Asymmetric Aldol−Ring-Closing Metathesis Strategy for the Enantioselective Construction of Six- to Nine-Membered Oxygen Heterocycles

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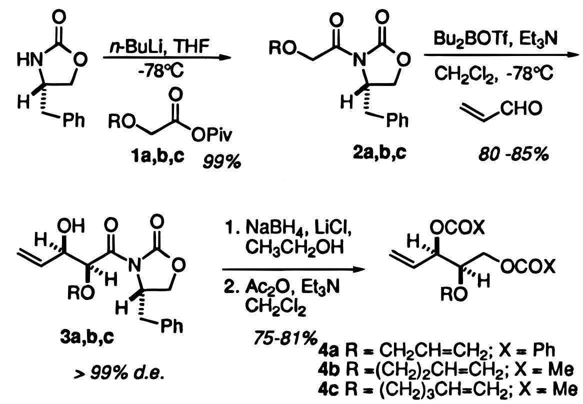
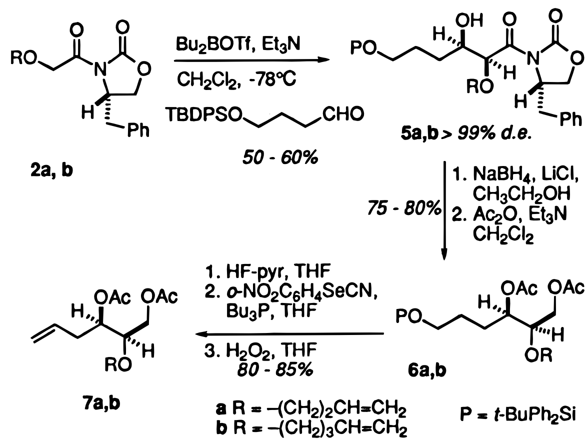
The ring closing metathesis reaction has rapidly become an important transformation in organic synthesis.[1] Examples of many ring sizes with a variety of functional appendages[2] have been constructed by this powerful method, largely because of the advent of the functionally tolerant ruthenium[3] and molybdenum[4] carbene complexes. Even kinetically and thermodynamically disfavored eight-membered rings have been prepared by ring- closing metathesis. However, virtually all[5] successful eight-membered ring closures have required the incorporation of cyclic conformational constraints[6] or rigid acyclic conformational control elements to avoid formation of dimers or oligomers.[7] It is noteworthy that cyclic constrained dienes underwent more efficient ring- closing metathesis to form eight-membered rings when the two olefinic chains were positioned trans on the cyclic constraint than when they were cis.[7] Grubbs[6a] has attributed this effect to a greater difference in energy between the diene and the cyclic olefin in the cis-substituted substrate. We reasoned that dienes with an appropriate acyclic conformational bias might allow eight (or nine)-membered ring formation and avoid the additional strain imposed by a fused ring attached to the newly formed cyclic olefin.

Scheme 1



Scheme 2



We recently reported an asymmetric aldol−ring-closing metathesis strategy for the enantioselective synthesis of the carbocyclic fragment of the nucleoside analogue 1592U89.[8] In view of the importance of enantioselective approaches to cyclic ethers of all sizes, particularly eight- and nine-membered ring metabolites that are abundant in marine algae,[9] an extension of the aldol−metathesis strategy to oxygen heterocycles seemed in order. We report here an efficient, general strategy for the asymmetric synthesis of six- to nine-membered cyclic ethers.[10]

The general strategy for the asymmetric construction of the required dienes is illustrated in Schemes 1 and 2. Treatment of 2-propen-1-ol, 3-buten-1-ol, and 4-penten-1-ol, respectively, with sodium hydride and bromoacetic acid in THF gave the α-alkoxy acids in nearly quantitative yield. Subsequent exposure of the acids to pivaloyl chloride and triethyl amine provided the mixed anhydrides **1a**−**c** in situ. Acylation of the lithium salt of (*S*)-2-benzyloxazolidinone with the mixed anhydrides **1a**−**c** provided the acyl oxazolidinones **2a**−**c** in greater than 90% yield in all cases. Formation of the dibutylboron

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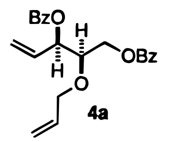
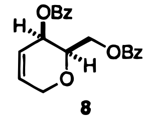
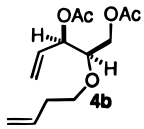
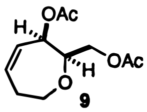
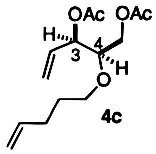
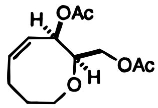
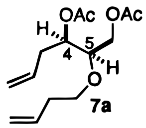
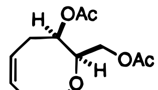
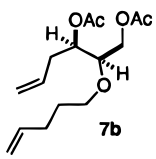
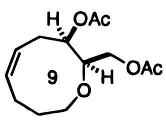
Table 1

Diene	Product	Yield[a,b]
 **4a**	 **8**	90% 1 h
 **4b**	 **9**	95% 2 h
 **4c**	 **10**	73% (17% dimer) 2 h
 **7a**	 **11**	94% 30 min
 **7b**	 **12**	89% (10% dimer) 1 h

[a] Reactions were carried out in dichloromethane at 40 °C with 5−7 mol % $(Cy_3P)_2Cl_2Ru{=}CHPh$. [b] Yields are for isolated, chromatographically purified products.

enolate according to the standard Evans[11] protocol and addition of acrolein gave the syn aldol products **3a**−**c** as single detectable isomers by 300 MHz NMR. Reductive removal of the chiral auxilliary ($LiBH_4$, MeOH, THF) followed by acylation of the resultant diols produced the required dienes **4a**−**4c** each in five synthetic steps in good overall yield[12] (>99% ee). The homologous dienes **7a,b** were prepared (Scheme 2) from 4-[(*tert*-butyldiphenylsilyl)oxy]butanal. Aldol addition of the boron enolate of **2a** or **2b** to 4-[(*tert*-butyldiphenylsilyl)oxy]butanal as described above produced the aldol products **5** with excellent stereoselectivity. Subsequent removal of the auxilliary and acylation of the resultant diols gave the diacetates **6**. Cleavage of the silyl ether with HF−pyridine in THF, conversion of the primary alcohol to the corresponding aryl selenide, and oxidative elimination under standard conditions[13] provided the dienes **7a** and **7b**.

Ring-closing metathesis reaction of diene **4a** (CH_2Cl_2, 0.1 M, 40 °C) was carried out with 4 mol % of the Grubbs catalyst $\{[(C_6H_{11})_3P]_2Cl_2Ru{=}CHPh\}$. The reaction was complete in 30 min and produced the dihydropyran **8** (see Table 1) in 90% yield after chromatography. Under similar conditions, treatment of the diene **4b** resulted in predominant formation of the dimer. Fortunately, when the concentration was lowered (0.003 M CH_2Cl_2, 40 °C, 5−7 mol % catalyst), the reaction resulted in exclusive formation of the oxepene **9** in 95% yield after 2 h. More interestingly, when diene **4c** was exposed to the ruthenium carbene (0.003 M CH_2Cl_2, 40 °C), an excellent yield (73%) of the Δ-4-oxocene **10** was realized together with 17% of a dimer. An even more impressive result was obtained upon exposure of diene **7a** to ring-closing metathesis (5−7 mol % catalyst, 0.003 M, CH_2Cl_2, 40 °C). Nearly quantitative conversion (94% yield) to the Δ-4-oxocene **11** was observed in less than 30 min with no recovered diene and no detectable dimerization. Cyclic ether **11** contains all the required functionality with the exception of the C8 alkyl group, needed for the synthesis of a variety of marine metabolites such as laurencin and prelaureatin. The contrast in efficiency between the ring-closing metathesis of diene **7a** to Δ-4-oxocene **11** and diene **4c** to oxocene **10** can be rationalized by the relative energies of the products. The position of the olefin has a dramatic effect on the relative energy of the oxocene. Oxocene **11** was calculated[14] to be on the order of 3−4 kcal lower in energy than oxocene **10**. This difference in energy is presumably reflected in the transition states for formation of the metallocyclobutane intermediates. Also, the vicinal stereogenic centers in dienes **4c** and **7a** provide access to the conformations where the olefinic chains are gauche, which are required to facilitate ring closure, by minimizing the difference in energy of the three staggered conformations about the C3−C4 bond of **4c** (C4−C5 bond of **7a**). The dipolar stabilization that results from the anti disposition of the two oxygens may contribute substantially to the stabilization of one of the conformations with the olefinic chains *gauche*.

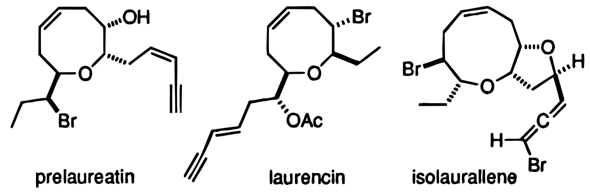


Figure 1.

Finally, when diene **7b** was exposed to ring-closing metathesis conditions (0.003 M CH_2Cl_2, 40 °C, 5−7 mol % catalyst), the nine-membered cyclic ether **12** was obtained as the major product in 89% yield accompanied by 10% dimers. Cyclic ether **12** is similar in substitution to the known metabolite isolaurallene. To our knowledge, this is the first example of the formation of a nine-membered ring by ring-closing metathesis without a cyclic conformational constraint.[6f]

In summary, a general, enantioselective synthesis of six-, seven-, eight- and nine-membered cyclic ethers has been achieved through the exploitation of an asymmetric aldol−ring-closing metathesis strategy. Eight- and nine-membered cyclic ethers have been prepared without the need for a rigid cyclic conformational constraint by incorporation of two stereogenic centers that provide sufficient acyclic conformation bias to facilitate ring closure. Application of this strategy to the synthesis of a variety of pharmacologically and structurally interesting molecules is underway.

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Supporting Information Available: Spectral data (^1H, ^{13}C NMR, IR) for compounds **4a**−**c**, **7a**−**c**, and **8**−**12** (12 pages).

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