Resolution of 2-Silyloxy-1-oxiranyl-4-pentenes by HKR: Total Synthesis of (5*S*,7*R*)-Kurzilactone

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Abstract: Enantiomerically pure *syn*- and *anti*-2-silyloxy-1-oxiranyl-4-pentenes were prepared by using Jacobsen's hydrolytic kinetic resolution (HKR) method. A resolved epoxypentenol generated in this fashion was used in the total synthesis of (5*S*,7*R*)-kurzilactone by a pathway employing epoxide ring-opening and RCM reactions in key steps.

Key words: epoxides, hydrolytic kinetic resolution, kurzilactone, metathesis, total synthesis

1,3-Diol subunits are present in numerous biologically active natural products and pharmaceuticals.[1] As a result, a large effort has been devoted to the development of methods for the stereoselective synthesis of 1,3-diols.[2] Common procedures developed to date rely on chiral pool strategies[3] or asymmetric reaction methodologies[4] for the introduction of the first asymmetric centers in these substances. Installation of the second asymmetric centers is typically orchestrated by the initial hydroxyl group by using various 1,3-*syn*- or *anti*-selective ketone reduction methods.[5]

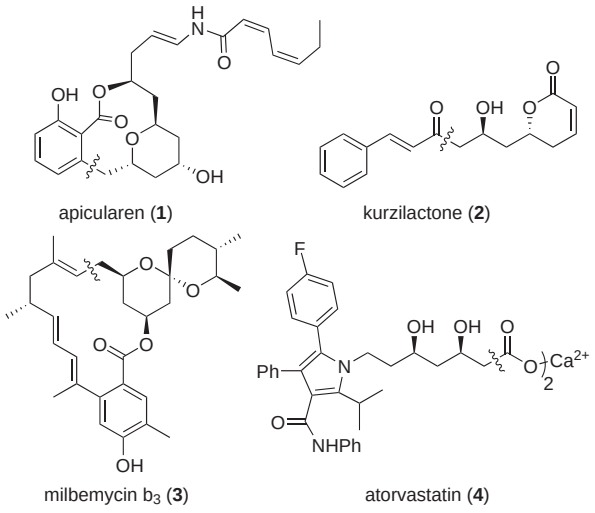
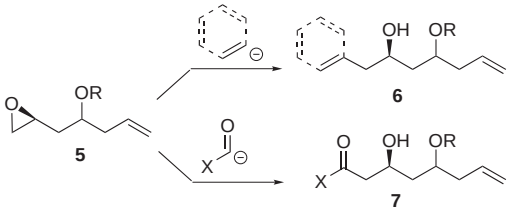


Figure 1

Jacobsen's method for hydrolytic kinetic resolution (HKR) of 2-hydroxy-1-oxiranes[6] represents another potential enantiocontrolled strategy for 1,3-diol synthesis. Importantly, nucleophilic ring-opening reactions of the epoxides formed in this way could enable easy access to structurally diverse 1,3-diol units found in many biologically active compounds (Figure 1), exemplified by apicularen (**1**),[7] kurzilactone (**2**),[8] milbemycin β_3 (**3**),[9] and atorvastatin (**4**).[10] Only few examples, in which the HKR method has been used to prepare enantiomerically pure 2-hydroxy-1-oxirane units, have been reported thus far. However, in these cases the alcohol moieties were introduced first by using known asymmetric methods and then HKR was employed to resolve the diastereomeric epoxides.[11] Consequently, the two asymmetric centers were installed separately through the use of two asymmetric reactions.

We envisioned an alternative approach to chiral 1,3-diol synthesis that utilizes kinetic resolution of racemic *syn*- or *anti*-2-hydroxy-1-oxirane derivatives. In this strategy, the relative stereochemistry between the alcohol and the epoxide groups is established prior to the HKR step and in this way a single asymmetric reaction can be used to form the key enantiomerically pure 2-hydroxy-1-oxirane intermediates. Below, we describe the results of studies of HKR reactions of racemic *syn*- and *anti*-2-hydroxy-1-oxiranes and an application to the asymmetric synthesis of (5*S*,7*R*)-kurzilactone.

Enantiomerically pure *syn*- and *anti*-2-alkoxy-1-oxiranyl-4-pentenes **5** (Scheme 1) are versatile synthetic building blocks. Ring-opening reactions of these substances with aryl or vinyl nucleophiles could lead to alkenyl-1,3-diols **6**, structural units found in apicularen (**1**) and milbemycin β_3 (**3**). In addition, carbon frameworks found in kurzilactone (**2**) and atorvastatin (**4**) could be accessed by ring-opening reactions of **5** with acyl anion equivalents (Scheme 1).



Scheme 1

Existing methods for asymmetric synthesis of **5** have utilized (*S*)-malic acid as a chiral pool[12] reactant or enzyme-catalyzed asymmetric epoxidation of 1,6-hepta-

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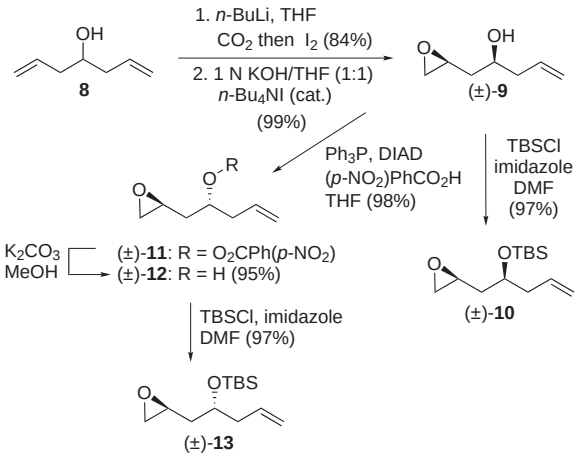
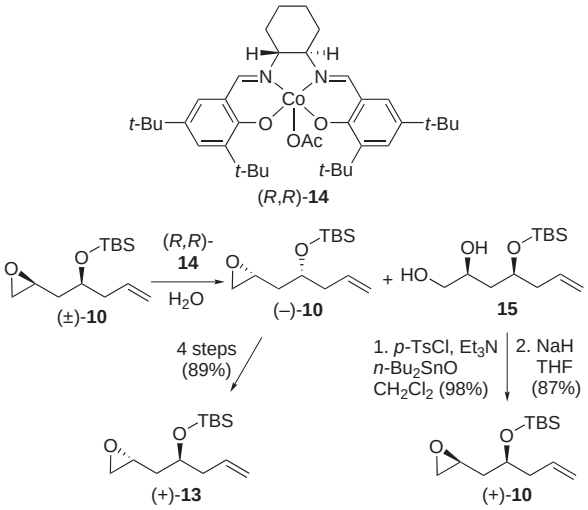
dien-4-ol.[13] The later method gives **5** in only a 65% ee and general methods to prepare both enantiomers of *syn*- and *anti*-**5** have not yet been described. We envisioned that application of the HKR method would enable access to both enantiomers of *syn*- and *anti*-**5** depending on the chiral ligand chosen. To test this proposal, we prepared the *syn*-epoxide (±)-**9** by using a modification of the literature procedure[14] starting from 1,6-heptadien-4-ol (**8**, Scheme 2). The *anti*-epoxide (±)-**12** was generated by Mitsunobu inversion reaction of (±)-**9**. The racemic TBS-protected epoxides (±)-**10** and (±)-**13** were then prepared for the HKR studies.



Scheme 2

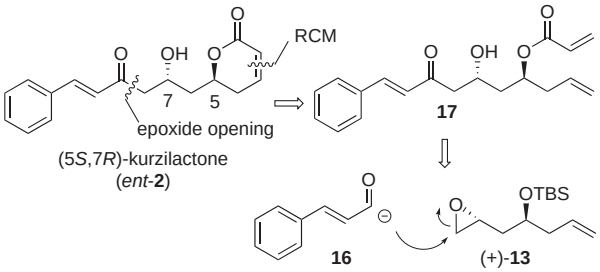
The activated Jacobsen's (*R*,*R*)-(–)-Co(salen) catalyst (*R*,*R*)-**14** and general conditions described earlier were used for the resolution studies.[6b] Treatment of *syn*-epoxide (±)-**10** with (*R*,*R*)-**14** (0.3–0.5 mol%) and H_2O (0.8 equiv) at room temperature led to formation of the epoxide (–)-**10** in good yield (42–48%) and high enantiopurity (98–99% ee) as shown in Table 1 (entries 1 and 2).[15] The diol **15** was also formed in 48–49% yield and 93–94% ee. In contrast, hydrolytic resolution of the *anti*-epoxide (±)-**13** was much less enantiospecific (69–88% ee) when conducted under the same conditions (Table 1, entries 3 and 4). Variations in catalyst loading and reaction time had little impact on the enantiospecificities of these reactions. Therefore, the *syn*-epoxide (±)-**10** is superior to the *anti*-epoxide (±)-**13** in the HKR reaction.[16]

The *anti*-epoxide (+)-**13** can be prepared from the resolved *syn*-epoxide (–)-**10** by using a four step route: (1) TBAF, THF, 99%; (2) DIAD, PPh_3, (*p*-NO_2)$PhCO_2H$, THF, 98%; (3) K_2CO_3, MeOH, 95%; (4) TBSCl, DMAP, imidazole, DMF, 97% (Scheme 3). Also, the diol **15** can be recycled to (+)-**10** by using known conditions (*p*-TsCl, Et_3N, *n*-Bu_2SnO in CH_2Cl_2).[17]



Scheme 3

This new enantiocontrolled method for 2-silyloxy-1-oxiranyl-4-pentene preparation should have wide applications in synthesis. Kurzilactone (**2**), which has strong cytotoxicity against KB cells (IC_{50} = 1 μg/mL), is an ideal target on which to test this proposal. The relative C(5)–C(7) stereochemistry of this substance was incorrectly assigned as *syn*[8] initially and then corrected to be *anti* by using total synthesis.[18] As shown in the retrosynthetic plan given in Scheme 4 for preparation of the enantiomeric form of natural kurzilactone (*ent*-**2**), our strategy relies on two key transformations. The first involves ring-opening reaction of the epoxide (+)-**13** with the acyl anion equivalent **16** and the second RCM reaction of **17**.

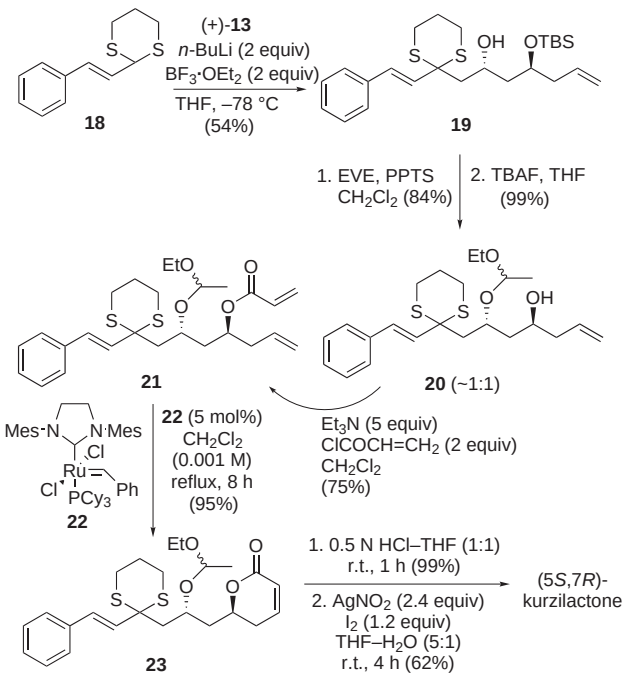


Scheme 4 Retrosynthetic plan for preparation of (5*S*,7*R*)-kurzilactone (*ent*-**2**)

Table 1 Hydrolytic Kinetic Resolution (HKR) of *syn*- and *anti*-**5**

Entry	Substrate	(*R*,*R*)-**14** (mol%)	H_2O (equiv)	Reaction time (h)	Epoxide yield (%, ee)	Diol yield (%, ee)
1	(±)-**10**	0.3	0.8	16	48 (98)	48 (94)
2	(±)-**10**	0.5	0.8	18	42 (99)	49 (93)
3	(±)-**13**	0.3	0.8	18	49 (88)	42 (99)
4	(±)-**13**	0.5	0.8	18	46 (69)	41 (99)

The synthetic pathway begins with reaction of the acyl anion equivalent, generated from the thioacetal **18**, with (+)-**13** in the presence of $BF_3{\cdot}OEt_2$ to afford **19** in 54% yield (Scheme 5). Protection of the secondary alcohol of **19** proved to be critical for the success of the synthesis. For example, acetate protection was problematic since removal of the TBS group (*n*-Bu_4NF in THF) was accompanied by acetate migration to give a ca. 1:1 mixture of hydroxyacetates. Protection with a MOM group was complicated by low yields (ca. 20%) of the protection processes carried out under several known conditions. A solution to this problem was found by using an ethoxyethyl group introduced using ethylvinyl ether (EVE) in the presence of catalytic PPTS (pyridine/*p*-TsOH). This produced **20** as a ca. 1:1 mixture of diastereomers in 84% yield. Removal of the TBS group followed by introduction of the acryloyl group afforded the RCM precursor **21**. Ring-closing metathesis[19] of **21**, utilizing the second generation Grubbs'catalyst **22**, furnished the lactone **23** in 95% yield. The ethoxyethyl ether was then cleaved with 0.5 N HCl–THF (1:1) at room temperature in good yield. Removal of thioketal by using $Hg(ClO_4)_2$, $CaCO_3$ in THF–H_2O (5:1)[20] took place in 10 minutes at 0 °C but the isolated yield of (5*S*,7*R*)-kurzilactone (*ent*-**2**) was low (20–38%). To solve this problem, we screened several conditions and found that the $AgNO_2$–I_2 method[21] is highly efficient. Accordingly, treatment of thioacetal **23** with $AgNO_2$–I_2 in THF–H_2O (5:1) at room temperature for 4 hours led to formation of *ent*-**2** in 62% yield. The synthetic material was shown to have the same spectroscopic properties as with the natural product. The observed optical rotation {$[\alpha]_D^{20}$ –85 (*c* 0.235, $CHCl_3$)} was found to be opposite to that reported for natural (5*R*,7*S*)-kurzilactone {$[\alpha]_D^{20}$ +84 (*c* 0.231, $CHCl_3$)}.[18]



Scheme 5 Asymmetric total synthesis of (5*S*,7*R*)-kurzilactone

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