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A cross-metathesis approach to the synthesis of new etretinate type retinoids, ethyl retinoate and its 9Z-isomer

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ABSTRACT

Two aromatic retinoids were synthesized from styrene derivatives using a novel strategy with a cross-metathesis reaction as a key step. The biological activity of the new etretinate analogues was tested. Cross-metathesis reactions were also employed for the preparation of ethyl retinoate and its 9Z-isomer via the $C_{15} + C_5$ route.

Retinoids are natural and synthetic analogues of retinoic acid. They play an essential role in a variety of biological processes such as vision, reproduction, cell differentiation, and immune responses.[1] The scope of natural retinoid therapy is limited by their susceptibility to double bond isomerization and oxidation by cytochrome P450 enzymes, which affects their activity and selectivity of action. Modification of the structure of natural retinoids to overcome these problems has resulted in the synthesis of atypical second generation retinoids, in which the trimethylcyclohexenyl unit was replaced by a functionalized benzene ring, and third generation retinoids with robust polyaromatic systems (Fig. 1).[2] These aromatic derivatives are more stable as well as more active and selective. Several such synthetic retinoids (etretinate, acitretin, tezarotene, bexarotene, adapalene) along with all-*E*-retinoic acid are used clinically. Numerous synthetic methods were elaborated to prepare natural and atypical second generation aromatic retinoids. Traditionally, polyene chain construction was accomplished using Wittig, Horner-Wadsworth-Emmons (HWE), Julia, and Stobbe reactions; more recently palladium-catalyzed cross-coupling reactions were applied.[3]

The arsenal of polyene synthesis methods has been extended to include olefin metathesis, which after the discovery of active and stable second generation catalysts has become a powerful synthetic tool in the hands of organic chemists.[4]

In our previous studies,[5] we proved that cross-metathesis (CM) may be applied to the synthesis of different apocarotenoids, including retinoids from β-carotene or retinyl acetate. However, in the case of these polyene substrates the reaction course depends

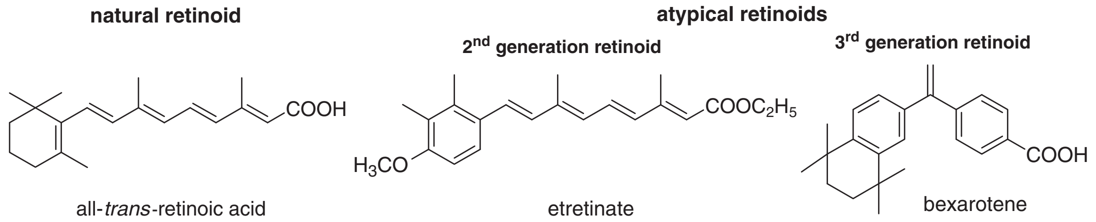

Figure 1. Natural and atypical retinoids.

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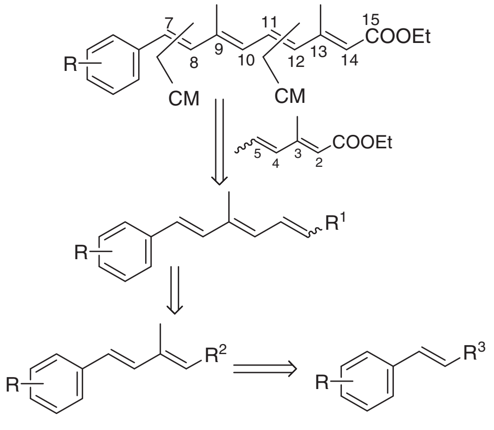
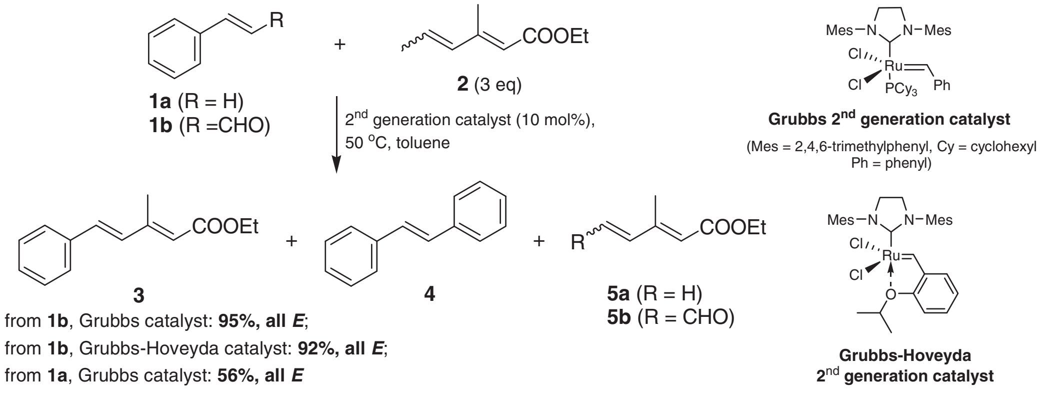


Scheme 1. Retrosynthesis of etretinate analogue.

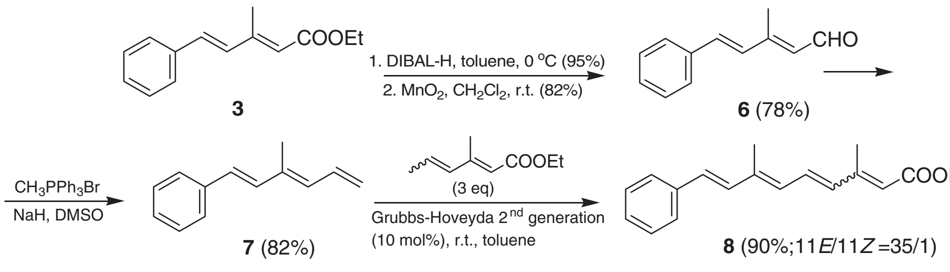
largely on the structure of the cross-metathesis partner and the reaction conditions. Herein, we present a novel protocol for the synthesis of aromatic retinoids using a CM reaction to extend the polyene chain. We have also synthesized ethyl retinoate and its 9*Z*-isomer employing the $C_{15} + C_5$ route, that is, the CM reaction between a substrate donating a fifteen-carbon atom fragment (C_{15}-synthon) and the other one being a donor of a five-carbon atom fragment (C_5-synthon).

The retrosynthetic analysis of etretinate analogues is shown in Scheme 1. Assuming that the disubstituted double bonds of the retinoid chain are more accessible than the trisubstituted ones by the CM approach, in order to build a polyene chain of aromatic retinoids from a styrene derivative, a CM coupling with partners bearing a 2-methylbuta-1,3-diene moiety was considered. Based on our previous experience,[5] we chose readily available ethyl 3-methylhexa-2,4-dienoate, as it has been proved that its CM reactions occur regioselectively at the terminal C4–C5, while its dimerization (self-metathesis) is slow. Additionally, the ester functionality present in this compound allows for convenient elongation of the unsaturated chain by a sequence of simple transformations. At first we investigated the CM reactions of styrene (**1a**) and cinnamaldehyde (**1b**) with ethyl (2*E*,4*E*/*Z*)-3-methylhexa-2,4-dienoate (**2**) promoted by second generation catalysts (Scheme 2). In all the experiments, apart from the major reaction product — the aromatic ester (**3**), side products: *E*-stilbene (**4**) and the non-aromatic ester (**5**) were formed. The desired CM product **3** was obtained in a better yield by coupling with cinnamaldehyde than with styrene. Probably, competitive self-metathesis of styrene is faster than that of cinnamaldehyde, and for this reason a significant lowering of the CM product yield was observed in the former case. Both second generation catalysts (Grubbs and Grubbs–Hoveyda complexes) efficiently promoted the reaction of cinnamaldehyde with the dienoate affording the desired CM product with complete diastereoselectivity — the all-*E*-isomer[6] was obtained in yields above 90% (Scheme 2).

In the next step the ester group of the CM product **3** was transformed into the corresponding aldehyde **6**[6b,7] by a known reduction–oxidation procedure (DIBAL-H, toluene, 0 °C, 2 h, then MnO_2, CH_2Cl_2, 16 h, rt.,).[8] The aldehyde was subjected to Wittig methylenation ($MePPh_3Br$, NaH, DMSO)[9] affording the all-*E*-triene **7**. The consecutive CM reaction of the triene with ethyl (2*E*,4*E*/*Z*)-3-methylhexa-2,4-dienoate (**2**) provided the etretinate analogue **8**[10] in 90% yield under optimized conditions (10 mol % of the 2nd generation Grubbs–Hoveyda catalyst, slow addition of 3 equiv of the diene partner at rt., 16 h) with high stereoselectivity (11*E*/11*Z* = 35/1). The aromatic retinoid **8** was synthesized in 55% total yield from cinnamaldehyde (Scheme 3). Using the same strategy, its analogue with a substituted phenyl ring (**12**) was synthesized from 5-but-1′-enyl-1,2,3-trimethoxybenzene (**9**)[11] (Scheme 4). As in the previous case, both CM steps were efficient and highly *E*-stereoselective. Both synthesized etretinate analogues **8** and **12** were screened against various tumor cells



Scheme 2. CM reaction between styrene or cinnamaldehyde and ethyl (2*E*,4*E*/*Z*)-3-methylhexa-2,4-dienoate.



Scheme 3. Synthesis of the phenyl analogue of etretinate.