



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

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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, allenates or oxetanes resulting from anionic domino reactions can be readily available with high to complete diastereoselectivities.

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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 allenates 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 TBAF⁵ or by Lewis acids,⁶ the reactivity of alkynyl esters tethered to 2-methyl-1,3-cycloalkanediones caught our attention.⁷

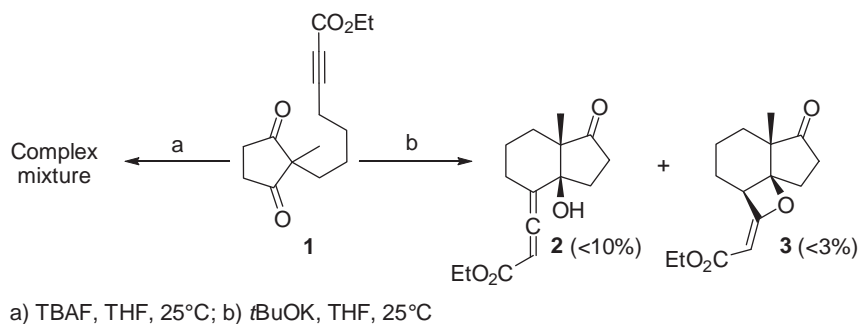
2. Results and discussion

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 allenates were easily obtained when alkynyl esters tethered to cycloalkanones were treated with TBAF.⁵ On the other hand, the addition of ^tBuOK to compound **1** led to a complex mixture of compounds from which it was possible to isolate very small quantities of allenates **2** (<10%) and trace amounts of oxetanes **3**. Once again, this result was in sharp contrast with our previous results (Scheme 1).⁵

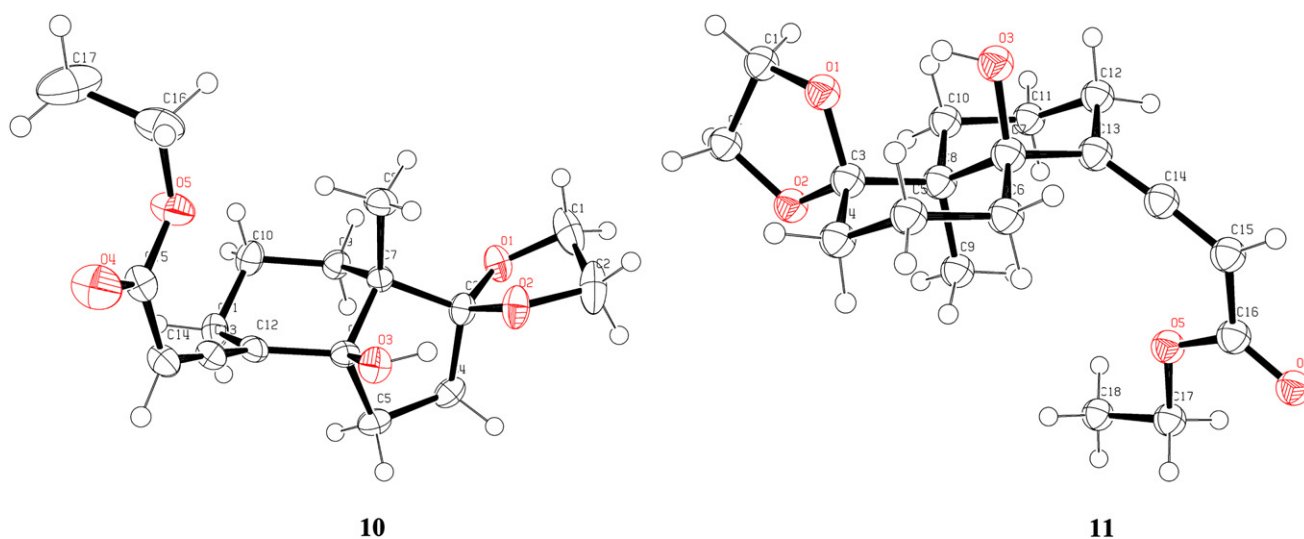
To solve this problem, the monoprotected acetylenic ω -ketoesters **4–7** were utilized as starting material. When TBAF was added to the latter, the formation of the allenates **8–11** as major compounds took place. Unreacted starting material was also recovered (5–20%) despite the addition of excess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

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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 allenolates **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

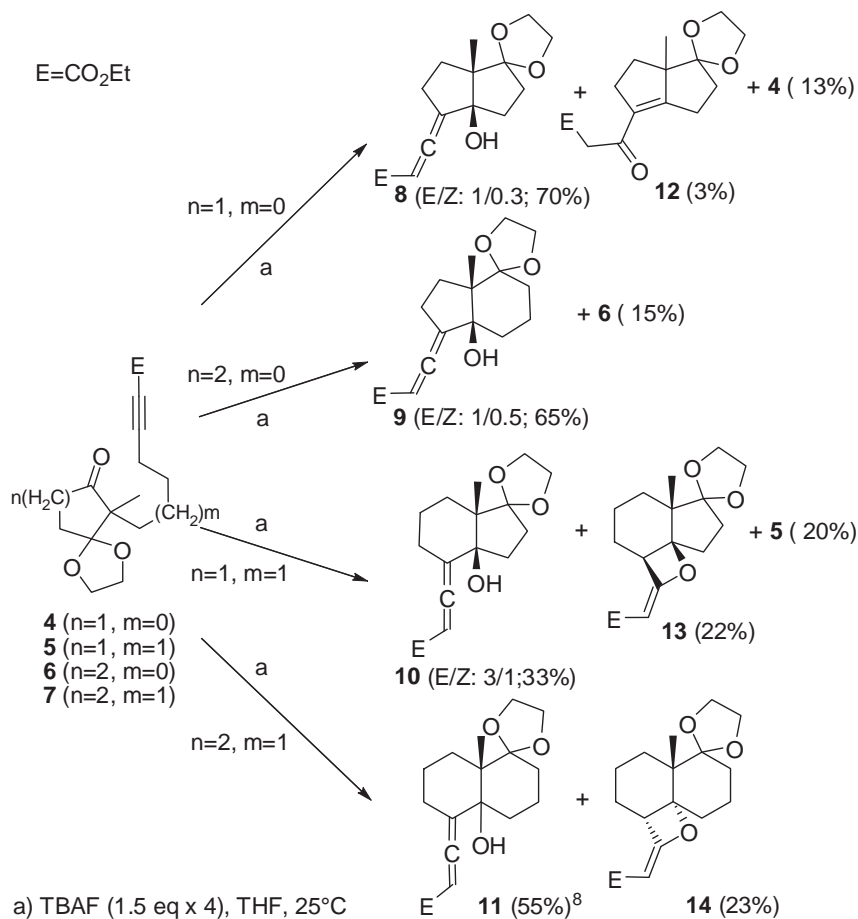
2.2. TBAF addition to alkynyl esters tethered to 2-methyl-3-oxocyclopentyl acetate

Five-membered rings allenolates were obtained in higher yield than the corresponding six-membered rings, the lowest yield being observed for the formation of allenolate **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 allenolate **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 allenolate **22** (15%) and oxetane **23** (12%) and recovered starting material (40%). Thus, the formation of

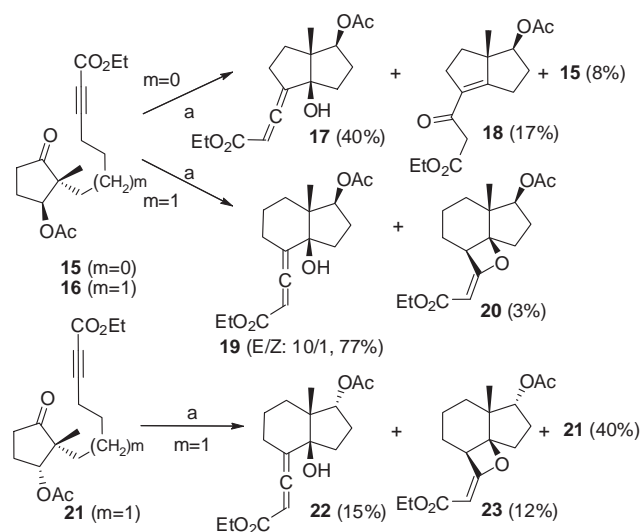
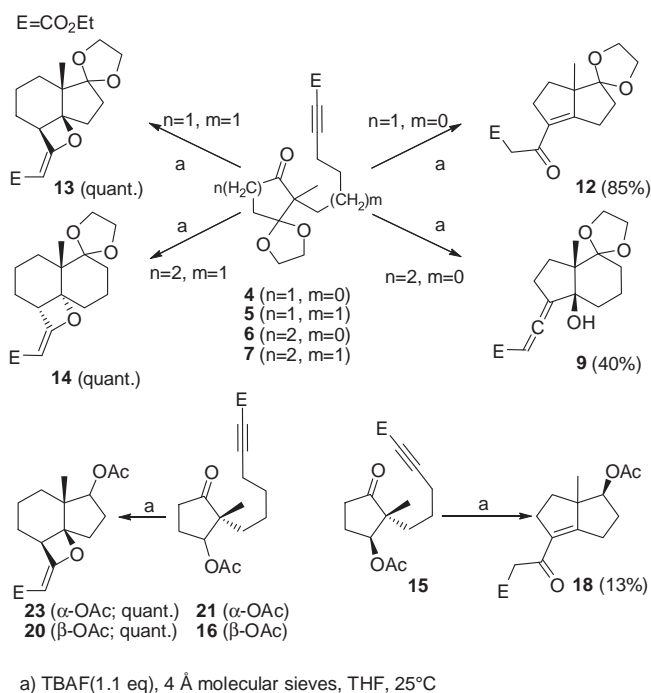
2.3. TBAF addition to alkynyl esters tethered to 2-methyl-1,3-cycloalkanediones in the presence of molecular sieves

To improve the yield of the anionic domino reaction leading to the allenolates, the TBAF reaction was performed in the presence of 4 Å molecular sieves¹³ 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 allenolates 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 allenolates or oxetanes at least when the formation of a six-membered ring took place. A mechanism was previously proposed for the formation of the allenolates,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**.

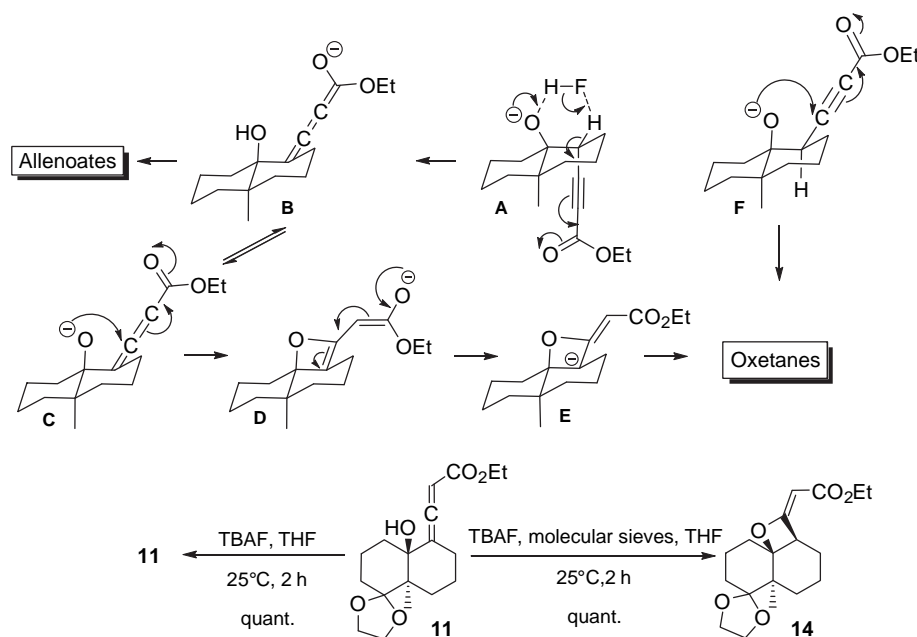
to the allenates. On the other hand, **B** can be in equilibrium with **C**, which undergoes a nucleophilic attack on the central carbon of the allenate affording the oxetene derivative **D**. The latter evolves toward carbanion **E** to yield finally the oxetane derivatives after protonation. It is 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 allenates and oxetanes. Moreover, we have shown that the addition of TBAF to the allenate **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 allenates and oxetanes (Scheme 5).

3. Conclusions

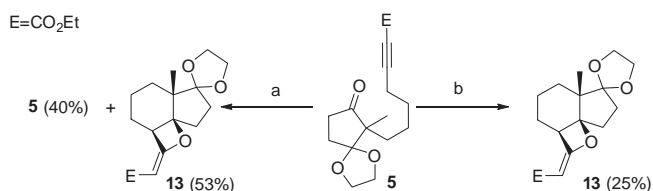
In summary, starting from alkynyl esters tethered to 2-methyl-1,3-cycloalkanediones, TBAF in the presence of 4 Å molecular sieves exclusively promoted a 4-*exo*-dig cyclization to afford polyfunctionalized oxetanes at least when the formation of six-membered rings was involved. In the absence of molecular sieves, TBAF promoted a highly chemoselective reaction leading to polyfunctionalized allenates; 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: polyfunctionalized diquinanes, oxetanes, hydrindane, and hydronaphthalene 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 allenates/oxetanes.

2.4. Triton B and ^tBuOK 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 ^tBuOK 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 allenates (Scheme 6).



a) Triton B (40% in water), THF, 25°C; b) ^tBuOK, THF, 25°C

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

4. Experimental section

4.1. General

Et₂O and THF were distilled from Na/benzophenone, CH₂Cl₂ over P₂O₅. 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. ¹H NMR spectra were recorded at 300 MHz and ¹³C NMR spectra at 75 or 125 MHz using the signal of the residual nondeuteriated solvent as the internal reference. Significant ¹H 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 CCl₄ 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 allenates

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 NaHCO₃ (15 mL). The aqueous layer was extracted with diethyl ether (3 × 15 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated. The crude material was purified by chromatography on silica gel (EtOAc/petroleum ether 1/9).

4.2.1. Ethyl-3-(3'-hydroxy-7'-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 (ABX₃, $J_{AB}=10.8$ Hz, $J_{BX}=7.1$ Hz, $J_{AX}=7.1$ Hz, $\Delta\nu=0.018$ ppm, $\delta_A=4.17$ ppm, $\delta_B=4.15$ 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). ¹³C NMR (CDCl₃, 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 C₁₇H₂₅O₅(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 NaHCO₃ (15 mL). The aqueous layer was extracted with diethyl ether (3 × 15 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated. The crude material was purified by chromatography on silica gel (EtOAc/petroleum ether 1/9).

4.3.1. (E)-ethyl-2-(5'-methylhexahydrospiro[[1,3]dioxolane-2,6'-indeno[4-b]oxete]-2'(2'A'H)-ylidene) acetate (13). Yield: quant.; colorless oil; IR (ATR): ν 1701, 1651 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ : 5.12 (d, $J=1.9$ Hz, 1H), 4.11 (ABX₃, $J_{AB}=10.8$ Hz, $J_{BX}=7.1$ Hz, $J_{AX}=7.1$ Hz, $\Delta\nu=0.030$ ppm, $\delta_A=4.13$ ppm, $\delta_B=4.09$ 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); ¹³C NMR (CDCl₃, 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 C₁₇H₂₅O₅ (M+H)⁺: 309.1696; found: 309.1692.

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Supplementary data

Experimental procedures and analytical data for compounds **11**, **14–16**, **19**, **21** are provided as well as copies of ¹H NMR and ¹³C NMR

spectra for compounds **9**, **11**, **13**, **14**, **19**, and **20**. 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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- The *E/Z* ratios were determined from ¹H NMR spectra. Allenate **11** was isolated as a mixture of two isomers bearing a *cis* ring junction (yield: 21%; ratio: 1/1.3) along with 1 isomer bearing a *trans* ring junction (34%).
- Allenate **11** bearing a *trans* ring junction and *E* allenate was obtained by column chromatography of the crude mixture of allenate. 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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