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Employment of a cyclobutene ring-opening metathesis reaction towards a concise synthesis of (±)-sporochnol A

Martin J. Bassindale,[a] Peter Hamley[b] and Joseph P. A. Harrity[a,*]

[a]*Department of Chemistry, University of Sheffield, Brook Hill, Sheffield S3 7HF, UK*
[b]*Department of Medicinal Chemistry, AstraZeneca Charnwood, Bakewell Road, Loughborough LE11 5RH, UK*

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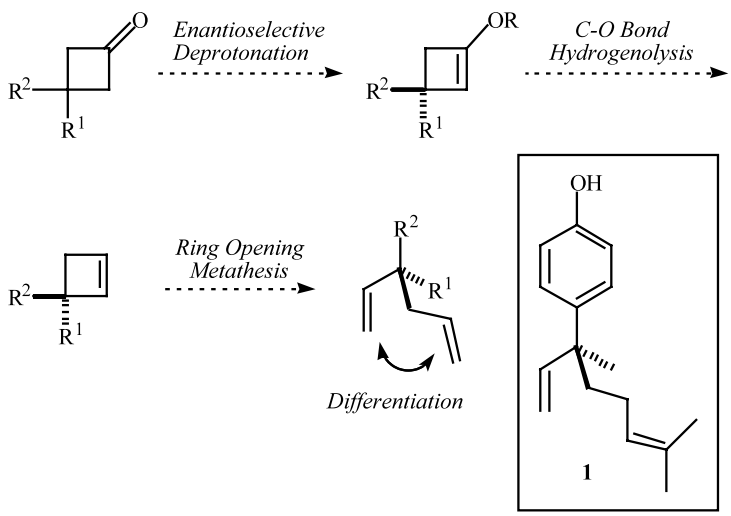
Abstract—A concise formal synthesis of (±)-sporochnol A **1**, a naturally occurring feeding deterrent towards herbivorous fish, is described. The target compound was prepared by the employment of a Ru-catalysed cyclobutene ring-opening metathesis reaction with gaseous ethylene followed by a site selective hydroboration reaction as the key steps. The optimisation of the metathesis process regarding the Ru-catalyst and reaction conditions is also delineated. © 2001 Elsevier Science Ltd. All rights reserved.

The development of efficient techniques for the construction of quaternary centres remains a significant challenge in organic chemistry, particularly when control of absolute stereochemistry is required.[1] In this context, we have recently initiated studies towards the development of a new approach to quaternary centre containing synthetic intermediates through the employment of desymmetrisation of *meso*-ketones[2] followed by a ring-opening metathesis (ROM) reaction, the general strategy is illustrated in Scheme 1. As well as the key ring-opening metathesis process, the differentiation of the two newly formed alkene units is pivotal to the independent and two directional elaboration of the resulting diene intermediate. We wish to report herein our initial observations regarding the ring-opening metathesis of 3,3-disubstituted cyclobutenes with ethylene and the differentiation of the olefin units through a site selective hydroboration reaction. Additionally, the application of this method to the short formal synthesis of (±)-sporochnol A **1**, a naturally occurring compound isolated from the Caribbean marine alga *Sporochnus bolleanus*, which exhibits significant feeding deterrence toward herbivorous fish, is described.[3,4]



Scheme 1.

Keywords: cyclobutenes; ring-opening metathesis; hydroboration; sporochnol A.
* Corresponding author. E-mail: j.harrity@sheffield.ac.uk

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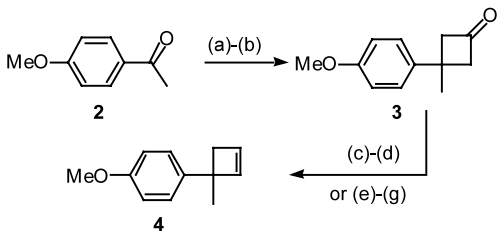
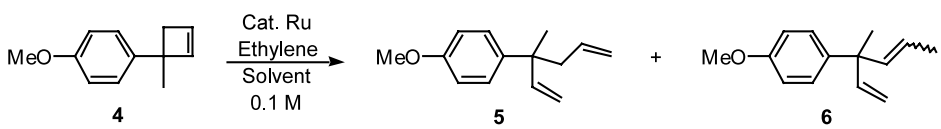
We began our studies with the preparation of cyclobutene **4** which we anticipated would be a suitable substrate to examine the ROM reaction as well as providing an appropriate substrate for the synthesis of sporochnol A. Cyclobutene **4** was prepared in a five-step sequence starting from commercially available 4-methoxyphenyl methyl ketone **2**, as outlined in Scheme 2. Accordingly, methylenation of **2** proceeded efficiently and the resulting alkene underwent clean α,α-dichlorocyclobutanone formation with trichloroacetyl chloride in the presence of a freshly prepared Zn–Cu couple. Subsequent dechlorination with Zn powder and NH_4Cl provided ketone **3** in 70% yield over the two steps.[5] We investigated two approaches for the conversion of **3** to the desired cyclobutene. Firstly, we hoped to employ a two-step approach using a Shapiro reaction.[6] Therefore, we prepared the *p*-toluenesulfonyl hydrazone of **3** and subjected this to 3 equiv. of *n*-BuLi. In the event, the reaction was very slow and was found to proceed only after heating the THF solution at reflux for over 2 h. Nonetheless, the cyclobutene could be isolated in 74% yield after chromatographic purification. Our second approach employed the sodium borohydride reduction of ketone **3**, which proceeded in excellent yield to give the corresponding alcohol as a 1:1 mixture of diastereoisomers. Subsequent tosylation followed by base-induced elimination furnished **4** in 59% overall yield over the three steps.



Scheme 2. *Reagents and conditions*: (a) Ph_3PMeBr, KOBu-*t*, THF–toluene, 25°C, 99%. (b) (i) Cl_3CCOCl, Zn–Cu, Et_2O, 25°C, (ii) Zn, NH_4Cl, MeOH, 70%. (c) $TsNHNH_2$, MeOH, 84%. (d) BuLi (3 equiv.), THF, −78 to 70°C, 74%. (e) $NaBH_4$, MeOH, 96%. (f) TsCl, pyr., 95%. (g) KOBu-*t*, DMSO, 70°C, 65%.

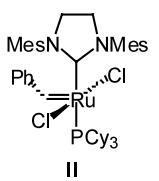
With cyclobutene **4** in hand, we turned our attention to the ROM step. The ROM of cyclobutenes has been studied extensively by Snapper and co-workers and provided firm precedent for successful incorporation of ethylene towards the desired diene.[7] Surprisingly, however, the metathesis of **4** with ethylene in the presence of 10 mol% of commercially available Grubbs' catalyst $Cl_2(Cy_3P)_2Ru{=}CHPh$ **I**[8] proved to be very sluggish and low conversion of **4** (<30%) to diene **5** was observed over a period of 16 h. Moreover, **5** could not be readily separated from the starting cyclobutene **4**. In an effort to force the ROM reaction to higher conversion, we examined the effects of reaction temperature and catalyst loading. As outlined in Table 1, complete conversion of **4** to diene **5** was only achieved using 45 mol% **I**, which had to be added to the reaction mixture in 5–10 mol% portions over 5 days. The unacceptably high catalyst loadings and reaction times required to complete the ROM reaction prompted us to examine the recently developed and more active 4,5-dihydroimidazol-2-ylidene-Ru catalyst **II**[8] for this conversion. Gratifyingly, as outlined in entry 4 of Table 1, much higher conversions were achieved with lower catalyst loadings over a significantly shorter time period. Unfortunately, however, the desired diene was contaminated with the product of olefin isomerisation **6**.[9] Since **6** must result from diene **5**, this observation suggested that the ROM reaction had proceeded to significant conversion well

Table 1. Ethylene-mediated ROM reaction of cyclobutene **4**

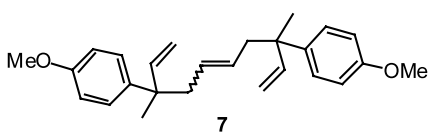


Entry	Catalyst	Conditions	Conversion	Yield (**5**:**6**)
1	10 mol% **I**	CH_2Cl_2, 20 °C, 16 h	<30%	-
2	25 mol% **I**	$Cl(CH_2)_2Cl$, 60 °C, 120 h	>90%	-
3	45 mol% **I**	CH_2Cl_2, 20 °C, 120 h	>95%	65% (>95:5)
4	10 mol% **II**	Toluene, 80 °C, 48 h	>95%	81% (70:30)
5	5 mol% **II**	$Cl(CH_2)_2Cl$, 60 °C, 3 h	>95%	52% (>95:5)
6	7 mol% **II**	$Cl(CH_2)_2Cl$, 60 °C, 16 h[a]	>95%	73% (>95:5)

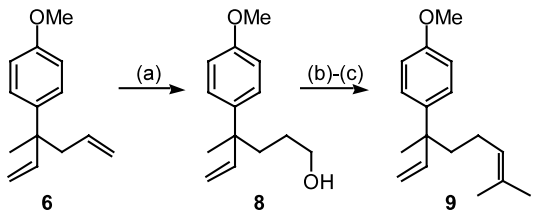
[a]Reaction carried out at 0.01 M concentration, 9% dimer **7** was also isolated.



II



7



Scheme 3. *Reagents and conditions*: (a) (i) 9-BBN, THF, 25°C, (ii) H_2O_2, 6 M NaOH, 50%. (b) Dess–Martin periodinane, 77%. (c) $Me_2C{=}PPh_3$, toluene, 59%.

within the 48 h time period employed. Indeed, we were pleased to find that the reaction was in fact complete within 3 h at 60°C and allowed us to isolate **5** with <5% **6** present in the reaction mixture (as judged by 250 MHz ^{1}H NMR). Having achieved efficient consumption of cyclobutene **4** and circumvented alkene isomerisation, we were disappointed to find that the diene **5** was only returned in 52% yield. The remainder of the mass balance comprised of dimer **7**, which was characterised on the basis of its ^{1}H NMR and mass spectrum.[10] Accordingly, the metathesis process was carried out under more dilute conditions, which provided **5** in 73% yield albeit over a longer reaction time.

Having demonstrated the effectiveness of the ROM methodology, it remained only to differentiate the alkene units of the diene product. We anticipated that the different steric environments around the alkenes would allow ready differentiation upon treatment with a bulky reagent. Indeed, treatment of **5** with 9-BBN proceeded smoothly to provide alcohol **8** in 50% isolated yield (60% based on recovered starting material) after oxidation. We were pleased to find that products of hydroboration of the more hindered alkene were not observed under these conditions.[11] We envisage that the ease of independent manipulation of the alkene and alcohol units in **8** will permit a two directional elaboration of this and related systems and this concept is currently under investigation. Nonetheless, the formal synthesis of sporochnol A was completed upon oxidation of **8** followed by Wittig olefination to provide diene **9**, which showed analytical and spectroscopic data in accordance with those previously reported (Scheme 3).[4a]

In conclusion, we have demonstrated that the ROM of 3,3-disubstituted cyclobutenes with ethylene proceeds efficiently with recently reported and highly active Ru-catalyst **II** and that the olefin units of the resulting diene can be readily differentiated by site selective hydroboration. Studies towards developing efficient enantioselective routes to 3,3-disubstituted cyclobutenes from the appropriate *meso*-ketones with a view to controlling the stereochemistry of chiral quaternary centre containing intermediates are underway and will be reported in due course.

Acknowledgements

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10. Subjection of the dimer **7** to 5 mol% **II** under an ethylene atmosphere at 60°C in DCE for 48 h resulted in 17% conversion to **5**. This suggests that dimer formation is reversible in the presence of ethylene and **II** and that isomerisation (**5→6**) highlighted in entry 4, Table 1 prevents significant quantities of dimerised product from being isolated in this case.
11. The employment of excess 9-BBN resulted in hydroboration of the remaining alkene moiety.