Kinetic Resolution of Racemic Chromenes via Asymmetric Epoxidation: Synthesis of (+)-Teretifolione B

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Kinetic resolution stands as a viable strategy for accessing chiral compounds in enantiomerically enriched form, particularly in cases where effective methods are not available for direct asymmetric synthesis from the chiral pool or from achiral precursors.[1] In this context, the enantioselective construction of compounds that contain quaternary stereocenters remains a difficult challenge in asymmetric synthesis.[2] Given the remarkably high levels of enantioselectivity attainable in the (salen)Mn-catalyzed epoxidation of prochiral 2,2-dimethylchromene derivatives,[3] we evaluated whether chiral 2,2′-dialkylchromenes, which bear quaternary stereocenters adjacent to an oxidizable olefinic moiety, might be good candidates for kinetic resolution with these catalysts. We report here the successful implementation of this strategy and its application to the first asymmetric synthesis of teretifolione B, the monomer component of the potent anti-HIV agent conocurvone.[4,5]

Compound **1** was evaluated as a model substrate for the kinetic resolution reactions (Scheme 1). Epoxidation of (±)-**1** with (salen)Mn catalyst **5** under standard NaOCl conditions[6] led to formation of diastereomeric epoxychroman products **2** and **2′** with very high (>97%) enantioselectivity for each one. The relative and absolute stereochemistry of **2** and **2′** was established by circular dichroism and NOE measurements (see supporting information). At partial conversions of **1**, epoxide **2** was generated preferentially; however, the enantiomeric olefins exhibited similar reactivity under these reaction conditions (k_{rel} = 1.7).[1b] These results reflect highly effective discrimination between *pro-S* and *pro-R* faces of the alkene in the epoxidation reaction, but little influence of the stereocenter in the substrate (i.e., epoxidation syn to the methyl group is similar in rate to epoxidation syn to the isobutyl group).

Scheme 1

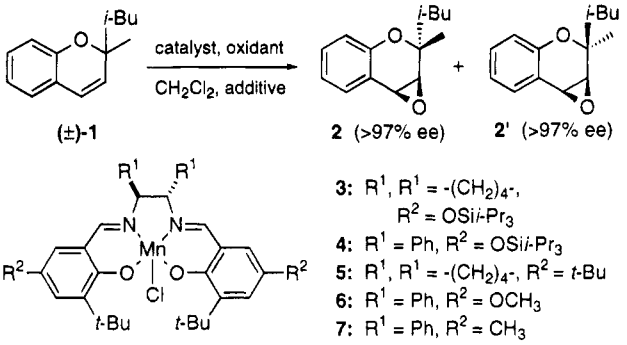

Table 1. Kinetic Resolution of 1

entry	catalyst	oxidant	T (°C)	additive	k_{rel}[a]
1	**5**	NaOCl	0	4-PhC$_5$H$_4$NO	1.7
2	**3**	*m*-CPBA	−78	NMO	6.9
3	**4**	*m*-CPBA	−78	NMO	5.4
4	**5**	*m*-CPBA	−78	NMO	3.1
5	**6**	*m*-CPBA	−78	NMO	3.9
6	**7**	*m*-CPBA	−78	NMO	3.4

[a] The extent of the reaction was followed by GC using an internal standard. Methods employed for determination of olefin ee are described in the supporting information. The relative rate was calculated by the equation $k_{rel} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$ where C is the fraction of **1** remaining and ee is the percent enantiomeric excess/100 (from ref 1b).

The difference in reactivity between the enantiomeric olefins could be enhanced by effecting the reaction at low temperature with the recently-discovered protocol for epoxidation under anhydrous conditions[7] (Table 1). Thus, kinetic resolution with catalyst **5** was improved slightly (k_{rel} = 3.1) using *m*-CPBA/NMO at −78 °C.[8] Further improvement in selectivity was achieved by tuning the catalyst's steric and electronic properties. Enantioselectivity in the epoxidation of chromene derivatives is particularly sensitive to the presence of electron-donating groups on the catalyst.[9] Thus, the most effective catalyst for the low-temperature kinetic resolution of **1** was identified to be the sterically hindered, electron-rich complex **3**.[10] Cyclohexanediamine-derived catalysts generally afforded slightly higher selectivities than the corresponding diphenyldiamine-derived catalysts (e.g., entries 2 and 3, Table 1).

The kinetic resolution of a range of racemic chromene derivatives was carried out using the conditions optimized for **1**. As illustrated in Table 2, moderate kinetic resolution efficiencies were observed with several 2-alkyl-2-methylchromene derivatives (k_{rel} = 4.5–9.3), with selectivities improving with increasing steric demand in the alkyl substituent. Thus, the isopropyl-substituted derivative **8** underwent resolution with substantially higher selectivity than the unbranched derivative **10**. Although olefin **9** underwent kinetic resolution with reasonable selectivity (k_{rel} = 6.1) and the same sense of induction as bicyclic olefins **1**, **8**, and **10**, reaction of the

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(2) Recent discussions of successful catalytic methods for the asymmetric construction of quaternary centers include: (a) Overman, L. E. *Pure Appl. Chem.* **1994,** *66,* 1423. (b) Fuji, K. *Chem. Rev.* **1993,** *93,* 2037. (c) Wantanabe, N.; Ohtake, Y.; Hashimoto, S.-i.; Shiro, M.; Ikegami, S. *Tetrahedron Lett.* **1995,** *36,* 1491. (d) Kondo, K.; Sodeoka, M.; Mori, M.; Shibasaki, M. *Synthesis* **1993,** 920. (e) Martin, S. F.; Spaller, M. R.; Liras, S.; Hartmann, B. *J. Am. Chem. Soc.* **1994,** *116,* 4493. (f) Hübscher, J.; Barner, J. *Helv. Chim. Acta* **1990,** *73,* 1068.

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(5) Racemic synthesis of teretifolione B: Cannon, J. R.; Joshi, K. R.; McDonald, I. A.; Retallack, R. W.; Sierakoski, A. F.; Wong, L. C. H. *Tetrahedron Lett.* **1975,** *32,* 2795.

(6) Deng, L.; Jacobsen, E. N. *J. Org. Chem.* **1992,** *57,* 4320.

(7) Palucki, M.; Pospisil, P. J.; Zhang, W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994,** *116,* 9333.

(8) .Reactions were quenched at partial conversion at −78 °C by addition of dimethyl sulfide. This workup procedure led to more reproducible results and higher selectivities than experiments where the extent of conversion was controlled by limiting the amount of oxidant employed.

(9) Jacobsen, E. N.; Zhang, W.; Güler, M. L. *J. Am. Chem. Soc.* **1991,** *113,* 6703

(10) Chang, S.; Heid, R. M.; Jacobsen, E. N. *Tetrahedron Lett.* **1994,** *35,* 669.

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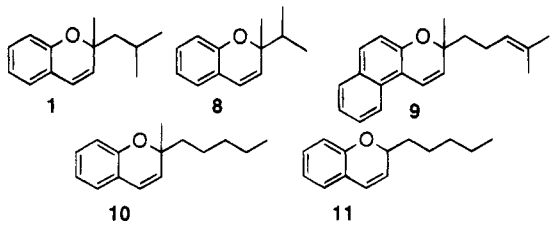
Table 2. (salen)Mn-Catalyzed Kinetic Resolution of Racemic Chromene Derivatives[a]



entry	substrate	k_{rel}[b]
1	**1**	6.9
2	**8**	9.3
3	**9**	6.1
4	**10**	4.5
5	**11**	2.7

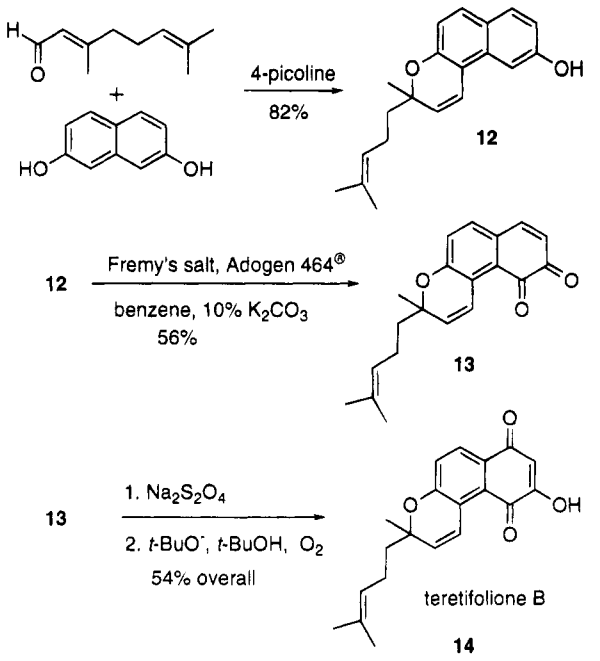
[a] Reactions were carried out using the conditions shown in Table 1, entry 2. [b] Substrate conversion was followed by HPLC or GC by integration against an internal quantitative standard. In all cases, olefin ee's were determined chromatographically (HPLC or GC). Details are provided in the supporting information.

tricyclic substrate was observed to proceed much more slowly than bicyclic analogs. Using 4 mol % catalyst, reactions with bicyclic substrates proceeded to >80% conversion within 10 min, but stopped at 60% conversion with tricyclic **9** even with prolonged reaction times. The resolution of the 2-pentylchromene derivative **11** occurred with very poor selectivity. This was attributable to a competitive, nonasymmetric aromatization pathway which led to multiple unidentified products.

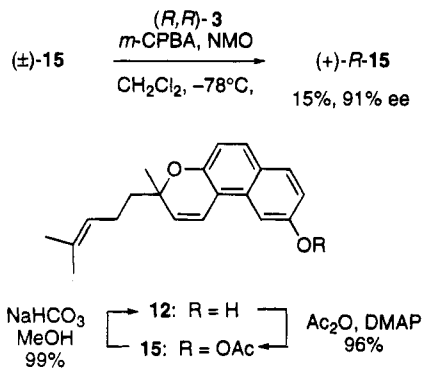
The kinetic resolution methodology was applied to the synthesis of teretifolione B (**14**). An efficient three-step synthesis of racemic **14** was devised by modification of the published procedure (Scheme 2).[5] Unfortunately, neither of the two intermediate products **12** or **13**, nor **14** itself, were suitable substrates for the kinetic resolution reaction due to the sensitivity of the phenol and/or quinone groups to overoxidation under epoxidation conditions. However, the resolution could be carried out effectively on the acetate-protected derivative **15** using relatively high catalyst loading (10 mol %) (Scheme 3). In reactions carried out to high conversion (≈80%), recovered **15** could be isolated in 15% yield (30% of theoretical) and 91% ee. Thus, although the efficiency of the resolution process (k_{rel} = 3.4) was poorer than that observed with the closely-related model substrate **9**, material of high enantiomeric purity could be obtained by this method. Deprotection of the acetate afforded **12**, and further transformation according to Scheme 1 led to **14** with the same absolute configuration as the natural product.

This work demonstrates the first application of the (salen)Mn-catalyzed epoxidation reaction to the kinetic resolution of olefins. High catalyst-induced selectivity but moderate substrate-induced selectivity has been

Scheme 2



Scheme 3



attained in the examples uncovered thus far. Nonetheless, this methodology has been shown to be adaptable to the resolution of olefins which are otherwise difficult to access in enantioenriched form.

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Supporting Information Available: Chromatographic analyses of all racemic and enantiomerically enriched olefins in Table 2 and of **15**; NOE data for epoxide **2**; circular dichroism spectra of **2** and **2'**; experimental procedures for the preparation of **1**, **8**–**11**, **14**, and teretifolione B; ^{1}H NMR and ^{13}C NMR spectra of new compounds (39 pages).

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