Rules of Stereoselectivity in Tandem Oxidative Polycyclization Reaction with Rhenium(VII) Oxides

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Received April 17, 1998

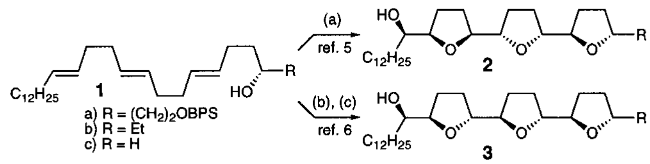
The tandem oxidative polycyclization reaction with rhenium(VII) reagents, first reported in 1995,[1] represents a powerful methodology by which polyene alcohols can be converted into poly-THF products with very high diastereoselectivity in a single step.

Kennedy's pioneering work on the monocyclization reaction with simple bis-homoallylic alcohols has suggested that the stereochemical outcome of this reaction leads consistently to *trans*-THF products.[2] We have confirmed this general rule in our early studies with mono- and also with a few bis-cyclization reactions,[1,3] and similar results were also reported by McDonald.[4] Therefore, we were surprised to observe the exclusive formation of **2a**, rather than its expected isomer **3a**, in the triple oxidative cyclization reaction with **1a** and trifluoroacetylperrhenate ($CF_3CO_2ReO_3$) (Scheme 1).[5] What we discovered was inconsistent with the findings of an independent study by McDonald who reported that the reaction of very similar trienol substrates, **1b** and **1c**, with the same oxidant, $CF_3CO_2ReO_3$, afforded the all-*trans* products, **3b** and **3c**, respectively.[6]

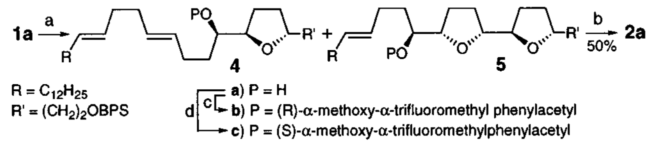
Considering the immense synthetic importance of the tandem oxidative polycyclization reaction, we felt that the discrepancy between ours and McDonald's results had to be resolved. More importantly, to allow the use of this reaction in a stereochemically predictable way, one must understand the stereochemical relationship between the polyenol substrate and the poly-THF product. Here, on the basis of a systematic study, we confirm that the polycyclization of **1** with $CF_3CO_2ReO_3$ produces **2** and not **3**. Moreover, we propose a set of rules for predicting the stereochemistry of the poly-THF products obtained by tandem oxidative cyclization reaction with $CF_3CO_2ReO_3$.[7]

The relative and absolute stereochemistries of the triple cyclization product **2a** were elucidated by carrying out the reaction in a stepwise manner (Scheme 2). Partial oxidative cyclization of **1a** with $CF_3CO_2ReO_3$ afforded a mixture of the mono- and bis-THF products, **4a** and **5a**, along with recovered starting material. The reaction of the mixture of **4a** and **5a** with an additional amount of $CF_3CO_2ReO_3$ afforded **2a**. The stereochemistry of the free hydroxyl group in **2a**, **4a**, and **5a** was determined on the basis of ^{19}F NMR spectral data of their (*R*) and (*S*) Mosher's esters (see Supporting Information).[8] The structure of **2a** was further corroborated by 2D $^1H-^1H$ COSY, TOCSY, and ROESY experiments with the bis-benzoate ester of **2a**. Finally, we prepared both compounds **2a**[9] and **3a**[10] by independent asymmetric synthesis. These experiments confirmed unequivocally that the tris-THF product obtained by the tandem oxidative cyclization of **1a** is **2a** and not **3a**.

Scheme 1. Oxidative Cyclization of **1** with $CF_3CO_2ReO_3$

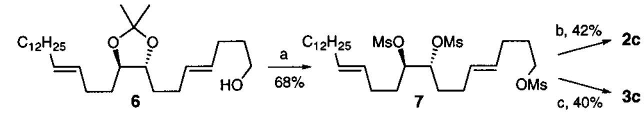


Scheme 2. Stepwise Oxidative Polycyclization of **1a** with $CF_3CO_2ReO_3$[a]



[a] Prepared in situ from 1 equiv of Re_2O_7 and 1.2 equiv of TFAA. Key: (a) $CF_3CO_2ReO_3$ (2 equiv), TFAA (2.6 equiv), CH_2Cl_2, 2 h, (Yield: **4a**, 11%; **5a**, 28%, recovered **1a**, 37%); (b) $CF_3CO_2ReO_3$ (1.5 equiv), TFAA (2 equiv), CH_2Cl_2, 6 h; (c) (*S*)-PhC(OMe)(CF_3)COCl, DMAP, CH_2Cl_2; (d) (*R*)-PhC(OMe)(CF_3)COCl, DMAP, CH_2Cl_2.

Scheme 3. Synthesis of **2c** and **3c** from L-(+)-diethyl tartrate[a]



[a] Key: (a) i. TsOH, MeOH-H_2O, rt, 16 h. ii. MsCl, Et_3N, CH_2Cl_2, 0 °C, 2 h. (b) i. AD-mix-β, $MeSO_2NH_2$, tert-BuOH-H_2O, 18 h. ii. Pyridine, reflux, 2 h. (c) i. AD-mix-α, $MeSO_2NH_2$, tert-BuOH-H_2O, 18 h. ii. Pyridine, reflux, 2 h.

Compound **2b** was easily prepared from **2a** *via* a three-step sequence, desilation to produce corresponding diol, selective monotosylation of the primary alcohol, and LAH reductive cleavage of the tosylate function. Compounds **2c** and **3c** were prepared from the enantiomerically pure acetonide **6** (Scheme 3) which was synthesized from L-(+)-diethyl tartrate (see Supporting Information). Comparison of the spectral properties of our compounds, **2b**, **2c**, and **3c**, with the original spectra kindly provided by McDonald revealed that the correct structures of compounds **49** and **48** described in ref 6 are also **2b** and **2c**, respectively, and not **3b** and **3c** as reported.

The above-described observation that *trans,trans,trans*-trienols **1a**−**c** underwent stereoselective triple cyclization to give a *trans,-cis,cis*-tris-THF product was quite intriguing considering our previously reported observations with a *cis,cis*-(4,8)-dienol substrate that afforded *trans,trans*-bis-THF product.[1] Apparently, the relative configuration of the resultant THF rings strongly depends on the configuration of the vicinal oxygen functions formed in

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(7) In contrast to other rhenium(VII) oxidants, polycyclization with trifluoroacetylperrhenate was found to proceed with high stereoselectivity and high yields, particularly with acid-sensitive substrates (ref 6). Therefore, this study was carried out with trifluoroacetylperrhenate.
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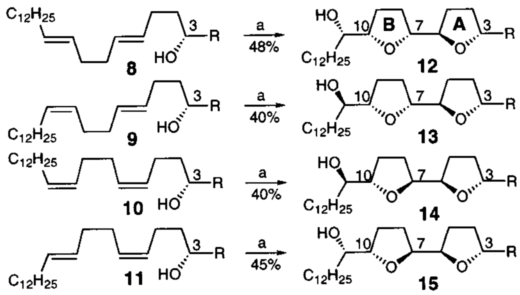
(9) For an asymmetric synthesis of **2a**, see: ref 5 (Supporting Information).
(10) . For an asymmetric synthesis of **3a** see: Sinha, S. C.; Sinha, A.; Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1998**, *120*, 4017.

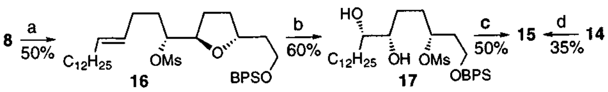
S0002-7863(98)01324-9 CCC: $15.00
Published on Web 08/20/1998

Scheme 4. Tandem Oxidative Cyclization Reactions with $CF_3CO_2ReO_3$[a]



[a] Key: R═$(CH_2)_2$OBPS (a) $CF_3CO_2ReO_3$ (2.5 equiv) and TFAA (3 equiv), CH_2Cl_2, 6 h.

Scheme 5. Synthesis of **15**[a]



[a] Key: (a) i. $CF_3CO_2ReO_3$, lutidine, CH_2Cl_2, 18 h. ii. MsCl, Et_3N, CH_2Cl_2, 0 °C, 2 h. (b) AD-mix-α, $MeSO_2NH_2$, tert-BuOH−H_2O, 18 h. (c) Pyridine, reflux, 2 h. (d) i. *p*-Nitrobenzoic acid, DEAD, PPh_3, C_6H_6, 3 h, ii. LiOH, THF-H_2O (1:1), 60 °C, 3 h.

previous cyclizations, which arises from the geometry of the double bonds in the polyenol substrate.

To further understand the stereochemical rules of this reaction, we have prepared four dienol substrates **8**−**11** (see Supporting Information) and subjected them to the tandem oxidative biscyclization reaction with trifluoroacetyl perrhenate ($CF_3CO_2ReO_3$), which yielded the only isolatable products **12**−**15** (Scheme 4) in 40−48% yields. We used both NMR spectroscopy and independent asymmetric synthesis to determine the stereochemistries of the products. For example, the structures of compounds **12**−**14** were determined on the basis of 2D ^{1}H−^{1}H COSY, TOCSY, and ROESY of their bis-nitrobenzoate derivatives. We used 2D ^{1}H−^{1}H COSY and TOCSY to locate the signals of H-7 and H-10 which show an nOe correlation in the case of the bis-benzoate esters of **12** and **13** and no such correlation in the case of **14**. This analysis clearly indicated that the B-ring is *cis* in **12** and **13** and is *trans* in **14**. The structure of **15** was determined by an independent synthesis starting with compound **8** (Scheme 5). Compound **14** was converted to **15** in two steps (Scheme 5), reinforcing our NMR structure determination of **14**.

On the basis of the stereochemical relationships between **8**−**11** and **12**−**15** as well as our previously reported results, we propose the following rules for the single step polycyclization of polydisubstituted alkenols with $CF_3CO_2ReO_3$:

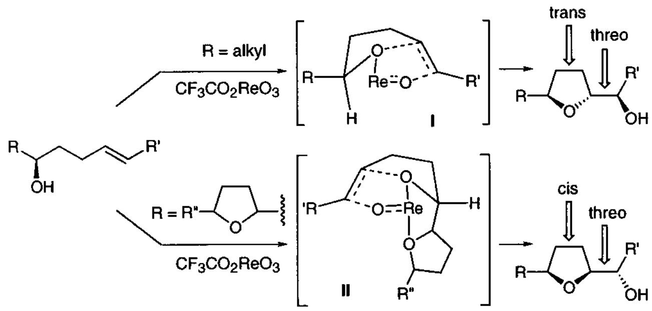
1. With simple bishomoallylic alcohol (where the hydroxyl group is the only strong coordination site of rhenium), the first THF ring is always produced with *trans* configuration.

2. If the two vicinal oxygen functions formed in the first cyclization have a *threo* relationship, the next cyclization produces a *cis*-THF ring.

3. If the vicinal oxygen functions formed in the first cyclization have an *erythro* relationship, the next cyclization produces a *trans*-THF ring.

The above rules reflect a dramatic change in the stereochemical course of the tandem oxidative cyclization reaction when proceeding from the first cyclization to the subsequent ones. A plausible explanation for this phenomenon arises from the ability of the newly formed THF ring to chelate the Re atom during the next oxidative cyclization. As illustrated in Scheme 6 (top), in the first cyclization step, the noncoordinating alkyl group has a high preference to take a less sterically demanding pseudoequatorial position in the proposed 3 + 2 transition state (**I**),[11] leading to a *trans*-THF ring. However, in cases where the group R possesses

Scheme 6. Plausible Transition States for Oxidative Cyclization with Re(VII) considering a 3 + 2 Addition Mechanism[a]



[a] The other ligands on Re are omitted for clarity.

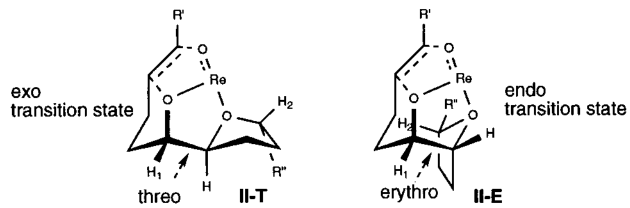


Figure 1.

a potential coordination site, the substrate may become a bidentate ligand to rhenium. In that case, a pseudoaxial position would be energetically preferred in the transition state (**II**), leading to a *cis*-THF ring. Nevertheless, the coordinating efficiency of this bidentate ligand depends on the relative configuration of the two oxygen functions. With a *threo* relative configuration the reaction proceeds via a sterically favored *exo*-type transition state, **II-T**. By contrast, the *erythro* configuration requires a sterically disfavored *endo*-type transition state, **II-E**, rendering the nonchelated structure, **I**, energetically more favorable.

Another observation of *cis*-THF rings in the tandem oxidative cyclization reaction with Re(VII) has been recently reported by Morimoto and Iwai who studied highly substituted systems (tertiary alcohols and trisubstituted double bonds).[12] Their results are consistent with our model. (1.) As observed in our less substituted substrates, the first cyclization produces predominantly a *trans*-THF ring. (2.) The second cyclization produces predominantly a *cis*-THF ring. This may be expected for tertiary alcohols because, for substrates having an alkyl group instead of H_1, there is no steric advantage of **I** over **II**. Yet, when coordination to Re becomes highly sterically demanding, e.g. with the *erythro* substrate **8** in ref 1, the transition state is **II-E** (having a methyl group instead of H_1 and H_2 and R″ = ^{i}Pr) which results in rather low *cis* selectivity (2:1).

In conclusion, we propose here a set of stereochemical rules for the tandem oxidative cyclization reaction with $CF_3CO_2ReO_3$. Theoretical calculations that support these rules are underway.

Acknowledgment. We thank the U.S.-Israel Binational Science Foundation, the Israel Cancer Research Fund, PharMore Biotechnologies, and the Skaggs Institute for Chemical Biology for financial support. We thank Prof. F. E. McDonald for copies of NMR spectra. E. K. is incumbent of the Benno Gitter & Ilana Ben-Ami chair of Biotechnology, Technion.

Supporting Information Available: Synthetic scheme of compounds **6** and **8**−**11**; ^{19}F NMR spectral data of both Mosher's esters of **2a**, **4**, **5** and two model compounds **I** and **II**; ^{1}H and ^{13}C NMR data of compounds **8**−**15**, ^{1}H and 2D ^{1}H−^{1}H NMR spectra of bis-nitrobenzoate derivatives of **12**−**14** (15 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA981324E

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