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# Synthesis of 'inside–outside' medium-sized rings via ring-closing metathesis

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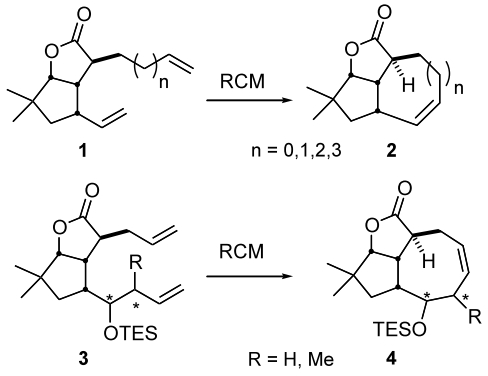
**Abstract**—Functionalized and unfunctionalized dienes were synthesized from lactones **7** and **6**, respectively, which were subjected to ring-closing metathesis (RCM) using Grubbs' catalysts. These dienes provide a systematic study of the stereochemical requirements for efficient cyclization. Moreover, it has been established that, within a uniquely defined oxabicyclo[3.3.0]octane template, medium sized rings bearing an 'in–out' intrabridgehead stereochemical relationship can been synthesized in good yield.


The construction of bridging medium-sized ring systems which exhibit an 'inside–outside' intrabridgehead stereochemical relationship remains a considerable synthetic challenge. Potential problems when designing a strategy lie in the fact that such ring systems can often undergo 'in–out'/'out–out' isomerization[1] which can give rise to mixtures or, in the worst case, exclusively the 'out–out' epimer. Research efforts on the 'in–out' ingenane tricyclic system by Winkler,[2] Funk,[3] Rigby,[4] Kuwajima[5] and Wood[6] illustrate different strategies to this unusual ring system. The first total synthesis of (±) ingenol has recently been reported by Winkler and co-workers.[2] The many recent advances in RCM,[7] in particular in the synthesis of medium-sized rings,[8] has underscored its wide applicability and potential in addressing this issue of 'in–out' isomerism.

In our recent synthesis of asteriscanolide we reported the first synthesis of an 'inside–outside' eight-membered ring by ring-closing metathesis.[9] The key ring forming event occurred in a highly efficient manner without isomerization which proved to be an intriguing result and one that warranted further investigation. The aim of this work was to establish some of the regio- and stereochemical requirements for efficient formation of 'inside–outside' medium sized rings within a stereochemically defined oxabicyclo[3.3.0]octane template. We therefore prepared a series of dienes such as **1** and **3** and subjected them to RCM and herein present our results (Scheme 1).

**Preparation of dienes**: The dienes used in this study were derived from lactones **6** and **7** respectively; both of which were key intermediates in our total synthesis of asteriscanolide.[9] Lactone **6** was prepared from enone **5** in seven steps (56%) and lactone **7** was obtained by ozonolysis of **6** followed by reductive workup with dimethyl sulfide (quant).[9] The stereodefined oxabicyclo[3.3.0]octane which is incorporated in lactones **6** and **7** ensures that alkylation of the lactone enolate will proceed on the convex face leaving the appendage *trans* to the side-chain at C-4 thus setting the 'in–out' stereochemistry prior to formation of the bridging ring. Alkylation of lactone **6** with four different alkenyl halides provided dienes **8**–**11**. The yields for these reactions varied from excellent to moderate depending on the alkenyl halide. These substrates contain no functionality along the alkene side chains and thus provide a




**Scheme 1.**

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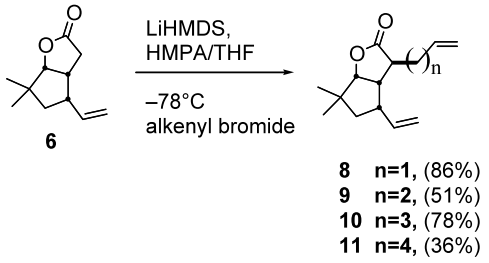
PII: S0040-4039(02)02639-4



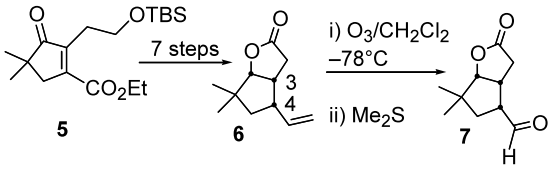

**Scheme 3.**

comparison of the effect of chain length for the generation of six-, seven-, eight- and nine-membered rings with an 'inside–outside' intrabridgehead relationship (Schemes 2 and 3).

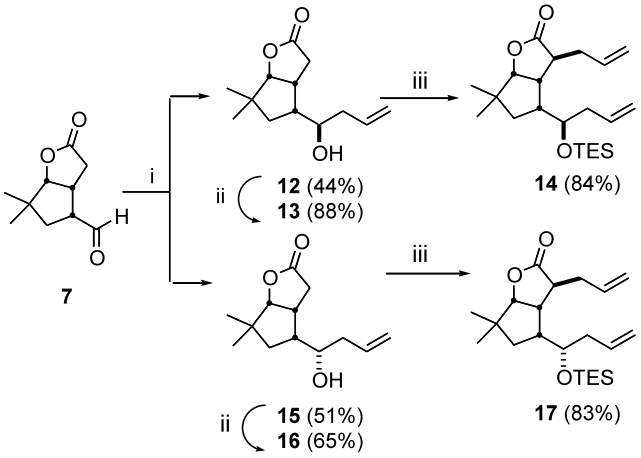
Lactone **7** provided a means to introduce functionality in the lower side-chain. This was achieved by treatment of aldehyde **7** with allylboronic acid pinacol cyclic ester which gave two diastereoisomeric alcohols **12** and **15** (1:1 ratio) that were separated by flash chromatography (Scheme 4). Homoallylic alcohols **12** and **15** were subjected in turn to reaction with TESOTf in pyridine to give the corresponding TES ethers **13** (88%) and **16** (65%). Deprotonation of **13** and **16**, in turn, at –78°C with LiHMDS/THF/HMPA, followed by alkylation with allyl bromide gave the corresponding dienes **14** (84%) and **17** (77%). Alkylation of lactone **13** proceeded smoothly at –78°C, whereas lactone **16** required warming to room temperature. The relative stereochemistry of the homoallylic alcohols was determined by evaluation of $^1$H NOE difference data of the corresponding 'inside–outside' tricycles (see Table 2).

Treatment of aldehyde **7** with (*Z*)-2-butenyl boronic acid pinacol cyclic ester gave the two *syn* homoallylic alcohols **18** (24%) and **21** (47%) in a ratio of 1:2. These alcohols were separated by flash chromatography and were similarly converted to dienes **20** and **23**, respectively (Scheme 5).

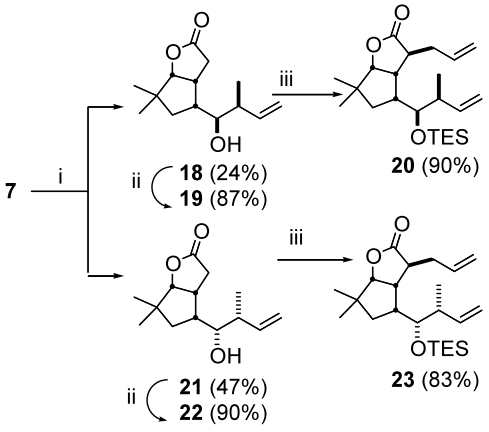
(*E*)-Crotylboration of aldehyde **7** gave a 4:1 ratio of *anti* homoallylic alcohols **24** and **27** (Scheme 6) which were separated by flash chromatography and converted to the corresponding dienes **26** and **29** via silylation and lactone alkylation. The relative stereochemistry of the substituents at the allylic and homoallylic position for these crotylboration reactions was determined by evaluation of the $^1$H NOE difference spectra of the corresponding 'inside–outside' tricycles after ring-closing metathesis.



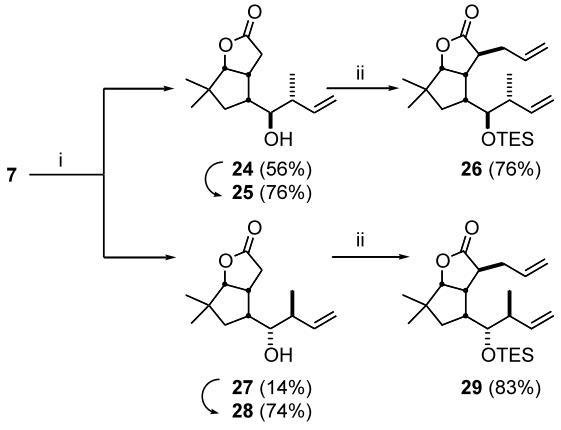

**Scheme 2.**




**Scheme 4.** *Reagents and conditions*: (i) allyl boronic acid pinacol cyclic ester; (ii) TESOTf, py.; (iii) LiHMDS, HMPA/THF –78°C; allyl bromide.




**Scheme 5.** *Reagents and conditions*: (i) (*Z*)-2-butenyl boronic acid pinacol cyclic ester; (ii) TESOTf, py.; (iii) LiHMDS, HMPA/THF –78°C; allyl bromide.



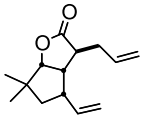
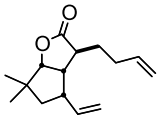
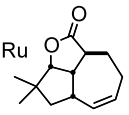
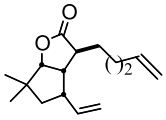
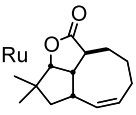
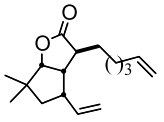
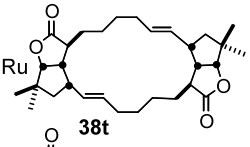
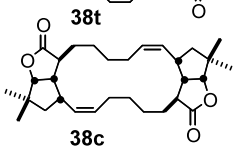

**Scheme 6.** *Reagents and conditions*: (i) (*E*)-2-butenyl boronic acid pinacol cyclic ester; (ii) TESOTf, py.; (iii) LiHMDS, HMPA/THF –78°C; (iv) allyl bromide.

Finally, treatment of aldehyde **7** with vinylmagnesium bromide gave a 2:1 ratio of allylic alcohols **30** and **33** in 47% overall yield (Scheme 7). These alcohols were converted to dienes **32** and **35**, respectively, via silylation and alkylation thus providing dienes for the synthesis of the seven-membered bridging ring bearing an inside–outside intrabridgehead relationship.

### Ring-closing metathesis of dienes

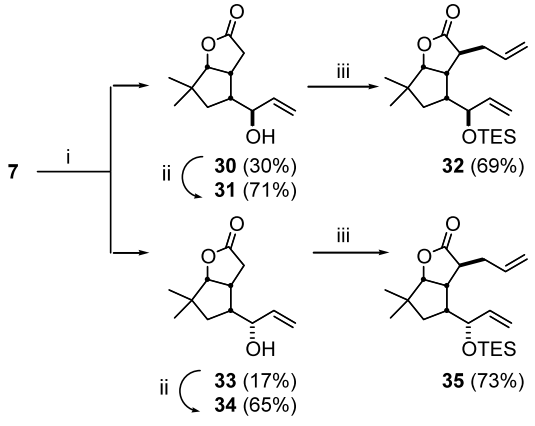
Results from ring-closing metathesis reactions of dienes **8**–**11** are summarized in Table 1. Highly efficient RCM was observed for the formation of 'inside–outside' seven- and eight-membered rings (entries 2 and 3). These reactions proceeded under mild conditions and over relatively short reaction times, between 2–3 h, using Grubbs' second generation catalyst.[10] In entry 1, the effect of ring strain in the attempted formation of a six-membered in–out bridging ring was evident as only a complex mixture of products was obtained from the reaction of diene **8**. In entry 4, the flexibility of the chains undoubtedly contributed to the formation of dimerization products **38c** and **38t** rather than ones resulting from RCM in the reaction of diene **11**. The structures of **38c** and **38t** as well as a diol of **36** were unambiguously determined by single crystal X-ray crystallography.[11] The relative ease of cyclization of **9** and **10** may be attributed to the unique conformational requirements imposed by the oxabicyclo[3.3.0]octane template. 'Inside–outside' tricycles **36** and **37** contain the core carbon framework of a number of cycloheptanoid and cyclooctanoid natural products such as rameswaralide[12] and the ophiobolins[13] and ceroplastins,[14] and this underscores the wide potential of this work.

**Table 1.**

| Entry | Diene | Conditions[a] | Product |
|---|---|---|---|
| 1 |  **8** | 20 mol% Ru, 3 h | Complex mixture of products |
| 2 |  **9** | 10 mol% Ru, 2 h |  **36** (88%) |
| 3 |  **10** | 10 mol% Ru, 2 h |  **37** (85%) |
| 4 |  **11** | 10 mol% Ru, 3 h |  **38t**<br>  **38c**<br>**38t** : **38c** 1.0 : 1.4 92% |

[a] All reactions were performed in refluxing $CH_2Cl_2$ at 0.007M or 0.015M concentration. Ru = Grubbs' second generation catalyst, ref 9.

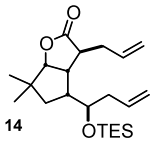
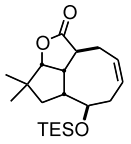
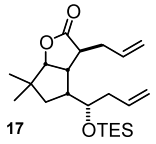
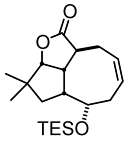
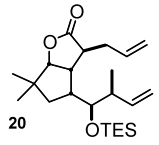
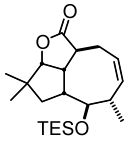
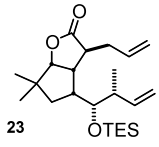
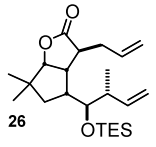
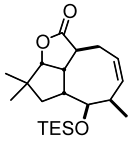
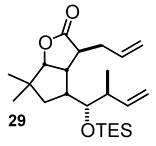
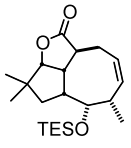
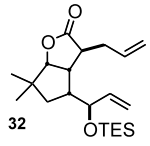
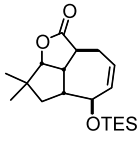
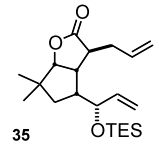
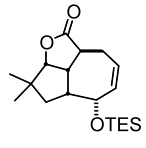
The results in Table 2 provide further insights into the effects of relative stereochemistry and the number of stereocenters on the alkenyl side-chain. One observation was the effect of the stereochemistry of the homoallylic alcohol in **14** and **17**. This is illustrated by entries 1 and 2, where the reaction of **14** with TES group in the β-configuration proceeded faster than the corresponding α-diastereoisomer in refluxing methylene chloride. We rationalized that this was due to the TES ether of diene **17** being on the concave face of the newly forming tricyclic ring system which leads to a more sterically demanding system. On this basis, we had originally envisioned that diene **17** may not cyclize and would probably undergo dimerization. Although initial studies indicated that reactions occurred at room temperature for dienes **14** and **17**, the reactions did not proceed with complete consumption of starting material. We therefore performed these and all latter reactions in refluxing methylene chloride. In entries 3 and 4 we observed a clear effect of the stereochemistry of two substituents in the homollylic and allylic position of the lower alkene side chain. To our good fortune substrate **20** had the correct orientation for the C-7 methyl for elaboration to asteriscanolide after RCM.[9] At this point we do not have an explanation for why diene **23** does not cyclize. Another surprising result is entry 5 where diene **26** was the slowest substrate to cyclize (3 days), whereas in entry 6 cyclization of diene **29** occurs relatively smoothly to give the tricycle **43**. The effect of stereochemistry of the TES ether is even more pronounced when entries 7 and 8 are considered. Lactone **32** cyclizes with high efficiency, however, diene **35** gives




**Scheme 7.** *Reagents and conditions*: (i) vinylmagnesium bromide/THF 0°C; (ii) TESOTf, py.; (iii) LiHMDS, HMPA/THF −78°C; allyl bromide.

mainly starting material along with a small amount of tricycle **45**. We believe that this is a result of a combination of increased ring strain and the α-orientation of the TES ether which would favor ring opening of the desired product **45** via ring-opening metathesis.

**Table 2.**

| Entry | Diene | Conditions[a] | Product | Yield |
|---|---|---|---|---|
| 1 |  **14** | 23 mol% Ru reflux 8 h |  | **39** (86%) |
| 2 |  **17** | 20 mol% Ru reflux 24 h |  | **40** (80%) |
| 3 |  **20** | 50 mol% Ru reflux 24 h |  | **41** (92%) |
| 4 |  **23** | 50 mol% Ru reflux 24 h | No Reaction | |
| 5 |  **26** | 60 mol% Ru reflux 3 d |  | **42** (60%) |
| 6 |  **29** | 50 mol% Ru reflux 26 h |  | **43** (69%) |
| 7 |  **32** | 40 mol% Ru reflux 16 h |  | **44** (90%) |
| 8 |  **35** | 40 mol% Ru reflux 17 h |  | **45**(12%) + s/m (33%) |

[a] All reactions were performed in $CH_2Cl_2$ at 0.007M or 0.015M concentration Ru = $(PCy_3)_2Ru(CHPh)Cl_2$

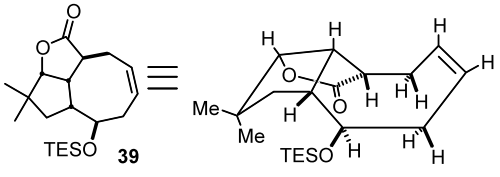


**Figure 1.**

## Confirmation of 'inside–outside' stereochemistry

The stereochemistry of all tricycles with an 'in–out' intrabridgehead relationship was confirmed by $^1H$ NOE spectroscopic studies. Furthermore these studies suggested basically two types of conformations for the newly formed eight-membered ring which are illustrated by the proposed conformations of **39**, **40** and **41**. In both tricycles **39** and **40**, the bridging eight-membered ring adopts a boat,boat conformation (tub-like) (Figs. 1 and 2). Both **39** and **40** were desilylated to the corresponding alcohols **46** and **47**, respectively, which were oxidized, in turn, to the keto-lactone **48** (Scheme 8). The structure of **48** was solved by X-ray crystal analysis[9] which confirmed the 'in–out' intrabridgehead stereochemistry and also showed that the eight-membered ring adopted a boat,boat conformation (Fig. 3).

We found from NOE studies of tricycle **41** that the eight-membered ring adopted a different boat,boat con-

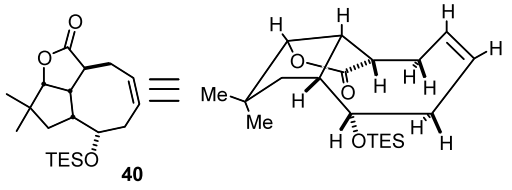
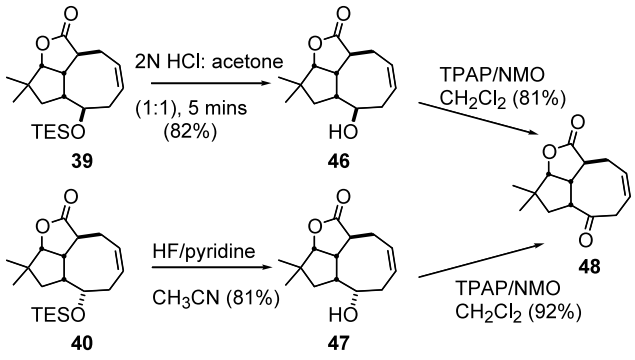


**Figure 2.**



**Scheme 8.**

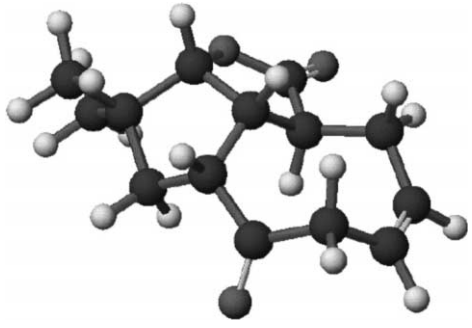


**Figure 3.**

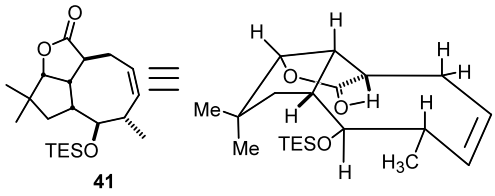



**Figure 4.**

formation (Fig. 4). This enables both the TES and methyl groups to be on the convex face of the molecule thus minimizing steric requirements on the concave face.

In summary, these studies on the RCM of dienes attached to a stereodefined oxabicyclo[3.3.0]octane template have furnished a number of 'inside–outside' seven- and eight-membered rings. We rationalize that the unique conformational constraints imposed by this bicyclic template provide a major contributing factor towards efficient cyclization to give the unusual 'in–out' intrabridgehead stereochemistry. In the case of the more functionalized dienes, we have established some of the stereochemical requirements for allylic and homoallylic substituents on one side chain. We are currently applying this work towards the synthesis of cycloheptanoid and cyclooctanoid containing natural products.

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