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Ring-Size-Selective Enyne Metathesis as a Tool for Desymmetrization of an Enantiopure C_2-Symmetric Building Block

Bernd Schmidt* and Lucia Staude

Institut fuer Chemie, Organische Synthesechemie, Universitaet Potsdam, Karl-Liebknecht-Strasse 24-25, D-14476 Golm, Germany

bernd.schmidt@uni-potsdam.de

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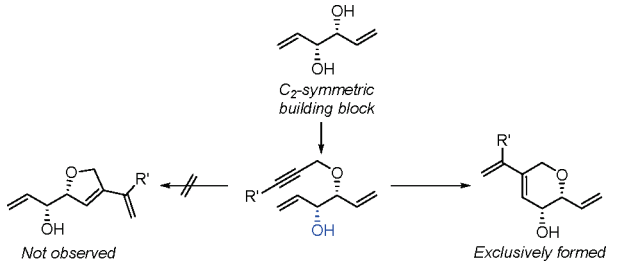
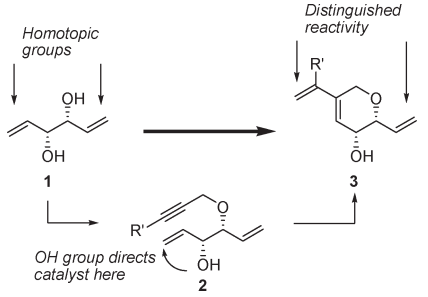


The enantiomerically pure C_2-symmetrical hexa-1,5-diene-3,4-diol is selectively monopropargylated. The products undergo ring-closing enyne metathesis to give exclusively dihydropyrans as single stereoisomers. An unprotected hydroxy group is identified as the factor controlling the ring-size selectivity.

Over the past few years the control of selectivity issues in olefin metathesis reactions has attracted more and more attention. In particular, diastereoselective,[1] enantioselective,[2] and ring-size-selective[3] olefin metathesis reactions were investigated.[4] Recently, unprotected hydroxy groups in close proximity to a C−C double bond were identified as crucial factors for selectivity control in some cases. A strong catalyst directing and activating effect exerted by an allylic hydroxy group has been proposed by us as a rationale for a remarkably high selectivity in the formation of six-membered rather than the normally preferred five-membered oxacycles[5,6] in the RCM of trienes derived from the C_2-symmetric diene **1**.[7] Hoveyda et al. described very recently a highly diastereoselective ring-opening/cross-metathesis reaction with allylic alcohols and strained cyclic olefins. They provide a mechanistic model that is supported by theoretical calculations. Notably, there is strong evidence for the formation of hydrogen bonding between the OH group and one chloride ligand in the carbene complex. The resulting alteration in charge values can account for both the observed diastereoselectivity and rate enhancement.[8] Previous investigations had already revealed the beneficial role of unprotected hydroxy groups on the reactivity of alkenes in olefin metathesis reactions. For instance, Hoye and Zhao reported a striking rate accelerating effect of allylic OH groups in ring-closing metathesis reactions, compared to the analogous methyl ethers.[9] More recently, Imahori et al. discovered that allylic alcohols as substrates in ring-closing enyne metathesis (RCEYM) reactions lead to excellent yields[10] even without an ethylene atmosphere, which is normally considered to be mandatory for obtaining preparatively useful results.[11] Simultaneously, a similar effect for intermolecular enyne metathesis was discovered by Diver et al.[12] However, these authors point out that the presence of an allylic alcohol moiety in the substrate might also have detrimental effects under certain circumstances, as a result of substrate-induced catalyst decomposition to Ruthenium hydrides.[13]

In this Note we present results that indicate not only a remarkable rate-accelerating[10] but also a strong selectivity-controlling effect of an allylic alcohol in ring-closing enyne metathesis reactions. This work was inspired by ongoing target molecule projects in our group, which aim at the enantioselective synthesis of natural products with a 2,5-disubstituted tetrahydropyran core.[14] The envisaged enantiomerically pure starting materials are either the C_2-symmetrical hexadienediol **1**,[7b,15] conveniently available from

SCHEME 1. Desymmetrization of 1 via RCEYM



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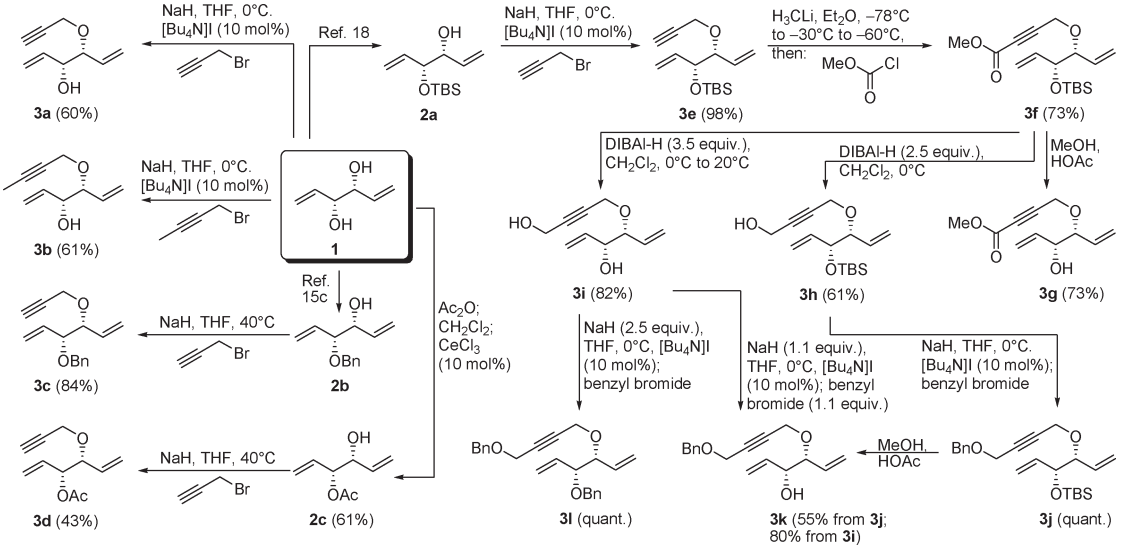
SCHEME 2. Synthesis of RCEYM Precursors from 1



D-mannitol, or *ent*-**1**,[6] which is synthesized from L-tartrate. Obviously, utilization of **1** or its enantiomer requires strategies for the differentiation of the two homotopic double bonds. We planned to achieve this goal by a selective propargylation of one OH group and utilization of the remaining one as a catalyst directing group, to ensure control of ring-size selectivity in the subsequent RCEYM (Scheme 1).

Starting from diene **1**, the two RCEYM precursors **3a** and **3b** were obtained in fair yield by treatment with NaH and propargyl bromide or 1-bromo-2-butyne, respectively. In both cases considerable amounts of unreacted starting material and bis-propargylated product were obtained. However, the desired products are easily separated, which makes this synthesis overall more efficient than alternative routes using sterically demanding protecting groups or stannylene acetals.[16] Two protected propargyl ethers **3c** and **3d** were also synthesized from **2b**[15c] and **2c** via Williamson ether synthesis. Synthesis of **2c** was achieved from **1** using Clarke's monoacylation protocol.[17] For the synthesis of RCEYM precursors with other substituents at the alkyne, the TBS-protected derivative **2a**[18] was used. Conversion to the propargyl ether **3e** was achieved in nearly quantitative yield. Lithiation of **3e** and subsequent trapping of the resulting acetylide with methyl chloroformate gave **3f**, which was desilylated to **3g** using acidic conditions. Reduction of **3f** was performed with DIBAl-H under two different conditions: with 2.5 equiv of DIBAl-H, short reaction times, and low temperatures, only the ester group was reduced and the alcohol **3h** was isolated in fair yield, whereas larger amounts of reducing agent, longer reaction times, and warming the reaction mixture to ambient temperature resulted in a concomitant desilylation to diol **3i** in good yield. Depending on the reaction conditions, **3i** was converted in good yield to **3k** or, with larger amounts of NaH and benzyl bromide, selectively to **3l** in quantitative yield; **3k** was also obtained via desilylation of **3j**, which was in turn synthesized from **3h** (Scheme 2).

Ring-closing enyne metathesis of precursors with the general structure **3** may result in the formation of four different products (Scheme 3).

The selectivity of the reaction will mainly depend on the site of initiation: initial attack at the alkyne, which was for quite some time believed to be the preferred pathway ("yne-then-ene" pathway),[19] can explain all four products, whereas the alternative "ene-then-yne" pathway can result only in products **4** and **5** because of steric constraints.[20] Evidence for a partial contribution of an yne-then-ene pathway in enyne metathesis reactions was provided by Mori et al., who obtained considerable amounts of exomethylene products for certain substitution patterns.[21] On the other hand, the results of NMR-studies[10b,22] and isotopic labeling experiments[23] clearly support an ene-then-yne pathway. We reasoned that a hydroxy group directing effect should induce

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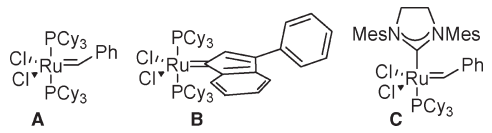
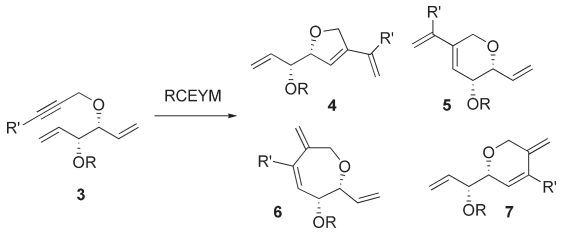


FIGURE 1. Catalysts for olefin metathesis reactions.

SCHEME 3. Possible Regioisomers from RCEYM of 3



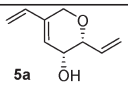
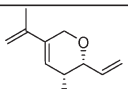
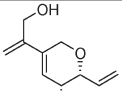
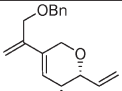
initiation at the double bond closest to the hydroxy group, which would ultimately lead to a six- rather than a five-membered ring.

Ring-closing enyne metathesis reactions were performed using three different catalysts (Figure 1).

Apart from the established first (**A**)[24] and second (**C**)[25] generation Grubbs' catalysts, the less common indenylidene complex **B**[26] was used. Feasibility and selectivity of RCEYM reactions with precursors **3** were first investigated for **3a** (Table 1). With 5 mol % of **A** approximately 80% of the starting material was converted to dihydropyran **5a** in refluxing toluene. NMR spectra of the crude reaction mixture indicated only unreacted starting material and dihydropyran **5a**. After chromatography, **5a** was obtained in 64% yield from this reaction. Evidence for the assigned dihydropyran structure **5**, rather than the alternative dihydrofuran structure **4**, comes from the $\delta(^{13}C)$ value for the -CH_2O- moiety. The observed chemical shift value of 65.7 ppm is in the typical range for dihydropyrans. For comparison, 75 ppm would be a typical value for the dihydrofuran isomer. Similarly, the geminal coupling constant of 15.6 Hz for the two diastereotopic protons in the -CH_2O- group is characteristic for a six- rather than a five-membered oxacycle.[7b,27] Structures **6** and **7** were immediately excluded, because no signals for an exomethylene group were found in the ^1H NMR spectrum. In accord with Imahoris observations, conversions lower than 5% were observed for the analogous benzyl ether **3c** and the acetate **3d**, irrespective of the catalyst used.

Although the ring-size selectivity observed in our initial experiment was fine, we were not satisfied with the conversion of 80%. No improvement was observed after longer reaction times, and increasing the catalyst loading was disregarded as economically unattractive. Therefore, we considered the use of an activating additive such as phenol. The beneficial effect of phenol on the performance of

TABLE 1. RCEYM of Precursors 3

3	Product	Catalyst (mol-%)	additive (conversion)[a]	Isolated Yield
3a	 **5a**	**A** (5)	none (80%)	64%
		A (5)	0.5 equiv. phenol (100%)	93%
		B (4)	0.5 equiv. phenol (100%)	63%
		C (5)	none (100%)	n. d.
3b	 **5b**	**A** (5)	none (80%)	n. d.
		A (5)	0.5 equiv. phenol (100%)	94%
		C (5)	none (100%)	n. d.
3c	Unreacted starting material	**C** (5)	none (< 5%)	--
3d	Unreacted starting material	**A** (5)	none (< 5%)	--
		C (5)	none (< 5%)	--
3g	**8** (see discussion and Scheme 4)	**A** (5)	0.5 equiv. phenol (100%)	72%
		B (5)	0.5 equiv. phenol (100%)	n. d.
		C (5)	0.5 equiv. phenol (100%)	--[b]
3h	Unreacted starting material	**A** (5)	0.5 equiv. phenol (< 5%)	--
		B (5)	0.5 equiv. phenol (< 5%)	--
3i	 **5i**	**A** (5)	0.5 equiv. phenol (100%)	60%
		B (5)	0.5 equiv. phenol (100%)	79%
3k	 **5k**	**A** (5)	0.5 equiv. phenol (100%)	53%
		B (5)	0.5 equiv. phenol (100%)	n. d.
3l	Unreacted starting material	**A** (5)	0.5 equiv. phenol (< 5%)	--

[a]Conversions were obtained from the ^1H NMR spectra of the crude reaction mixtures. Only the corresponding dihydropyran **5** and/or unreacted starting material **3** were detected, unless otherwise stated. [b]A complex mixture of products was observed with second generation catalyst **C** for this particular example.

Grubbs' catalysts was demonstrated a few years ago by Forman et al. This effect was rationalized by proposing a hydrogen bonding between one chloro ligand and phenol, facilitated dissociation of one phosphine ligand, and stabilization of the 14 electron species by complexation of phenol.[28] We were quite confident that addition of phenol would improve the conversion but feared that the presence of a competing hydrogen bond donor might lead to a diminished ring-size selectivity. Therefore, the amount of phenol was limited to 0.5 equiv. Gratifyingly, this led to full conversion while retaining the high level of selectivity observed in the absence of phenol. When indenylidene complex **B** was used, the outcome was very similar. Interestingly, second generation catalyst **C** can also be successfully used for this enyne metathesis. Here, complete conversion to the dihydropyran **5a** was observed even without any additive. This is remarkable, because a number of reports have been published in the literature detailing that the significant rate enhancement observed for metathesis catalysts with NHC ligands is associated with much lower diastereoselectivity, ring-size

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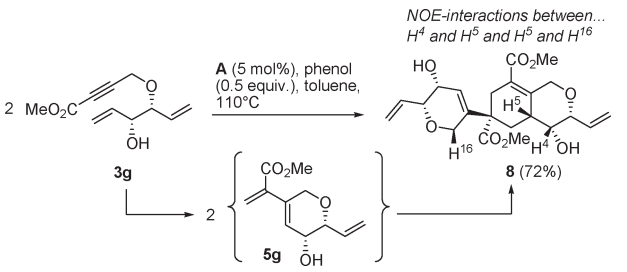
SCHEME 4. RCEYM of 3g and Spontaneous Dimerization to 8



selectivity, or *E*/*Z* selectivity.[29] In the following experiments, the combination of first generation catalysts **A** or **B** and phenol as an additive was applied to other precursors **3** listed in Table 1. Generally, derivatives **3b**, **3i**, and **3k** with an unprotected allylic alcohol reacted under these conditions with complete conversion to the corresponding dihydropyrans **5**. For **3i**, with an additional propargylic OH group, selectivity was slightly lower, presumably due to formation of small amounts of dihydrofuran product **4i**. Evidence for the formation of **4i** was observed in the NMR spectra of the crude mixture. In particular, in the ether region of the ^{13}C NMR spectrum, characteristic signals for five-membered ring products are present. It was, however, not possible to separate a pure sample of **4i** for unambigous structure elucidation. Derivatives **3h** and **3l**, with a TBS or benzyl protecting group, respectively, turned out to be unreactive under the established conditions. The failure observed for **3h**, with a free primary propargylic alcohol, parallels observations published by Imahori et al.[10b] and may be interpreted in terms of a ene-then-yne pathway. A remarkable case that merits a special comment is the ring-closing enyne metathesis of **3g** with an electron-deficient triple bond. While the reactivity of **3g** is similar to the other derivatives with an allylic OH group, we were unable to isolate the expected dihydropyran **5g**. Monitoring the reaction by TLC reveals that an initially formed product undergoes a consecutive reaction to a much more polar product **8**, which was identified as a dimer of **5g** using mass spectrometry. In the NMR spectra of the crude reaction mixture only one isomer could be detected. On the basis of one- and two-dimensional NMR spectroscopy, we assign the structure depicted in Scheme 4 to compound **8**. Although Diels–Alder reactions are commonly used to further functionalize enyne metathesis products,[30] we were surprised to find that all attempts to isolate the monomer **5g** failed. Even if **5g** was detected in highly diluted solutions, its dimer **8** was the only product obtained upon evaporation. Interestingly, the use of second generation catalyst **C** instead of **A** or **B** results in the formation of a complex mixture of products.

In conclusion, we used a sequence of monopropargylation and ring-closing enyne metathesis for the desymmetrization of a C_2-symmetrical, enantiomerically pure diene. The ring-closing enyne metathesis step is highly ring-size-selective, and we propose a strong hydroxy group directing effect as a rationale for the observed selectivity.

Experimental Section

Representative Procedure. (2*R*,3*R*)-2,5-Divinyl-3,6-dihydro-2*H*-pyran-3-ol (5a). To a solution of **3a** (200 mg, 1.3 mmol) and phenol (61 mg, 0.7 mmol) in toluene (20 mL) was added precatalyst **A** (53 mg, 5 mol %). The solution was heated to reflux for 3–5 h, then cooled to ambient temperature, and washed with aqueous $NaHCO_3$ solution. The solvent was evaporated, and the residue was purified by column chromatography on silica to give **5a** (185 mg, 93%) as a colorless solid, mp 46 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 6.27 (ddd, J = 0.6, 10.9, 18.1, 1 H), 6.01 (ddd, J = 5.3, 10.7, 17.5, 1 H), 6.01 (d, J = 5.5, 1 H), 5.42 (dt, J = 1.6, 17.5, 1 H), 5.33 (dt, J = 1.5, 10.8, 1 H), 5.14 (s, 1 H), 5.09 (d, J = 6.1, 1 H), 4.54 (d, J = 15.8), 4.28 (d, J = 15.8, 1 H), 4.00 (dm, J = 5.3, 1 H), 3.94 (bs, 1 H), 1.08 (bs, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.0 (0), 135.1 (1), 134.8 (1), 126.4 (1), 117.4 (2), 114.3 (2), 78.6 (1), 65.6 (2), 64.7 (1); $[\alpha]^{26}_D$ 288.0° (*c* 0.64, CH_2Cl_2); IR (KBr disk) ν 3420 (bm), 3088 (w), 2982 (w), 2832 (m), 1098 (s); LRMS (EI) m/z 135 (M^+ − OH, 100%); HRMS (ESI) calcd for $C_9H_{13}O_2$ (M^+ + H) 153.0916, found 153.0906.

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Supporting Information Available: Full experimental details, characterization data, and copies of ^1H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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