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Rhodium-Catalyzed *Endo*-Selective Epoxide-Opening Cascades: Formal Synthesis of (−)-Brevisin

Kurt W. Armbrust, **Matthew G. Beaver**[†], and **Timothy F. Jamison**[*]

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States

Abstract

$[Rh(CO)_2Cl]_2$ is as an effective catalyst for *endo*-selective cyclizations and cascades of epoxy-(*E*)-enoate alcohols, thus enabling the synthesis of oxepanes and oxepane-containing polyethers from di- and trisubstituted epoxides. Syntheses of the ABC and EF ring systems of (−)-brevisin via all *endo*-diepoxide-opening cascades using this method constitute a formal total synthesis and demonstrate the utility of this methodology in the context of the synthesis of marine ladder polyether natural products.

Introduction

The unique structural features, limited abundance, and potent biological activity of the marine ladder polyether family of natural products have inspired many innovative achievements in total synthesis enabled by the development of new methodology.[1] Guided by the biogenesis proposed for these compounds,[2] several groups have investigated the feasibility of all-*endo*[3] epoxide-opening cascades as a potentially rapid and general approach to these polyethers.[4] An ongoing challenge, these kinetically disfavored processes have been addressed in part by previous methodology developed in our laboratory.[5] Enabling expeditious synthesis of polytetrahydropyran fragments, template-guided, water-promoted cascades nevertheless as yet do not appear to be amenable to the synthesis of oxepanes, 7-membered rings that represent an important motif present in every natural ladder polyether isolated to date. Herein we demonstrate a new tactic that not only constructs oxepane rings, but also provides a new means for selective initiation of epoxide-opening cascades, as embodied by a formal synthesis of (−)-brevisin.

In the same vein as the use of epoxides and allylic alcohols as sites for selective initiation of polyene cyclizations towards sterols,[6] we envisioned that an appropriately substituted alkenyl epoxide[7] with a suitable activator might play a similar role in epoxide-opening

Corresponding Author:tfj@mit.edu.

[†]**Present Addresses:** Amgen, 360 Binney Street, Cambridge, MA 02142.

ASSOCIATED CONTENT

Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Notes

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cascades. Previous examples of selective initiation of epoxide-opening cascades include the Holton synthesis of hemibrevetoxin B, wherein an electrophilic selenium reagent triggered nucleophilic attack by an epoxide,[8] the photochemical generation of an oxocarbenium described by Floreancig and Houk,[9] and bromonium formation in a epoxide-opening cascade we utilized en route to dioxepandehydrothyrsiferol.[10] Finally, although the Lewis acid-promoted epoxide-opening cascades developed by McDonald did not utilize a site-selective initiation mechanism, they nevertheless demonstrated an important and unusual *endo* selectivity in the construction of trans-fused bis-oxepanes.[11]

Our design is depicted in Scheme 1 and can be summarized as follows: incorporation of an electronically tailored alkene at the distal[12] epoxide would provide a specific site for complexation and activation by a transition metal. The use of transition metals to selectively activate alkenyl epoxides for nucleophilic attack has excellent and diverse precedents. Although Pd catalysis is the most well known,[13] we eschewed this path because of the limited examples of oxygen nucleophiles in this context and, more importantly, the likelihood that an undesired stereochemical outcome would be observed, i.e., net retention (double inversion) at the site of epoxide opening, rather than the necessary inversion of configuration. In contrast, $[Rh(CO)_2Cl]_2$ has been shown to activate alkenyl epoxides for intermolecular opening by alcohol and amine nucleophiles with inversion of stereochemistry.[14] Further development by Ha and coworkers led to cyclizations of *trans*-disubstituted enoate epoxy-alcohols and carbamates to provide five- and six-membered saturated heterocycles.[15] Prior to our investigations, however, no examples of oxepane formation via $[Rh(CO)_2Cl]_2$ catalysis, activation of trisubstituted epoxides, or its use in initiation of epoxide-opening cascades had been reported.

Important in these designs was consideration of the natural product (−)-brevisin (**1**), isolated by Wright and Baden in 2008 from the dinoflagellate *Karenia brevis*.[16] The use of two cascades as described above (and shown in Scheme 2) would intercept two tricyclic intermediates (**2** and **3**) in the only previous total synthesis of (−)-brevisin from Tachibana and coworkers.[17]

Results and Discussion

Before embarking on epoxide-opening cascades towards (−)-brevisin, we first explored the feasibility of oxepane formation from epoxy alcohols promoted by $[Rh(CO)_2Cl]_2$.. Subjecting *trans*-disubstituted epoxy alcohol **6b** with the required enoate π-activating group[18] to conditions for $[Rh(CO)_2Cl]_2$ catalysis provided the desired oxepane **7b** as the only observable product (Table 1, entry 3). This combination of alkenyl epoxide and Rh catalysis provides rapid access to oxepanes from relatively simple starting materials[19] via *endo*-cyclization with stereospecific inversion observed at the formed O–C bond.

Noteworthy by contrast were the results observed under Brønsted acid catalysis. For example, subjecting epoxy alcohol **6b** to (±)-CSA activation conditions afforded primarily the smaller ring (*exo*), THP **8b**, consistent with results reported Nicolaou and coworkers (Table 1, entry 4).[20] The reversal of regioselectivity by $[Rh(CO)_2Cl]_2$ relative to acid catalysis supports an alternative mechanism for epoxide activation beyond a typical Lewis

acid. We found similar direct comparisons in these studies to be useful measures of the biasing ability of the enoate and $[Rh(CO)_2Cl]_2$ combination on regioselectivity.

Critical to the success of this method toward the synthesis of the ABC tricycle of (−)-brevisin, distal methyl substitution was well tolerated under $[Rh(CO)_2Cl]_2$ promotion, providing complete *endo* selectivity for the synthesis of both tetrahydropyran (**7c**) and oxepane (**7d**) from epoxy alcohols **6c** and **6d** respectively (Table 2, entries 1 and 3). In comparison, promotion with (±)-CSA yielded a mixture of *endo*- and *exo*-products, albeit with a slight improvement in regioselectivity compared to disubstituted epoxides **6a** and **6b**. Encouraged by these one-oxepane studies, we turned our attention to epoxide-opening cascades.

Toward the EF fragment, the route illustrated in Scheme 3 allowed for rapid access to the desired cascade precursor **5**. Ozonolysis of known enoate **9**,[21] followed by nucleophilic addition of isopropenyl magnesium bromide and a tandem vinylation–Claisen process[22] afforded aldehyde **10**. Olefination of **10**[23] and subsequent asymmetric Shi epoxidation[24] and TBAF desilylation rapidly provides cascade precursor **5** in six steps from enoate **9**.[25]

Investigation of cascade promoters for diepoxy alcohol **5** containing an (*E*)-enoate revealed $[Rh(CO)_2Cl]_2$ to be a highly chemo-, stereo-, and regioselective promoter – in the desired fashion. For example, $[Rh(CO)_2Cl]_2$ catalyzed the regioselective epoxide-opening cascade of (*E*)-enoate-diepoxy alcohol **5** to provide the desired product **11** in 38% isolated yield (Table 3, entry 1). Further optimization by employing 1,4-dioxane as the solvent and performing the reaction at elevated temperatures (65 °C) provided a 61% yield. Lewis or Brønsted acid activation, which we and others have employed in other all-endo epoxide-opening cascades, provided none of the desired product for enoate diepoxide **5**, again highlighting the exquisite selectivity of $[Rh(CO)_2Cl]_2$ catalysis (entries 3 and 4). The ester functional group is critical to the success of the method; vinyl-diepoxide **13** under $[Rh(CO)_2Cl]_2$ catalysis provided lower yields (entry 5). Alternatively, conditions utilized by McDonald in methyl-[11b] or vinyl-directed[11c] epoxide-opening cascades led to the desired product (**3**), but also in a lower yield (entries 6–8). These results support the mechanistic hypothesis of Rh(I) activation of alkenyl epoxides via π-coordination and oxidative addition into the vinylic C–O bond of the epoxide, which contrasts the generally non site-selective epoxide activation with Lewis acids. Importantly, these results represent the first examples of both a cascade process and a seven-membered ring formation using this method. By ozonolysis followed by Wittig reaction, (*E*)-enoate **11** was converted to **3**, corresponding to the EF-ring system of (−)-brevisin (**1**).

Toward the ABC fragment, synthesis of the A ring proceeded via the previously reported route to lactone **14**[17c] (Scheme 4). This lactone was elaborated by diastereoselective dihydroxylation, and the incipient side chain installed through allyl Grignard addition. Triethylsilane reduction of the intermediate lactol, and acetylation provided the fully elaborated A ring (**15**).

Elaboration of the allyl group of **15** was accomplished via cross metathesis with **18**,[26] giving trisubstituted alkene **19**, albeit in only 31% yield. Motivated by reports of higher yields in

cross metathesis of allyl groups with increased steric hindrance,[27] alkene **16** was prepared from **15** via cross metathesis with 2-methyl-2-butene.[28] In comparison, cross metathesis of **18** and trisubstituted alkene **16** provided a significantly higher yield, particularly when performed in the absence of additional solvent. Despite the modest stereoselectivity, the 2:1 *E:Z* mixture of alkene isomers could be separated by column chromatography. The enoate-directing group was installed by desilylation of **19**, alcohol oxidation, and in-situ stabilized-Wittig olefination. Asymmetric Shi epoxidation, and acetate ethanolysis provided the diepoxide cascade precursor **21**.

Exposure of diepoxide **21** to catalytic $[Rh(CO)_2Cl]_2$ at ambient temperature in THF led to full conversion and 78% yield of the desired ABC tricycle (**22**). Efforts directed toward lowering the catalyst loading led to inferior yields. Brønsted acid promotion with (±)-CSA did not provide any desired product, further differentiating $[Rh(CO)_2Cl]_2$ from acid promoted conditions. Completion of the formal synthesis of (−)-brevisin (**1**) was achieved by benzylation of both hydroxyl groups, oxidative cleavage of the pendant enoate via dihydroxylation and diol cleavage,[29] and finally aldehyde reduction to provide alcohol **2**, corresponding to the ABC-ring system of (−)-brevisin (**1**).

To help further our understanding of these successful diepoxide-opening reactions, we have put forth a mechanism for the ABC-ring cascade, shown in Scheme 5. The proposed epoxonium pathway invokes formation of a bicyclo[4.1.0] epoxonium by $[Rh(CO)_2Cl]_2$ activation of the distal epoxy-enoate, subsequent attack by the central epoxide, then rapid trapping by the A-ring hydroxyl. We favor the epoxonium pathway versus a related stepwise transformation[30] as it provides a more consistent explanation of the high yield obtained under what would generally be regarded mild conditions.

Further insight into the putative mechanism is suggested by our initial cyclization studies of epoxides with proximal methyl substitution. These substrates, which represent one of the most challenging substitution patterns to achieve high *endo* selectivity in epoxy alcohol cyclizations,[31] have shown significant promise thus far. For example, use of the enoate and $[Rh(CO)_2Cl]_2$ overrides the near complete *exo*-selectivity observed with CSA for proximal methyl substitution, (Table 4, entries 1 and 2). Notably, however, measurable quantities of the exo products are observed – in contrast to the previous substrates tested (vide supra). Higher catalyst loadings and heating are required for full conversion in these cases. While the yield and selectivity are lower in the case of formation of oxepane **7f** (Table 4, entry 3), this result suggests nevertheless an alternative approach to override the *exo*-directing methyl group in this very challenging case of oxepane formation. These results together with the diepoxide cascades further suggest that $[Rh(CO)_2Cl]_2$ is activating alkenyl epoxides via a distinct mechanism relative to Brønsted or Lewis acid catalysis.

Conclusions

In summary, the combination of an enoate group and $[Rh(CO)_2Cl]_2$ catalysis is effective not only for the synthesis of 6- and 7-membered oxygen heterocycles from epoxy alcohols bearing a variety of substitution patters, but also cascades of diepoxides where control of the sequence of epoxide opening events is tantamount to success. The high yield, stereo-

specificity, functional group compatibility, and *endo*-selectivity make this approach particularly well suited for target-directed synthesis, as highlighted by the formal synthesis of (−)-brevisin. Further application of this methodology towards other oxepane-containing natural products is an active area of research, as is investigation of other Rh(I) catalysts and alkene directing groups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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12. Distal is defined as the epoxide furthest from the terminating alcohol nucleophile.

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18. "π-Activating group" refers to the group distal to furthest epoxide relative to trapping nucleophile.
19. See the Supporting Information for complete details of synthetic procedures and compound characterization towards epoxy alcohols 6a–6f.
20. Alkenes other than enoates are superior π-activating activating groups for endo-selective epoxy-alcohol cyclizations promoted by Brønsted acids. See:(a) Nicolaou KC, Prasad CVC, Somers PK, Hwang C-K. J Am Chem Soc. 1989; 111:5330.(b) Nicolaou KC, Prasad CVC, Somers PK, Hwang C-K. J Am Chem Soc. 1989; 111:5335.
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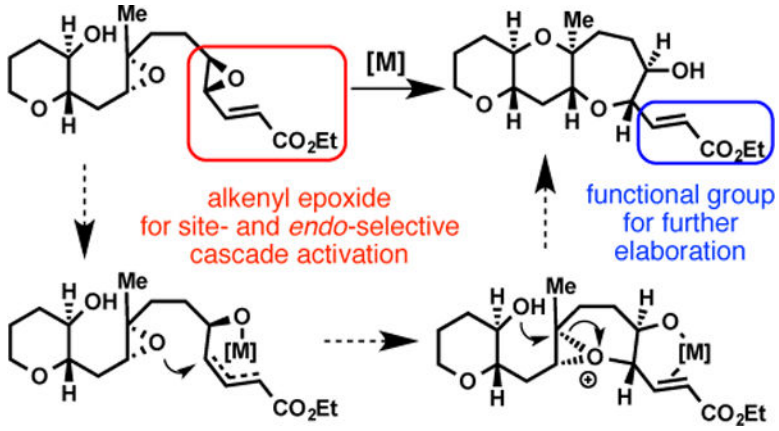
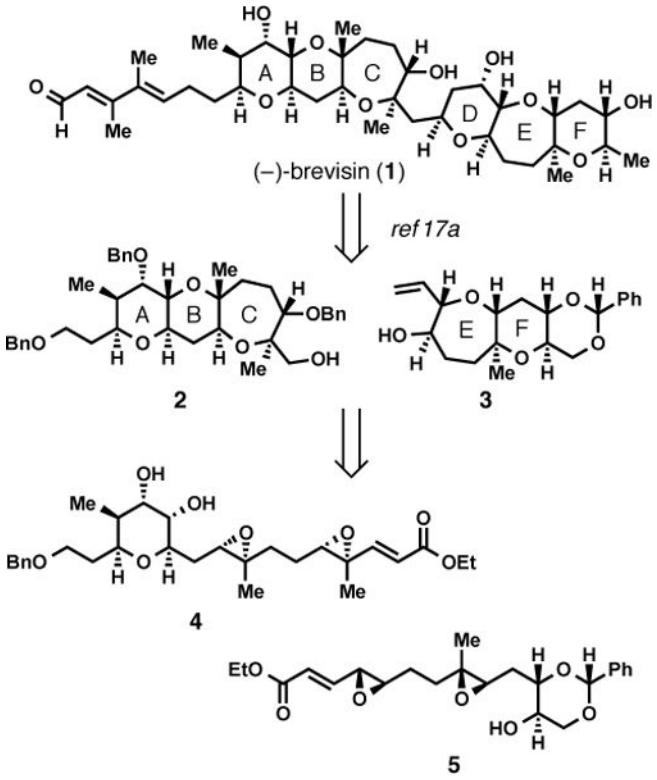
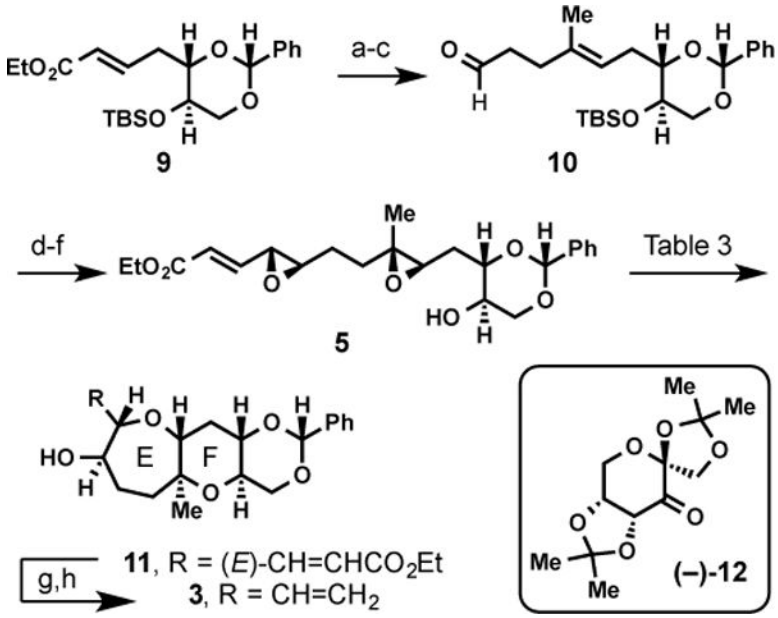


Scheme 1.

Substrate and promoter combination designed for selective initiation of all-*endo* epoxide-opening cascades

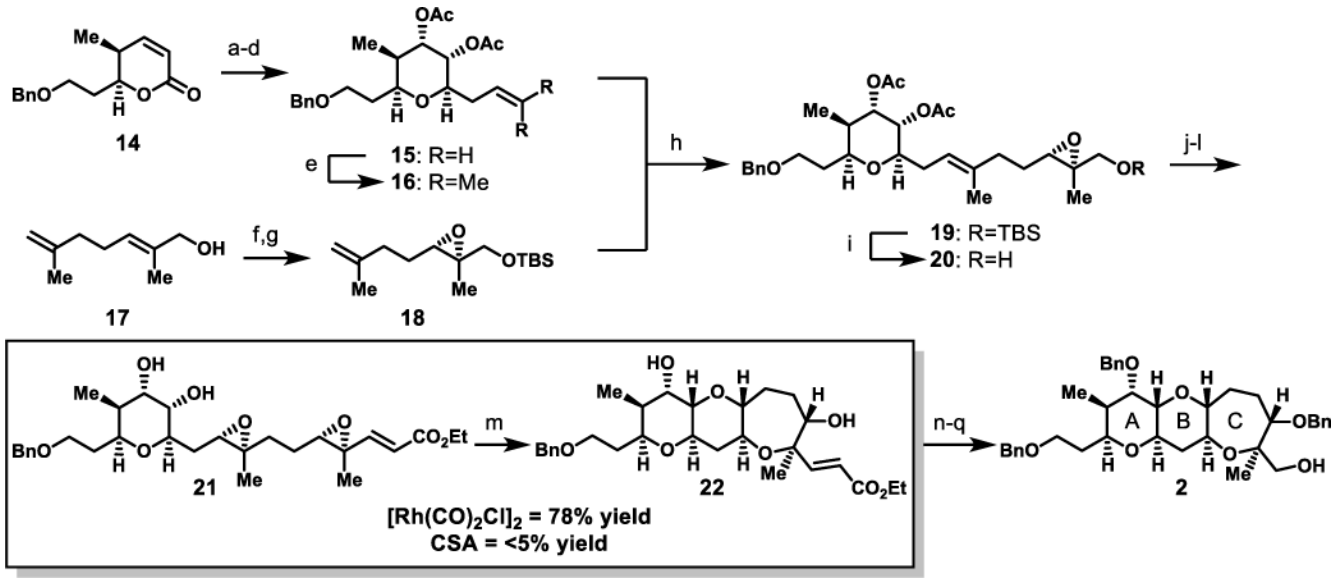


Scheme 2.
Retrosynthetic Analysis of (−)-Brevisin (1)



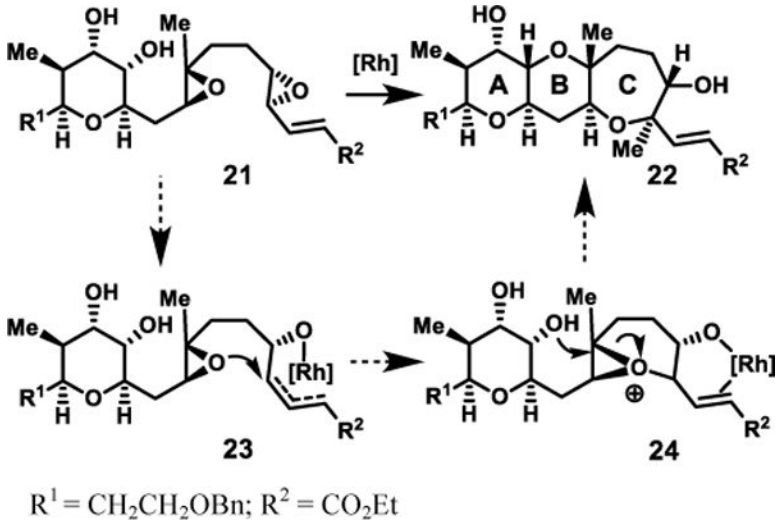
Scheme 3. Synthesis of EF diepoxy cascade precursors and formal synthesis target

Reaction conditions: a) O_3, CH_2Cl_2, −78 °C; then Me_2S, 82%; b) $H_2C{=}C(CH_3)MgBr$, THF, −78 °C to 0 °C, 1:1 dr, 89%; c) Triethyleneglycol divinyl ether, (1,10-phenanthroline)$Pd(OAc)_2$, 80 °C, 7:1 *E*/*Z*, 63%; d) LDA, $(MeO)_2P(O)CH_2CH{=}CHCO_2Et$, −78 °C to rt, 2:1 *E*/*Z*, 84%; e) (−)-**12**, $KHSO_5$, Bu_4NHSO_4, K_2CO_3, pH 10.5, DMM/CH_3CN (2:1), 22%; f) TBAF, THF, rt, 69%; g) O_3, CH_2Cl_2/MeOH (4:1), −78 °C; Ph_3P, −78 °C to rt; h) Ph_3PCH_3Br, KO*t*-Bu, THF, 0 °C to rt, 84% (over 2 steps).



Scheme 4. Synthetic route to ABC diepoxide-opening cascade precursor and formal synthesis target

a) OsO_4, NMO, Acetone/H_2O (4:1), 95%; b) CH_2=$CHCH_2MgBr$, THF, −78 °C; c) Et_3SiH, TMSOTf, MeCN, 44% (over 2 steps); d) Ac_2O, pyr, DMAP, CH_2Cl_2, 87%; e) 2-methyl-2-butene, Hoveyda-Grubbs cat. (2nd generation), Benzoquinone, 87%; f) L-(+)-DET, $Ti(OiPr)_4$, TBHP, CH_2Cl_2, −20 °C, 49%, 93% e.e.; g) TBSCl, Et_3N, CH_2Cl_2, 86%; h) Hoveyda-Grubbs cat. (2nd generation), Benzoquinone, 80 °C, 78%, 2:1 *E*/*Z*; i) TBAF, THF, 84%; j) pyr•SO_3, DMSO, Et_3N, CH_2Cl_2, rt; then Ph_3PCHCO_2Et, rt, 91%; k) (+)-**12**, $KHSO_5$, Bu_4NHSO_4, K_2CO_3, pH 10.5, DMM/CH_3CN (2:1), 84%, 3:1 d.r.; l) Guanidine•HCl, NaOEt, EtOH, 77%; m) $[Rh(CO)_2Cl]_2$ (10 mol%), THF, rt, 78%; n) NaH, BnBr, TBAI, THF, 60 °C, 75%; o) $K_2OsO_2(OH)_4$, Citric Acid, NMO, t-BuOH/H_2O; p) Ph_3BiCO_3, CH_2Cl_2, reflux; q) $NaBH_4$, MeOH, 0 °C, 60% (over 3 steps).

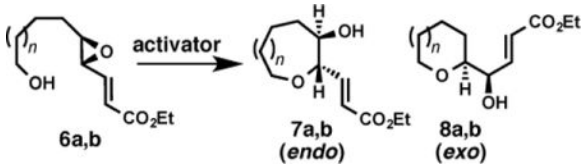


$R^1 = CH_2CH_2OBn$; $R^2 = CO_2Et$

Scheme 5. Proposed mechanism for Rh-promoted epoxide-opening cascade of diepoxide 22

Table 1

Trans-disubstituted epoxy alcohol cyclizations under $[Rh(CO)_2Cl]_2$ and (±)-CSA promotion



entry	substrate	activator	7/8	yield 7 (%)[a]
1	**6a**, n = 0	$[Rh(CO)_2Cl]_2$[b]	>20 : 1	94
2	**6a**, n = 0	(±)-CSA[c]	1 : 1	–
3	**6b**, n = 1	$[Rh(CO)_2Cl]_2$[d]	>20 : 1	81
4	**6b**, n = 1	(±)-CSA[e]	1 : 3	–

[a] Isolated yield.

[b] $[Rh(CO)_2Cl]_2$ (2.5 mol %), THF, rt.

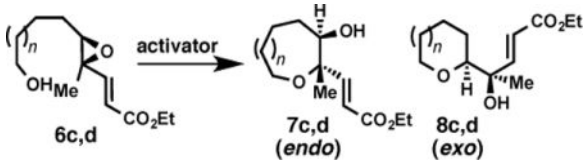
[c] (±)-CSA (10 mol %), CH_2Cl_2, rt.

[d] $[Rh(CO)_2Cl]_2$ (5 mol %), THF, rt.

[d] (±)-CSA (100 mol %), CH_2Cl_2, rt.

Table 2

Trisubstituted epoxy alcohol cyclizations under $[Rh(CO)_2Cl]_2$ and (±)-CSA promotion



entry	substrate	activator	7/8	yield 7 (%)[a]
1	**6c**, n = 0	$[Rh(CO)_2Cl]_2$[b]	>20: 1	93
2	**6c**, n = 0	(±)-CSA[c]	3.4: 1	–
3	**6d**, n = 1	$[Rh(CO)_2Cl]_2$[d]	>20: 1	88
4	**6d**, n = 1	(±)-CSA[e]	1: 1.8	–

[a] Isolated yield.

[b] $[Rh(CO)_2Cl]_2$ (1 mol %), THF, rt.

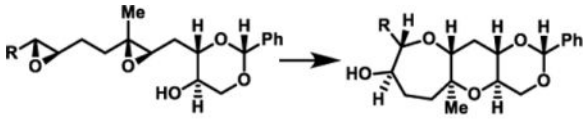
[c] (±)-CSA (10 mol %), CH_2Cl_2, rt.

[d] $[Rh(CO)_2Cl]_2$ (2.5 mol %), THF, rt.

[d] (±)-CSA (100 mol %), CH_2Cl_2, rt.

Table 3

Investigation of diepoxide cascade towards EF Fragment



5, R = (*E*)-CH=CHCO$_2$Et
13, R = CH=CH$_2$

11, R = (*E*)-CH=CHCO$_2$Et
3, R = CH=CH$_2$

entry	substrate	conditions	product	yield (%)
1	**5**	[Rh(CO)$_2$Cl]$_2$, THF, rt	**11**	38[a]
2	**5**	[Rh(CO)$_2$Cl]$_2$, Dioxane, 65°C	**11**	61[a]
3	**5**	BF_3•OEt_2, CH_2Cl_2, −78°C	**11**	–[b,c]
4	**5**	CSA, CH_2Cl_2, rt	**11**	–[b,c]
5	**13**	[Rh(CO)$_2$Cl]$_2$, THF, rt	**3**	21[a]
6	**13**	BF_3•OEt_2, CH_2Cl_2, −78°C	**3**	23[a]
7	**13**	Yb(OTf)$_3$, CH_2Cl_2, rt	**3**	38[b]
8	**13**	Eu(OTf)$_3$, CH_2Cl_2, rt	**3**	26[b]

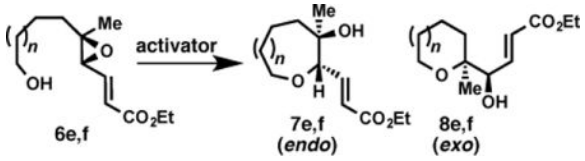
[a] Isolated yield.

[b] Yield determined by ^{1}H NMR against mesitylene standard.

[c] – represents no observed product.

Table 4

Proximal-methyl (*E*)-trisubstituted epoxy alcohols cyclizations under $[Rh(CO)_2Cl]_2$ and (±)-CSA promotion



entry	substrate	activator	7: 8	yield 7 (%)[a]
1	**6e**, n = 0	$[Rh(CO)_2Cl]_2$[b]	12: 1	81
2	**6e**, n = 0	(±)-CSAc	1: >20	–
3	**6f**, n = 1	$[Rh(CO)_2Cl]_2$[d]	4: 1	21
4	**6f**, n = 1	(±)-CSAe	1: >20	–

[a] Isolated yield.

[b] $[Rh(CO)_2Cl]_2$ (10 mol %), 1,4-Dioxane, 80 °C.

[c] (±)-CSA (10 mol %), CH_2Cl_2, rt.

[d] $[Rh(CO)_2Cl]_2$ (10 mol %), THF, 60 °C.

[e] (±)-CSA (100 mol %), CH_2Cl_2, rt.