# Biomimetic reactions in organic synthesis: Semi-pinacol rearrangements of some spirocyclic epoxyalcohols derived from Juliá–Colonna asymmetric epoxidations

**Bernhard Hauer, Jamie F. Bickley, Julien Massue, Paula C. A. Pena, Stanley M. Roberts, and John Skidmore**

**Abstract**: Epoxy *tert*-alcohols have been prepared from (*E*)-enones in a two-step approach consisting of Juliá–Colonna asymmetric epoxidation followed by Grignard alkylation of the epoxyketone. On treatment with sub-stoichiometric amounts of $Yb(OTf)_3$ these *trans*-epoxyalcohols underwent efficient stereoselective semi-pinacol rearrangement to afford *anti*-α-phenyl-β-hydroxy-ketones (aldols). Under the same conditions, spirocyclic epoxyalcohols derived from 1-tetralone and 1-benzosuberone undergo either ring contraction (via semi-pinacol rearrangement) or fragmentation. A mechanistic rationale is presented to explain the formation of the various products.

*Key words*: Juliá–Colonna reaction, asymmetric epoxidation, epoxy *tert*-alcohols, semi-pinacol rearrangement.

**Résumé** : Faisant appel à l'approche en deux étapes de Juliá–Colonna impliquant une époxydation asymétrique suivie d'une alkylation de Grignard de l'époxycétone, on a préparé des époxy *tert*-alcools à partir de (*E*)-énones. Le traitement de ces *trans*-époxyalcools avec des quantités sous-stoechiométriques d'$Yb(OTf)_3$ provoque un réarrangement semi-pinacolique stéréosélectif et efficace qui conduit aux *anti*-α-phényl-β-hydroxycétones (aldols). Dans les mêmes conditions, les époxyalcools spirocycliques obtenus à partir de la 1-tétralone et de la 1-benzosubérone donnent lieu soit à une contraction de cycle (par le biais d'un réarrangement semi-pinacolique) ou à une fragmentation. On propose un mécanisme qui permet de rationaliser la formation des divers produits.

*Mots clés* : réaction de Juliá–Colonna, époxydation asymétrique, époxy *tert*-alcools, réarrangement semi-pinacolique.

[Traduit par la Rédaction]

## Introduction

Epoxides are among the most widely used functional groups in modern synthetic chemistry. This reflects the existence of numerous reliable, highly enantioselective methods for epoxidation, and the wealth of chemistry that epoxides can undergo, allowing a wide range of compounds to be prepared in an efficient and stereoselective manner (1). Amongst the reactions of epoxides, rearrangements have been widely used as key steps in the synthesis of biologically active targets and natural products. Several different modes of epoxide rearrangement have been identified (2); in substrates where the epoxide is flanked by an alcohol, or a silyl-protected alcohol, treatment with a suitable Lewis acid can lead to a semi-pinacol rearrangement (3), in which 1,2-migration of one of the alcohol substituents opens the epoxide, generating an α-substituted-β-hydroxyketone (aldol) in a stereoselective manner. Various Lewis acids have been used, in stoichiometric quantities, to facilitate this rearrangement, including $TiC1_4$ (4), $BF_3{\cdot}OEt_2$ (3, 5, 6), $Ti(i\text{-}PrO)_2C1_2$ (5), $Ti(i\text{-}PrO)_3C1$ (7), and $SnC1_4$ (8). Until recently, catalytic variants of this rearrangement required a silyl-protected epoxyalcohol, using either TMSI or TMSOTf as the Lewis acid (9). Our recent report (10) and that of Tu et al. (11) have shown, however, that rare-earth triflates and $ZnBr_2$ are capable of catalyzing semi-pinacol rearrangements of unprotected epoxyalcohols.

Some of the epoxy *tert*-alcohol substrates used in semi-pinacol rearrangements may be prepared in enantiomerically enriched form by a five-step Sharpless AE–oxidation–alkylation–oxidation–alkylation strategy (4, 5). An alternative approach to prepare such substrates is the use of a polyleucine-catalyzed asymmetric epoxidation of an enone (Juliá–Colonna epoxidation) (12–14) followed by a

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*Dedicated to Professor J. Bryan Jones on the occassion of his 65th birthday.*

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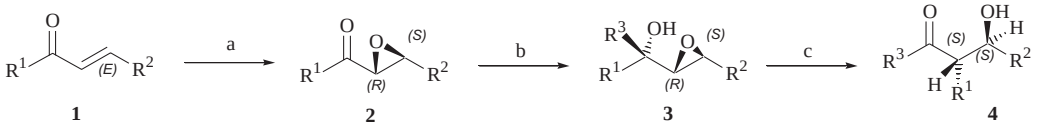
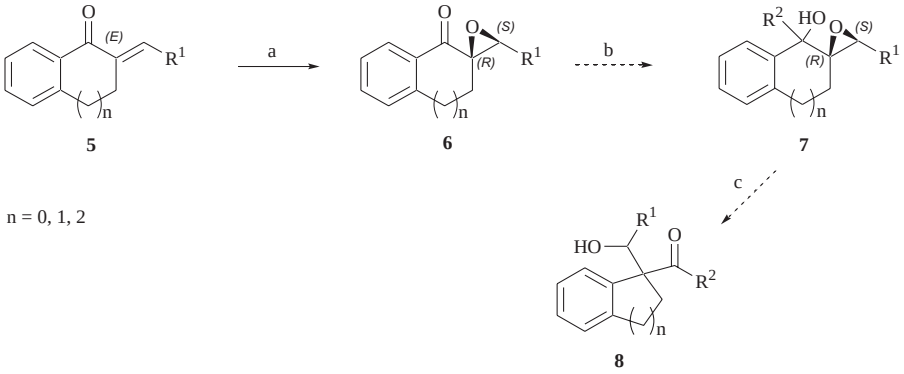
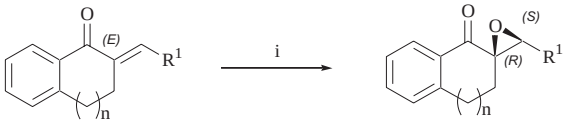
**Scheme 1.** (*a*) Asymmetric epoxidation; (*b*) Grignard alkylation; (*c*) $Yb(OTf)_3$ catalyzed rearrangement.



**Scheme 2.** (*a*) Asymmetric epoxidation; (*b*) Grignard alkylation; (*c*) $Yb(OTf)_3$ catalyzed rearrangement.

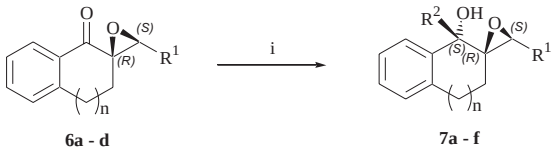


**Scheme 3.** Reagents and conditions: (*i*) urea–$H_2O_2$, BEMP, $SiO_2$-poly-L-leucine, THF, room temp.



| | | |
|---|---|---|
| **5a** | n = 1, $R^1$ = Et | **6a** |
| **5b** | n = 0, $R^1$ = *i*-Pr | **6b** |
| **5c** | n = 2, $R^1$ = *i*-Pr | **6c** |
| **5d** | n = 1, $R^1$ = Ph | **6d** |

**Scheme 4.** Reagents and conditions: (*i*) $R^2MgBr$, $Et_2O$–THF, –78°C.



diastereoselective Grignard alkylation of the resultant epoxyketone (15, 16). This method entails conversion of achiral enones **1** into optically active epoxides **2**, which are transformed with high stereoselectivity into enantiomerically enriched diastereomerically pure epoxyalcohols **3**. We have shown that such epoxyalcohols are efficiently rearranged to afford aldols **4** in reactions catalyzed by rare-earth triflates (Scheme 1) (10).

Recent work has extended the Juliá–Colonna epoxidation to cyclic enones possessing an exocyclic olefin unit; thus epoxidation of ketones **5** using urea–$H_2O_2$ and DBU in the presence of poly-L-leucine affords spirocyclic epoxides **6** in 63–85% yield and 59–94% ee (Scheme 2) (17).

It was anticipated that alkylation of spirocyclic epoxyketones **6** would afford epoxy alcohols **7** (step b) in which the aromatic ring is the group with the highest migratory aptitude in a semi-pinacol rearrangement unless stereochemical constraints become dominant. Thus, treatment of 1,2,3,4-tetrahydronaphthalene epoxyalcohols (**7**, *n* = 1) with rare-earth triflates was expected to result in ring contraction to afford indans (**8**, *n* = 1) bearing a quaternary chiral center (step c); such systems are not readily accessible, in enantiomerically enriched form, using conventional methodology. We report herein the outcome of Lewis acid catalyzed rearrangements of compounds of type **7**.

## Results

*E*-3,4-Dihydro-2-propylidene-2*H*-naphthalen-1-one (**5a**) was converted into the epoxide **6a** in 75% yield and 85% ee employing silica-supported poly-L-leucine as the catalyst with urea–$H_2O_2$ (UHP) as the oxidant and sub-stoichiometric quantities of BEMP as the base (Scheme 3). Using similar reaction conditions,indanone epoxide **6b** was prepared from enone **5b** with good stereoselectivity (74% yield, 81% ee), whilst the epoxidation of alkylidene–benzosuberone **5c** under these conditions proved to be very slow and to generate racemic product **6c** (62% yield). This result contrasts with our previously reported asymmetric epoxidation of **5c** (under different conditions), which generated the product in 74% yield and 59% ee. The synthesis of epoxide **6d** (76% yield and 84% ee) was reported previously, employing poly-L-leucine as the catalyst, UHP as the oxidant in isopropyl acetate containing DBU (17). The alternative use of sub-stoichiometric quantities of BEMP as the base and silica-supported poly-L-leucine as the catalyst led to a quantitative yield of **6d** having the same optical purity.

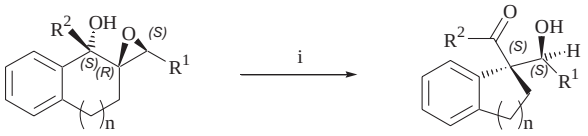
Epoxyketones **6a**–**d** were alkylated with methylmagnesium bromide to afford the epoxyalcohols **7a**–**d**, respectively; compounds **6a** and **6d** were also reacted with phenylmagnesium bromide to afford the tertiary alcohols **7e** and **7f** (Scheme 4 and Table 1).

All the ketones gave the appropriate product as a single diastereoisomer. The operation of a Cram-chelate mode of

**Table 1.** Reaction of epoxyketones **6a–d** with Grignard reagents $R^2MgBr$.

| Epoxyketone | $R^1$ | $R^2$ | *n* | Epoxyalcohol (yield %) |
|---|---|---|---|---|
| **6a** | Et | Me | 1 | **7a** (82) |
| **6b** | *i*-Pr | Me | 0 | **7b** (66) |
| **6c** | *i*-Pr | Me | 2 | **7c** (57) |
| **6d** | Ph | Me | 1 | **7d** (97) |
| **6a** | Et | Ph | 1 | **7e** (69) |
| **6d** | Ph | Ph | 1 | **7f** (94) |

**Scheme 5.** Reagents and conditions: (*i*) $Yb(OTf)_3$, $CH_2Cl_2$, room temp., 1 h.




| | | |
|---|---|---|
| **7a** | n = 1, $R^1$ = Et, $R^2$ = Me | **8a** |
| **7c** | n = 2, $R^1$ = *i*-Pr, $R^2$ = Me | **8c** |
| **7e** | n = 1, $R^1$ = Et, $R^2$ = Ph | **8e** |

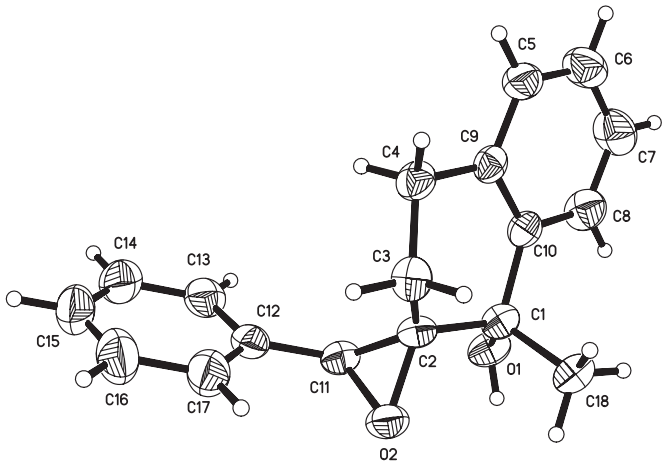
addition (16) was confirmed by X-ray analysis of the epoxyalcohol **7d** (Fig. 1).[2]

To effect the desired semi-pinacol rearrangement, tertiary alcohol **7a** was treated with Yb $(OTf)_3$ (20 mol %) in dichloromethane for 1 h. The formation of the expected methyl ketone **8a** (Scheme 5) was supported by NMR spectroscopy (three-proton singlet at δ 2.03 inter alia) and by a strong signal at 1693 $cm^{-1}$ in the IR spectrum. Under the same reaction conditions, indan-epoxide **7b** gave a complex mixture, whereas treatment of the benzosuberan-epoxide **7c** with $Yb(OTf)_3$ gave the ring-contracted product **8c** in 60% yield.

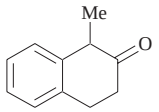
Similarly, treatment of **7e** with $Yb(OTf)_3$ (20 mol %) in dichloromethane, followed by purification of the crude product by chromatography over silica gel led to the isolation of a rearranged product. The structure of the isolated product **8e** (58% yield) was initially suggested by IR spectroscopy ($\lambda_{max}$ = 1661 $cm^{-1}$), corroborated by NMR spectroscopy, and firmly established by X-ray crystallography (Fig. 2). As expected, the epoxide ring opening had occurred with inversion of configuration.

Treatment of alcohol **7f** with $Yb(OTf)_3$ (20 mol %) gave a mixture of products from which the indan-1-yl phenyl ketone (**9**) was isolated in 63% yield (Scheme 6). Ketone **9** is most probably formed by retroaldol fragmentation of the initially formed ring-contracted product **8f**. To try to provide proof for this hypothesis, the reaction was repeated but quenched after a much shorter period of time. Purification of the crude material led to the isolation of a major product — the $^1H$ NMR spectrum of which was closely analogous to those of the ring-contracted products **8a** and **8e**. FAB mass spectrometry displayed a molecular-ion peak corresponding to compound **8f**. This material was unstable (decomposing readily but cleanly to ketone **9** and benzaldehyde), which prevented more extensive characterization. With this additional evidence, however, it seems highly likely that the well-precedented semi-pinacol rearrangement forms during the first part of the reaction.

**Fig. 1.** X-ray crystal structure of compound **7d**.




Surprisingly, epoxyalcohol **7d** did not produce ring-contracted material, but instead, formed two major products, 1-methyl-2-tetralone (**10**) (40% yield) and benzaldehyde, which were identified by $^1H$ NMR and by comparison with authentic materials (10).




**10**

## Discussion

Indans **8a** and **8e** are clearly formed by the expected ring-contraction process, whilst the fragmentation product **9** is assumed to be generated from indan **8f**. The fact that indan-epoxide **7b** fails to undergo ring contraction is presumably due to a high-energy transition state caused by ring strain. The key stereoelectronic requirement for the semi-pinacol rearrangement is that the migrating group should be anti-periplanar to the breaking C–O bond. Note that compound **7e** undergoes ring contraction rather than phenyl migration. Although no crystal structure data are available for **7e**, inspection of the X-ray crystal structure of the analogous methyl substituted epoxyalcohol **7d** (Fig. 1) suggests an origin for the selectivity. Thus whilst the dihedral angle between the epoxide C–O and the methyl group C–C [O(2)-

[2] Supplementary material may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0S2, Canada. For information on obtaining material electronically go to http://www.nrc.ca/cisti/irm/unpub_e.shtml. Crystallographic information has also been deposited with the Cambridge Crystallographic Data Centre (CCDC Nos. 181123 and 181124). Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

**Scheme 6.** Reagents and conditions: (*i*) $Yb(OTf)_3$, $CH_2Cl_2$, room temp.

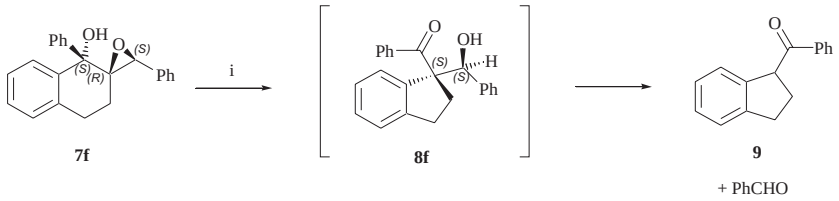
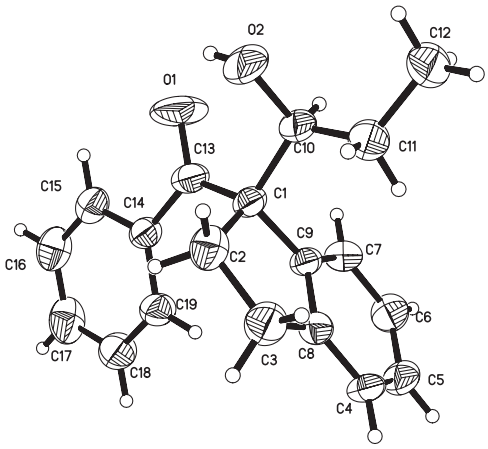



**Fig. 2.** X-ray crystal structure of compound **8e**.




C(2)-C(1)-C(18)] is 61.0°, the dihedral angle between the epoxide C–O and the migrant C–C [O(2)-C(2)-C(1)-C(10)] is 178.45°, i.e., anti-periplanar. The required alignment of the migrating C–C with the C–O $s^*$ of the epoxide dictates the outcome of these semi-pinacol rearrangements.

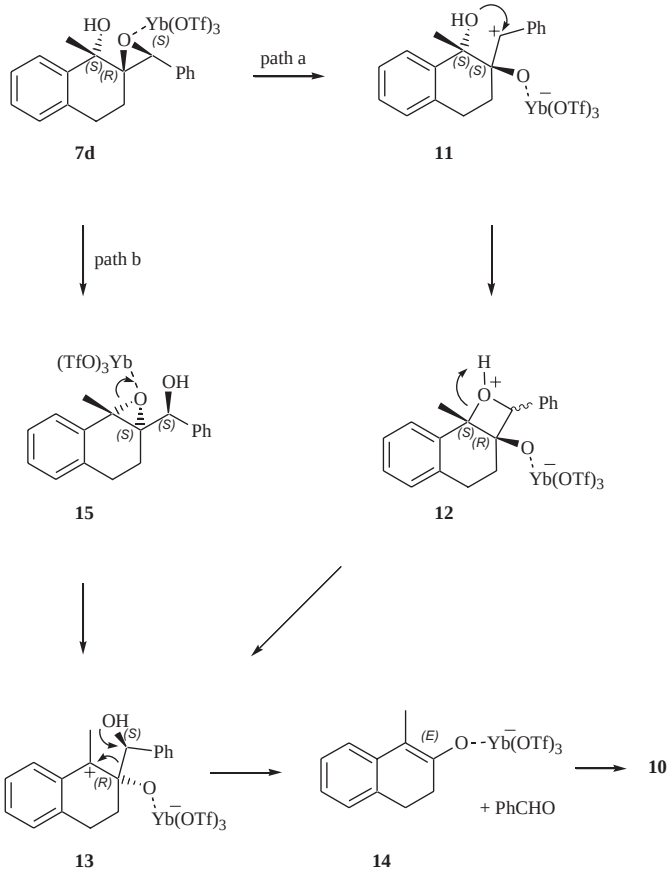
The mechanism by which 1-methyl-2-tetralone (**10**) is formed from epoxyalcohol **7d** is less clear; two possibilities are outlined in Scheme 7. Coordination of the $Yb(OTf)_3$ to the epoxide moiety should assist ring opening to reveal benzylic carbocation **11** (Scheme 7, path a). It is possible that this cation can rearrange via oxetane **12** to generate tertiary benzylic carbocation **13**. This would readily undergo a fragmentation reaction to generate benzaldehyde and the enolate (**14**) of 1-methyl-2-tetralone. An alternative approach to benzylic carbocation **13** is via a Lewis acid-catalyzed Payne rearrangement generating epoxyalcohol **15** followed by epoxide opening (Scheme 7, path b).

Work is in progress to try to distinguish between these two possibilities and the outcome of these experiments will be reported in a full paper.

## Conclusions

Application of Juliá–Colonna asymmetric epoxidation followed by Grignard alkylation has been used to prepare epoxyalcohols in enantiomerically enriched form, both from acyclic enones and from cycloalkanones bearing exocyclic olefin units. The spirocyclic epoxyalcohols prepared from the latter substrates undergo either ring contraction or fragmentation processes, depending on the substituents present and the size of the ring. $Yb(OTf)_3$ has been shown to be an excellent catalyst for epoxyalcohol semi-pinacol rearrangements.

**Scheme 7.**

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