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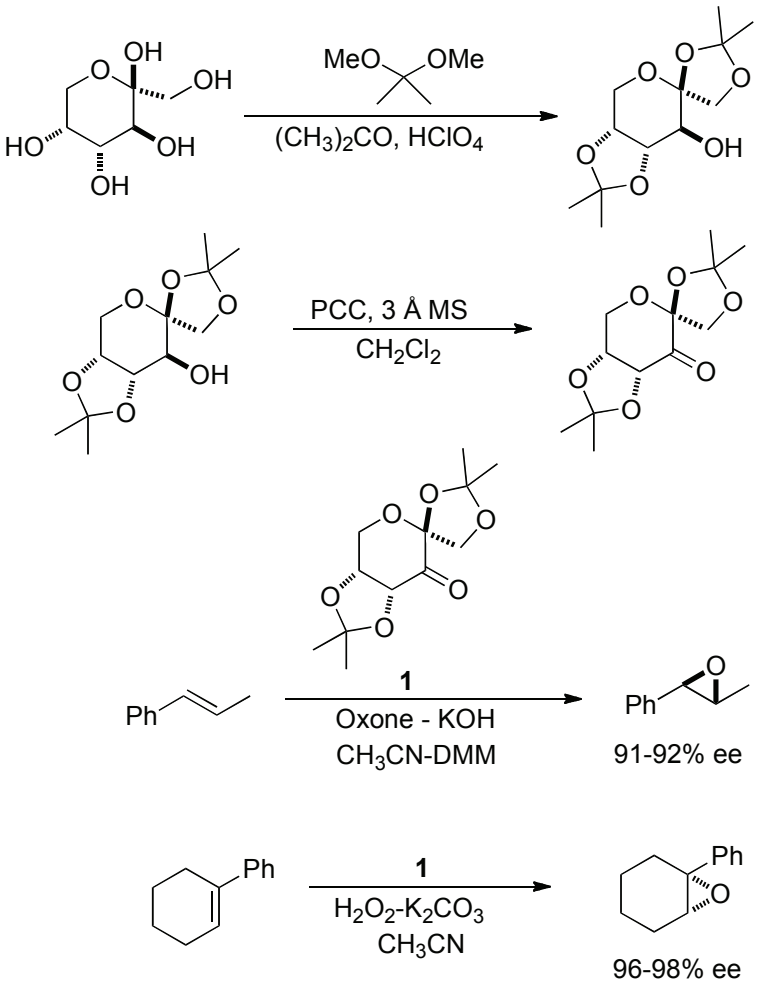
Discussion Addendum for: Synthesis of 1,2:4,5-Di-*o*-isopropylidene–D-erythro-2,3-hexodiulo-2,6-pyranose. A Highly Enantioselective Ketone Catalyst for Epoxidation/Asymmetric Epoxidation of *trans*-β-Methylstyrene and 1-Phenylcyclohexene using a D-Fructose-derived Ketone: (*R*,*R*)-*trans*-β–Methylstyrene Oxide and (*R*,*R*)-1-Phenylcyclohexene Oxide



Prepared by Thomas A. Ramirez, O. Andrea Wong, and Yian Shi.*[1]
Original articles: Tu, Y.; Frohn, M.; Wang, Z.-X.; Shi, Y. *Org. Synth*. **2003**, *80*, 1. and Wang, Z.-X.; Shu, L.; Frohn, M.; Tu, Y.; Shi, Y. *Org. Synth*. **2003**, *80*, 9.

Prior to and subsequent to the original reports in *Organic Syntheses*, we have reported a number of carbohydrate-derived ketone epoxidation

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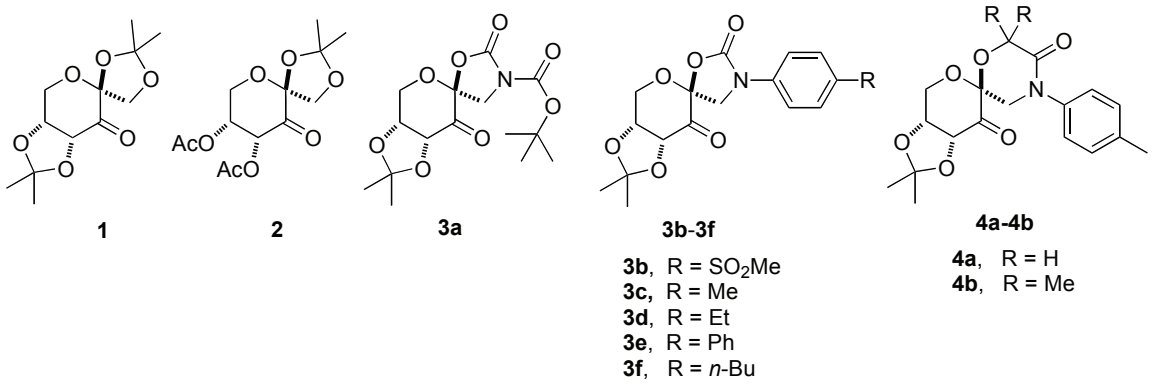
catalysts[2] including **1**-**4** (Figure 1). Epoxidation of olefins catalyzed by these ketones has become a valuable tool for the synthetic organic chemist.[2]

Figure 1. Four Generations of Ketone Catalysts



Generations of Catalysts:

*Ketone **1**:*

The synthesis and use of ketone **1** was reported in the original *Organic Syntheses* articles. Ketone **1** is an effective catalyst for the epoxidation of a variety of *trans*- and tri-substituted olefins,[3] vinylsilanes,[4] hydroxy alkenes,[5] dienes,[6] enynes,[7] enol ethers, and enol esters.[8,9] A procedure for the preparation of *ent*-ketone **1** from L-sorbose has also been developed.[3b,10] Ketone **1** and *ent*-ketone **1** have been successfully used in various synthetic applications.[2h-k]

*Ketone **2***:

Ketone **2** has proven to be a more reactive analogue of ketone **1**, particularly in the reaction of electron-deficient olefins. It is derived from ketone **1** through a selective deketalization followed by acetylation.[11]

*Ketones **3***:

Ketones **3** mediate the highly stereoselective epoxidation of conjugated *cis*-, terminal, tri-substituted, and some tetra-substituted double bonds.[12-21] While ketone **3a** is highly effective, **3c**-**3f** were developed due to their streamlined syntheses.[13] Ketones **3a** and **3f** have also found efficacy in the epoxidation of non-conjugated, amphiphilic *cis*-olefins.[22]

*Ketones **4***:

Ketone **4a** has extended the capability of the epoxidation system to geminally-disubstituted terminal olefins and also works well in the epoxidation of some *cis*- and tri-substituted olefins.[23] Ketone **4b** has proven effective in the reaction of *trans*- and tri-substituted double bonds.[23]

Ketone **1**, *ent*-ketone **1**, **3c**, and **3d** are now commercially available. Our group website now features "Guidelines for Asymmetric Epoxidation"[24] which includes instructive illustrations and tips for running the epoxidation reactions, and the document addresses frequently asked questions.

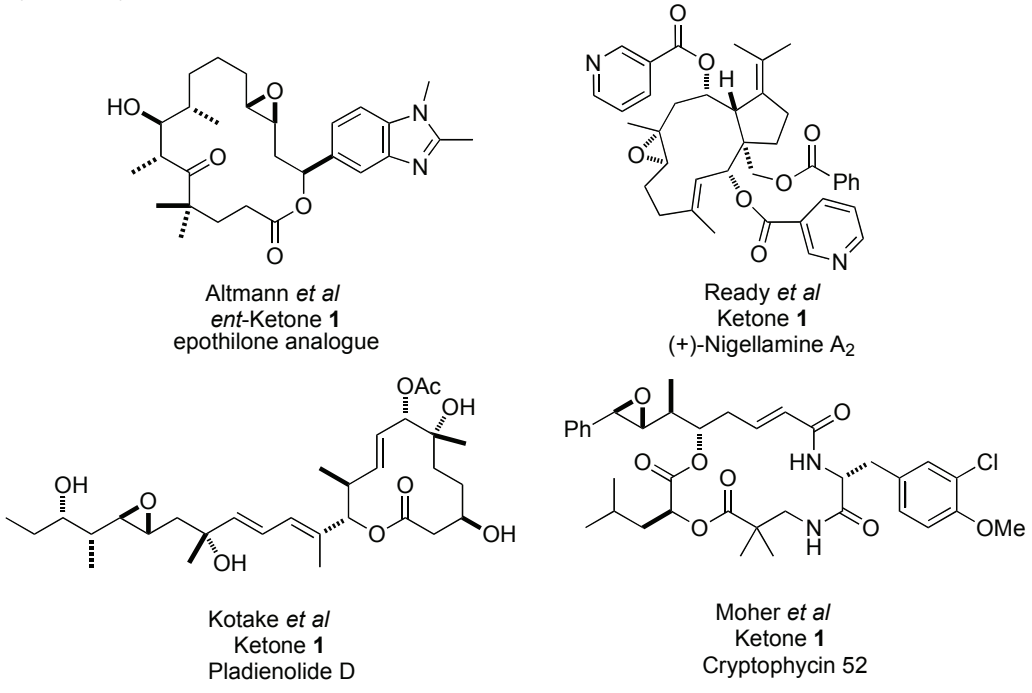
Synthetic Applications:

Previously published reviews provide a detailed discussion of the development of the catalysts and their respective substrate scopes.[2b-e, 2g-k] This update will focus primarily on the wealth of synthetic applications of ketone **1** and *ent*-ketone **1**.

Ketone 1:

The epoxidation with ketone **1** is practical and has been used in undergraduate teaching laboratories,[25] academic research laboratories,[2b-e,g-k] and in industry.[26] Along with other proven asymmetric epoxidation systems, ketone **1** has validated the use of stereoselective epoxidation in endgame approaches as well as those invoking the epoxide's manipulability. In addition, the ketone-catalyzed epoxidation is a process that can be used for discriminant or indiscriminant (poly-) epoxidation which can be further utilized in the rapid construction of complex molecules via cascade cyclization reactions.

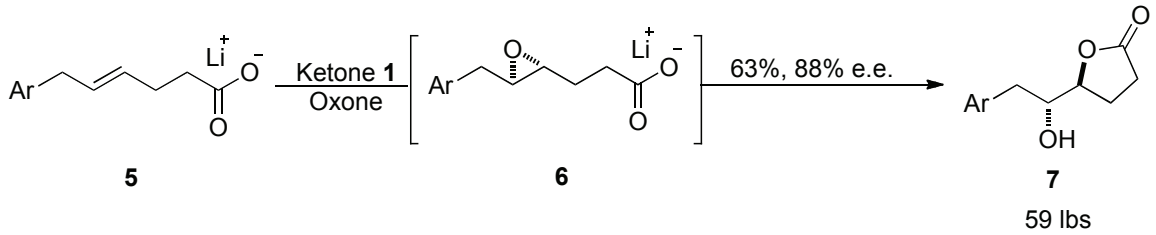
Figure 2. Examples of Target Molecules Synthesized with Epoxidation Catalyzed by Ketone **1** or *ent*-Ketone **1**



Some examples of the use of ketone **1** in the selective installation of the epoxide functional group in biologically active molecules are shown in Figure 2. Altmann and coworkers used *ent*-ketone **1** for the epoxidization of an unsaturated macrolide to afford an epothilone analogue as a single isomer.[27] Ready and coworkers utilized ketone **1** for a highly discriminant epoxidation in their synthesis of (+)-nigellamine A_2.[28] Moher,[29] Kotake,[30] and others[31,32] have used ketone **1** to stereoselectively install epoxides in the side chains of target molecules.

The ketone-catalyzed epoxidation has found use in industry.[26] A team at DSM Pharma Chemical obtained lactone **7** in 63% overall yield and 88% ee when crude γ,δ-unsaturated carboxylate was subjected to the reaction conditions (Scheme 1).[26] The intermediate epoxide was opened by an intramolecular attack by the carboxylate anion.[22,26] After the product was crystallized from heptane, 59 lbs of lactone were obtained.

Scheme 1. Industrial Scale Synthesis of Lactone **7** via Epoxidation/Epoxide Opening

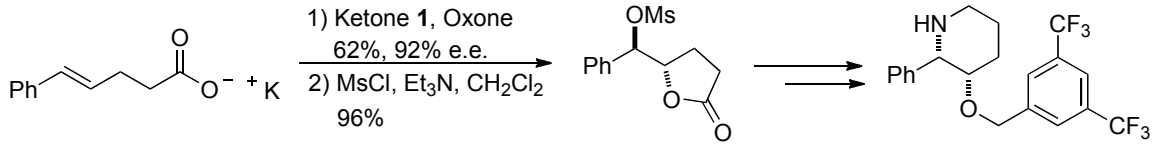


5 **6** **7**

59 lbs

Sudalai and coworkers have used a similar process in their synthesis of (+)-L-733,060 (**10**), an antitumor agent with activity against retinoblastoma (Scheme 2).[33] The γ,δ-unsaturated carboxylate **8** was stereoselectively epoxidized and then underwent *in situ* lactonization.

Scheme 2. Synthesis of (+)-L-733,060

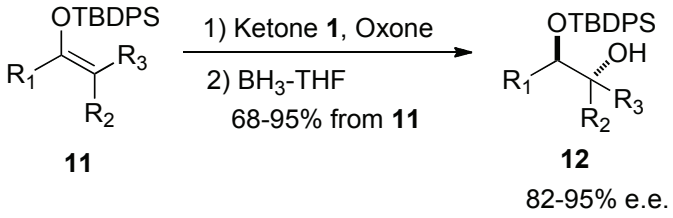


8 **9** **10**

(+)-L-733,060

Myers and coworkers developed a method to synthesize *trans*-1,2-diol derivatives **12** using ketone **1**-catalyzed epoxidation of cyclic *E* and acyclic *E* and *Z* silyl enol ethers followed by reduction mediated by an internal hydride delivery (Scheme 3).[34,35]

Scheme 3. Epoxidation/Reduction For 1,2-Diols

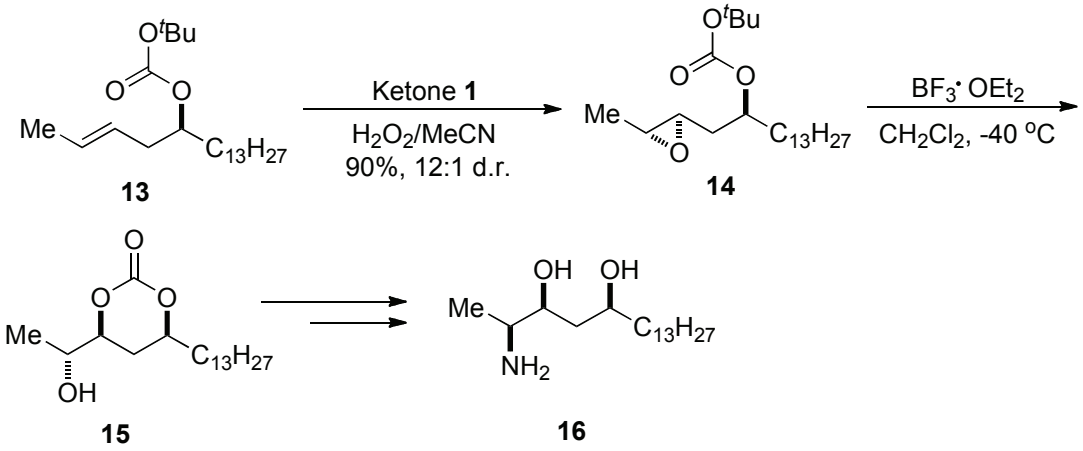


11 **12**

82-95% e.e.

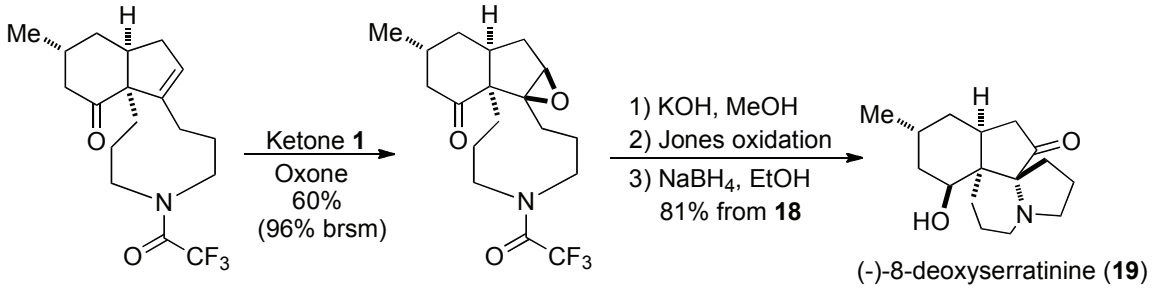
McDonald and coworkers used ketone **1**-catalyzed epoxidation to access potentially antineoplastic 1-deoxy-5-hydroxysphingosine analogue **16** (Scheme 4).[36] Lewis acid catalyzed cyclization led to cyclic carbonate **15**. The resulting alcohol was then activated and displaced by an azide to yield the 2-amino-3,5-diol motif. The C-5 epimer of **16** was also synthesized when *ent*-**13** was used as the starting template.

Scheme 4. Synthesis of 1-Deoxy-5-Hydroxysphingosine Analogue



13 **14** **15** **16**

Scheme 5. Synthesis of (-)-8-Deoxyserratinine



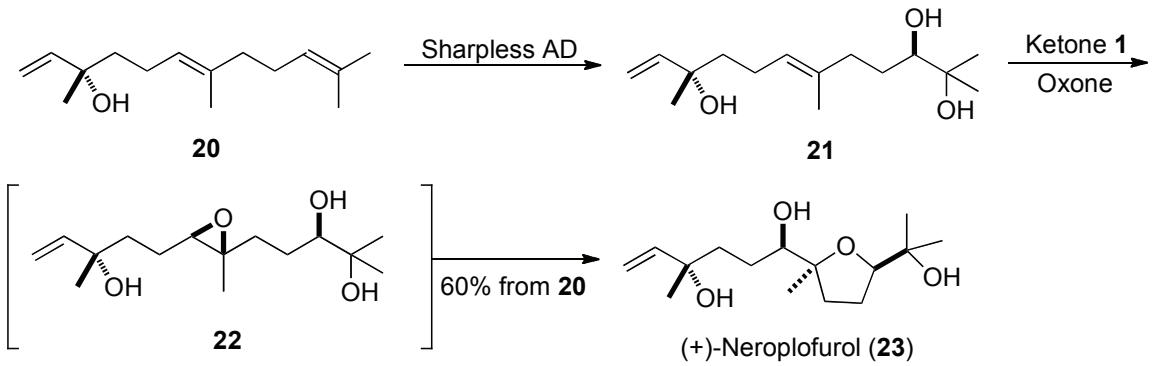
17 **18** (-)-8-deoxyserratinine (**19**)

Yang and coworkers recently reported the total synthesis of (−)-8-deoxyserratinine (**19**) (Scheme 5).[37] Ketone **1** allowed them to overcome the

substrate-induced facial bias in the epoxidation of **17** which afforded **18** as the sole isomer.

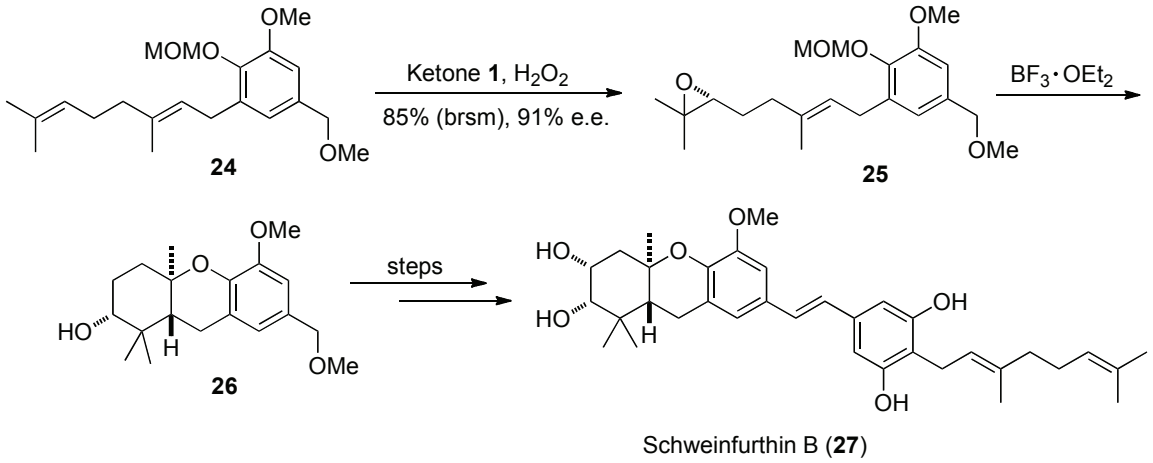
Huo and coworkers recently synthesized (+)-neroplofurol (**23**) in two operations and 60% overall yield from the naturally (and commercially) available (+)-nerolidol (Scheme 6).[38] Upon epoxidation of **21**, cyclization took place *in situ*.

Scheme 6. Synthesis of (+)-Neroplofurol (**23**)



Wiemer and coworkers have also investigated the use of cascade cyclizations in the syntheses of schweinfurthins.[39] A ketone **1**-catalyzed highly site- and stereo-selective epoxidation followed by a Lewis acid catalyzed cyclization allowed them to synthesize schweinfurthin B (**27**)[39] (Scheme 7) and a diverse array of derivatives.

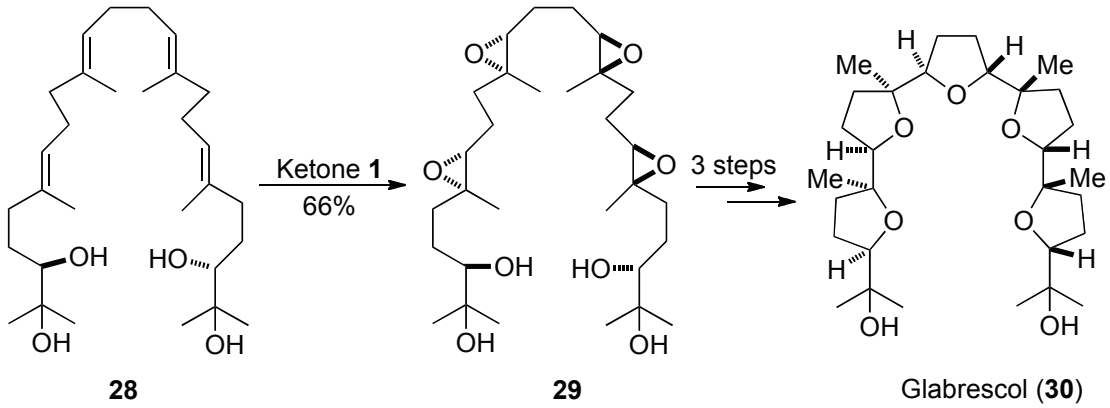
Scheme 7. Synthesis of Schweinfurthin B (**27**) via Epoxidation/Cascade Cyclization



In an effort to confirm the absolute stereochemistry of glabrescol (**30**), Corey and coworkers obtained the poly-tetrahydrofuran via the tetra-

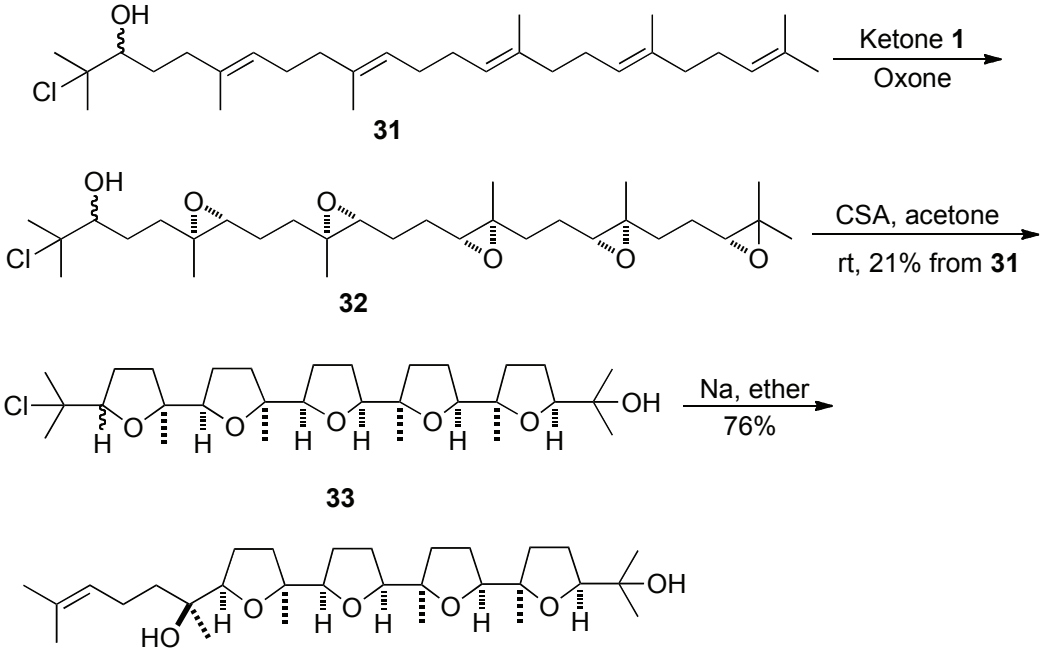
epoxidation of tetra-ene **28** followed by a CSA-mediated cyclization (Scheme 8).[40,41]

Scheme 8. Synthesis of Glabrescol (**30**)



In 2010, (+)-omaezakianol was obtained by Xiong, Busch, and Corey via penta-epoxidation of **31** followed by cascade cyclization and dehalogenation (Scheme 9).[42]

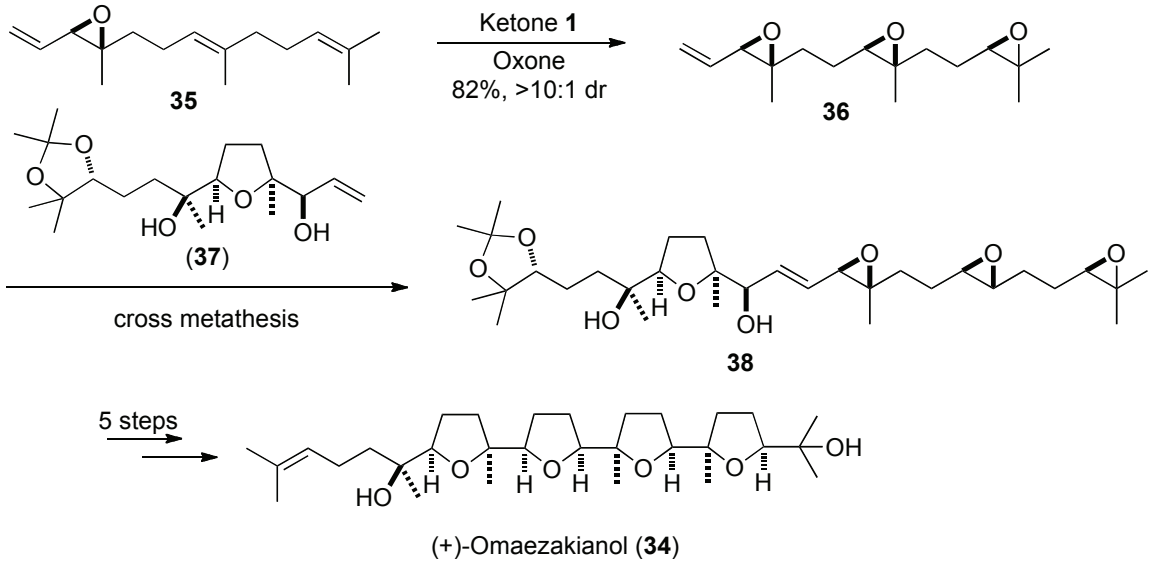
Scheme 9. Synthesis of (+)-Omaezakianol (**34**)



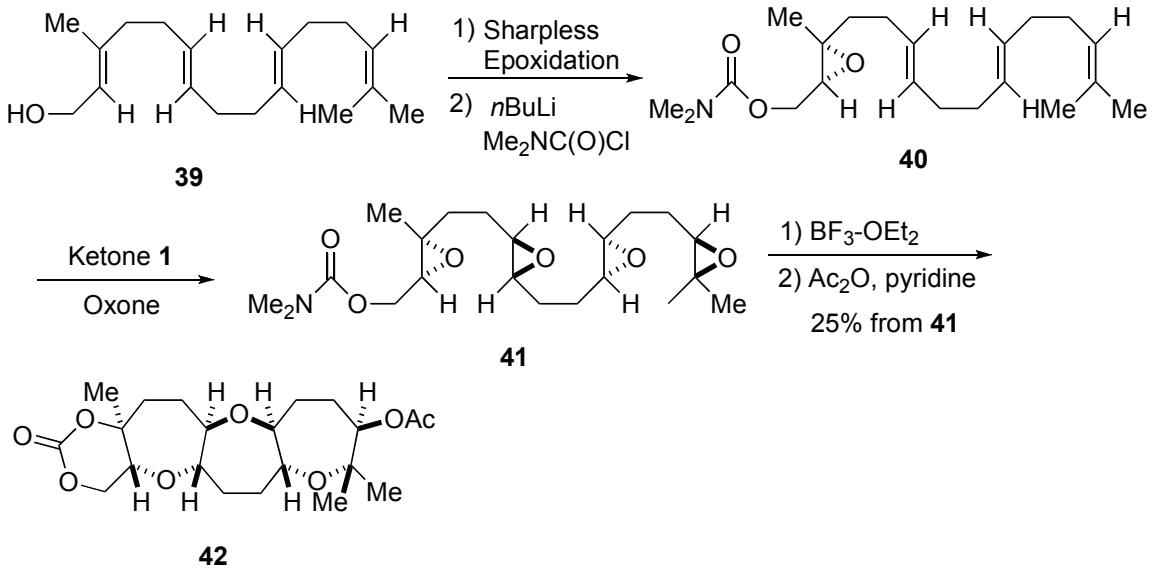
In 2009, Morimoto and coworkers accomplished a synthesis of (+)-omaezakianol (**34**) using a convergent approach (Scheme 10).[43] Ketone **1** promoted a *bis*-epoxidation of **35** in high yield and diastereoselectivity.

Compound **37** was assembled, in part, by an *ent*-ketone **1** catalyzed epoxidation. Epoxide **36** and **37** were cross-coupled and a cascade cyclization along with some additional steps afforded the target product.

Scheme 10. Synthesis of (+)-Omaezakianol (**34**)



Scheme 11. Polyepoxide Cyclization

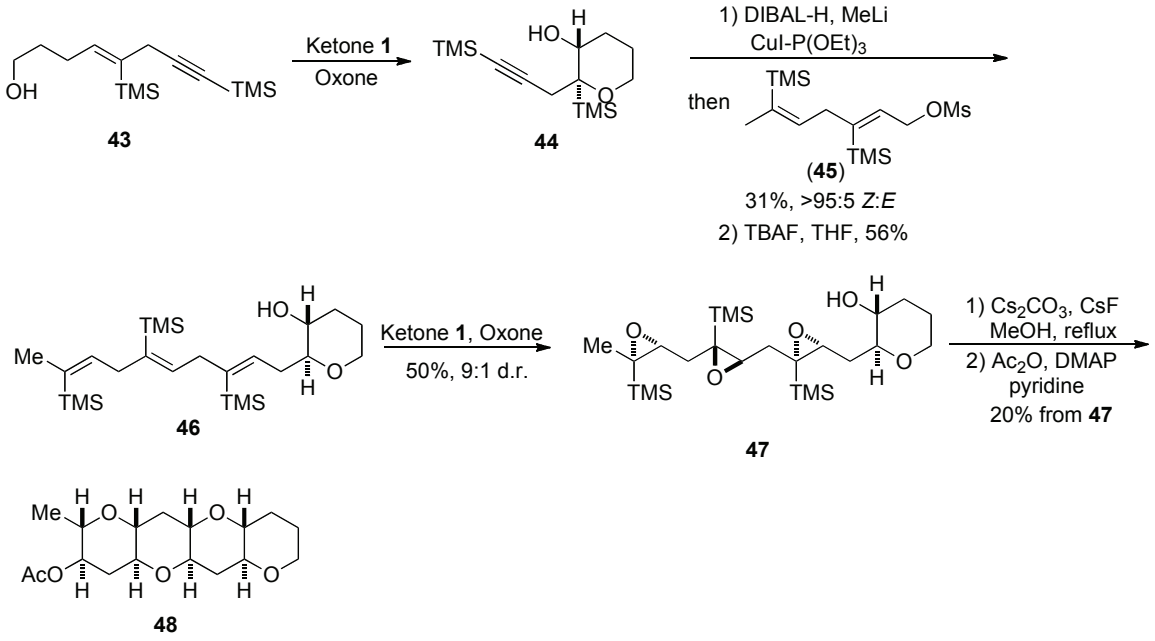


McDonald and coworkers have reported on a series of biomimetic cascade cyclizations of poly-epoxides to access complex polycyclic ethers. An example is shown in Scheme 11.[44a] The Sharpless methodology was used to epoxidize the allylic alcohol and ketone **1** facilitated the tris-

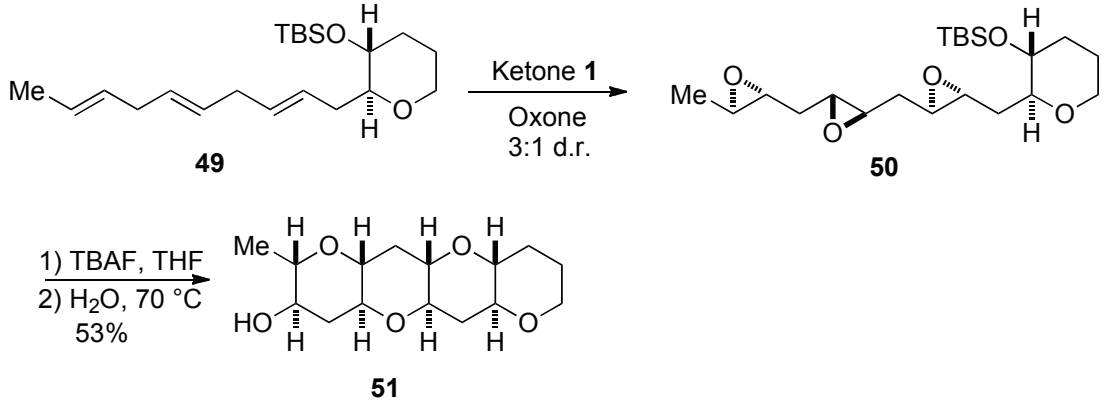
epoxidation of **40**. The carbamate was used to trigger the cascade cyclization under Lewis-acidic conditions to afford fused tetracycle **42**.[44]

Jamison and coworkers have shown that poly-vinyl silane **46** can be poly-epoxidized to afford **47**, which was converted to a ladder polyether under basic conditions in methanol. The trimethylsilyl groups directed the 6-*endo* attack and then "disappeared" (Scheme 12).[45]

Scheme 12. Stereoselective *Tris*-Epoxidation and Subsequent TMS-Directed Cyclization



Scheme 13. Stereoselective *Tris*-Epoxidation and Subsequent Water-Promoted *Endo*-Cyclization

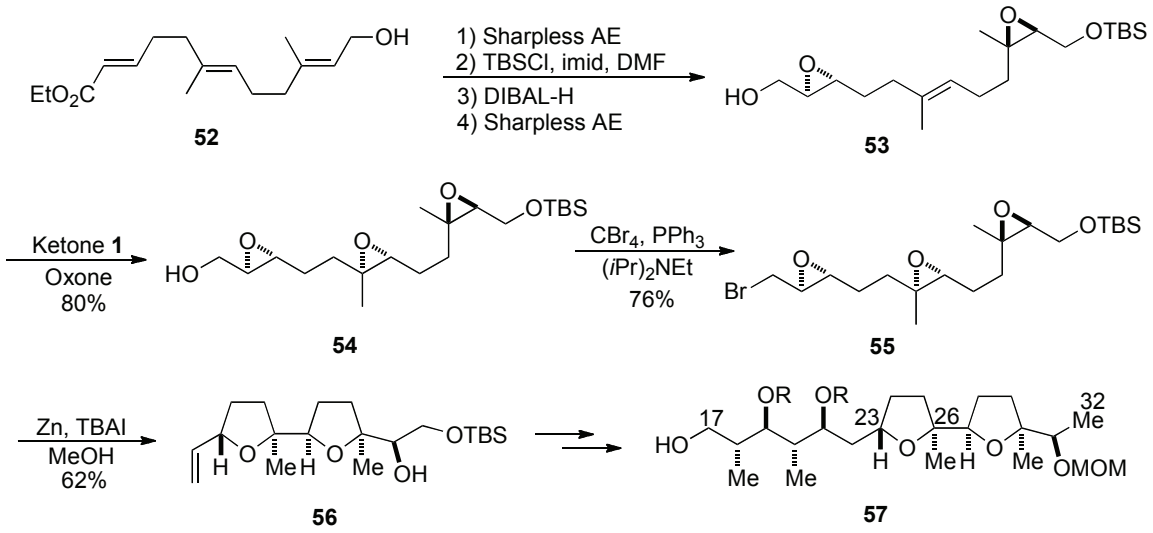


In their subsequent studies, Jamison and coworkers have reported that water can promote the highly regioselective 6-*endo* cyclization of tethered di-and tri-epoxides thus bypassing the need for the TMS-directing groups

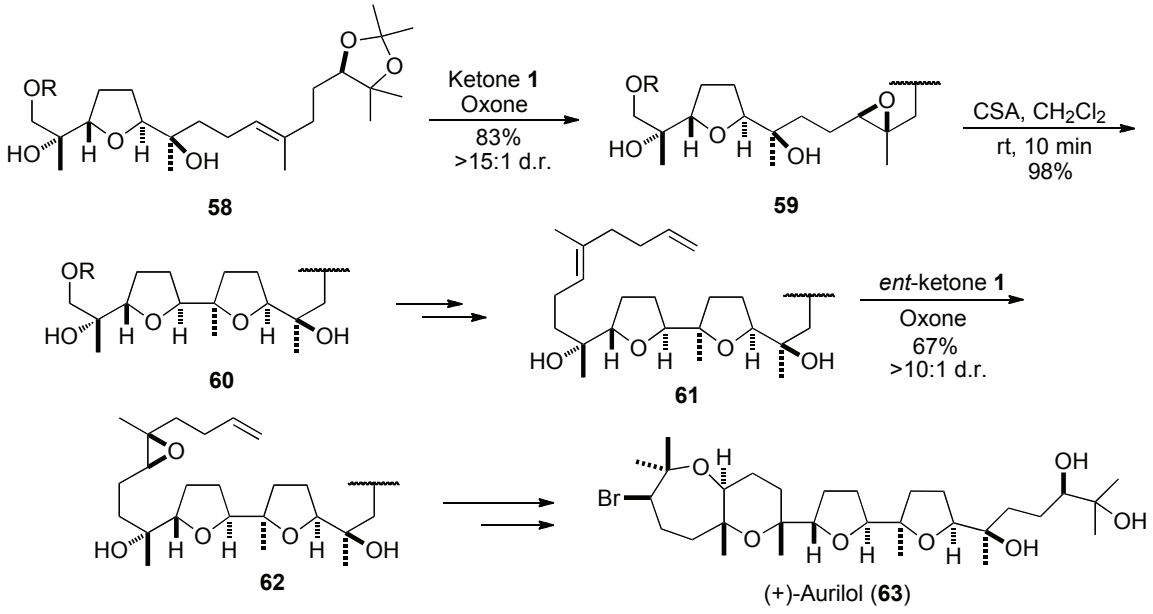
(Scheme 13).[46] Additionally, the water allows the 6-*endo* cyclization to override regioselective bias induced by methyl groups on the epoxides.[46c] They have also shown that the 1,3-dioxane group can be a suitable template for *endo*-selective cyclizations of epoxides.[46f,47-49]

Marshall and coworkers assembled the C17-C32 fragment of the antibiotic ionomycin (Scheme 14).[50] Sharpless epoxidation installed the peripheral epoxides in **53** and ketone **1** catalyzed the epoxidation of the internal double bond, resulting in **54**.[50-52] The zinc debrominates **55** and facilitates the cascade cyclization.

Scheme 14. Synthesis of C17-C32 Fragment of Ionomycin



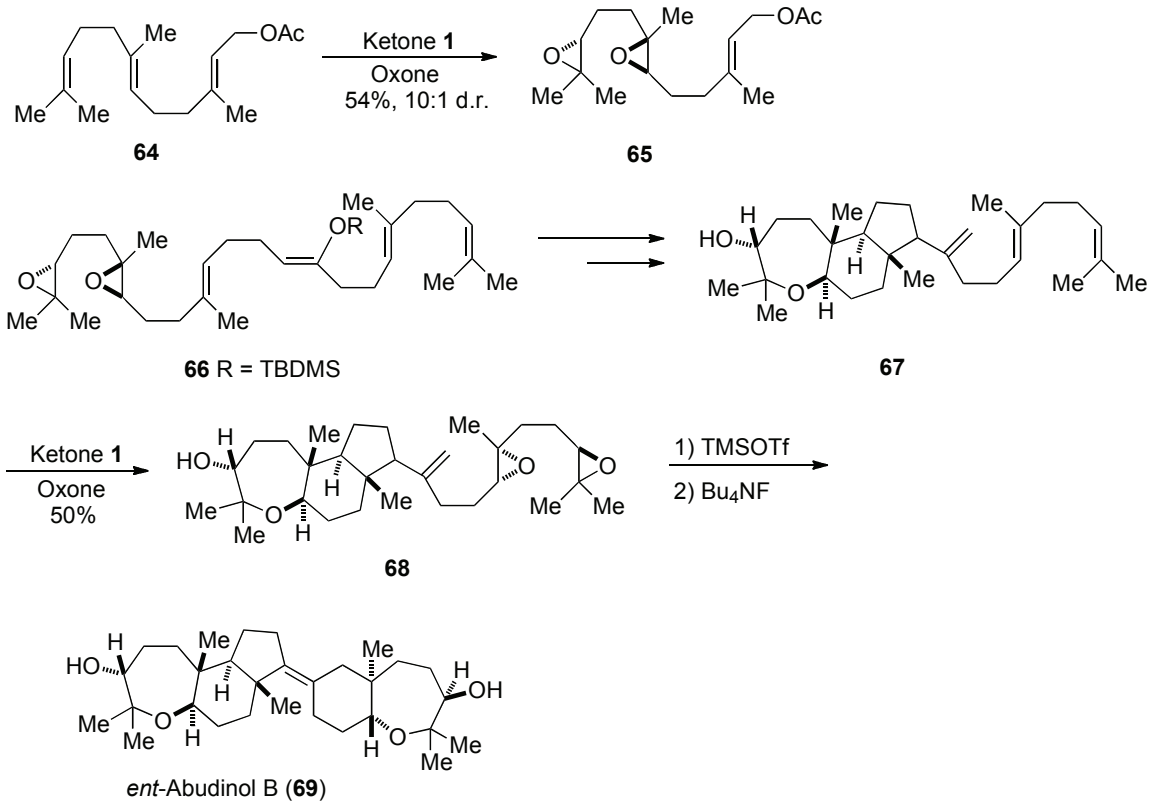
Scheme 15. Synthesis of (+)-Aurilol (**63**)



In 2005, Morimoto and coworkers reported the first total synthesis of (+)-aurilol (**63**) (Scheme 15).[53] A series of epoxidations catalyzed by ketone **1** and *ent*-ketone **1** allowed them to construct the cyclic ethers in a regio- and stereo-controlled fashion.

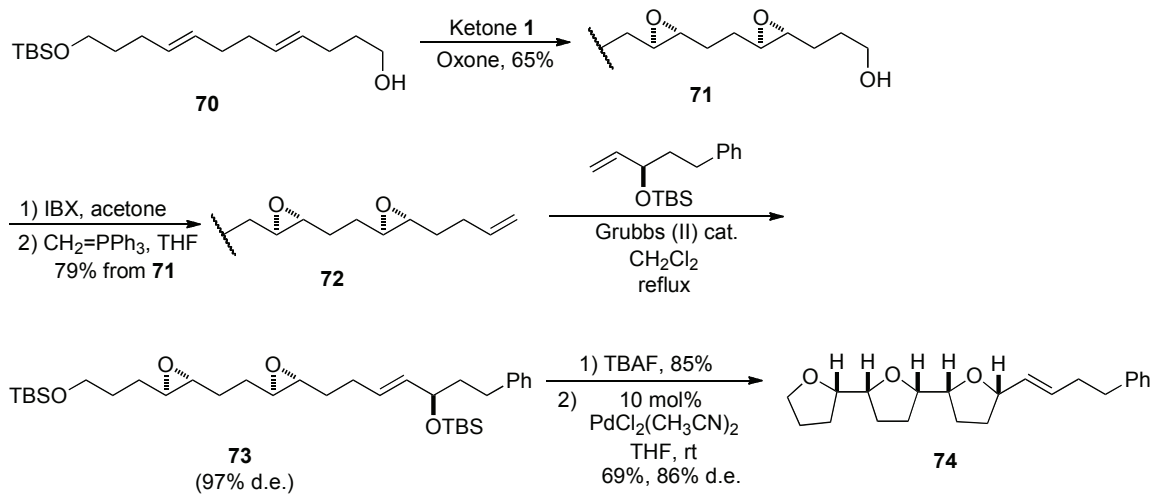
McDonald and coworkers synthesized *ent*-abudinol B (**69**) utilizing epoxidation/cascade cyclization (Scheme 16).[54] *Bis*-epoxidation of **64** with ketone **1** resulted in high diastereoselectivity in the formation of **65**. A second iteration of *bis*-epoxidation resulted in **68** which formed **69** upon treatment with TMSOTf. They had reported an earlier synthesis of the same molecule which also employed ketone **1**-catalyzed epoxidation.[54d]

Scheme 16. Synthesis of *ent*-Abudinol B (**69**)



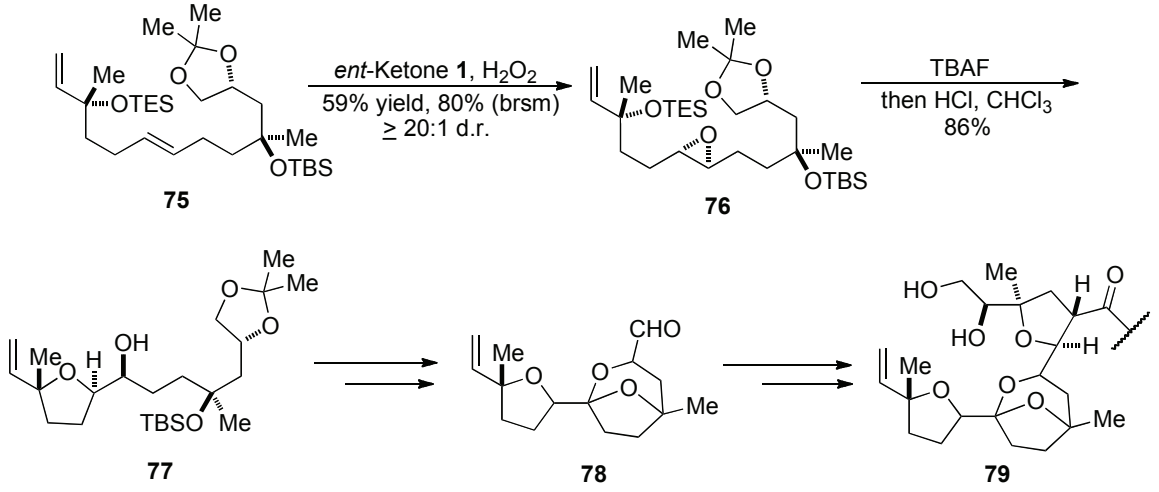
Uenishi and coworkers stereoselectively constructed linked tetrahydrofurans with a Pd(II)-catalyzed cascade cyclization (Scheme 17).[55] The metal serves to activate the epoxide while controlling the regioselectivity and also to catalyze and transfer the chirality of the displaced allylic alcohol in the S_N2'-type reaction.

Scheme 17. Pd(II)-Catalyzed Formation of Linked Tetrahydrofurans



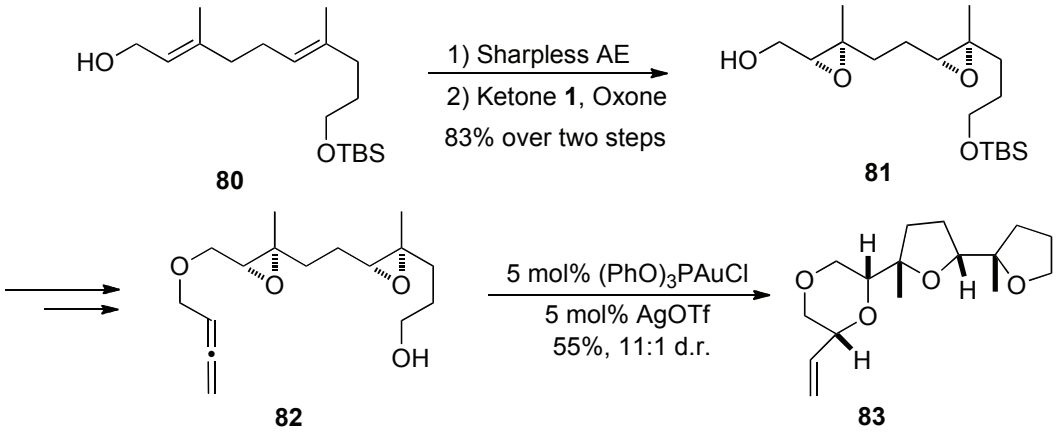
Micalizio and coworkers synthesized a tetracyclic fragment **79** of pectenotoxin-2 (Scheme 18).[56] *Ent*-Ketone **1**/H_2O_2 epoxidized the double bond in **75** with excellent diastereoselectivity and subsequent deprotection of the TES-protected alcohol led to formation of THF **77**. Deprotection and oxidation of the TBS-protected alcohol led to a domino condensation/cyclization to form **78**.

Scheme 18. Synthetic Work Toward Pectenotoxin-2



Lee, Gagné, and coworkers have shown that allenes can also initiate these cascade reactions.[57] In the example shown in Scheme 19, a tandem of Sharpless and ketone **1**-catalyzed epoxidations set the stereochemistry in **81**, and upon treatment with Au(I), the allene reacts with the proximal epoxide to set off the cascade. The product was obtained in good yield and high d.r.

Scheme 19. Allene-Initiated Cascade Cyclization

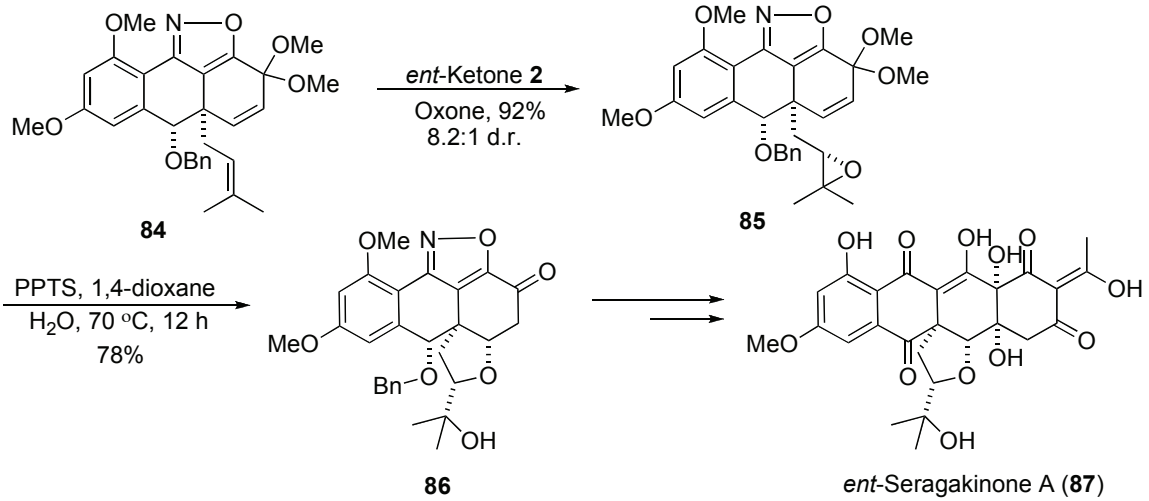


The previous section has given a snapshot of the synthetic utility of ketone **1** and *ent*-ketone **1**. The use of this methodology in synthesis[58] and dynamic method developments[58-61] are anticipated to undergo continued growth.

Ketone 2:

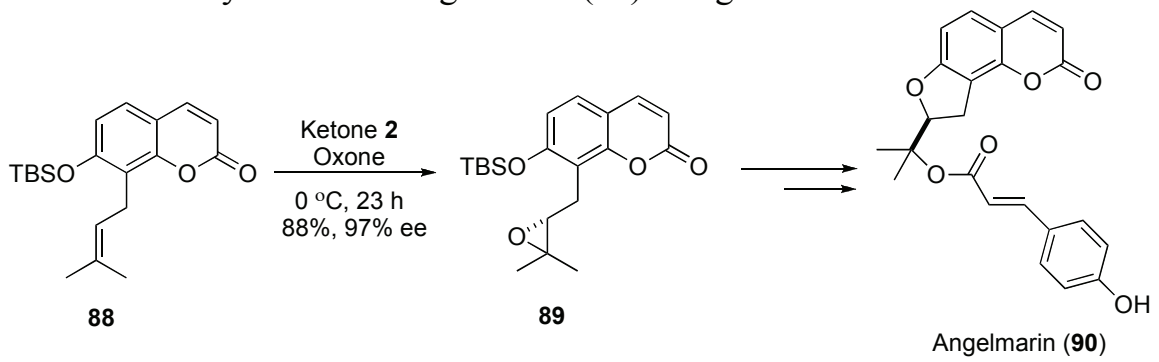
Ketone **2** has recently begun to receive more attention in organic synthesis. Suzuki and coworkers completed the first synthesis of *ent*-seragakinone A (**87**) (Scheme 20) and confirmed its absolute stereochemistry.[62] Substrate-controlled epoxidation of **84** resulted in low diastereoselectivity, however *ent*-ketone **2** induced good diastereoselectivity (8.2:1 d.r.). Acid-promoted hydration of the epoxide and subsequent conjugate addition provide the THF in compound **86**. This provided the tetracyclic core which was further elaborated to **87**.

Scheme 20. Synthesis of *ent*-Seragakinone A (**87**)



Hamada and coworkers have used ketone **2** to synthesize precursors to valuable compounds such as angelmarin, (+)-marmesin, (−)-(3'R)-decursinol, and (+)-lomatin.[63] Synthetic work toward angelmarin, a chemical that displays activity against PANC-1 cancer cells, is shown in Scheme 21.[63] Epoxidation with ketone **2** led to the formation of **89** in 88% yield and 97% e.e. Employing a two-step process for the removal of the TBS group and cyclization at low temperatures allows for highly selective (and complementary) dihydrobenzopyran formation.[63] Kan and coworkers have used ketone **2**-catalyzed epoxidation to synthesize epimeric epigallocatechin gallates.[64]

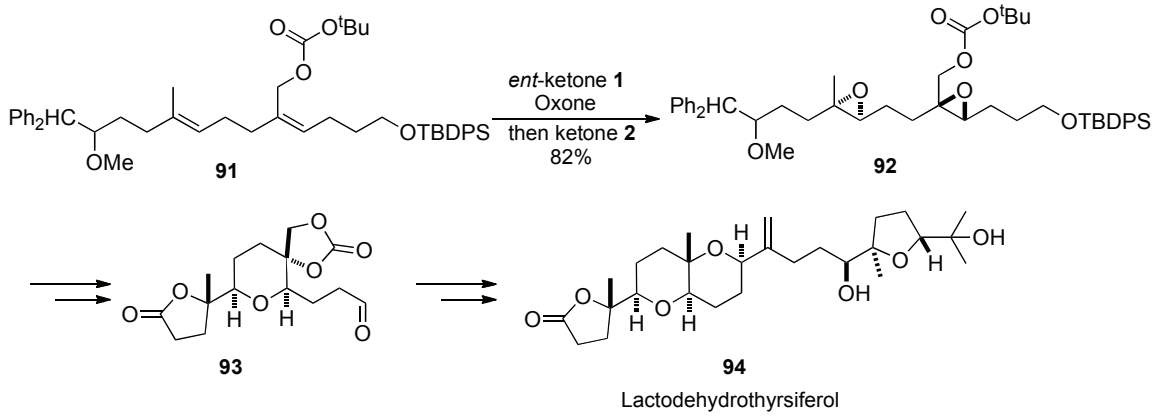
Scheme 21. Synthesis of Angelmarin (**90**) using Ketone **2**



88 **89** Angelmarin (**90**)

Yadav and coworkers have achieved an expedient formal synthesis of diastereomeric Hagen's gland lactones using ketone **2**.[65] Bruner and coworkers epoxidized *trans*-ethyl cinnamates and saponified the esters to study the products' ability to inhibit *Sg*TAM, an MIO-based aminomutase.[66]

Scheme 22. Synthesis of Lactodehydrothyrsiferol (**94**)



91 **92** **93** **94**

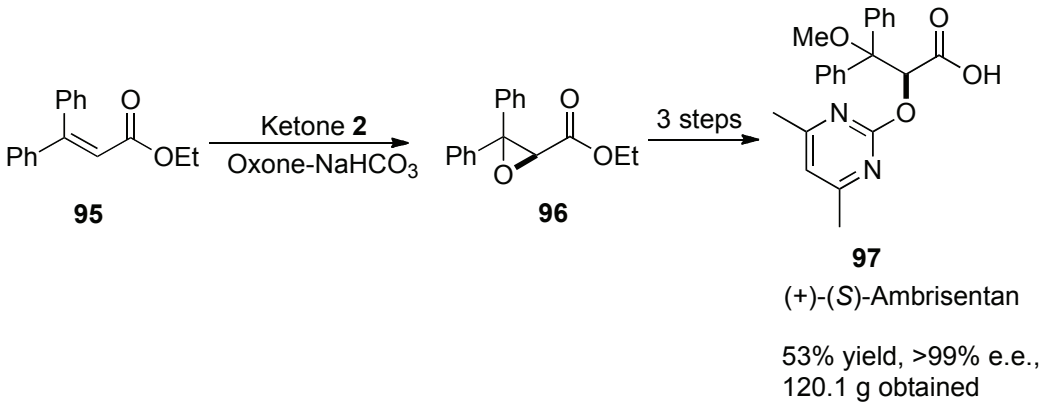
Lactodehydrothyrsiferol

Floreancig and coworkers recently accomplished the *bis*-epoxidation of **91** in high stereoselectivity using *ent*-ketone **1** and ketone **2** (Scheme 22).

Ent-ketone **1** catalyzed the epoxidation of the more reactive double bond, and upon completion, ketone **2** was added to the pot to facilitate epoxidation of the less reactive site. They then further elaborated **92** to lactodehydrothyrsiferol (**94**).[67]

Shi and coworkers recently obtained 120 g of virtually enantiopure (+)-ambrisentan (**97**) without the need for column chromatography (Scheme 23).[68] (+)-Ambrisentan, an endothelin-1 receptor antagonist, is currently used to treat hypertension. Ketone **2**-catalyzed epoxidation afforded **96** in 90% conversion and 85% ee. Compound **97** was further enriched via precipitation and filtration of the racemate.

Scheme 23. Synthesis of (*S*)-Ambrisentan



*Ketones **3**:*

Ketones **3** have been used in the asymmetric epoxidation/rearrangement of benzylidene cyclopropanes to synthetically valuable cyclobutanones and lactones and in the transformation of benzylidene cyclobutanes to cyclopentanones.[18-20] In addition, they have been used for the synthesis of oxindoles from indoles[69] and for the desymmetrization of *meso*-hydrobenzoins and the kinetic resolution of racemic hydrobenzoins.[70] They can also catalyze the stereoselective epoxidation of amphiphilic olefins; in the case of carboxylic acids, the carboxyl group can provide a directing effect as well as serve as a trigger for *in situ* lactonization.[22]

1. Department of Chemistry, Colorado State University, Fort Collins, CO 80523. We are grateful for the generous financial support provided by the General Medical Sciences of the National Institutes of Health (GM59705).

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