$ (15 mL). The aqueous layer was extracted with diethyl ether (3×15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by chromatography on silica gel (EtOAc/petroleum ether 1/9).

*4.2.1. Ethyl-3-(3a′-hydroxy-7a′-methylhexahydrospiro[[1,3]dioxolane-2,1′-indene]-4′(2′H)-ylidene)acrylate (**10**).* Yield: 33% (3/1 mixture of isomers); mp 69–70 °C; IR (ATR): ν 3527, 1964, 1702 cm^{-1}; 5.73 (d, J=3.7 Hz, 1H, minor isomer), 5.64 (d, J=3.9 Hz, 1H major isomer), 4.16 (ABX_3, J_{AB}=10.8 Hz, J_{BX}=7.1 Hz, J_{AX}=7.1 Hz, $\Delta\nu$=0.018 ppm, δ_A=4.17 ppm, δ_B=4.15 ppm, 2H major isomer), 4.16 (q, J=7.1 Hz, 2H, minor isomer), 4.01–3.87 (m, 4H), 3.18 (s, 1H), 3.14 (s, 1H), 2.43–1.46 (m, 10H), 1.27 (t, J=7.2 Hz, 3H), 1.26 (t, J=7.1 Hz, 3H), 1.04 (s, 3H), 0.95 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 208.4, 166.6, 119.7, 110.4, 89.3, 80.9, 64.9, 60.6, 52.5, 32.1, 32.8, 32.6, 29.17, 22.4, 14.2, 11.4. HRMS (ESI): m/z calcd for $C_{17}H_{25}O_5(M+H)^+$: 309.1696; found: 309.1697.

4.3. General procedure for the synthesis of oxetanes

To a solution of acetylenic ω-ketoesters **4**–**7** (1 equiv) in anhydrous THF (0.07 M) containing molecular sieves (4 Å, 1 g) was added at room temperature a solution of TBAF in THF (1 M, 1.1 equiv). After 0.5 h the mixture was quenched with a saturated solution of $NaHCO_3$ (15 mL). The aqueous layer was extracted with diethyl ether (3×15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by chromatography on silica gel (EtOAc/petroleum ether 1/9).

*4.3.1. (E)-ethyl-2-(5a′-methylhexahydrospiro[[1,3]dioxolane-2,6′-indeno[4-b]oxete]-2′(2a′H)-ylidene) acetate (**13**).* Yield: quant.; colorless oil; IR (ATR): ν 1701, 1651 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 5.12 (d, J=1.9 Hz, 1H), 4.11 (ABX_3, J_{AB}=10.8 Hz, J_{BX}=7.1 Hz, J_{AX}=7.1 Hz, $\Delta\nu$=0.030 ppm, δ_A=4.13 ppm, δ_B=4.09 ppm, 2H), 3.96–3.89 (m, 4H), 3.57 (td, J=7.4, 2.1 Hz, 1H), 2.31–2.20 (m, 2H), 2.10 (td, J=14.7, 8.4 Hz, 1H), 1.88 (td, J=12.8, 8.8 Hz, 1H), 1.70–1.31 (m, 5H), 1.38–1.32 (m, 1H), 1.25 (t, J=7.1 Hz, 3H), 1.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 180.8, 167.6, 118.0, 96.4, 90.2, 65.0, 64.7, 59.2, 49.1, 47.3, 35.3, 30.8, 29.7, 24.3, 19.8, 17.9, 14.4. HRMS (ESI): m/z calcd for $C_{17}H_{25}O_5$ $(M+H)^+$: 309.1696; found: 309.1692.

Acknowledgements

Support for this work was provided by Université de Strasbourg, CNRS and ANR (N°07-PCVI-0016). M-P.B. thanks MRT for a research fellowship. The authors thank Dr. Jennifer Wytko for her assistance in preparing this manuscript.

Supplementary data

Experimental procedures and analytical data for compounds **11**, **14**–**16**, **19**, **21** are provided as well as copies of ^1H NMR and ^{13}C NMR spectra for compounds **9**, **11**, **13**, **14**, **19**, and **2**0. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.06.025. These data include MOL files and InChIKeys of the most important compounds described in this article.

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10. Allenoate **11** bearing a trans ring junction and *E* allenoate was obtained by column chromatography of the crude mixture of allenoate. CCDC-705046 contains the supplementary crystallographic data for compound **11**. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif. CCDC-637164 contains the supplementary crystallographic data for compound **10**. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.
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