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Unified Approach towards Medium Ring Allylic Ethers. Stereoselective Synthesis of 2,10-Dialkylated (*E*)-Oxacyclodec-3-enes by Palladium Catalyzed Cyclization.

H. M. R. Hoffmann* and J. Pohlmann

Institut für Organische Chemie, Universität Hannover, Schneiderberg 1B, 30167 Hannover, Germany

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Abstract: Δ^3-Unsaturated 10-membered ring ethers (5,6,7,8,9,10-hexahydro-2*H*-oxecins) **11a** and **11b** have been prepared by intramolecular Pd-catalyzed allylic alkylation. The ethers are formed with *E*-configurated olefinic double bond and with the chiral centre at carbon C2 intact.

Keywords: oxygen heterocycles; stereocontrol; mechanisms

We have recently reported the synthesis of Δ^3-unsaturated 8-membered (3,4,5,8-tetrahydro-2*H*-oxocins)[1] and 9-membered ring ethers (2,3,4,5,6,9-hexahydro-oxonins)[2] relevant to marine natural products. Key reactions were BF_3-mediated regio- and stereoselective ring opening of glycidol tosylates by secondary alcohols[1-3] to establish the chirality at the carbon atoms α and α' to the ether oxygen. Ring closure was accomplished by palladium catalyzed allylic alkylation.[4]

In view of the surprising loss of stereochemistry and epimerization at the allylic ether carbon C2 on formation of 8- and 9-membered ring ethers[1,2,5] it was of obvious interest to prepare appropriate Δ^3-unsaturated 10-membered ring ethers and to probe the stereochemical fate of the corresponding carbon C2.

Epoxidation of *trans*-crotyl alcohol and tosylation provided epoxy tosylate **2**, which was allowed to react with monoprotected butane-1,2-diol **1** in the presence of $BF_3{\cdot}OEt_2$ (Scheme 1). The resulting hydroxy tosylate was treated directly with alkali, giving α,α'-disecondary epoxy ether **3**. One-carbon homologation by epoxide opening with cyanide ion and subsequent protection of the resulting secondary hydroxy group yielded oxynitrile **4**, which in two steps was reduced to primary alcohol **5**. After conversion into the corresponding primary iodide the 1,1-bis(phenylsulfonyl) moiety was introduced *via* S_N2 displacement[6] giving **6**. Further elaboration to allylic alcohol required a differentiation of two protected hydroxy groups. Selective debenzylation of the primary alcohol by standard palladium mediated hydrogenation was not successful, perhaps due to catalyst poisoning by the sulfur containing substrate. Since the hard-soft combination $BF_3{\cdot}SMe_2$ also caused desilylation, the allylic alcohol was reprotected (PivCl, pyridine) and the secondary alcohol resilylated. Removal of the ester group (DIBAH), oxidation and Horner reaction provided the α,β-unsaturated ester **9**.

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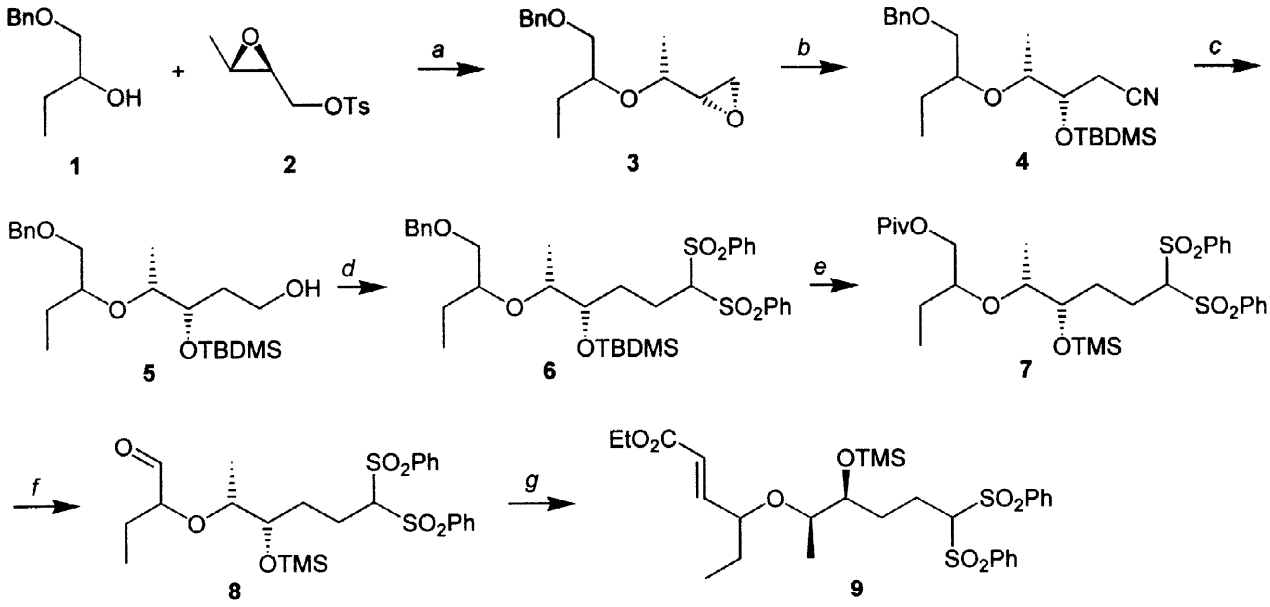
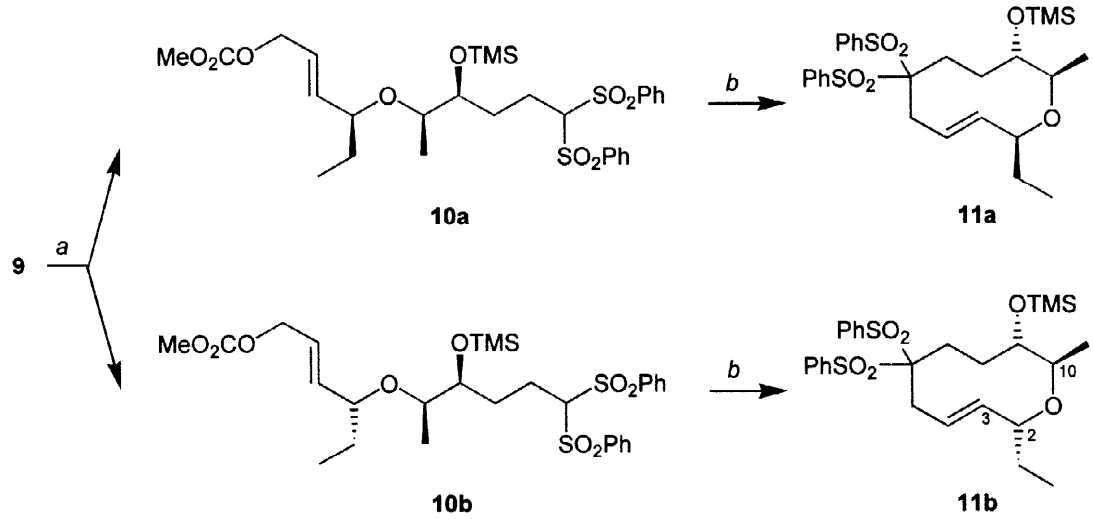


Scheme 1. *a*) 1. BF_3·OEt_2, CH_2Cl_2, 0 °C to r.t.; 2. K_2CO_3, MeOH, r.t., 63%. *b*) 1. KCN, 18-crown-6, MeOH, r.t., 90%; 2. Imidazole, TBDMSCl, DMF, 60 °C, 87%. *c*) 1. DIBAH, PE, –70 °C to r.t., 70%; 2. $NaBH_4$, *i*-PrOH, r.t., 87%. *d*) 1. PPh_3, imidazole, I_2, E/MeCN, 34 °C; 2. TBA-CH(SO_2Ph)$_2$, DMF/benzene, 110 °C, 68%. *e*) 1. BF_3·OEt_2, DMS, CH_2Cl_2, r.t., 81%; 2. PivCl, pyridine, CH_2Cl_2, r.t., 83%; 3. TMSCl, NEt_3, THF, 40 °C. *f*) 1. DIBAH, CH_2Cl_2, –70 °C; 2. SO_3·py, DMSO, Et(*i*-Pr)$_2$N, CH_2Cl_2, 0 °C. *g*) *t*-BuOK, $(EtO)_2POCH_2CO_2Et$, THF, 0 °C, 62% from **7**.

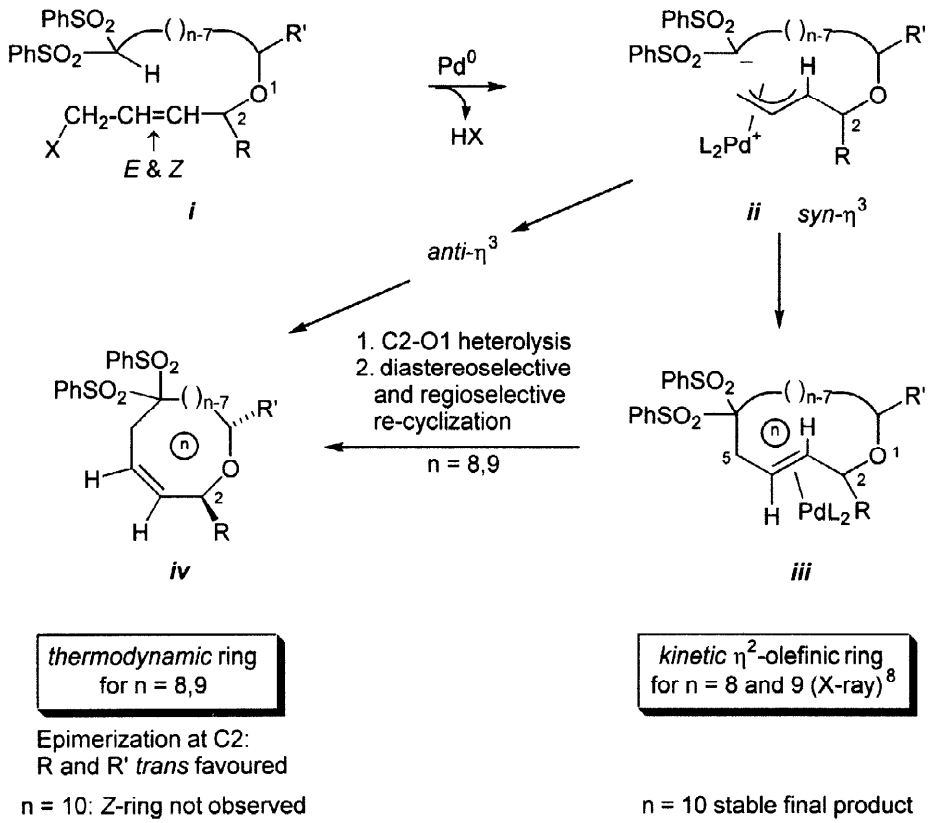
Reduction afforded the allylic alcohol as a mixture of diastereomers, which were separated and then converted into allylic carbonates **10a** and **10b**. The two diastereomers **10a** and **10b** were cyclized separately by slow addition to a refluxing solution of the catalyst in THF (Scheme 2).



Scheme 2. *a*) 1. DIBAH, CH_2Cl_2, –70 °C, 69%, separation of diastereomers. 2. MeO_2CCl, pyridine, CH_2Cl_2, 0 °C, **10a** (87%), **10b** (89%). *b*) $Pd_2(dba)_3CHCl_3$, dppe, THF, 66 °C, **11a** (80%), **11b** (81%).

The 10-membered ring ethers **11a** and **11b** were obtained in good yield and as *single* diastereomers. Starting with enantiopure epoxy tosylate **2**, the resulting ethers **11a** and **11b** were obtained enantiomerically pure. The configuration at allylic carbon C2 was *retained* completely.[7]

A simplified mechanism for these cyclizations is shown in Scheme 3.



Scheme 3. Simplified Mechanism for the Synthesis of Δ^3-Unsaturated Ringethers (n = 8,9,10).

For n = 9 and n = 8, the corresponding *E*-configurated ring ***iii***, although strained, is formed as significant intermediate. In fact, starting from acyclic precursor ***i*** (n = 9) with *Z-olefinic double bond* and strongly back-bonding, monodentate ligand L = $P(OEt)_3$, the *E*-ring ether ***iii*** could be isolated as major product (76%) under kinetic control. Its structure was corroborated by X-ray diffraction.[8] Unsaturated ethers ***iii*** (n = 8,9) are sufficiently strained for palladium-catalyzed allylic C2-O1 bond heterolysis to occur, with alkoxide ion as a leaving group under salt-free conditions and under thermodynamic control. Re-cyclization[9] (***iii*** → ***iv***) is *regioselective* and thought to involve *ion pair return*.[10,11] For 8-membered ring ***iii*** (n = 8) re-closure to ***iv*** is accompanied by complete epimerization at C2 to give the stereoisomer with *trans* arrangement of R and R' at C2 and C8, respectively.

For n = 10 the *E*-configurated 10-membered ring ***iii***, i.e. **11a** and **11b**, is isolated and formed from *syn*-η^3 allyl complex ***ii***. This first cyclization concludes the reaction and the configuration at C2 is not altered.[12]

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* Tel: 0049 (0)511 762 4611, Telefax: 0049 (0)511 762 3011, E-mail: hoffmann@mbox.oci.uni-hannover.de.

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6 See ref. 2, footnote 11.

7 *(2R,3S,10S)-6,6-Bis-(phenylsulfonyl)-10-ethyl-2-methyl-3-trimethylsiloxy-8E-5,6,7,8,9,10-hexahydro-2H-oxecin* (**11a**). ^{1}H NMR (200 MHz, C_6D_6) δ –0.01 (s, 9 H, $Si(CH_3)_3$), 0.94 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.32 (d, J = 6 Hz, 3 H, $CHCH_3$), 1.39 - 1.78 (m, 2 H, CH_2CH_3), 2.11 - 2.35 (m, 1 H, H8), 2.44 - 2.82 (m, 3 H, H7, H8), 3.16 - 3.32 and 3.37 - 3.69 (m, 5 H, H2, H5, H9, H10), 5.49 (br. dd, J = 16, 9 Hz, 1 H, H3), 5.74 - 5.93 (m, 1 H, H4), 7.02 - 7.18 (m, 6 H, arom. H), 8.15 - 8.31 (m, 4 H, arom. H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 0.01 (–, $Si(CH_3)_3$), 9.81 (–, CH_2CH_3), 18.69 (–,$CHCH_3$), 23.23 (+, CH_2CH_3), 25.02 (+, C8), 27.50 (+, C7), 32.92 (+, C5), 72.73 (–, C9), 74.23, 83.29 (–, C2, C10), 89.77 (+, C6), 123.08 (–, C3), 128.48, 128.55, 130.96, 131.43, 134.37. 134.40 (–, arom. CH), 136.00, 137.43 (+, arom. C), 141.02 (–, C4). *(2R,3S,10R)-6,6-Bis-(phenylsulfonyl)-10-ethyl-2-methyl-3-trimethylsiloxy-8E-5,6,7,8,9,10-hexahydro-2H-oxecin* (**11b**). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.01 (s, 9 H, $Si(CH_3)_3$), 0.87 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 1.01 - 1.18 (m, J = 6 Hz, 3 H, $CHCH_3$), 1.40 - 1.95 (m, 4 H, CH_2CH_3, H8), 2.05 - 2.53 (m, 2 H, H7), 2.67 - 2.86 (m, 1 H, H5), 3.15 - 3.55 (m, 3 H, H5, H9, H10), 3.94 - 4.15 (m, 1 H, H2), 5.28 - 5.57 and 5.77 - 6.25 (m, 2 H, H3, H4), 7.50 - 7.79 (m, 6 H, arom. H), 7.89 - 8.26 (m, 4 H, arom. H); ^{13}C NMR (50 MHz, $CDCl_3$) δ –0.01 (–, $Si(CH_3)_3$), 10.06 (–, CH_2CH_3), 21.04 (–,$CHCH_3$), 25.02 (+, CH_2CH_3), 25.34 (+, C8), 27.26 (+, C7), 36.15 (+, C5), 65.69 (–, C9), 75.37, 78.09 (–, C2, C10), 91.23 (+, C6), 128.64, 131.21, 131.40 (–, arom. CH), 132.04 (–, C3), 134.48, 136.01 (–, arom. CH), 136.01 (+, arom. C), 137.37 (–, C4), 137.43 (+, arom. C).

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12 For simple 2,n-dialkylated oxacycloalkanes (ring size n) the *cis* arrangement of alkyl groups is usually favoured thermodynamically, as in 2,6-*cis*-diequatorial tetrahydropyrans. The 2,n-*trans* arrangement, as observed here for n = 8 and n = 9 is usually contrathermodynamic.