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Synthesis of 2,6-dioxabicyclo[3.3.0]octenes by tandem ring-rearrangement/cross metathesis

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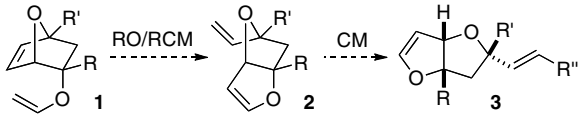
ABSTRACT

A facile synthesis of stereodefined 2,6-dioxabicyclo[3.3.0]octene derivatives from the vinyl ether of *endo*-7-oxanorbornen-2-ol via tandem ring-opening/ring-closing(ring-rearrangement)/cross metathesis is reported.

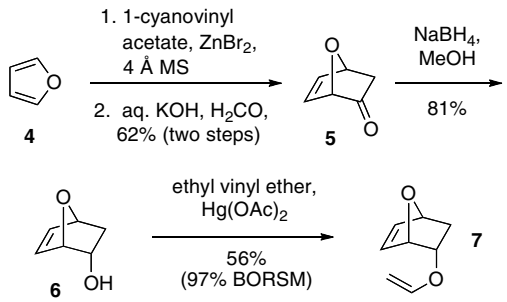
The use of tandem olefin metathesis sequences, in which multiple C=C bonds are formed/broken in a single catalytic step, has become an increasingly powerful strategy for the construction of complex molecular architectures.[1] While the design and implementation of metathesis cascades can be demanding, the benefits of efficiency, economy, and elegance that result are undeniable. Tandem ring-opening/ring-closing metathesis (RO/RCM) results in exchange of one cycloalkene for another and is often referred to as ring-rearrangement metathesis.[2] The potential of such ring-rearrangement processes to produce ring systems common to natural products from readily available cyclic precursors make them particularly useful.

Encouraged by previous studies on metathesis reactions of 7-oxanorbornenes and related bridged bicyclic ring systems, we envisioned the approach to the synthesis of 2,6-dioxabicyclo-[3.3.0]octenes (**3**) based on RO/RCM of *endo*-7-oxanorbornen-2-yl vinyl ethers (**1**) outlined in Scheme 1.[3] Specifically, thermodynamically driven ring-rearrangement of vinyl ether **1** would produce fused enol ether **2**, and subsequent cross metathesis (CM) of the terminal olefin of **2** with an alkene coupling partner would complete the sequence to afford chain-extended dioxabicycle **3**. Enol ethers have been employed as substrates for RCM[4] and as coupling partners in CM;[5] however, their use in RO/RCM has not been reported. The tandem ring-rearrangement/CM shown in Scheme 1 represents a useful extension of enol ether metathesis capable of providing highly functionalized 2,6-dioxabicyclo[3.3.0]octene derivatives (**3**) well-suited for use in total synthesis of a large number of butyrolactone- and THF-containing natural products.



Scheme 1. 2,6-Dioxabicyclo[3.3.0]octene synthesis by RO/RC/CM.

In this Letter, we report our studies on the ring-rearrangement/CM of 7-oxanorbornen-2-yl vinyl ether **7**, the synthesis of which is outlined in Scheme 2. Following known protocols, furan (**4**) was elaborated to *endo*-7-oxanorbornen-2-ol (**6**) via cycloaddition with 1-cyanovinyl acetate, basic hydrolysis, and carbonyl reduction.[6] Treatment of **6** with ethyl vinyl ether and a catalytic amount of mercuric acetate provided a mixture of starting alcohol and vinyl ether **7** from which a 56% yield of the desired product could be isolated (95% yield based on recovered starting material, BORSM).[7]



Scheme 2. Preparation of metathesis substrate **7**.

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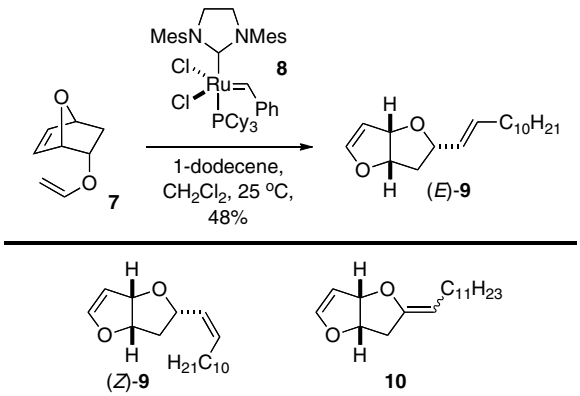


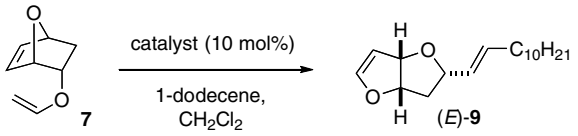
Scheme 3. RO/RC/CM of **7** with 1-dodecene.

This short and efficient route allowed for ready access to gram quantities of metathesis substrate **7**.

A preliminary examination of the metathesis reactivity of **7** was undertaken in which it was treated with 10 mol % of the second-generation Grubbs' catalyst (**8**)[8] and 5 equiv of 1-dodecene at room temperature (Scheme 3). We were gratified to observe the formation of desired bicycle **9** as a separable mixture of geometric isomers from which 48% yield of (*E*)-**9** could be isolated. Quantification of the yield of (*Z*)-**9** was complicated by the fact that it could not be easily separated from isomerized product **10**. Alkene isomerization of this type is not unusual in metathesis reactions and has been developed into a synthetically useful transformation.[9]

Although the observed yield of **9** was modest in our initial attempt, we felt that careful optimization of reaction conditions could provide enhancements, particularly if isomerization could be suppressed. Our results are outlined in Table 1. A typical procedure involved dropwise addition of 10 mol % of a metathesis catalyst as a 0.01 M solution over 6 h via syringe pump to a 0.02 M methylene chloride solution of vinyl ether **7** in the presence of 5 equiv of 1-dodecene. For consistency in catalyst evaluation, all reactions were allowed to run for a total of 14 h. The first-generation Grubbs' catalyst[10] proved ineffective at promoting the tandem ring-rearrangement/CM, affording a maximum of 8% isolated yield of (*E*)-**9** at 40 °C (entries 1 and 2). This outcome is consistent with

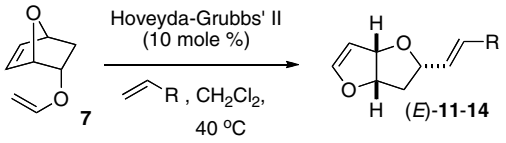
Table 1
Optimization of RO/RC/CM of **7** with 1-dodecene[14]



Entry	Catalyst[a]	Temperature (°C)	Additive	Yield of (*E*)-**9** (%)
1	Grubbs' I	25	—	0
2	Grubbs' I	40	—	8
3	**8**	25	—	48
4	**8**	40	—	61
5	**8**	40	1,4-Benzoquinone	75
6	Hoveyda–Grubbs' II	25	—	74
7	Hoveyda–Grubbs' II	40	—	83
8	Hoveyda–Grubbs' II	40	1,4-Benzoquinone	82
9[b]	Hoveyda–Grubbs' II	80	—	72

[a] Grubbs' I catalyst: $PhCH{=}RuCl_2(PCy_3)_2$; Hoveyda–Grubbs' II catalyst: *o*-isopropoxyPhCH=$RuCl_2$(IMes).
[b] Reaction run in benzene.

Table 2
RO/RC/CM of **7** with various alkenes[16]



Entry	R	Product, yield (%)
1	CH_2OAc	**11**, 85
2	Ph	**12**, 66
3	CO_2Me	**13**, 72
4	CN	**14**, 11[a]

[a] (*Z*)-**14** isolated as the major product in 16% yield.

previous reports on attempted enol ether RCM with the first-generation Grubbs' catalyst.[11] The second-generation Grubbs' catalyst was found to be much more effective and provided a maximum yield of 75% when the reaction was performed at 40 °C in the presence of 10 mol % 1,4-benzoquninone (entry 5), which is known to inhibit alkene isomerization by Ru metathesis catalysts.[12] We found the second-generation Hoveyda–Grubbs' catalyst[13] to be the most efficient initiator affording (*E*)-**9** in as high as 83% yield (entry 7). It is noteworthy that no products of isomerization were detected when the second-generation Hoveyda–Grubbs' catalyst was used. As such, addition of 1,4-benzoquinone had no effect on the reaction yield. In all cases, experiments performed at 40 °C showed increased yields relative to those performed at room temperature. We observed diminished yield for the reaction with the second-generation Hoveyda–Grubbs' catalyst upon increasing the reaction temperature to 80 °C (entry 9). We believe this is due to an increased rate of catalyst decomposition at elevated temperature.

With optimal reaction conditions established, we surveyed the series of terminal alkene CM coupling partners shown in Table 2. As we had previously observed for **9**, geometric isomers of metathesis products **11**–**14** were separable by column chromatography, and yields reported in Table 1 refer to isolated yields of (*E*)-isomers. Reactions of **7** with allyl acetate, styrene and methyl acrylate (entries 1–3) provided good yields of the corresponding side-chain extended products (*E*)-**11**–**13**. These examples demonstrate that synthetically useful functionality can be introduced stereoselectively in the CM step of the metathesis sequence. Interestingly, CM with acrylonitrile led to formation of the (*Z*)-isomer of **14** as the major product with (*E*)-**14** isolated in only 11% yield. Similar low yields and modest (*Z*)-selectivities in CM reactions of nitriles have been reported.[15]

In summary, we have demonstrated an efficient approach to the synthesis of stereodefined 2,6-dioxabicyclo[3.3.0]octenes from the vinyl ether of *endo*-7-oxanorbornen-2-ol via ring-rearrangement/CM. The flexibility of this route and the ease of substrate preparation make it broadly applicable. Studies on the use of this methodology in natural product synthesis are currently underway and will be reported in due course.

Acknowledgments

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7. *Preparation of vinyl ether* **7**: A solution of alcohol **6** (630 mg, 5.62 mmol) and mercuric acetate (448 mg, 1.40 mmol) in 100 mL of ethyl vinyl ether was heated to reflux for 28 h. After cooling to room temperature, the yellow solution was filtered through a short pad of Celite, and the filtrate was concentrated in vacuo. Purification by silica gel chromatography (4:1 pentane/Et_2O) gave unreacted **6** (258 mg, 41% recovery) and vinyl ether **7** (435 mg, 56%, 95% BORSM) as a colorless oil. Data for **7**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.55 (dd, J = 5.9, 1.8 Hz, 1H), 6.35 (dd, J = 14.8, 6.9 Hz, 1H), 6.33 (m, 1H), 5.06 (ddd, J = 4.4, 1.8, 0.6 Hz, 1H), 4.98 (ddd, J = 4.8, 1.8, 0.6 Hz, 1H), 4.54 (ddd, J = 7.9, 4.4, 2.4 Hz, 1H), 4.25 (dd, J = 14.8, 2.1 Hz, 1H), 4.05 (dd, J = 6.9, 2.1 Hz, 1H), 2.26 (ddd, J = 11.9, 7.9, 4.8 Hz, 1H), 1.16 (dd, J = 11.9, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.7, 137.6, 132.3, 88.4, 79.5, 78.1, 74.3, 33.4; HRMS calcd for $C_8H_{11}O_2$ (MH^+) 139.0759, found 139.0755.
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14. *Optimized procedure of ring-rearrangement/CM of* **7** *and 1-dodecene*: To a solution of vinyl ether **7** (109 mg, 0.79 mmol) and 1-dodecene (0.88 mL, 3.95 mmol) in refluxing CH_2Cl_2 (40 mL) was added second-generation Hoveyda–Grubbs' catalyst (50 mg, 0.08 mmol) in 8 mL of CH_2Cl_2 dropwise over six hours by syringe pump. Heating was continued for an additional 8 h after addition was completed. After cooling to room temperature, the brown solution was filtered through a short pad of silica gel, and the filtrate was concentrated in vacuo. Purification by silica gel chromatography (4:1 hexanes/Et_2O) gave RO/RC/CM product (*E*)-**9** (182 mg, 83%) as a pale yellow oil. Data for (*E*)-**9**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.45 (d, J = 2.6 Hz, 1H), 5.70 (dt, J = 15.2, 6.7 Hz, 1H), 5.49 (ddt, J = 15.2, 7.8, 1.3 Hz, 1H), 5.23 (t, J = 2.6 Hz, 1H), 5.06 (dd, J = 7.0, 2.6 Hz, 1H), 5.00 (td, J = 7.0, 4.1 Hz, 1H), 4.27 (td, J = 7.8, 6.2 Hz, 1H), 2.51 (ddd, J = 13.5, 7.0, 6.2 Hz, 1H), 2.00 (br q, J = 7.0 Hz, 2H), 1.88 (ddd, J = 13.5, 7.8, 4.1 Hz, 1H); 1.36–1.25 (m, 16H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.8, 134.5, 129.8, 102.3, 86.1, 84.7, 79.3, 40.7, 32.4, 32.1, 29.8, 29.7, 29.5, 29.3, 29.2, 29.1, 22.9, 14.3; HRMS calcd for $C_{18}H_{31}O_2$ (MH^+) 279.2324, found 279.2329.
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16. Compounds (*E*)-**12**–**14** and (*Z*)-**14** were characterized by ^{1}H NMR, ^{13}C NMR and HRMS, and the assigned structures are consistent with spectroscopic and analytical data.