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Cross metathesis of β-carotene with electron-deficient dienes. A direct route to retinoids

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ABSTRACT

Cross metathesis (CM) reactions of β-carotene and alkenes occur regioselectively in the presence of the Hoveyda second generation catalyst. Scission of the C15–C15′ and C11–C12 bonds of β-carotene in all CM reactions predominates. The reaction with ethyl (2*E*,4*E*/*Z*)-3-methylhexa-2,4-dienoate is both regio- and diastereoselective, and affords ethyl all-*trans*-retinoate as the major product, if suitable CM conditions are applied.

Retinol (vitamin A_1) along with its metabolites such as 11-*cis*-retinal, all-*trans*-retinoic acid and 9-*cis*-retinoic acid are involved in regulating many biological processes including vision, reproduction, cell differentiation and growth.[1] Besides being essential to normal cell function, all-*trans*-retinoic acid and its natural and synthetic analogues show antitumour activity.[2] One of them, *N*-(4-hydroxyphenyl)retinamide (fenretinide), is currently undergoing clinical trials for treatment of breast, bladder, renal and neuroblastoma malignancies (Fig. 1).[3]

Despite the long history of these compounds, there is still a need for effective and fast methods for the preparation of retinoids for biological and structural studies.[4] Retrosynthetic analysis revealed that the synthesis of all-*trans*-retinoids could be achieved in one simple step by regioselective cross metathesis of β-carotene with an appropriate olefinic partner. Olefin metathesis[5] provides a useful synthetic tool for such transformations, since this method enables the formation of new carbon–carbon bonds under mild conditions and in relatively short times, which is especially important for unstable compounds such as β-carotene and retinoids.

CM reactions of β-carotene, a symmetric polyene containing eleven conjugated double bonds, may produce a complex mixture of products. However, our preliminary studies on β-carotene ethenolysis proved that only three double bonds of the polyene system are cleaved under CM conditions, with scission of the C11–C12 double bond predominating (Scheme 1).[6] Assuming the same regioselectivity for CM between β-carotene and other olefins, the synthesis of retinoids would require suitably functionalized 1,3-diene cross partners showing preference for terminal double bond cleavage in CM reactions.

Ethyl (2*E*,4*E*)-3-methylhexa-2,4-dienoate[7] was chosen as a suitable substrate for the β-carotene CM reaction. The reaction was carried out with the second generation Hoveyda catalyst (Hoveyda II, 15 mol %) in toluene at room temperature for 24 h. The reaction appeared to be relatively clean, but unexpectedly, ester **2** (Scheme 2) was formed as the major product by cleavage of the β-carotene C15–C15′ double bond (38%).[8] The all-trans isomer **2** predominated (>92%) as was determined by ^{1}H NMR analysis. The desired ethyl retinoate (**1**) was obtained in 9% yield as the all-trans isomer (~89%).

The main reaction products were accompanied by a number of by-products, such as tetraene **3** (3%; a mixture of *E*/*Z* isomers in the ratio 3:1), triene **4** (5%; a mixture of *E*/*Z* isomers in the ratio 2:1) and ester **5** (less than 1%, a mixture of isomers with one of them, probably the all-trans, predominating). The amounts of these by-products varied with time. The hydrocarbon products **3** and **4** were formed by cleavage of the C11–C12 or C9–C10 double bond, respectively. Compound **5** was apparently formed by double scission of β-carotene. The products obtained were detected and analyzed by GC–MS method,[9] esters **1**, **2** and **5** were additionally isolated by preparative HPLC or column chromatography. Increasing the reaction time resulted in a decrease in yield of ester **2** in favour of ethyl retinoate (**1**). Most likely, the initially formed products (including **2**) underwent consecutive CM reactions producing **1** (this was proved in a separate experiment). After 96 h, a 31% yield of the desired retinoate **1** (isolated by HPLC) was achieved, whereas the yield of ester **2** decreased to 15%. The influence of the reaction time on the product distribution is shown in

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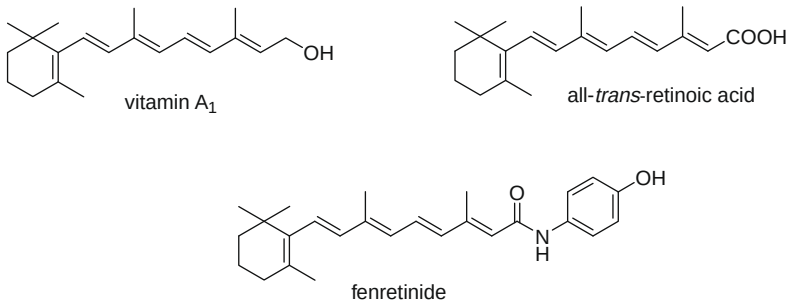
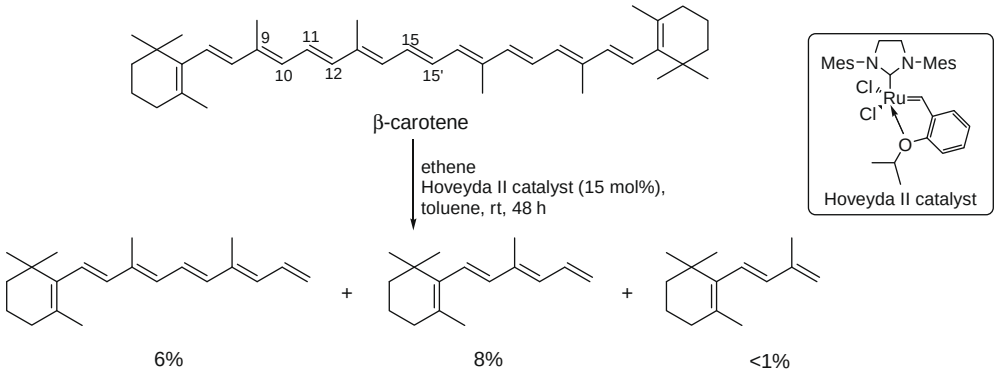
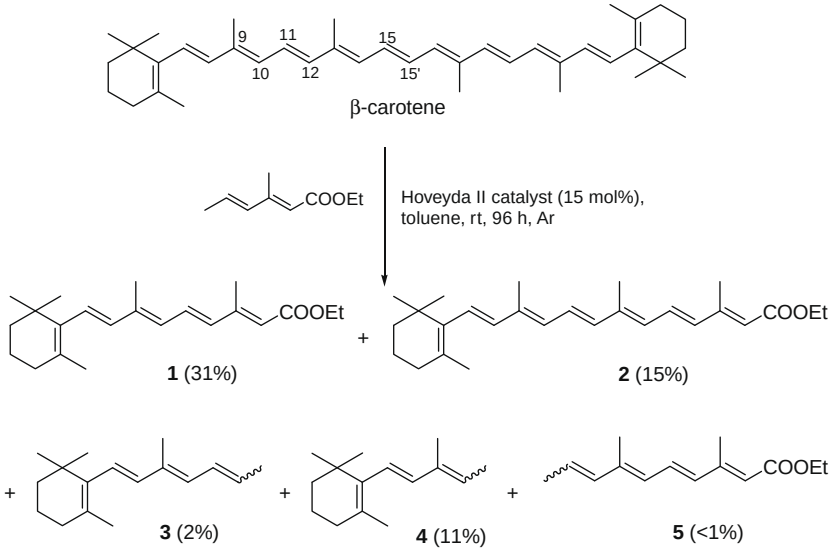


Figure 1. Structures of vitamin A_1, all-*trans*-retinoic acid and fenretinide as examples of natural or synthetic retinoids.



Scheme 1. Ethenolysis of β-carotene.



Scheme 2. CM of β-carotene with (2*E*,4*E*)-3-methylhexa-2,4-dienoate.

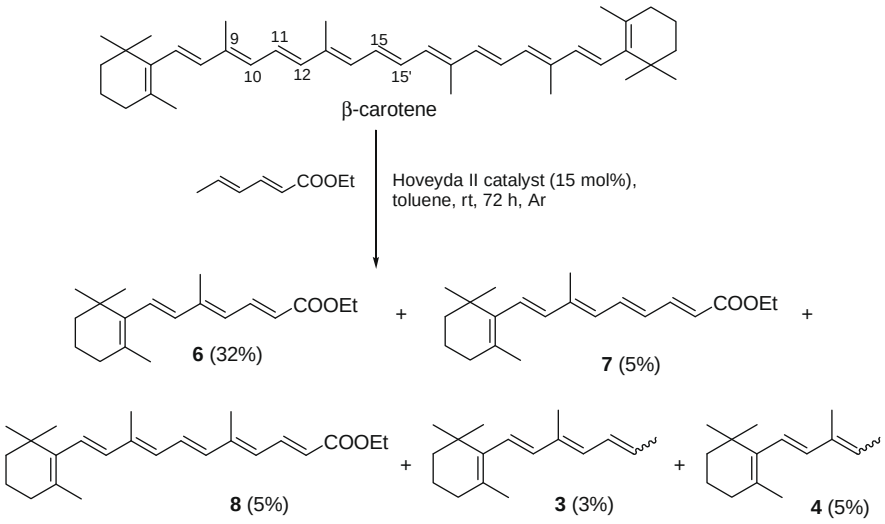
Table 1. The optimal reaction time was 96 h; at least 80% of β-carotene was consumed in four days. Further extension of the reaction time led to a diminished yield of ethyl retinoate (**1**), probably due to secondary CM reactions of this compound.

Similar results were obtained when a stereoisomeric mixture of ethyl 3-methylhexa-2,4-dienoate (2*E*,4*Z* and 2*E*,4*E* in the ratio 5:3) was used instead of a single stereoisomer (2*E*,4*E*) as the cross partner for metathesis reactions. This is not surprising since blank experiments revealed that the mixture of stereoisomeric esters undergoes fast isomerization to the more stable (2*E*,4*E*)-3-methyl-

Table 1
Influence of the reaction time on the product distribution of the CM between β-carotene and ethyl (2*E*,4*E*)-3-methylhexa-2,4-dienoate (4 equiv) in the presence of the second generation Hoveyda catalyst (15 mol %) in dry toluene at room temperature

Time (h)	24	48	72	96	120
Ester **1** yield (%)*	9	13	23	31[a]	21
Ester **2** yield (%)*	38	17	12	15[a]	10

* Yields obtained by quantitative HPLC analysis.
[a] Isolated yield following HPLC.



Scheme 3. CM of β-carotene with ethyl sorbate.

Table 2
Influence of the reaction conditions on the CM of β-carotene and ethyl (2*E*,4*E*/*Z*)-3-methylhexa-2,4-dienoate, analyzed after 72 h

Conditions				Yield* (%)	
β-Carotene concentration (M)	Catalyst	Cross partner (equiv)	Solvent	Ethyl retinoate (**1**)	Ester **2**
4.9×10^{-2}	Hoveyda II (15 mol %)	4 equiv	Toluene	14	34
9.7×10^{-2}	Hoveyda II (15 mol %)	4 equiv	Toluene	23	12
9.7×10^{-2}	Hoveyda II (7.5 mol %)	4 equiv	Toluene	7	18
9.7×10^{-2}	Hoveyda II (4 mol %)	4 equiv	Toluene	1	8
9.7×10^{-2}	Hoveyda II (15 mol %)	4 equiv	CH_2Cl_2	1	4
9.7×10^{-2}	Hoveyda II (15 mol %)	2 equiv	Toluene	12	9
9.7×10^{-2}	Grubbs II (15 mol %)	4 equiv	Toluene	3	11
9.7×10^{-2}	Modified Hoveyda II (15 mol %)	4 equiv	Toluene	<1	5

* Yields obtained by quantitative HPLC analysis.

hexa-2,4-dienoate stereoisomer under CM conditions. It should be noted that during CM reactions with dienic esters highly regioselective cleavage of the γ–δ double bond occurred, as was expected from earlier studies on CM of substituted 1,3-dienes.[10] Only a trace amount of a CM product originating from scission of the C11–C12 bond in β-carotene and the α–β bond of the dienic ester was detected by GC–MS analysis. CM reactions of β-carotene with ethyl sorbate [ethyl (2*E*,4*E*)-hexa-2,4-dienoate], carried out under the same conditions, showed opposite regioselectivity with respect to the dienic partner (Scheme 3). In this case, CM products formed by cleavage of the C11–C12 double bond of β-carotene and the γ–δ (compound **7**) or α–β (compound **6**) double bond of sorbate were isolated from the reaction mixture (reaction time 72 h) in 5% or 32% yields. In addition to these two products, a hexadienic ester **8** was also formed in 5% yield by cleavage of the C15–C15′ double bond of β-carotene and the α–β double bond of ethyl sorbate. This example emphasizes the importance of the detailed structure of the dienic partner for obtaining regioselectivity in the reaction.

Other commercially available second generation catalysts were also tested for their ability to promote the CM reactions of β-carotene. The second generation Grubbs' catalyst (Grubbs II) proved to be much less efficient than the Hoveyda II catalyst. The yield of retinoate **1** decreased from 23% to 3%, while the yield of ester **2** remained roughly the same. The recently introduced modified Hoveyda catalyst with toluyl groups in place of mesityl substituents on the NHC ligand was even less active. Only a 5% yield of ester **2** and below 1% of retinoate **1** were achieved under similar conditions. The solvent effect on the reaction course was also examined. A dramatic change was observed when toluene was replaced by dichloromethane; conversion was much lower and the yield of retinoate **1** amounted to only 1%. A drop in yield was also noticed when the catalyst loading or amount of the cross partner was decreased. These results are summarized in Table 2.

This is the first report on CM reactions of β-carotene with electron-deficient dienes. In spite of the fact that there are many alternative reaction sites in the polyene system a reasonable yield of the desired product can be achieved by appropriate selection of the CM conditions. Although there are two double bonds in β-carotene (C15–C15′ and C11–C12), which are preferably cleaved during CM reactions, the reaction course can be controlled to some extent. Short reaction times, low catalyst loading, a less active catalyst or lower concentration of reagents favour formation of ester **2** as the kinetic product. This product may react further with an excess of a dienic ester in consecutive CM reactions. Therefore, more forcing conditions are advantageous for formation of retinoate **1**. However, compound **1** cannot be considered as a thermodynamic product, since CM processes may progress even further, for example, with scission of the C9–C10 double bond. Nevertheless, the studies performed allowed determination of the optimal conditions for preparation of ethyl all-*trans*-retinoate **1**. The methodology developed will be applied to the synthesis of other retinoids, including fenretinide and other retinoic acid derivatives.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.032.

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8. Yields were calculated in relation to β-carotene. However, yields were divided by two due to the symmetry of the β-carotene molecule.
9. *GC–MS analysis*: Aliquots (50 μL) of the reaction mixture in dichloromethane (450 μL) were prepared. Internal standard (methyl myristate, 0.2 equiv) was added to each sample. Analytical conditions: GC–MS (EI) was carried out on a Perkin Elmer (AutoSystem XL) gas chromatograph coupled to an MS detector (Perkin Elmer TurboMass) running in electron impact mode (70 eV). A PE-5HT column (30 m × 0.25 mm × 0.1 μm) was used; carrier gas: helium (1 mL/min); the inlet mode was split: 50:1; the injector temperature was 250 °C. The initial column temperature was 60 °C, after 1 min the temperature was raised to 310 °C at a rate of 4 °C per min. Thereafter, the conditions were held for 6 min. The mass spectra were scanned from 40 to 600 *m/z*.
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