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Re_2O_7-Mediated Dehydrative Cyclization Reactions: Total Synthesis of Herboxidiene and Its 12-Desmethyl Analog

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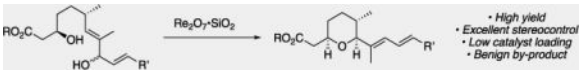
Abstract

Re_2O_7 catalysis effects efficient and stereoselective dehydrative cyclization reactions from monoallylic diols, with stereocontrol arising from thermodynamic equilibration. This method was applied to a rapid synthesis of the spliceosome inhibitor herboxidiene. The route was also utilized for the synthesis of an analog that highlights the importance of a single methyl group in biasing the conformation in the acyclic region of the molecule.

TOC Image

Water from a stone: Re_2O_7 is an extremely effective catalyst for promoting green dehydrative cyclization reactions. Stereochemical control can be achieved through thermodynamic product equilibration. The use of the method in a brief synthesis of the spliceosome inhibitor herboxidiene and an analog illustrated its functional group compatibility and applicability to complex targets. These compounds illustrate the importance of remote steric interactions in promoting biological activity.



Keywords

natural products; cyclization; solvolysis; oxygen heterocycles; conformational analysis

Catalytic dehydrative cyclization reactions are extremely attractive, green processes for synthesizing heterocycles because the only waste product is water and because the alcohol that serves as the nucleofuge requires no derivatization. Numerous approaches have recently been reported for achieving dehydrative cyclizations that proceed through either of two basic mechanisms. Soft electrophilic transition metal catalysts based on palladium,[1] gold,[2] or ruthenium[3] coordinate to the alkenes of allylic alcohols and promote cyclization/elimination sequences. Alternatively hard Lewis acids, including $FeCl_3$,[4] BF_3•OEt_2,[5] arylboronic acids,[6] $Bi(OTf)_3$,[7] and even hot water,[8] react with alcohols to form stablized carbocations that react with appended nucleophiles. Alkene coordination conditions allow

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for kinetic substrate- or ligand-based stereocontrol while hard Lewis acids allow for thermodynamic control through product equilibration.

We have been exploring[9] the use of Re_2O_7-catalyzed allylic alcohol transposition reactions[10] in complex molecule synthesis. These processes, in which allylic alcohols react with Re_2O_7 to form allylic perrhenate esters that rearrange and cleave to form isomeric allylic alcohols, employ appended electrophiles to dictate the regioselectivity of the transposition reaction. However we observed[9c] that allylic alcohols can also serve as precursors to allylic cations (Scheme 1) during an investigation of epoxides as electrophilic traps. This result is consistent with calculations that show substantial charge separation in the transition states of perrhenate ester rearrangements[11] and with the generation of highly stabilized carbocations from allylic alcohols in bimolecular processes.[12] Thus Re_2O_7 should serve as an effective catalyst for promoting dehydrative cyclizations from allylic alcohols with pendent nucleophiles.[13] This manuscript describes the realization of this objective and defines the structural features that promote high levels of stereocontrol. We apply the protocol to brief total syntheses of the naturally occuring spliceosome inhibitor herboxidiene and an analog that provides useful information regarding the importance of acyclic conformational constraints on biological activity in this compound class.

We utilized diol **1** as the initial substrate for developing the method (Scheme 2). Exposing **1** to Re_2O_7•SiO_2[9c] (5 mol%) at rt generated diastereomeric tetrahydropyrans **3** in <10 min through the putative carbocation intermediate **2**. While the diastereoselectivity improved at prolonged reaction times the epimerization proved to be too sluggish at ambient temperature for practical purposes. This was remedied by heating the reaction to 40 °C (capped vial). Stirring at this temperature for 20 h provided major product **2** in 82% yield as >30:1 ratio of diastereomers. The stereochemical assignment was based on coupling constants in the ^1H NMR spectrum and by analyzing a NOESY experiment.

Table 1 illustrates the scope of the process. All reactions were conducted at 40 °C for 20 h for consistent comparisons. Secondary allylic alcohol substrates cyclize with good to excellent levels of stereocontrol but primary allylic alcohols, while cyclizing efficiently, do not equilibrate as readily as the secondary alcohols (entries 1 and 2). This is consistent with a mechanism in which allylic cation stability dictates the isomerization rate. Silyl ethers serve as nucleophiles for the reaction (entry 3), albeit with a slight yield reduction (entry 3 relative to entry 4). Trisubstituted alkenes can be generated as single geometrical isomers (entries 3 and 4). The reaction works well when electron-withdrawing groups are proximal to the nucleophilic hydroxyl group (entries 5–9). Notably, these products correspond to common substitution patterns in tetrahydropyran-containing natural products.[14] The cyclization of triol substrate **14** (entry 6) highlights the selectivity of the ionization of allylic alcohols in the presence of non-allylic alcohols. The compatibility of the nitro group provides an entry to structures in which amino acids are incorporated into polyketide biosynthetic pathways.[15] Matching (entry 8) or mismatching influences (entry 9) dictate the degree of stereocontrol when two non-equilibrating stereocenters are present in the substrate.

Our success in the initial phase of this study led us to explore the applicability of the process to natural product synthesis. Herboxidiene (**22**), also known as GEX1A, provides an excellent opportunity to validate the capacity of the dehydrative cyclization to access an important synthetic target. Scientists at Monsanto isolated herboxidiene[16] and Oppolzer subsequently established the absolute stereochemistry through degradation and semisynthesis.[17] Yoshida demonstrated that **22** is a potent toxin against several tumor cell lines and enhances survival in murine cancer models.[18] Subsequent studies showed that **22** operates through spliceosome inhibition,[19] which is generating significant interest for selective cancer therapy.[20] Herboxidiene also inhibits angiogenesis,[21] providing further justification for developing a rapid approach to access this compound and its analogs. Several syntheses of **22** have been developed.[22] The dehydrative cyclization protocol, however, provides uniquely rapid access to **22** via diol intermediate **23** (Scheme 3).

The synthesis (Scheme 4) of the left-hand fragment commenced with known[23] aldehyde **24**, which can be prepared in one step from commercially available citronellene. Asymmetric cycloaddition[24] with AcCl provided β-lactone **25** with good stereocontrol and in high yield. Cross metathesis with methacrolein[25] generated aldehyde **26**. While the yield of this transformation is not high, throughput is sufficient since **25** can be recovered and resubjected to the reaction conditions. The synthesis of the right- hand fragment began with a vinylogous Mukaiyama aldol reaction between **27**[26] and **28**,[27] each available in two steps from commercially available materials, to yield **29** with excellent diastereocontrol in accord with studies by Kobayashi.[28] Conversion to iodide **30** proceeded through facile transformations. Evans alkylation[29] followed by a routine three step sequence generated alkyne **31**. Hydrozirconation of **31** followed by transmetalation with Me_2Zn[30] and quenching with **26** provided, after in situ β-lactone ethanolysis, cyclization substrate **32** as a mixture of diastereomers. Dehydrative cyclization proceeded extremely efficiently in the presence of Re_2O_7 (1 mol%). Prolonged exposure to the reaction conditions also effected silyl group cleavage to provide **33** in 82% yield upon increasing the Re_2O_7 loading to 3 mol %. Conducting this reaction with *p*-TsOH rather than Re_2O_7 resulted in a much slower and transformation with extensive by-product formation, demonstrating that Re_2O_7 is uniquely effective for allylic alcohol ionizations. Vanadium-mediated epoxidation and ester cleavage, in accord with established protocols,[22b,c] provided herboxidiene in 14 steps from commercially available materials for the longest linear sequence. This sequence matches the shortest reported linear sequence[22j] and sets a new standard for the lowest overall step count.

The capacity to form the tetrahydropyranyl group rapidly creates ample opportunities for analog synthesis. The structure-activity relationships for **22** have been explored,[22h,31] though the influence of the methyl group at C12 on potency has yet to be established. The considerable effort that is dedicated to introducing this group led us to investigate whether this group is necessary for biological activity. The synthesis of the 12-desmethyl analog (Scheme 5) began with allylic chloride **34**, which is available through a sequence that follows the preparation of **30**. The addition of lithiated 1-trimethylsilyl-1-propyne[32] followed by *in situ* silyl cleavage[33] yielded alkyne **35**. 12-Desmethyl herboxidiene (**36**) was accessed by following the route that was developed for the natural product synthesis. This

route is three steps shorter than the natural product synthesis and eliminates the need for a chiral auxiliary.

Access to herboxidiene and its desmethyl analog allowed for a comparison of their potencies as cytotoxins. These compounds were evaluated against HeLa (cervical cancer) and 4T-1 (breast cancer) cells using an MTT assay.[34] The IC_{50} values for **22** were 30 nM and 40 nM, repectively. Minimal cytotoxicity, however, was observed for desmethyl analog **36** at concentrations up to 500 nM, indicating that the absence of the C12 methyl group causes at least a 40-fold drop in potency. This result is remarkable in consideration of the distance of this methyl group from the polar functionality on the molecule.

A conformational analysis of **22** and **36** provided insights on the origin of the potency difference. The methyl group at C12 in **22** promotes the formation of a turn conformation, consistent with the crystal structure[17] and modeling studies. This is illustrated by structure **37** in Figure 1. Rotation of the C12–C13 bond by 120° in either direction generates a highly destabilizing *syn*-pentane interaction with the methyl group at C14, as illustrated by conformer **38**. ^{1}H NMR data support this analysis. The C13 hydrogens of **22** have coupling constants of 4.8 and 10.8 Hz to the C12 hydrogen, indicating a dominant conformation. Moreover the turn conformation enhances the energetic penalty for rotation around the C11–C12 bond since rotation would lead to enhanced steric clashes with the C10 alkenyl hydrogen, as illustrated by **39** (note the perspective change). Removal of the C12 methyl group eliminates the energetic penalty for the *syn*-pentane interaction, thereby making several additional conformations avaliable through rotation around the C12–13 and C11–C12 bonds.[35] ^{1}H NMR analysis again supports this hypothesis, with the coupling constants of the C12 and C13 hydrogens in **36** being 5.6 and 8.1 Hz, which correlates with a time averaged conformational ensemble. We postulate that **37** represents the binding conformation and removing the methyl group leads to a significant reduction in the population of conformers that interact with the spliceosome.

We have demonstrated that Re_2O_7 is an exceptional catalyst for dehydrative cyclization reactions of monoallylic diols. Stereochemical equilibration leads to high diastereocontrol for transformations in which the products can ionize to form sufficiently stabilized allylic cations. The process shows good functional group tolerance and is experimentally facile, requiring no special precautions to avoid oxygen or water. The method facilitates access to the natural product herboxidiene that validates its applicability to complex molecule synthesis. C12 desmethyl herboxidiene is accessible through a shorter sequence, though the product is less potent as a cytotoxin. The greater potency of the natural product is attributed to the turn conformation that results from the minimization of steric interactions with the C12 methyl group, highlighting the importance of remote steric effects in influencing biological activity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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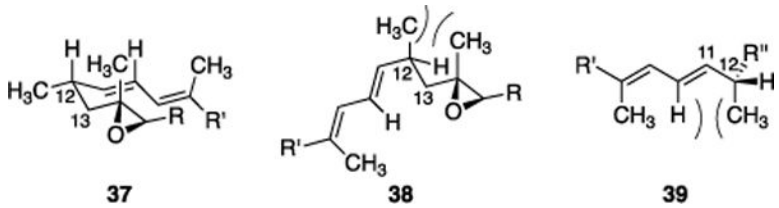
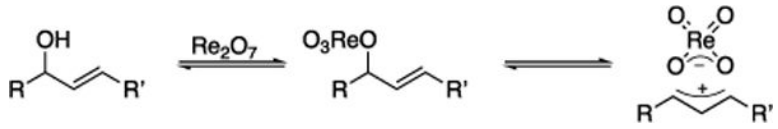
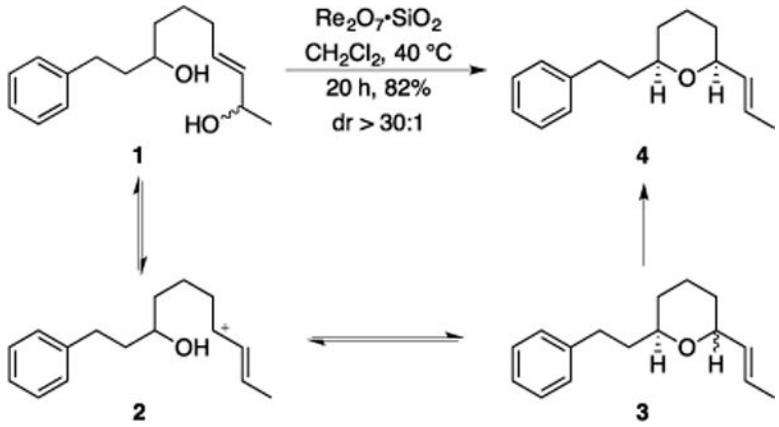


Figure 1.
Preference for the turn conformation at C12.

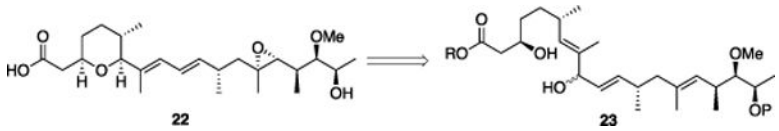


Scheme 1.

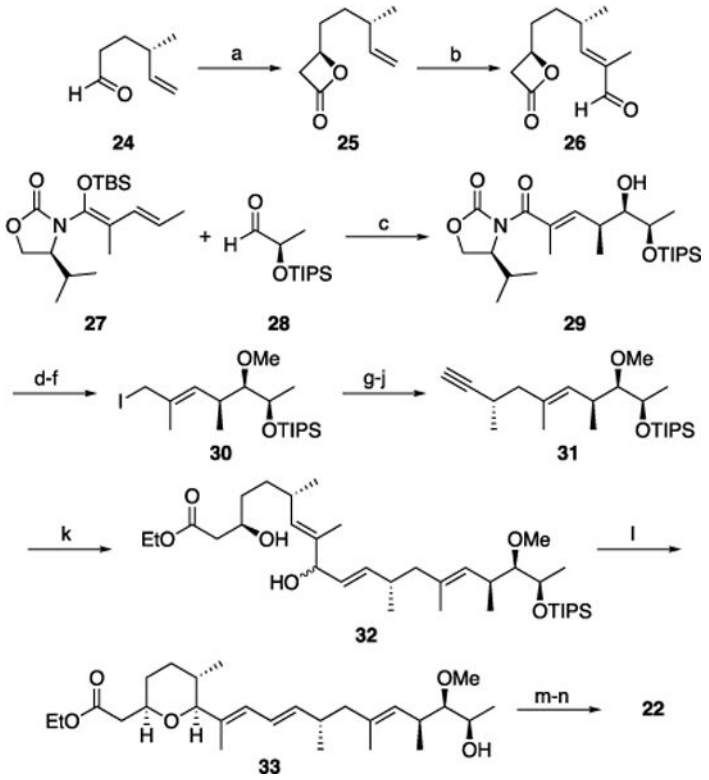
Re_2O_7-mediated allylic alcohol ionization.



Scheme 2.
Re_2O_7-mediated dehydrative cyclization.

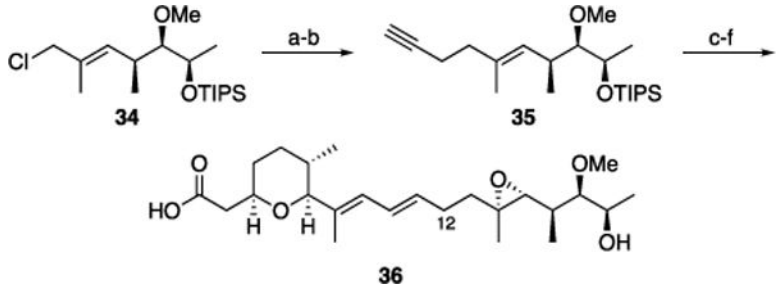


Scheme 3.
Herboxidiene retrosynthesis.



Scheme 4.

Total synthesis of herboxidiene. Reagents and conditions: a) AcCl, *i*Pr_2NEt, trimethylsilylquinidine, $LiClO_4$, CH_2Cl_2, Et_2O, 73%, dr = 9:1; b) Methacrolein, Hoveyda-Grubbs metathesis catalyst, 31%, 59% BRSM; c) $TiCl_4$, CH_2Cl_2, −78 °C, 71%; d) Me_3OBF_4, Proton Sponge®, CH_2Cl_2, 87%; e) $LiBH_4$, MeOH, Et_2O, 0 °C, 95%; f) I_2, Ph_3P, CH_3CN, Et_2O; g) (*R*)-4-Benzyl-3-propionyloxazolidin-2-one, NaHMDS, THF, −78 °C, 61% (two steps); h) $LiBH_4$, MeOH, Et_2O, 0 °C, 88%; i) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, 76%; j) Ohira-Bestmann reagent, NaOMe, THF, −78 C to −40 °C, 96%; k) $Cp_2Zr(H)Cl$, CH_2Cl_2, then Me_2Zn, then **26** then NaOEt, 72%; l) Re_2O_7•SiO_2, CH_2Cl_2, 82%; m) *t*BuOOH, $VO(acac)_2$, CH_2Cl_2, −15 °C, 64%; n) K_2CO_3, H_2O, MeOH, reflux, 85%.

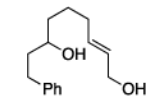
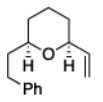
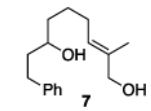
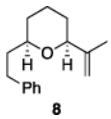
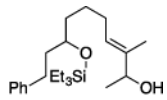
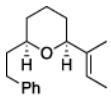
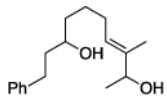
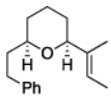
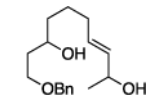
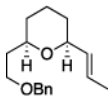
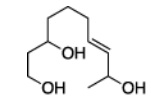
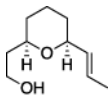
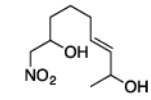
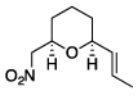
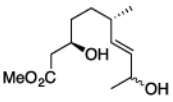
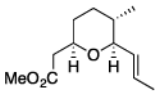
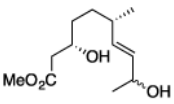
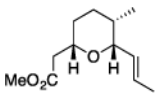


Scheme 5.

Synthesis of 12-desmethyl herboxidiene: a) 1-Trimethylsilyl-1-propyne, THF, −78 °C, then K_2CO_3, MeOH, 95%; b) $Cp_2Zr(H)Cl$, CH_2Cl_2, then Me_2Zn, then **26**, then NaOMe, 64%; c) Re_2O_7•SiO_2, CH_2Cl_2, 67%; d) *t*BuOOH, $VO(acac)_2$, CH_2Cl_2, −15 °C, 38%, 48% brsm; e) K_2CO_3, H_2O, MeOH, reflux, 85%.

Table 1

Dehydrative cyclization scope.[a]

Entry	Substrate	Product	Yield[b]	dr[c]
1	 **5**	 **6**	81%	1.7:1
2	 **7**	 **8**	81%	2.6:1
3	 **9**	 **10**	71%	>30:1
4	 **11**	 **10**	86%	>30:1
5	 **12**	 **13**	86%	7.6:1
6	 **14**	 **15**	85%	>15:1
7	 **16**	 **17**	84%	16:1
8	 **18**	 **19**	77%	>30:1
9	 **20**	 **21**	56%	2.9:1

[a] See the Supporting Information for experimental procedures and spectral data.

[b] Combined yield of the diastereomeric mixture.

[c] Determined by ^{1}H NMR analysis of the crude product mixture.