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Cross metathesis approach to retinoids and other β-apocarotenoids

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ABSTRACT

Cross metathesis (CM) reactions between polyenes, such as β-carotene, canthaxanthin or retinyl acetate, and various alkenes or dienes in the presence of second generation Hoveyda–Grubbs (H II) or Grubbs (G II) catalysts were investigated. Depending on the cross partner different apocarotenoids were obtained. Cross metathesis reactions of retinyl acetate proved to be fully regioselective. Carotenoid CM reactions afforded mixtures of two products due to competing cleavage of the C11–C12 and C15–C15′ double bonds. However, regioselectivity can be controlled by choice of appropriate reaction conditions. The reactions of polyenes with dienes worked better in respect of yields and diastereoselectivities than those with monounsaturated cross partners.

1. Introduction

Natural products containing a conjugated polyene system constitute a large and structurally diverse group of compounds.[1] Some of them, including eicosanolids,[2] polyene macrolides,[3] carotenoids,[4] apocarotenoids,[5] and retinoids[6] show interesting biological activity. Particularly, retinoids (Fig. 1) play an essential role in a variety of biological processes, such as vision, reproduction, cell differentiation, and immune response. Besides being important to normal cell function, all-*trans*-retinoic acid and its natural and synthetic analogues exhibit antitumor activity.[7] One of them, *N*-(4-hyroxyphenyl)retinamide (fenretinide) is currently undergoing clinical trials for the treatment of breast, bladder, renal, and neuroblastoma malignancies.[8]

Due to increasing application of polyenes in medicine, nonlinear optics, cosmetics, and the food industry, the search for efficient synthetic routes to these compounds is becoming increasingly important. Difficulties with controlling the olefin geometry and susceptibility of some polyenes to oxidation and isomerization make their synthesis a difficult and challenging task. Nowadays synthetic chemists are provided with a new tool to construct polyene compounds, i.e., olefin metathesis. Since the development of well defined molybdenum and ruthenium catalysts (Fig. 2), which are now commercially available, olefin metathesis has become one of the most valuable methods of C–C double bond formation.[9] It has found application in the synthesis of a variety of natural products.[10]

Although cross metathesis (CM) reactions of two alkenes, and recently also of an alkene and a conjugated diene, have already been studied,[11] the use of CM to construct longer conjugated polyene systems is very limited.[12] In our previous paper, we reported the CM reaction of β-carotene with ethyl (2*E*,4*E*/*Z*)-3-methylhexa-2,4-dienoate.[13] In spite of the fact that there are many alternative reaction sites in the polyene molecule, the reaction was regio- and diastereoselective. The major product was either ethyl all-*trans*-retinoate or 12′-β-apocaroten-12′-oate, depending on reaction conditions. With this promising preliminary result in hand, we decided

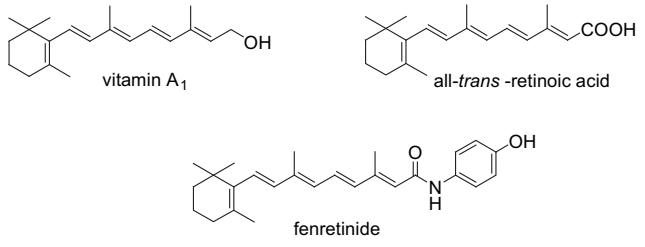

Fig. 1. Natural and synthetic retinoids.

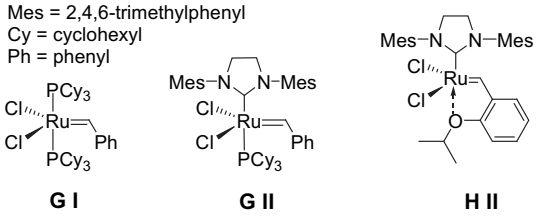

Fig. 2. Examples of the commercially available metathesis catalysts.

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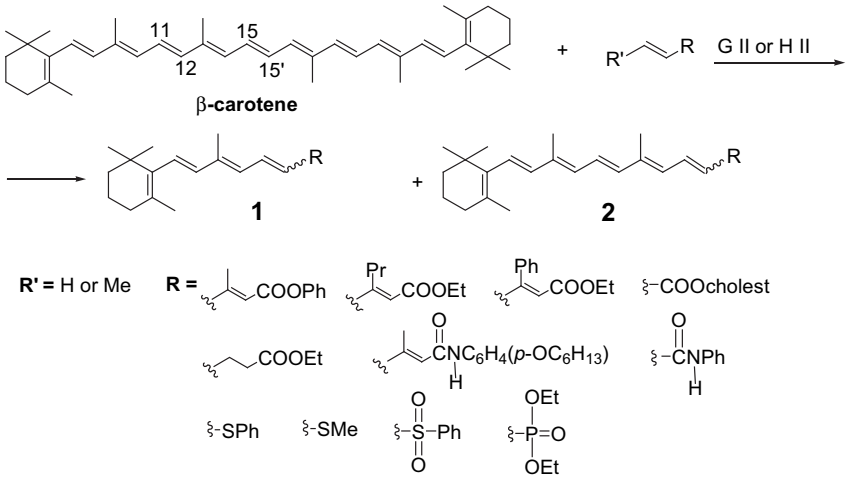
to define the scope and limitation of CM reactions of different polyenes in order to develop the CM methodology of retinoid synthesis, including fenretinide analogues and other apocarotenoids.

2. Results and discussion

Clearly our first goal was to find out if CM of β-carotene with different olefins can also be accomplished effectively and selectively. As cross partners alkenoic and dienoic acid esters, amides, as well as vinyl sulfide, sulfone, and phosphate were chosen (Scheme 1). The experiments were carried out under conditions elaborated in our preliminary study on the β-carotene reaction with ethyl (2*E*,4*E*/*Z*)-3-methylhexa-2,4-dienoate (polyene concentration 0.1 M, 4 equiv of a cross partner, second generation Hoveyda–Grubbs catalyst (H II), toluene, rt). In the case of a disappointing outcome, the reaction conditions were optimized. Various catalysts (G II, H II), catalyst loading (5–20 mol %), amount of a cross partner (1–4 equiv), solvents (CH_2Cl_2, toluene, MeOH), reaction temperature (rt, 40 °C, or 60 °C), and time (20 min–120 h) were tested. The results are summarized in Table 1.



Scheme 1. CM between β-carotene and different cross partners.

Table 1
CM reactions between β-carotene and different cross partners

Entry	Cross partner R'/R	Reaction conditions[a]	Yield[b,c] (*E*/*Z*)[d]	
			Product **1**	Product **2**
1[13]	**R'** = Me **R** = COOEt	H II, 4 equiv of olefin, toluene, 24 h, rt	9[e] (30:1)	38[e] (23:1)
2[13]	**R'** = Me **R** = COOEt	H II, 4 equiv of olefin, toluene, 96 h, rt	31%[f] (9:1)	15%[f] (>15:1)
3	**R'** = Me **R** = COOPh	H II, 4 equiv of olefin, toluene, 24 h, rt	6%[e] (20:1)	50%[e] (100:1)
4	**R'** = Me **R** = COOPh	H II, 4 equiv of olefin, toluene, 96 h, rt	33%[f] (30:1)	57%[f] (60:1)
5	**R'** = Me **R** = COOPh	G II, 4 equiv of olefin, toluene, 96 h, rt	4%[e] (30:1)	23%[e] (100:1)
6	**R'** = Me **R** = COOcholest	H II, 4 equiv of olefin, toluene, 24 h, rt	9%[e] (6:1)	30%[e] (10:1)
7	**R'** = Me **R** = COOcholest	H II, 4 equiv of olefin, toluene, 96 h, rt	12%[f] (5:1)	8%[f] (8:1)
8	**R'** = H **R** = COOEt	H II, 3 equiv of olefin, toluene, 96 h, rt	20%[d] (1.5:1)	6%[d] (5:1)
9	**R'** = H **R** = Pr, COOEt	Various conditions	<1%[e]	<1%[e]
10	**R'** = H **R** = Ph, COOEt	Various conditions	<1%[e]	<1%[e]
11	**R'** = Me **R** = CNC6H4(*p*-OC6H13)	H II, 2 equiv of olefin, CH_2Cl_2, 96 h, rt	22%[f] (>80:1)	32%[f] (20:1)
12	**R'** = Me **R** = CNPh	H II, 1.1 equiv of olefin, 72 h, rt, toluene/CH_2Cl_2	19%[f] (3:1)	21%[f] (3:1)

[a] Catalyst (15 mol %) was used in all experiments.
[b] Yields were calculated in relation to β-carotene and were divided by two due to the symmetry of β-carotene molecule.
[c] The remaining material was mainly the unreacted β-carotene, although its stereochemical purity was not analyzed.
[d] Diastereomeric ratio determined by NMR or HPLC analysis.
[e] Yield obtained by quantitative HPLC analysis.
[f] Isolated yield.