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Ring-closing metathesis for the synthesis of benzo-fused bicyclic compounds

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Abstract—Ring-closing metathesis (RCM) was used to synthesise five 4H-chromenes, a naphthol and an indenol. These are the first examples of RCM applied to the synthesis of such benzo-fused bicyclic compounds. © 2002 Elsevier Science Ltd. All rights reserved.

Small molecules with bicyclic skeletons are ubiquitous in Nature and often show interesting biological activities. This feature has been capitalised on in the pharmaceutical industry as bicyclic molecular scaffolds have been models for the design of interesting pharmacophores with a plethora of bioactivities.^{1,2} It should then come as no surprise that there is a wide range of approaches to the syntheses of these compounds, including the use of the versatile metathesis reaction using the Grubbs' catalysts.³⁻¹⁰ However, amongst the large numbers of examples described in reviews, relatively few examples utilise RCM for the synthesis of benzo-fused bicyclic molecules.^{11–17} As part of our ongoing interest^{18–20} in the synthesis of this class of compounds, we report our preliminary results on a general synthetic approach to a range of benzo-fused bicyclic molecules, using the Grubbs' second-generation catalyst 1 in the key ring-closing step. Using simple precursors we were able to synthesize specific examples of 4*H*-chromenes, naphthols and indenols, all of which are found as structural units in natural products.²¹



1. 4H-Chromenes

The 4*H*-chromenes (also known as 4*H*-1-benzopyrans), are interesting compounds that have been isolated from natural sources.²² We decided to examine the possibility of using the RCM strategy for the synthesis of this class of compounds. Three differently substituted phenols, 2, were subjected to O-allylation, followed by Claisen rearrangement to form the substituted phenols 3a-e in moderate yields (Scheme 1). Vinylation of 3a-e with tetravinyltin according to a recently published procedure²³ gave the bis-alkenes 4a-e in excellent vields. These compounds were then easily converted into their corresponding 4H-chromene derivatives 5a-eusing catalyst 1 under standard reaction conditions.²⁴ RCM using Grubbs' catalysts on substrates containing electron-rich vinylic olefins is known to be problematic^{25,26} and to our knowledge these results are the first examples of high-yielding metathesis reactions with phenolic vinyl ethers.



Scheme 1. Reagents and conditions: (a) K_2CO_3 , allyl bromide or crotyl bromide, acetone; (b) Δ (240°C), neat; (c) Cu(OAc)₂, Sn(vinyl)₄, acetonitrile, O₂; (d) 5% catalyst 1, toluene (for yields see Table 1).

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Table 1. Yields for Scheme 1

	2 → 3	3→4	4→5
a R^2 , $R^3 = OMe$, R^1 , R^4 , $R^5 = H$	45%	98%	90%
b R^1 , $R^3 = OMe$, R^2 , R^4 , $R^5 = H$	91%	99%	80%
c R^1 , $R^4 = OMe$, R^2 , R^3 , $R^5 = H$	63%	99%	85%
d R^2 , $R^3 = OMe$, R^1 , $R^4 = H$; $R^5 = Me$	65%	98%	98%
e R^1 , $R^3 = OMe$, R^2 , $R^4 = H$; $R^5 = Me$	42%	98%	82%

Although substituted 2*H*-chromenes have been synthesized before^{13–16} by the RCM approach, our strategy represents a direct synthesis of the related 4*H*chromene skeleton. In addition, we have achieved a concise synthesis of 6,7-dimethoxy-4*H*-chromene **5a**,²⁴ a natural product with interesting organoleptic properties,²⁷ isolated from *Wisteria sinensis*.²⁸

2. Naphthols

We also wish to report progress in the application of RCM to the synthesis of substituted naphthols. Treatment of readily available 6^{18} with vinylmagnesium bromide gave alcohol 7 in moderate yield (Scheme 2). Oxidation of 7 with MnO₂ gave the α , β -unsaturated system 8 and subsequent treatment with Grubbs' catalyst 1 afforded the naphthol $9a^{29}$ in good yield, while reaction of alcohol 7 under similar conditions gave naphthalene 9b as previously reported in the literature.¹¹ This facile method of synthesizing the naphthol is complementary to our previously reported naphthalene synthesis¹⁸ and is important in light of the common occurrence of the naphthol skeleton in natural products.³⁰ Another point to note is that when alcohol 7 was subjected to metathesis with catalyst 1, immediately followed by hydrogenation,³¹ the dihydronaphthalene 10 was obtained as an intermediate³² which readily



Scheme 2. Reagents and conditions: (a) vinyImagnesium bromide, THF, 0°C (50%); (b) MnO₂, benzene (54%); (c) 5% catalyst 1, dichloromethane; (d) 5% catalyst 1, dichloromethane; then H₂ (g) (65%, two steps).

aromatised to the corresponding naphthalene 9b in deuterated chloroform or on silica gel.^{33,34}

3. Indenols

Indenols and indenones are also important compounds as a result of their biological activities and they have been successfully used as intermediates in the syntheses of a variety of natural products.³⁵ The conjugated styrene system **11** was readily synthesized as previously reported.¹⁸ Addition of vinylmagnesium bromide to the aldehyde group of **11** then afforded alcohol **12** (Scheme 3). Subsequent RCM on substrate **12** then gave the indenol **13**³⁶ in reasonable yield. A noteworthy point is that this reaction worked unusually well considering the internal alkene involved in the metathesis.



Scheme 3. *Reagents and conditions*: (a) vinylmagnesium bromide, THF, 0°C (54%); (b) 5% catalyst 1, dichloromethane (67%).

We have thus shown that the versatile RCM reaction, with the Grubbs' second-generation catalyst 1, can be applied to the synthesis of a number of benzo-fused bicyclic compounds, namely 4H-chromenes, naphthols and indenols. The extension of this work to the synthesis of various natural products as well as other interesting systems is currently under investigation.

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 5a: ¹H NMR (CDCl₃, 200 MHz, assignments with superscripts can be interchanged): δ 3.31–3.33 (2H, m, H-4); 3.82 (6H, s, 2×OCH₃); 4.86–4.93 (1H, m, H-3); 6.42 (1H, s, H-8);^a 6.46 (1H, s, H-5);^a 6.42–6.46 (1H, m, H-2).
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