Synthesis of Unsaturated Nine-Membered Ring Ethers (Δ^3-Oxonenes) Containing a *Z*- or *E*-Configurated Double Bond: Thermodynamic versus Kinetic Control in Palladium-Catalyzed Allylic Cyclizations**

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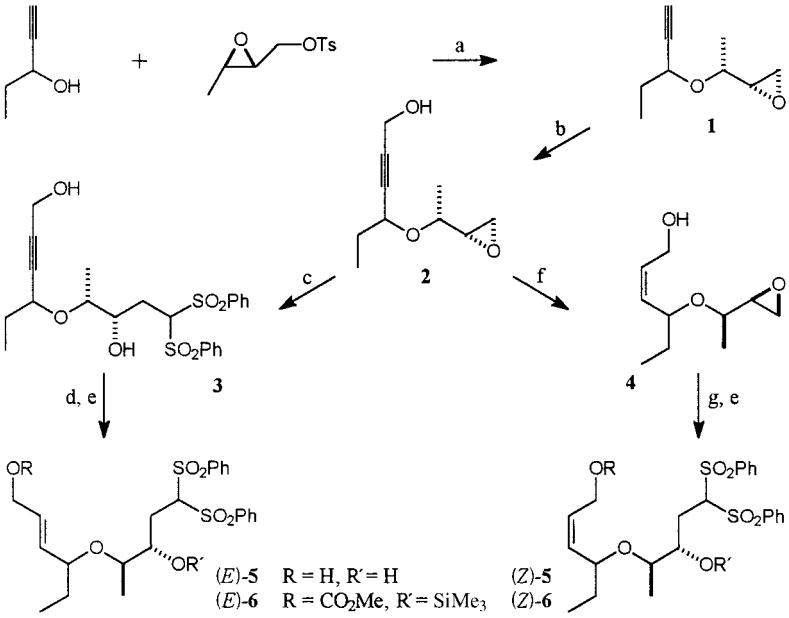
Dedicated to Professor Heribert Offermanns on the occasion of his 60th birthday

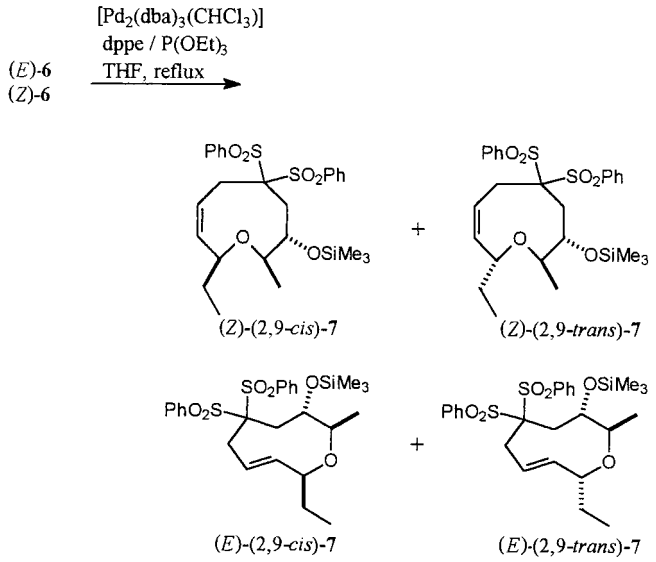
Medium-ring ethers ($n = 8-10$) occur in a variety of marine natural products, and efforts continue towards their total synthesis.[1] Of the currently known, unsaturated nine-membered ring ethers most contain *Z*-configurated double bonds. *E*-configurated, monocyclic Δ^3-oxonenes, either natural or unnatural, appear to be unknown.[2] We here report a simple and efficient stereoselective synthesis of both *Z*- and *E* -configurated Δ^3-oxonenes starting from a single advanced intermediate.

The cyclization precursors were prepared as outlined in Scheme 1. A key reaction was the BF_3-mediated regioselective opening of the crotyl alcohol derived epoxytosylate with 1-pentyn-3-ol. Although this secondary alcohol is a weak nucleophile and has to attack a secondary epoxide carbon in an S_N2-type displacement, the preparation of **1** proceeded with complete inversion and regioselectivity in 70% yield.[3] Thus the highly functionalized α,α'-di-*sec*-alkyl ether **1** is accessible in two steps with full control over two stereocenters by a simple procedure.[4] Hydroxymethylation of the triple bond provided propargylic alcohol **2**, which served as advanced intermediate en route to cyclization precursors (*E*)-**6** and (*Z*)-**6**.

Cyclization of (*E*)-**6** as well as (*Z*)-**6** with catalytic amounts of palladium(0) and in the presence of a ligand (1,2-bis(diphenylphosphanylethane (dppe), $P(OEt)_3$)[5] provided strained **7** in reproducible, good yield (Scheme 2, Table 1).[6] Seven-membered ring ethers are not formed, in agreement with early work on the preparation of related carbocycles.[5b, e] Separation and identification of the cyclization products was not trivial. Only the cyclic ether (*Z*)-(2,9-*cis*)-**7** could be purified by standard chromatography. The TLC plate showed an additional spot which could not be resolved further. NMR spectra were inconclusive but suggested that more than one isomer might be formed in dynamic distribution. Eventually, the experimental conditions in entry 8 provided a clue because the product mixture was rich in two *E*-configurated diastereomers. Recrystallization from ether gave single crystals of (*E*)-(2,9-*trans*)-**7** suitable for X-ray diffraction analysis.[7] Given the NMR spectrum of this diastereomer, the spectra of the *E*- and *Z*-configurated cyclic ethers **7** could be assigned.



Scheme 1. Synthesis of cyclization precursors (*E*)- und (*Z*)-**6**: a) 1. $BF_3 \cdot Et_2O$, CH_2Cl_2; 2. K_2CO_3, MeOH, 70%; b) *n*BuLi, $(CH_2O)_n$, THF, 98%; c) 1. ethyl vinyl ether, cat. *p*-TsOH, CH_2Cl_2; 2. $(PhO_2S)_2CH_2$, *n*BuLi, $BF_3 \cdot Et_2O$, THF; 3. aq. HCl, THF, 45%; d) Red-Al, THF, 62%; e) 1. MeO_2CCl, Py, CH_2Cl_2; 2. bis(trimethylsilyl)acetamide, THF, 77% (*E* isomer), 59% (*Z* isomer); f) Lindlar catalyst, H_2, MeOH, 97%; g) 1. ethyl vinyl ether, cat. *p*-TsOH, CH_2Cl_2; 2. $(PhO_2S)_2CH_2$, *n*BuLi, $BF_3 \cdot Et_2O$, THF; 3. aq. HCl, THF, 89%.



Scheme 2. Cyclization of (*E*)- and (*Z*)-**6**.

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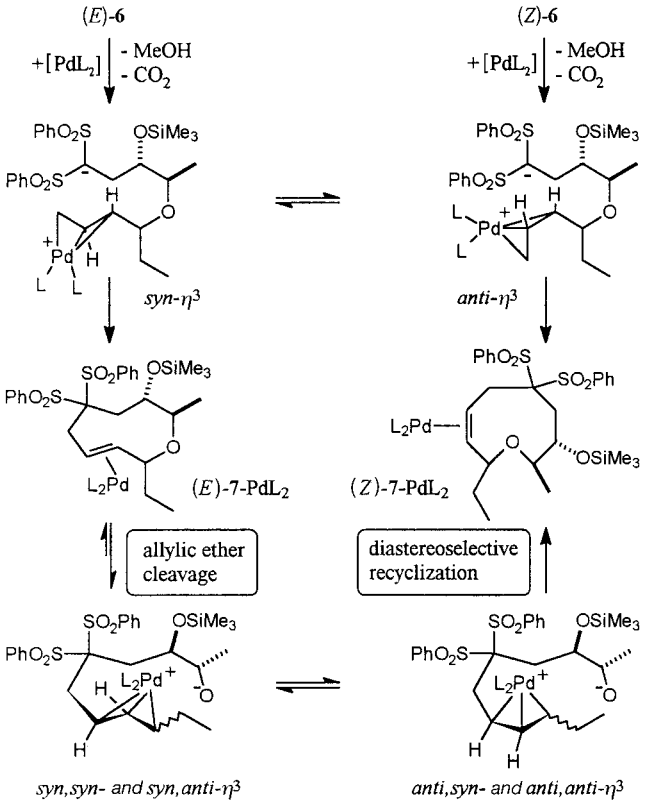
Table 1. Cyclization results.

Entry	Precursor	Ligand [mol%]	Cat. [mol%]	Add. time [h]	Reaction time [h]	(*Z*)-**7**:(*E*)-**7**	(*Z*)-(2,9-cis)-**7**: (*Z*)-(2,9-*trans*)-**7**	Yield [%]
1	(*E*)-**6**	dppe, 25	5	5.5	7	1.7:1	1:12	82
2	(*E*)-**6**	dppe, 45	10	6	17	2.5:1	1:12	83
3	(*E*)-**6**	dppe, 45	10	15	18	4.5:1	1:7	70
4	(*E*)-**6**	dppe, 45	10	13	17	7.5:1	1:4	67
5	(*E*)-**6**	$P(OEt)_3$, 50	5	5	8	0.25:1	1:10	68
6	(*E*)-**6**	$P(OEt)_3$, 50	5	5	20	0.75:1	1:5	53
7	(*Z*)-**6**	dppe, 22	5	7	8	7:1	1:3	80
8	(*Z*)-**6**	$P(OEt)_3$, 50	5	7	8.5	0.07:1	–	81

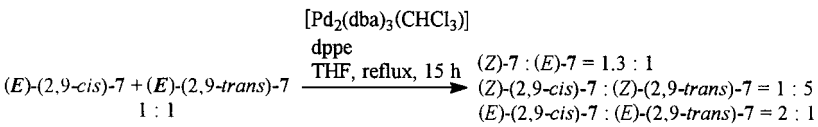
The product distribution depended on the type of ligand and reaction time. Surprisingly, the configuration of the double bond in the cyclization precursors (*E*)-**6** and (*Z*)-**6** also played an important role.[8] Proper choice of the reaction conditions allowed preparation of either predominantly *E*- or *Z*-configurated nine-membered ring ether. Furthermore, formation of (*Z*)-(2,9-*cis*)-**7** and (*Z*)-(2,9-*trans*)-**7** was diastereoselective with respect to the configuration at allylic carbon C-2. Epimer (*Z*)-(2,9-*trans*)-**7** was the major product (Table 1). The isolated *E*- and *Z*-configurated nine-membered ring ethers were resubjected to the conditions of allylic alkylation. Whereas the (*Z*) ethers were stable, the energy-rich (*E*) ethers isomerized to the less strained (*Z*) isomers. Furthermore, these experiments showed that (*E*)-(2,9-*trans*)-**7** (higher energy content) isomerized faster than (*E*)-(2,9-*cis*)-**7** (Scheme 3).

A unique feature of the cyclization is the palladium-mediated cleavage of the strained, nine-membered ring ethers (*E*)-(2,9-*cis*)-**7** and (*E*)-(2,9-*trans*)-**7** (Scheme 4).[9] This allylic ether cleavage and subsequent recyclization account not only for the observed *E*/*Z* isomerization of the olefinic double bond, but also for the diastereoselective formation of (*Z*) ethers. The C–O bond heterolysis generates at least four η^3-allylpalladium complexes (*syn,syn*, *syn,anti*, *anti,syn*, and *anti,anti*) in addition to the two initially formed η^3-complexes (*syn* and *anti*). Scheme 4 is simplified, since the allyl π-faces are diastereotopic. Hence, the number of η^3 complexes and therefore discrete allyl cation equivalents must be doubled from six to twelve. The presence of two and three further chiral centers along the carbon chain increases the manifold of possible organopalladium intermediates even further.

For the preparation of the more stable *Z*-configurated nine-membered ring ethers, the dppe ligand is advantageous, irrespective of the configuration of the double bond in the cyclization precursor (Table 1, entries 4 and 7). The precursor (*E*)-**6** requires extended reaction times for formation of the (*Z*) ether (cf. entry 4, $Z{:}E = 7.5{:}1$ and entry 1, $Z{:}E = 1.7{:}1$), presumably as a consequence of thermodynamic control. Comparison of entries 2 and 4 shows that the time required for the addition of the cyclization precursor to the catalyst solution also plays a role. Given a total reaction time of 17 h, fast addition (6 h vs. 13 h) increases the amount of (*E*) ether (cf. entry 2, $Z{:}E = 2.5{:}1$ and entry 4, $Z{:}E = 7.5{:}1$).[10] For the selective formation of the less stable (*E*) ether a maximum of kinetic control is required. Triethyl phosphite, a monodentate ligand with considerable backbonding capability, renders the η^3-allyl palladium complex more ionic and speeds cyclization. The effect of shortening the reaction time is shown in entries 5 and 6. The amount of (*E*) ether increases with shorter reaction times. The system of choice for high kinetic control and almost exclusive formation of *E*-configurated cyclic ether is the energy-rich precursor (*Z*)-**6** in combination with $P(OEt)_3$ as a ligand (entry 8).



Scheme 4. Simplified cyclization mechanism.



Scheme 3. Isomerization of *E*-configurated unsaturated ethers.

With a view to the synthesis of natural products and the *Laurencia* ethers, we examined the refunctionalization of the 1,1-bissulfone moiety of the cyclization products. Standard conditions for the reduction to a methylene group (NaHg in buffered methanol)[11] were unsatisfactory and led to partial cleavage

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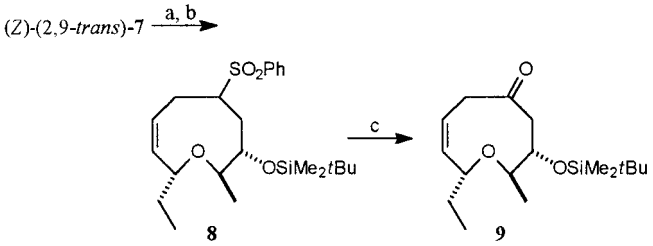
of the allylic ether. In contrast, reductive monodesulfonylation with SmI_2 provided sulfone **8**.[12] Subsequent oxidative desulfonylation[13] afforded the ketone **9** as a functionalized intermediate, well endowed for further synthetic manoeuvres (Scheme 5).



Scheme 5. Refunctionalization of 1,1-bissulfone. a) 1. SmI_2, MeOH, THF; 2. aq. HCl, THF, 87%; b) tBuMe$_2$SiCl, imidazole, DMF, 75%; c) lithium diisopropylamide (LDA), MoO_5/pyridine/hexamethylphosphoric triamide (MoOPH), THF, 70%.

The epoxyether alkynol **2** is readily accessible from inexpensive starting materials and serves as a key intermediate for preparing *E*- and *Z*-configurated cyclization precursors. Thanks to the installation of three stereochemical labels we have been able to unravel some of the beautiful mechanistic complexity of organopalladium catalysis. Intramolecular allylic alkylation has been tuned to both (*E*)- and (*Z*)-Δ^3-oxonenes with high stereocontrol. The chemical yield of the nine-membered ring products remains respectable throughout, especially in view of the cleavage of the allylic ether and subsequent recyclization. The weakened bond between the allylic carbon and oxygen in *E*-configurated ring ethers generates a cascade of stereo- and structurally isomeric organopalladium intermediates. Finally, the 1,1-bissulfone refunctionalization is valuable in the synthesis of naturally occurring *Z*-configurated cyclic ethers. Strained *E*-configurated monocyclic Δ^3-oxonenes, which have apparently been unknown, are higher in energy than the corresponding (*Z*) isomers[7] and of intrinsic general interest. They are also analogues of natural products for evaluation of biological activity.

Experimental Section

General procedure for the Pd^0-catalyzed cyclization: A flame-dried, two-necked flask was charged with [$Pd_2(dba)_3CHCl_3$] (dba = dibenzylideneacetone) and ligand. The apparatus was evacuated and refilled with N_2 three times. Solvent (THF) was added such that the solution was 0.02 M with respect to starting material. The reaction mixture was heated to reflux and the cyclization precursor (0.02 M in THF) was added by syringe. After complete addition, the reaction mixture was heated to reflux for a further 1–15 h. The solvent was removed and the crude product was purified by chromatography. For further experimental details and spectroscopic data see reference [14].

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