Communications to the Editor

Conformational Bias by a Removable Substituent. Synthesis of Eight-Membered Cyclic Ethers via Ring-Closing Metathesis

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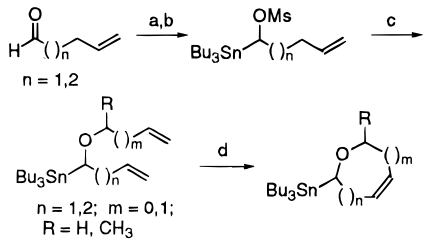
The synthesis of eight-membered rings from acyclic precursors is difficult due to conformational entropy factors and developing transannular repulsions as the ring is formed.[1] Grubbs and co-workers have developed a Ru−carbene complex[2] which has provided macrocyclic rings via ring-closing olefin metathesis; however, the synthesis of medium-sized rings has posed problems.[3] Several reports have revealed that eight-membered rings could be formed only if conformational restrictions imposed by an existing ring or other functional groups were present in the diene precursor.[4] Conformationally flexible acyclic dienes have not been successfully closed to eight-membered rings via metathesis with the exception of a tosyl amide derivative.[4d] We were intrigued with the possibility of using a large yet "removable" group to effect a conformational bias which would allow the synthesis of an eight-membered oxacyclic ring via metathesis from an acyclic diene. We previously reported the unique features imparted by a trialkylstannane substituent in stereocontrolled nucleophilic addition reactions to acyclic oxocarbenium ions.[5] We now report that ring-closing metathesis of acyclic α-(alkoxyalkyl)-stannyl-substituted dienes leads to the synthesis of six-, seven-, and eight-membered α-trialkylstannyl-substituted cyclic ethers in excellent yields.

The synthesis of the α-(alkoxyalkyl)stannane-substituted dienes **1**−**3** is shown in Scheme 1. Condensation of lithiotributylstannane with 4-pentenal provided the hydroxystannane which was immediately converted to the mesylate in 62% overall yield. Displacement of the mesylate with allyl alcohol or 3-butenol, following the conditions of Nakai and co-workers,[6] provided dienes **1** and **2** in 89% and 60% yield, respectively. An analogous sequence starting from 5-hexenal provided diene **3** in modest overall yield. The syntheses of dienes **4**−**6** by a more versatile approach are illustrated in Scheme 2. The mesylates were obtained from the TBS-protected hydroxy aldehydes in 60−65% overall yield. Subsequent steps shown in the scheme ranged from 85% to 90% yield. Generation of diene **4** was achieved via elimination of the ω-iodide[7] using KOtBu in DMSO/benzene.[8] Dienes **5** and **6** were obtained via olefination of the terminal aldehyde by the Lombardo procedure.[9]

Scheme 1[a]



[a] Reagents: (a) Bu_3SnLi, THF, −78 °C. (b) MsCl, Et_3N, −40 °C. (c) ROH, KH, Et_2O. (d) [Ru].

Initial metathesis reactions were carried out with the seven-membered ring precursor diene **1**. Reaction of **1** in benzene (0.03 M) with 3 mol % [bis(tricyclohexylphosphine)benzylidene]ruthenium dichloride ([Ru]) at room temperature for 30 min provided 92% of the cyclic ether **9**; see Table 1. Cyclization of diene **2** under similar conditions (10 mol % [Ru]) resulted in the eight-membered cyclic ether **10** in 74% yield with 16% recovered starting material. Only 10% of diene **2** had undergone polymerization, the main product observed in earlier attempts to form eight-membered rings via ring-closing metathesis.[4a,d] The cyclization reaction of **2** is essentially complete within 1 h (GC and TLC). In contrast, the methyl-substituted diene **3** cyclized to oxocene **11** in only 38% yield. Diene **4** cyclized to oxocene **12** in 84% yield, while the homoallylic stannane **5** provided the eight-membered cyclic ether **13** in 96% yield. Oxocene **12** was obtained as a 2.4:1 diastereomeric mixture (separable by chromatography) in which the relative stereochemistry of the Bu_3Sn and methyl groups in the major isomer is cis (NOE: C8, 8%; C2, 7%). Since the diene **4** subjected to the metathesis conditions was a 1:1 mixture of diastereomers, cyclization of the diastereomer of **4** leading to *cis*-**12** is somewhat favored over that leading to *trans*-**12**. Recovered **4** was significantly enriched in the less reactive diastereomer of **4**, >10:1 (GC). Eight-membered ring formation in the case of diene **4** was examined using 4−19 mol % [Ru] catalyst over reaction times ranging from 8 to 24 h without appreciable changes in the yield (80−84%) or diastereomeric ratio of the cyclized material. With the exception of diene **5**, the ring-closing metathesis reaction did not go to completion (12−24 h), providing approximately 15% of recovered starting material. We have not yet examined longer reaction times or higher catalyst loads in these cases. Cyclization of diene **6** cleanly provided the six-membered cyclic ether in 96% yield after only 30 min of reaction time.

Two *tert*-butyl-substituted dienes **7** and **8** were also prepared, and subjected to the ring-closing metathesis reaction conditions

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(9) Lombardo, L. *Tetrahedron Lett.* **1982**, *23*, 4293−4296.

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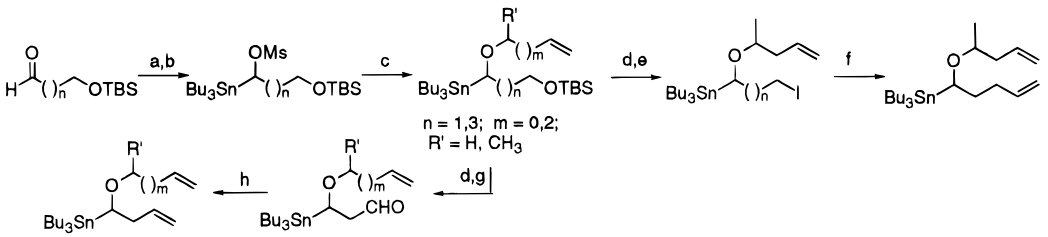
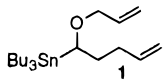
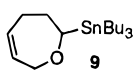
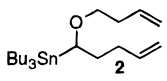
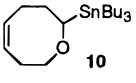
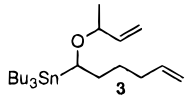
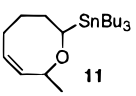
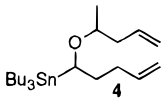
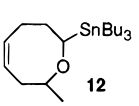
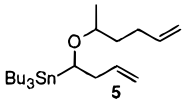
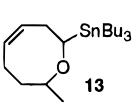
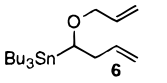
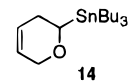
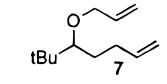
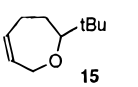
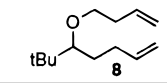
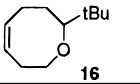
Scheme 2[a]



[a] Reagents: (a) Bu_3SnLi, THF, −78 °C. (b) MsCl, Et_3N, −40 °C. (c) ROH, KH, Et_2O. (d) HF, py, THF, 0 °C. (e) $(PhO)_3PMeI$, DMF. (f) *t*-BuOK, DMSO, PhH. (g) Dess−Martin. (h) Zn, CH_2Br_2, $TiCl_4$, RT.

Table 1. Ring-Closing Metathesis of Acyclic Tributylstannyl-Substituted Dienes

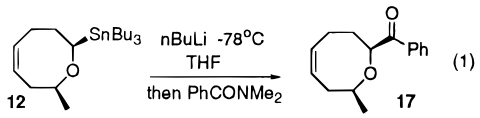
Entry	Diene	Product	Conditions[a] / Yields[b]
1			30 min 92% (0%)
2			12h 74% (16%)
3			12h 38% (20%)
4			12h 84% (15%)
5			12h 96% (0%)
6			30 min 96% (0%)
7			6h 73% (0%)
8			12h 0% (0%)

[a] Reaction conditions: 0.01-0.015 M PhH, RT, 3-10 mol % $[(PCy_3)_2RuCHPh]Cl_2$. [b] Isolated yield and, in parentheses, the yield of the recovered starting material.

employed for the tin-substituted dienes. Oxepene **15** was obtained from diene **7** in 73% yield after 6 h (longer reaction times to 24 h did not increase the yield), while oxocene **16** was not obtained from diene **8**. Diene **8** underwent polymerization exclusively. In both of these reactions, complete consumption of the diene starting material was observed within 12 h. Note, in comparison, that the stannyl-substituted oxepene **9** was obtained in 92% yield after only 30 min of reaction time and oxocene derivatives **10**, **12**, and **13** were obtained in high yields.

The Bu_3Sn group favors intramolecular cyclization over polymerization in the metathesis reaction compared to the *t*-Bu substituent. Initial examination of the relative sizes of these two groups may be misleading. The *A* value for the *t*-Bu group is significantly greater than that for a R_3Sn group due to the length of the C−Sn bond (2.16 Å).[10] However, the long C−Sn bond will minimize a potential gauche interaction energy in the butyl ligands and provide a lower rotational barrier for the Sn−C^1-alkyl bond. Given the atomic size of Sn vs C coupled with enhanced rotation of the Bu groups on tin, the Bu_3Sn group is effectively larger than the *t*-Bu group. Therefore, the Bu_3Sn group may restrict conformational freedom in the acyclic precursor, overcoming the entropic factors which disfavor cyclization, without introducing additional unfavorable enthalpic factors. The possibility of a unique stereoelectronic effect[5] due to the interaction of the Sn and O atoms or a possible interaction of the Sn and [Ru] carbene cannot be ruled out at this stage. Further work will determine if an α-heteroatom is required.

The synthetic utility of the α-(alkoxyalkyl)stannane moiety in transmetallation reactions and electrophilic cleavage reactions is well demonstrated.[11] As an example, *cis*-oxocene **12** can undergo transmetallation with butyllithium (−78 °C, THF) followed by condensation of the anion with *N*,*N*-dimethylbenzamide to provide the benzoyl-substituted oxocene (80% yield) (eq 1). The reaction sequence occurred predominantly



with retention of configuration,[11c−e] leading to the *cis*-oxocene **17** in 75% isolated yield and 5% isolated yield of the trans isomer. The Bu_3Sn group therefore functions as a removable substituent for conformational bias in acyclic systems.

Acknowledgment. J.M.S. thanks the Burroughs Wellcome Fund and Glaxo for fellowships.

Supporting Information Available: Experimental procedure for the metathesis reaction and spectral data for all dienes and cyclized products (37 pages). See any current masthead page for ordering and Internet access instructions.

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(10) *A* values (kcal/mol): *t*-Bu, 4.7 (ref 1a); Me_3Sn, 1.0; *i*-Pr_3Sn, 1.1. Kitching, W.; Olszowy, H. A.; Harvey, K. *J. Org. Chem.* **1982**, *47*, 1893−1904.

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