Simple Synthesis of Conjugated All-(*E*)-Polyenic Aldehydes, Ketones, and Esters Using Chemoselective Cross-Metathesis and an Iterative Sequence of Reactions: Application to the Synthesis of Navenone B

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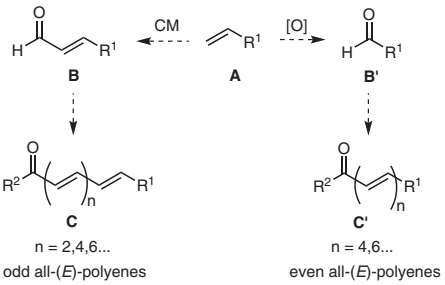
Abstract: By using a very simple sequence of reactions such as allylation, acetylation, chemoselective cross-metathesis, and elimination, even and odd conjugated all-(*E*)-polyenes can be synthesized from very simple alkenes.

Key words: polyenes, cross-metathesis, elimination, allylation, navenone B

Conjugated all-(*E*)-polyenes are present in a great variety of natural products of biological interest such as, for example, antibiotics[1] (filipin III), immunosuppressive agents (pseudotrienic acid),[2] and anticoagulants (tetrafibricin)[3] (Figure 1). Among the different protocols that have been reported to synthesize conjugated all-(*E*)-polyenes, we can cite iterative Wittig–Horner reactions,[4] as well as the Corey–Schlessinger–Mills-modified Peterson olefination,[5] iterative Pd-catalyzed cross-couplings such as Stille coupling,[6] Suzuki–Miyaura coupling,[7] Negishi coupling,[8] Sonogashira coupling,[9] treatment of dienic benzoates with Na/Hg,[10] Julia–Lythgoe olefination,[11] or ring opening of bicyclo[4.2.0]octadiene acetate with $LiAlH_4$.[12]

Herein, we would like to report the synthesis of conjugated odd all-(*E*)-polyenes of type **C** as well as conjugated even all-(*E*)-polyenes of type **C′**[13] from simple alkenes of type **A** by using an iterative sequence of reactions involving allylations, acetylations, chemoselective cross-metatheses,[14] and domino elimination.

Depending on the first transformation of alkenes of type **A** either to an α,β-unsaturated aldehydes **B** (cross-metathesis) or to aldehydes of type **B′** (oxidative cleavage of the double bond), conjugated odd all-(*E*)-polyenes of type **C** or conjugated even all-(*E*)-polyenes of type **C′** were synthesized (Scheme 1).



Scheme 1

Alkene **A**, which at first was chosen to produce conjugated odd and even all-(*E*)-polyenes of type **C** and **C′**, was the protected but-1-en-3-ol **1**. We have to point out that the allylation of intermediate aldehydes of type **B** and **B′** were achieved using either allylmagnesium chloride or allyltrichlorosilane[15] in order to obtain the corresponding

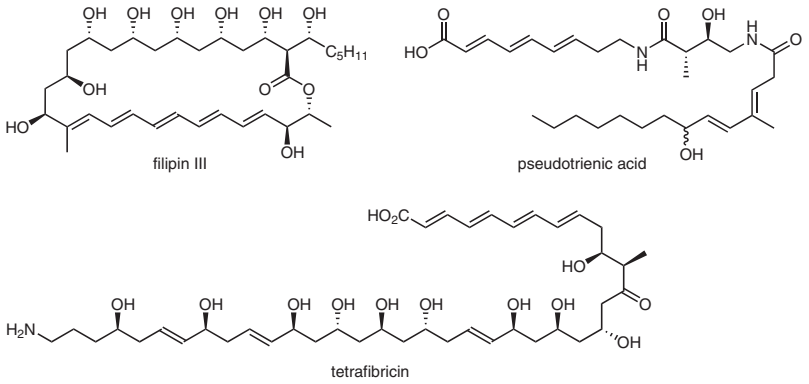


Figure 1

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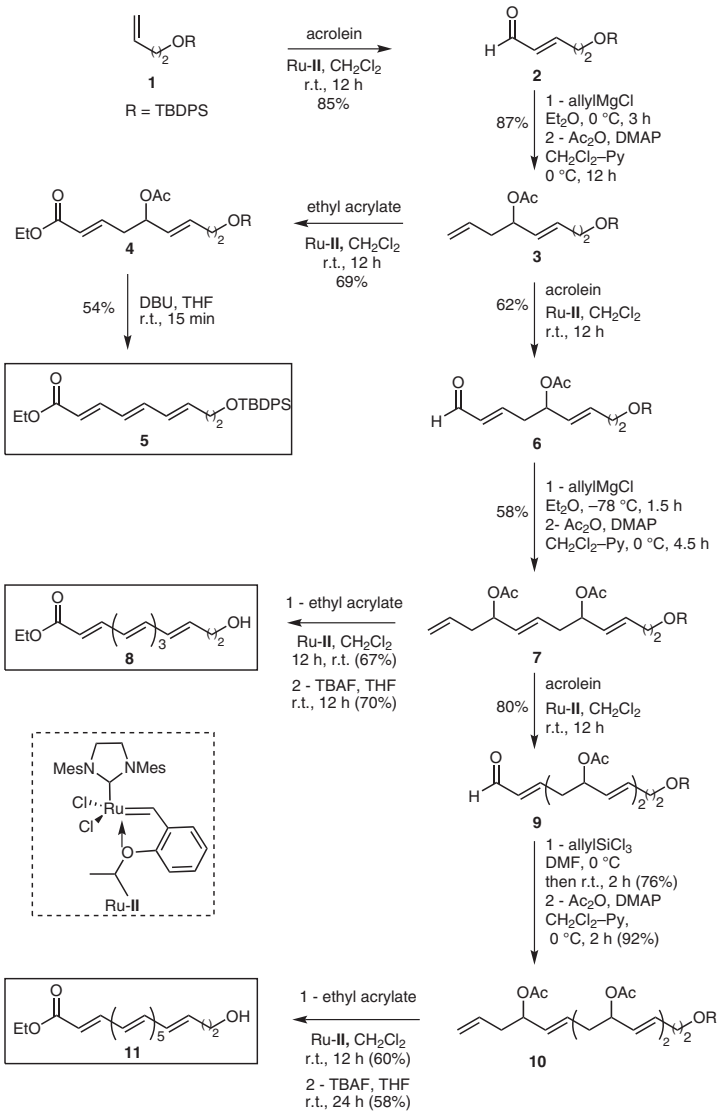
homoallylic alcohols. Concerning the elimination step, the reagents used were either DBU, TBAF, or $BF_3{\cdot}OEt_2$. Only the reagents producing the best yields for the allylation and the elimination are reported.

In order to obtain conjugated odd all-(*E*)-polyenes of type **C**, compound **1** was transformed to the unsaturated aldehyde **2** by treatment with acrolein (3 equiv) under cross-metathesis (CM) conditions [Hoveyda–Grubbs second-generation catalyst = Ru-**II** (5 mol%),[16] CH_2Cl_2, r.t., 85% yield]. Aldehyde **2** was then converted into triene **5** in four steps. After addition of allylmagnesium chloride (Et_2O, 0 °C), the obtained homoallylic alcohol was acetylated (Ac_2O, pyridine, DMAP, CH_2Cl_2, 0 °C) to produce the corresponding acetate **3** (for the two steps, 87%) which was then transformed to conjugated triene **5** in two steps. Due to the presence of the acetyl group, a chemoselective CM could be performed with ethyl acrylate[14] [Ru-**II** (5 mol%), CH_2Cl_2, r.t.] and this reaction resulted in the formation of the nonconjugated dienic ester **4**[17] (69% yield) which, after treatment with DBU (THF, 15 min), furnished conjugated triene **5**[18] in 54% yield. Having synthesized **3**, the latter compound was also transformed to pentaene **8** by realizing a CM/allylation/acetylation/CM/domino elimination sequence. Thus, after a chemoselective CM with acrolein [Ru-**II** (5 mol%), CH_2Cl_2, r.t.], α,β-unsaturated aldehyde **6** was formed, which after an allylation (allylMgCl, Et_2O, –78 °C)/acetylation sequence led to **7** (58%). The latter compound was then converted into **8** after a chemoselective CM with ethyl acrylate followed by an elimination step using TBAF. Another conjugated odd all-(*E*)-polyene, heptaene **11**, was also obtained from the previously synthesized trienic diacetate **7**. After a chemoselective CM with acrolein in the presence of Ru-**II**, followed by an allylation ($allylSiCl_3$, DMF, 0 °C)/acetylation sequence, **10** was isolated (70%) and then transformed to heptaene **11** after a CM (ethyl acrylate) followed by treatment with TBAF which induced a domino elimination (35% overall yield for the two steps) (Scheme 2).

Compound **3** can be considered as a cornerstone in the synthesis of conjugated odd all-(*E*)-polyenes, as it al-

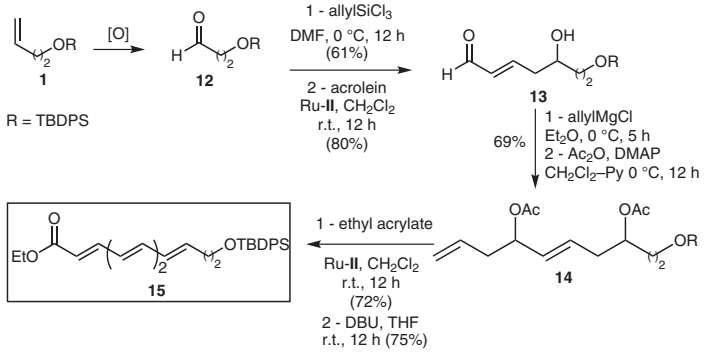


Scheme 2

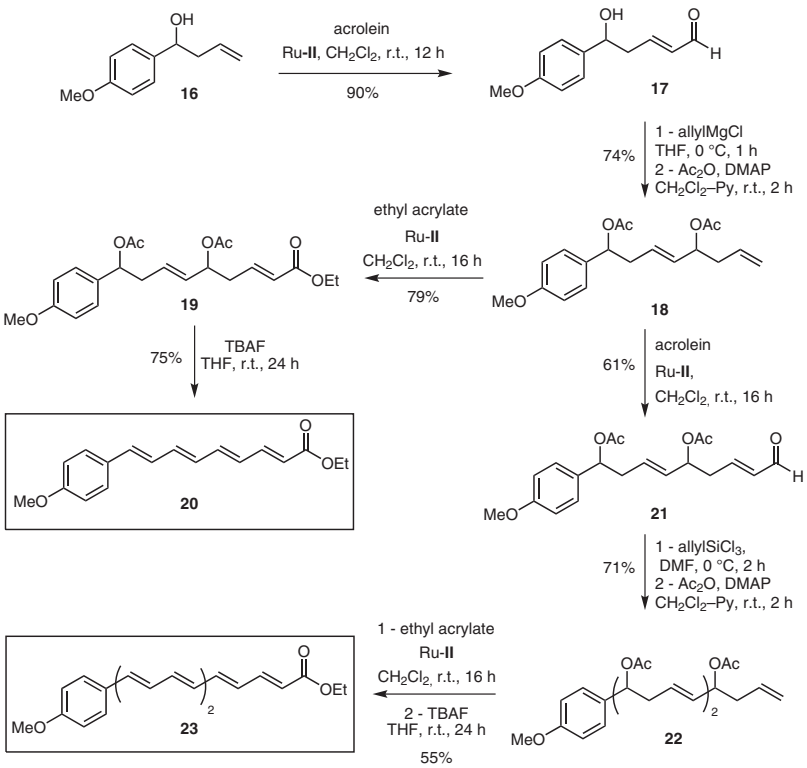
lowed an easy access to triene **5**, pentaene **8**, and heptaene **11** (Scheme 2).

In order to synthesize conjugated even all-(*E*)-polyenes of type **C′**, aldehyde **12** was prepared by oxidative cleavage of the double bond (OsO_4 then $NaIO_4$, *t*-BuOH/H_2O) of the protected but-3-en-1-ol **1**. As for the synthesis of conjugated odd all-(*E*)-polyenes, the same sequence of reactions was used. Thus, trichloroallylsilane was added to **12** and the resulting homoallylic alcohol was involved in a CM reaction with acrolein (3 equiv) in the presence of Ru-**II** (5 mol%, CH_2Cl_2, r.t.) leading to **13** (49% overall yield). Unsaturated aldehyde **13** was then transformed to **14** in two steps (allylation with allylMgCl and acetylation, 69% overall yield) and the latter compound was involved in a CM (ethyl acrylate)/elimination (DBU) sequence to afford the conjugated ester **15** (54% overall yield) (Scheme 3).

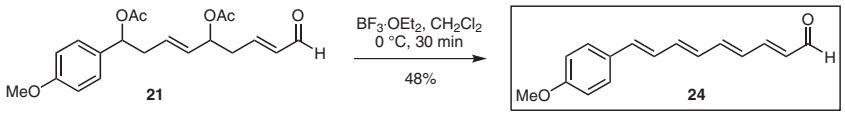
Other homoallylic alcohols than **1** can be used to prepare conjugated even all-(*E*)-polyenes. For example, homoallylic alcohol **16** (prepared from *p*-methoxybenzaldehyde) was transformed to **19** in five steps (Scheme 4). After a CM reaction in the presence of acrolein (3 equiv) and Ru-**II** (5 mol%, CH_2Cl_2, r.t.), homoallylic alcohol **16** was converted into unsaturated aldehyde **17** (90%) which was then treated with allylmagnesium chloride (Et_2O, 0 °C) and, the obtained diol was acetylated (DMAP, Ac_2O, CH_2Cl_2, r.t.) furnishing diacetate **18**. This latter compound was then treated with ethyl acrylate (3 equiv) in the presence of Ru-**II** (5 mol%, CH_2Cl_2, r.t.) and the resulting CM product **19** was transformed to tetraene **20** after a domino elimination performed with TBAF (59% overall yield from **18**). Compound **18** was also transformed to **23** in five steps. After a CM reaction with acrolein, **21** was isolated (61%) and this latter was transformed to **22** by addition of allyltrichlorosilane (DMF, 0 °C) and acetylation.



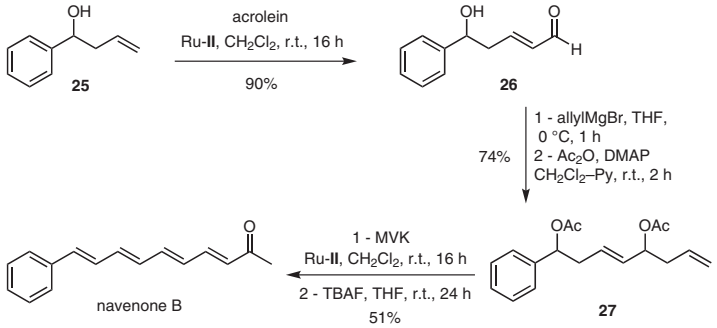
Scheme 3



Scheme 4



Scheme 5



Scheme 6

The resulting triacetate **22** (71% overall yield) was then converted into the conjugated hexaene **23** (55% yield) after a CM reaction realized with ethyl acrylate [Ru-**II** (5 mol%), CH_2Cl_2, r.t.] and an elimination step performed with TBAF (THF, r.t.) (Scheme 4).

If conjugated even all-(*E*)-polyenic esters, such as **15**, **20**, and **23**, were obtained easily when the last CM reaction was achieved by utilizing ethyl acrylate, conjugated all-(*E*)-polyenic aldehydes were also synthesized when the last CM reaction was achieved with acrolein. Thus, compound **21** was converted into **24** in 48% yield after treatment with $BF_3{\cdot}OEt_2$ (0 °C, CH_2Cl_2) (Scheme 5).

By using methyl vinyl ketone to achieve the last CM reaction, conjugated all-(*E*)-polyenic ketones can be isolated. This methodology was used to synthesize navenone B which is an alarm pheromone secreted by the blind Pacific opistobranch mollusk *Navanax inermis*.[19,20] When under duress, this mollusk secretes components which induce an alarm avoidance response in other *Navanax*, and among the compounds, navenone B was isolated. Navenone B was obtained in five steps from homoallylic alcohol **25**. After a CM with acrolein, **25** was transformed into **26** and by utilizing an allylation–acetylation sequence, **27** was formed (74% yield) and converted into navenone B using a chemoselective CM (involving methyl vinyl ketone)/elimination (TBAF) sequence (51% overall yield from **27**) (Scheme 6).

In conclusion, by using a very simple sequence of reactions mainly chemoselective CM, allylation of aldehydes, elimination, conjugated even and odd all-(*E*)-polyenes can be synthesized from very simple alkenes.

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(17) **Synthesis of Compound 4**
To a solution of alkene **3** (190 mg, 0.45 mmol) in CH_2Cl_2 (2.3 mL) was added at r.t. ethyl acrylate (0.15 mL, 1.35 mmol) and Ru-**II** (14 mg, 0.023 mmol). The reaction mixture was stirred at r.t. overnight and then concentrated in vacuo. Purification of the residue by flash chromatography (hexane/EtOAc, 99:1) afforded **4** (154 mg, 69%) as a yellow oil. R_f = 0.43 (hexane/EtOAc, 9:1). IR: 1739, 1720, 1656, 1232 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.66 (m, 4 H), 7.41 (m, 6 H), 6.83 (dt, *J* = 15.8, 7.2 Hz, 1 H), 5.85 (dt, *J* = 15.8, 1.5 Hz, 1 H), 5.76 (m, 1 H), 5.47 (dt, *J* = 15.5, 6.8 Hz, 1 H), 5.34 (m, 1 H), 4.18 (q, *J* = 6.8 Hz, 2 H), 3.69 (t, *J* = 6.4 Hz, 2 H), 2.49 (m, 2 H), 2.28 (q, *J* = 6.8 Hz, 2 H), 2.02 (s, 3 H), 1.26 (t, *J* = 6.8 Hz, 3 H), 1.04 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1, 166.2, 143.3, 135.6, 133.8, 131.6, 129.6, 129.1, 127.6, 124.2, 72.8, 63.1, 60.3, 37.3, 35.6, 26.8, 21.2, 19.2, 14.2. MS: *m/z* = 377, 241, 199, 105.

(18) **Synthesis of Compound 5**
To a solution of nonconjugated dienic ester **4** (147 mg, 0.30 mmol) in THF (1 mL) was added at r.t. DBU (1 mL, 6.7 mmol). The mixture was stirred for 15 min then neutralized with sat. aq NH_4Cl. The layers were separated, and the aqueous phase was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (hexane/EtOAc, 95:5) afforded conjugated triene **5** (70 mg, 54%) as a pale yellow oil. R_f = 0.61 (hexane/EtOAc, 9:1). IR: 1710, 1619, 1257 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.66 (m, 4 H), 7.41 (m, 6 H), 7.30 (dd, *J* = 15.5, 11.5 Hz, 1 H), 6.44 (dd, *J* = 15.1, 10.2 Hz, 1 H), 6.13 (dd, *J* = 15.1, 11.5 Hz, 1 H), 6.09 (dd, *J* = 14.8, 10.2 Hz, 1 H), 5.92 (dt, *J* = 14.8, 6.4 Hz, 1 H), 5.85 (d, *J* = 15.5 Hz, 1 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 3.69 (t, *J* = 6.4 Hz, 2 H), 2.39 (q, *J* = 6.4 Hz, 2 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.04 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.2, 144.7, 140.9, 136.6, 135.6, 133.8, 131.6, 129.6, 128.2, 127.6, 120.3, 63.2, 60.2, 36.3, 26.8, 19.2, 14.3. MS: *m/z* = 377, 227, 199, 105.

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