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# Enantioselective Synthesis of (+)- and (−)-Dihydroepiepoformin and (+)-Epiepoformin

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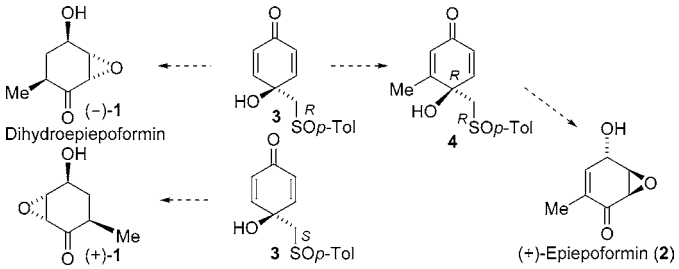
## ABSTRACT




**The enantioselective synthesis of both enantiomers of dihydroepiepoformin (1) and (+)-epiepoformin (2) was achieved from (*p*-tolylsulfinyl)-methyl-*p*-quinols (S*R*)- or (S*S*)-3 and (4*R*,S*R*)-4, respectively. Key features include the stereocontrolled conjugate addition of $AlMe_3$ to *p*-quinol 3 and retrocondensation to the ketone functionality, previous to oxidation of the *β*-hydroxy sulfoxide moiety of advanced intermediates to the corresponding sulfone.**

Dihydroepiepoformin (**1**) and (+)-epiepoformin (**2**) belong to a family of highly oxygenated cyclohexane-based metabolites that have been isolated from fungi and higher plants. These derivatives share a cyclohexene oxide skeleton, a recurring structural motif found in a number of natural products.[1] The wide range of biological properties that embrace these compounds have stimulated important synthetic efforts to achieve the stereoselective formation of this moiety.[2] Although several efficient solutions are now available, the development of new approaches are welcome.

Dihydroepiepoformin (**1**) was isolated by Kuo et al.[3] in 1995 from fermentation of *Penicillium patulum* and was found to have antagonistic activity for interleukin-1. Nevertheless, the authors did not report the specific rotation of the isolated compound or its absolute configuration. (+)-Epiepoformin (**2**) was isolated by Nagasawa[4] in 1978 from the culture filtrate of an unidentified fungus separated from a diseased leaf and showed marked inhibition activity against the germination of lettuce seeds.

(+)-Epiepoformin (**2**) has been previously synthesized by several authors using different strategies. Ogasawara et al. used a retro Diels−Alder reaction to recover the cyclohexenone fragment from a stereoselectively functionalized quinone Diels−Alder adduct.[5] The formation of a bicyclic adduct in the cinchonine-catalyzed reaction between 3-hydroxy-2-pyrone and an acrylamide derived from a chiral oxazolidinone was the key step in the more recent approach of Okamura et al.[6] In the synthesis reported by Maycock et al. in 2000,[7] (−)-quinic acid was the starting material,

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(2) Marco-Contelles, J.; Molina, M. T.; Anjum, S. *Chem. Rev.* **2004**, *104*, 2857−2859.

(3) Kuo, M.-S.; Yurek, D. A.; Mizsak, S. A.; Marshall, V. P.; Liggett, W. F.; Cyaldella, J. I.; Laborde, A. L.; Shelly, J. A.; Truesdell, S. E. *J. Antibiot.* **1995**, 888−890.

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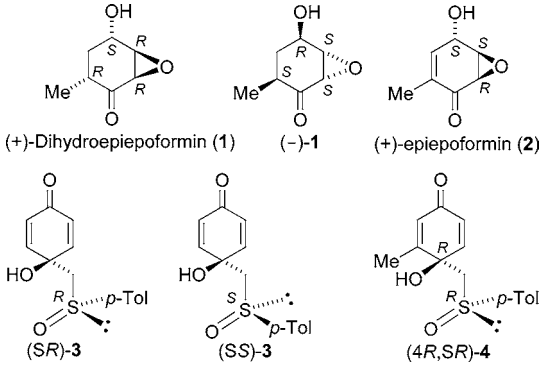
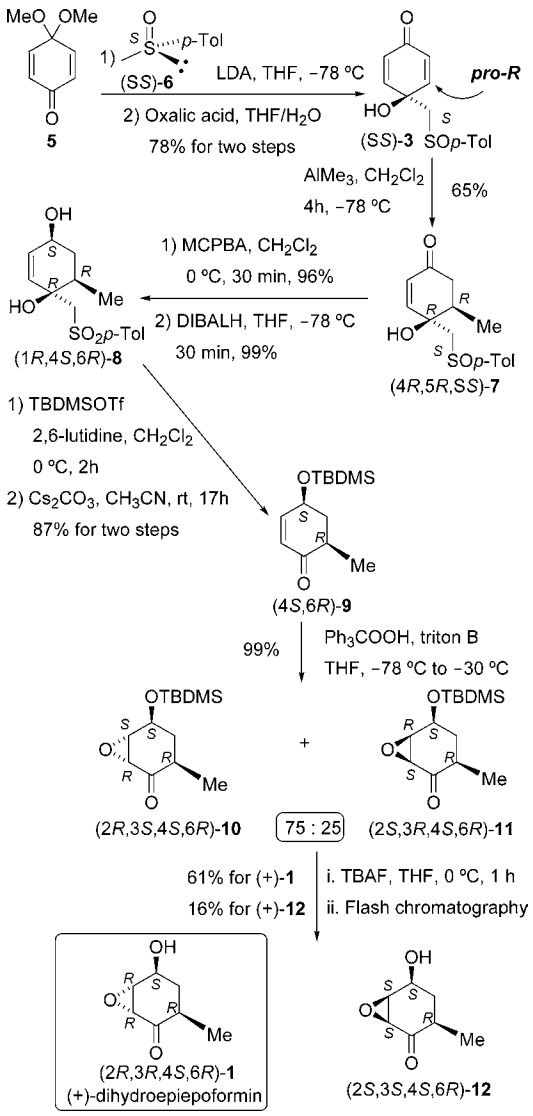
whereas a chiral building block obtained by enzymatic reduction was used by Kitahara et al.[8] to synthesize (+)-**2** in 2003. To the best of our knowledge, there is no synthetic approach to racemic or enantioenriched dihydroepiepoformin (**1**).

In connection with a program devoted to asymmetric synthesis mediated by sulfoxides,[9] we have recently reported that the $\beta$-hydroxysulfoxide moiety present in several (*p*-tolylsulfinyl)methyl-*p*-quinols such as **3** and **4** can be regarded as a chiral ketone equivalent,[10] opening an easy access to differently substituted enantiopure cyclic ketones by combining stereoselective organoaluminum conjugate additions,[11] stereoselective reductions, and elimination of the sulfur function by retrocondensation in a basic medium.[10,12] In this communication, we report the synthesis of several epoxy cyclohexene derivatives and their use as key intermediates for the first total synthesis and determination of the absolute configuration of both enantiomers of dihydroepiepoformin (**1**) and a new enantioselective approach to (+)-epiepoformin (**2**).




The synthesis of (+)-dihydroepiepoformin (**1**), depicted in Scheme 1, started with (*p*-tolylsulfinyl)methyl-*p*-quinol (*SS*)-**3**,[12] easily available in two steps and 78% yield by reaction of *p*-benzoquinone dimethyl monoacetal **5**[13] with the lithium anion derived from (*SS*)-methyl *p*-tolylsulfoxide (**6**),[14] followed by the hydrolysis of the acetal group using oxalic acid.

**Scheme 1.** Enantioselective Total Synthesis of (+)-Dihydroepiepoformin (**1**)




The diastereo- and chemoselective addition of $AlMe_3$ to (*SS*)-**3** occurred at the pro-*R* conjugate position, on the same face of the OH group of **3**, giving rise exclusively to cyclohexenone (4*R*,5*R*,*SS*)-**7**. After MCPBA oxidation to sulfone and stereoselective DIBALH reduction of the carbonyl group, cyclohexenoid derivative (1*R*,4*S*,6*R*)-**8** was obtained in excellent yield. Finally, protection of the carbinol at C-4 of **8** followed by elimination of methyl *p*-tolyl sulfone under $Cs_2CO_3$ conditions afforded cyclohexenone (4*S*,6*R*)-**9** in optically pure form.[12] The stereoselective epoxidation of the double bond of **9** was troublesome. After several trials using different epoxidation agents ($H_2O_2$/triton B,[15] TBHP/*n*-BuLi,[16] TBHP/triton B,[17] $CF_3COCH_3$/oxone[18]), the best

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(7) Okamura, H.; Shimizu, H.; Yamashita, N.; Iwagawa, T.; Nakatani, M. *Tetrahedron* **2003**, *59*, 10159−10164.
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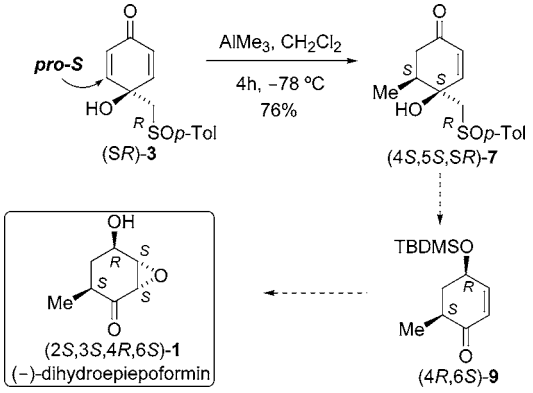
(9) Overviews: (a) Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717−1760. (b) Carreño, M. C.; Urbano, A. *Synlett* **2005**, 1−25. Recent work: (c) Carreño, M. C.; González-López, M.; Urbano, A. *Chem. Commun.* **2005**, 611−613. (d) Brinkman, Y.; Carreño, M. C.; Urbano, A.; Colobert, F.; Solladié, G. *Org. Lett.* **2004**, *6*, 4335−4338. (e) Carreño, M. C.; Des Mazery, R.; Urbano, A.; Colobert, F.; Solladié, G. *Org. Lett.* **2004**, *6*, 297−299. (f) Carreño, M. C.; Des Mazery, R.; Urbano, A.; Colobert, F.; Solladié, G. *J. Org. Chem.* **2003**, *68*, 7779−7787. (g) Carreño, M. C.; García-Cerrada, S.; Urbano, A. *Chem. Eur. J.* **2003**, *9*, 4118−4131. (h) Almorín, A.; Carreño, M. C.; Somoza, Á.; Urbano, A. *Tetrahedron Lett.* **2003**, *44*, 5597−5560. (i) Carreño, M. C.; García-Cerrada, S.; Sanz-Cuesta, M. J.; Urbano, A. *J. Org. Chem.* **2003**, *68*, 4315−4321.
(10) Carreño, M. C.; Pérez-González, M.; Ribagorda, M.; Somoza, A.; Urbano, A. *Chem. Commun.* **2002**, 3052−3053.
(11) (a) Carreño, M. C.; Pérez-González, M.; Ribagorda, M.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 3687−3693. (b) Carreño, M. C.; Pérez González, M.; Ribagorda, M.; Fischer, J. *J. Org. Chem.* **1996**, *61*, 6758−6759.
(12) Carreño, M. C.; Ribagorda, M.; Somoza, A.; Urbano, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 2755−2757.
(13) Buchanan, G. L.; Raphael, R. A.; Taylor, R. *J. Chem. Soc., Perkin Trans. 1* **1973**, 373−375.
(14) (*SS*)-**6** was prepared as previously described for the (*SR*)-enantiomer: Solladié, G.; Hutt, J.; Girardin, A. *Synthesis* **1987**, 173−175.
(15) Barros, M. T.; Matias, P. M.; Maycock, Ch. D.; Ventura, M. R. *Org. Lett.* **2003**, *5*, 4321−4323.

results were achieved in the presence of $Ph_3COOH$[19] and Triton B. Under these conditions (THF, −78 to −30 °C), an unseparable 75:25 mixture of diastereomeric epoxides **10** and **11** was obtained in quantitative yield. Deprotection of the OTBDMS of this mixture (TBAF in THF) followed by chromatographic separation furnished (+)-dihydroepiepoformin (**1**) (61% yield) and alcohol (2*S*,3*S*,4*S*,6*R*)-**12** (16% yield). Synthetic dihydroepiepoformin (**1**) {$[\alpha]^{20}_D$ +34 (*c* 0.1, $CHCl_3$), $[\alpha]^{20}_D$ +22 (*c* 0.1, acetone), 96% ee},[20] with the (2*R*,3*R*,4*S*,6*R*)- absolute configuration, showed NMR parameters identical to those described for the isolated natural product.[3]

The synthesis of (−)-dihydroepiepoformin (**1**), summarized in Scheme 2, required the use of (*SR*)-**3**[21] as starting material.

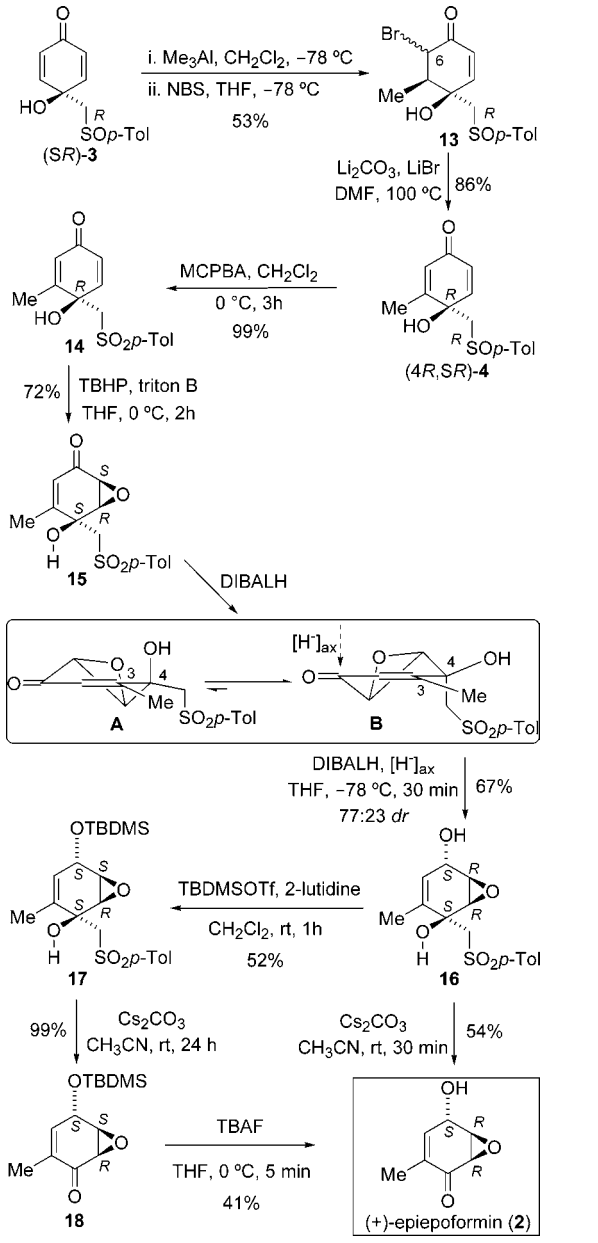
**Scheme 2.** Enantioselective Total Synthesis of (−)-Dihydroepiepoformin (**1**)




This enantiomer was synthesized following the sequence shown in Scheme 1 for (*SS*)-**3** but using (*SR*)-methyl-*p*-tolylsulfoxide (**6**)[14] as the source of chirality. Conjugate addition of $AlMe_3$ to (*SR*)-**3** occurred at the pro-*S* position.[11] The resulting compound (4*S*,5*S*,*SR*)-**7** was transformed, as described in Scheme 1 for the corresponding enantiomer, into cyclohexenone (4*R*,6*S*)-**9**[10] and further elaborated to (−)-dihydroepiepoformin (**1**). This enantiomer showed the same spectral data as the natural dihydroepiepoformin and a specific rotation value of {$[\alpha]^{20}_D$ −27 (*c* 1.2, $CHCl_3$), $[\alpha]^{20}_D$ −21 (*c* 1.2, acetone), 96% ee}[20] having the (2*S*,3*S*,4*R*,6*S*)-absolute configuration.

With both enantiomers of dihydroepiepoformin (**1**) synthesized, we turned out our attention to the other target structure, (+)-epiepoformin (**2**). The synthetic sequence to (+)-**2** is depicted in Scheme 3 and started with (*p*-tolylsulfinyl)methyl-*p*-quinol (*SR*)-**3**.[21] The stereoselective addition of $Me_3Al$ followed by trapping of the enolate intermediate with *N*-bromosuccinimide furnished α-bromoketone **13** as a mixture of epimers at C-6. After HBr elimination in the presence of lithium carbonate and lithium chloride, methyl-susbtituted *p*-quinol (4*R*,*SR*)-**4**[11] was obtained in good yield. Transformation of **4** into (+)-epiepoformin (**1**) was then achieved in only four steps. MCPBA oxidation of **4** gave rise to the sulfone **14** in nearly quantitative yield. The epoxidation of derivative **14** was carried out with *tert*-butylhydroperoxide (TBHP) in the presence of Triton B, affording epoxide **15** as the unique diastereoisomer in 72%

**Scheme 3.** Enantioselective Synthesis of (+)-Epiepoformin (**2**)

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(20) Optical purity of both enantiomers of dihydroepiepoformin (**1**) was determined by chiral HPLC: Daicel Chiralcel AD, *i*-PrOH/hexane 10:90, flow rate 0.7 mL/min, $t_R$ = 15.3 min for the (2*S*,3*S*,4*R*,6*S*)-enantiomer and 17.5 min for the (2*R*,3*R*,4*R*,6*S*)-enantiomer, 211 nm.

(21) Carreño, M. C.; Pérez-González, M.; Houk, K. N. *J. Org. Chem.* **1997**, *62*, 9128−9137.

yield. This highly stereoselective epoxidation took place on the more electrophilic unsubstituted double bond of **14** exclusively on the upper face of the enone system, which bears the OH group. The diisobutyl aluminum hydride (DIBALH) reduction of the carbonyl group of **15** afforded a 77:23 mixture of the two possible diastereoisomeric carbinols from which major compound **16**, bearing the (*S*)-absolute configuration at the newly created stereogenic center, could be isolated after flash chromatography in 67% yield. The diastereoselectivity of the reduction process could be explained from the axial attack of the small hydride DIBALH to the most stable B conformation of ketone **15**, where severe interactions between the methyl group at C-3 and the equatorial (*p*-tolylsulfonyl)methyl substituent at C-4 present in the other possible conformation **A**, are avoided (Scheme 3).

Further treatment of carbinol **16** with $Cs_2CO_3$ ($CH_3CN$, rt, 30 min) afforded, after elimination of methyl *p*-tolyl sulfone, a 54% yield of (+)-epiepoformin (**2**) {$[\alpha]^{20}_D$ +303 (*c* 1.1, EtOH), 96% ee}.[22] All physical and spectroscopic data of our synthetic compound were in agreement with those published in the literature for the natural enantiomer of epiepoformin.[4−8]

With the aim of increasing the yield of the elimination step, we performed the protection of the free OH group of **16** as TBDMS (TBDMSOTf, 2,6-lutidine, 52% yield). The elimination of methyl *p*-tolyl sulfone on the resulting compound **17** under mild basic conditions ($Cs_2CO_3$, $CH_3CN$, rt, 24 h) afforded ketone **18** in an excellent 99% yield. Final deprotection of the TBDMS group of **18** (TBAF, THF, 0 °C) yielded a 41% of (+)-epiepoformin (**2**). Regardless of the excellent yield achieved in the elimination of methyl *p*-tolyl sulfone on the TBDMS-protected carbinol **17**, the overall yield for the direct transformation of carbinol **16** into (+)-epiepoformin (**2**) was higher than that obtained in the three-step sequence through intermediates **17** and **18**.

In summary, we have reported that (*p*-tolylsulfinyl)methyl quinols such as **3** and **4** are useful starting materials for the asymmetric synthesis of naturally occurring cyclohexenone epoxides. We have described the first total synthesis of both enantiomers of dihydroepiepoformin (**1**) from known *p*-quinols (R*S*)- and (S*S*)-**3** in seven steps with 32% overall yield and established their absolute configuration, as well as a new enantioselective approach to (+)-epiepoformin (**2**) in only four steps from methyl-substituted *p*-quinol (4*R*,S*R*)-**4** with 26% overall yield.

Further applications of this methodology to the asymmetric synthesis of more functionalized cyclohexanes−epoxide natural products are now in progress.

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**Supporting Information Available:** Experimental procedures, spectroscopic data, and copies of $^1H$ NMR and $^{13}C$ NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Optical purity of (+)-epiepoformin (**2**) was determined after $^1H$ NMR analysis (500 MHz) from the corresponding Mosher's esters: Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519.