Pergamon

Tetrahedron Letters 43 (2002) 1561–1564

TETRAHEDRON LETTERS

Totally atom economical tandem-metathesis and Diels–Alder approach to polycyclic compounds

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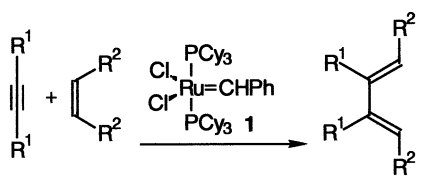
Received 12 November 2001; accepted 21 December 2001

Abstract—Norbornene derivatives bearing pendant alkynes undergo a series of tandem metathesis reactions when treated with Grubbs' catalyst. The products of this cascade are dienes which can be trapped in situ by dienophiles in Diels–Alder reactions to yield polycyclic compounds.

In recent years there has been enormous interest in the use of alkene-metathesis reactions in organic synthesis, largely sparked by the discovery of Grubbs' catalyst **1** which is a commercially available, air stable and functional group tolerant catalyst for a wide range of alkene metathesis reactions.[1] Grubbs' catalyst is also known to induce ene–yne metatheses,[1–3] reactions which, whilst not currently as widely exploited as alkene-metatheses, have the advantage of leading to products containing diene units[4] (Scheme 1). We have used catalyst **1** to initiate a variety of ring-opening-metathesis-polymerization reactions based on the use of norbornene (bicyclo[2.2.1]hept-2-ene) containing monomers.[5] Norbornene derivatives are particularly suitable substrates for metathesis reactions since they are readily prepared by Diels–Alder reactions and the release of strain energy during the metathesis of the double bond makes the reaction irreversible. In this communication we report our first results on the use of Grubbs' catalyst to induce highly selective tandem-alkene and ene–yne-metathesis reactions of norbornene derivatives.[6]

It was anticipated that the bis-propargyloxy-norbornene derivative **2** would be a suitable and interesting substrate for ene–yne metathesis reactions. In particular, there was literature precedent for the ring-opening–ring-closing metathesis of the corresponding bis-allyloxy-norbornene derivative using a chiral molybdenum based metathesis catalyst.[7] Compound **2** was readily prepared by treatment of known diol[8] **3** with propargyl bromide (Scheme 2).[9] Gratifyingly, treatment of compound **2** with 5 mol% of catalyst **1** under an ethene atmosphere[10] led to the isolation of tricyclic bis-diene **4** in 53% yield. Compound **4** subsequently underwent a double Diels–Alder reaction with maleic anhydride to give heptacyclic bis-anhydride **5a** as a single stereoisomer in 47% yield. The stereochemistry of compound **5a** is based on: the three-dimensional shape of bis-diene **4** resulting in a preference for the Diels–Alder reaction to occur on the *exo*-face of the dienes; the known kinetic preference for Diels–Alder reactions to occur through an *endo*-transition state; the symmetrical nature of compound **5a**; and the observation of an NOE between H_a and H_b, a result which a three-dimensional model showed was only consistent with the product shown. The conversion of compound **2** directly into product **5a** could also be achieved in one-pot simply by adding maleic anhydride to the metathesis mixture after 4 h. All of the atoms originally present in substrate **2**, maleic anhydride, and ethene are incorporated into heptacyclic derivative **5a**, making the process 100% atom economical. Compound **4** also underwent Diels–Alder reactions with di-isopropyl azodicarboxylate to give bis-hydrazine **5b** and with dimethyl acetylene–dicarboxylate to give bis-aromatic compound **5c** after aromatization of the bis-dihydrobenzene intermediate with DDQ. The synthesis of **5c** could also be accomplished in a one-pot reaction, directly from **2** by sequential addition of reagents in 30% overall yield.



Scheme 1.

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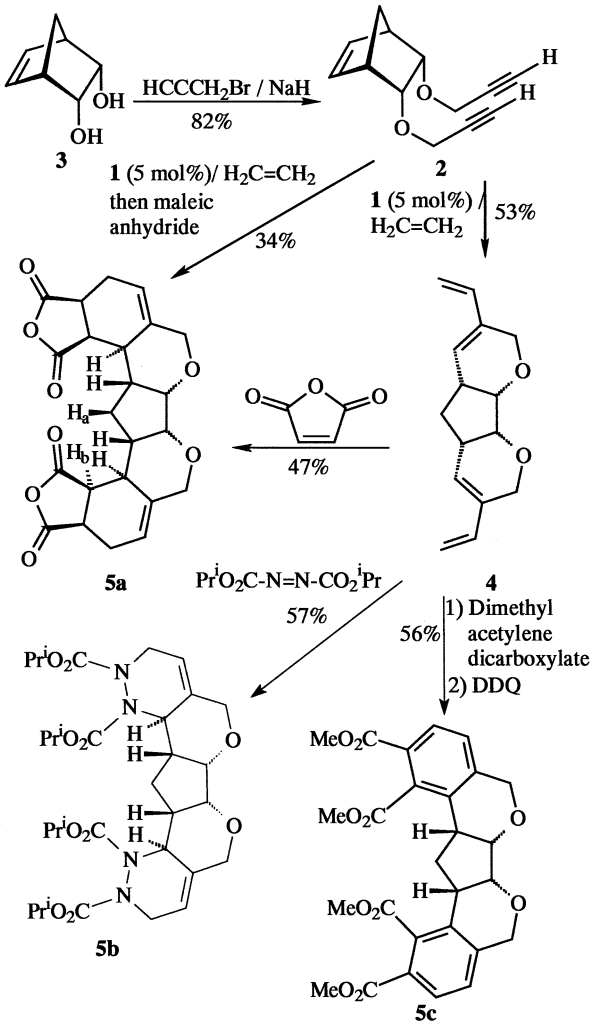
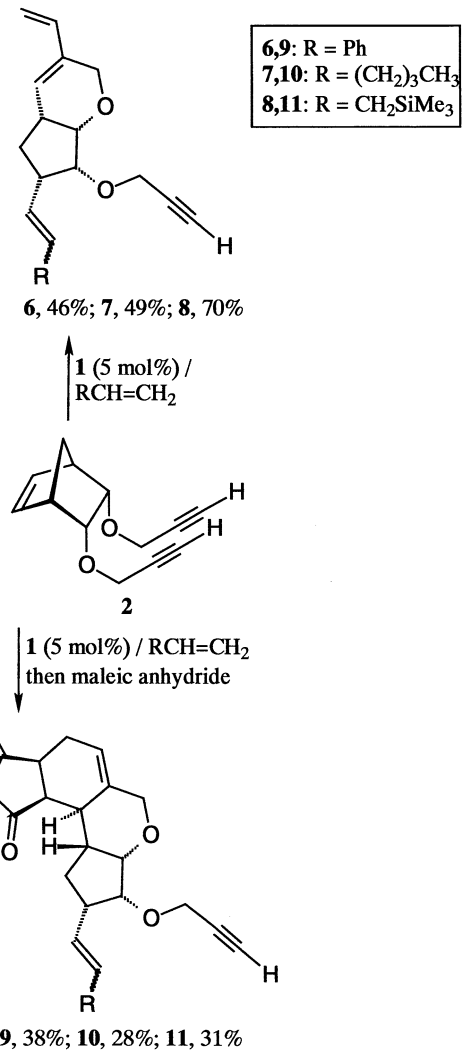


Scheme 2.

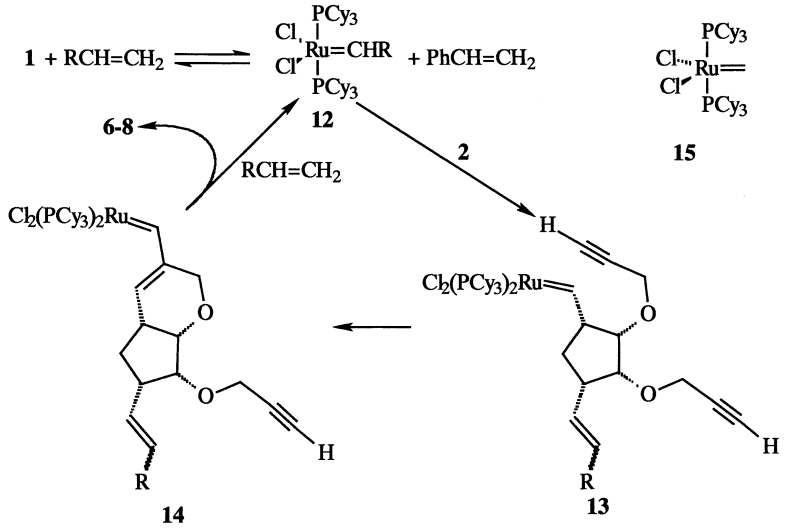
Encouraged by the facile formation of bis-diene **4** using ethene, the use of alternative unsymmetrical alkenes was investigated.[11] When substrate **2** was treated with Grubbs' catalyst in the presence of at least 2.5 equiv. of styrene, hexene or allyl trimethylsilane, dienes **6–8** were obtained (Scheme 3). Compounds **6–8** were each obtained as a mixture of *cis*- and *trans*-isomers (1:3–1:4 ratio) at the disubstituted double bond. In the case of compounds **7** and **8** these could be separated by flash chromatography. Whilst various ring-opening followed by ring-closing or cross metatheses of norbornene derivatives have been reported previously,[7,12,13] the inclusion of ring-closing ene–yne metathesis in this cascade sequence has not previously been reported.[14]

It was also possible to combine the metathesis reactions of compound **2** with a Diels–Alder reaction using maleic anhydride, all in one-pot (Scheme 3), leading to tetracyclic products **9–11**. Compounds **9–11** were again obtained as mixtures of *cis*- and *trans*-isomers at the disubstituted alkene, but were otherwise stereochemically pure. The stereochemistry of compounds **9–11** is assumed to be exactly analogous to that of compound **5a**.

The formation of compounds **6–8** requires a series of four tandem metathesis reactions as shown in Scheme 4. Thus, Grubbs' catalyst must initially react with the terminal alkene to generate a new metathesis catalyst **12**. When the alkene is styrene, this is a degenerate metathesis. The new catalyst then reacts with the strained disubstituted double bond of the norbornene ring to give ruthenium complex **13**. Compound **13** spontaneously undergoes a ring-closing ene–yne metathesis to generate bicyclic derivative **14**, which finally undergoes cross metathesis with another molecule of the terminal alkene to give the diene product **6–8** and regenerate metathesis catalyst **12**. Evidence to support the catalytic cycle shown in Scheme 4 was obtained from an NMR experiment in which Grubbs' catalyst and allyl trimethylsilane were mixed in $CDCl_3$. ^1H NMR spectroscopy of the resulting mixture (after 40 min) showed the presence of a 12:1 mixture of **12** ($R = CH_2SiMe_3$) and methylidene complex **15**. Hence, complex **12**, which is needed to initiate the catalytic cycle, is the major product from reaction of Grubbs' catalyst with a terminal alkene. A similar route forms compound **4** by a series of seven consecutive metathesis reactions.

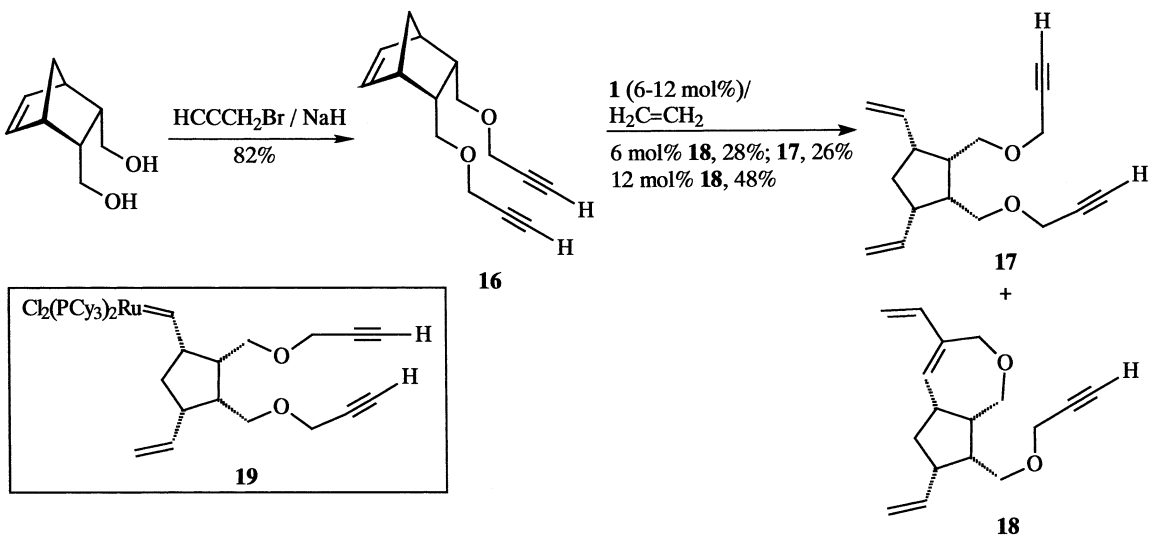


Scheme 3.



Scheme 4.

To further demonstrate the utility of this chemistry, its extension to the use of substrate **16** was investigated. Compound **16** can be prepared by reaction of *endo*,*endo*-2,3-bis-hydroxymethyl-norborn-5-ene[15] with propargyl bromide (Scheme 5) and is a more challenging substrate for the tandem-metathesis reactions since the product of ene–yne metathesis contains seven-membered rings. In the event, treatment of compound **16** with 6 mol% of metathesis catalyst **1** under an ethene atmosphere for 1 day gave a 1:1 mixture of compounds **17** and **18**, and none of the product arising from double ene–yne metathesis. Interestingly, the analogue of compound **16** in which both alkynes are reduced to alkenes is known to undergo a tandem ring-opening, double ring-closing metathesis cascade leading to a 7,5,7 fused ring system.[13] To form compound **17**, Grubbs' catalyst must first undergo a metathesis reaction with ethene to give the highly reactive and unstable ruthenium methylidene complex[16] **15**, which then initiates the ring-opening metathesis of the norbornene ring. The resulting ruthenium–alkylidene complex **19** must then undergo metathesis with ethene to give compound **17** rather than ring-closing ene–yne metathesis. Compound **18** can be formed in two ways: direct ring-closing ene–yne metathesis of complex **19**, or metathesis between complex **1** or **15** and compound **17** to reform alkylidene **19** which can then undergo ring-closing ene–yne metathesis. In both cases, trapping of the ring-closed ruthenium–alkylidene with ethene would give compound **18**. Evidence for the latter route was obtained by carrying out a reaction in which a second 6 mol% batch of catalyst **1** was added to a reaction after 24 h and the reaction left for a further 24 h. Under these conditions, the ratio of compound **18** to **17** increased to greater than 4:1 and compound **18** was isolated in 48% yield. Hence, the reactions of substrate **16** provide further support for the catalytic cycle shown in Scheme 4, and in particular, prove that for these norbornene derivatives, the initial metathesis reaction is between the ruthenium–alkylidene and the alkene rather than with the alkyne.



Scheme 5.

In summary, we have demonstrated that Grubbs' catalyst can be used to transform readily available norbornene derivatives into highly-functionalized polycyclic systems in a rapid and completely atom-economical process. Studies aimed at further extending the scope of this chemistry and the development of methodology to allow the preparation of enantiomerically pure compounds using ene–yne metathesis of norbornene derivatives are currently underway.

Acknowledgements

The authors thank King's College London for a studentship (D.B.) and generous financial support, and Professor V. C. Gibson and Dr. E. Marshall of Imperial College London for their help and advice in the preparation of Grubbs' catalyst. Mass spectra were recorded by the EPSRC mass spectrometry service based at the University of Wales, Swansea.

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