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ONE-POT SYNTHESIS OF DIHYDROXYCYCLOPENTANES FROM ALLYLSULFONES AND CHIRAL DIEPOXIDES

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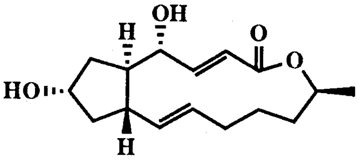
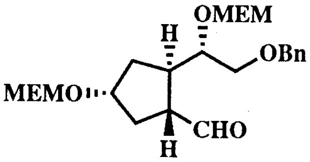
Allylphenylsulfonyl lithium, generated from allyl phenyl sulfone and ^{n}BuLi, reacts with chiral diepoxides to give dihydroxycyclopentane derivatives in good yields. The synthesis of the aldehyde **2**, which is a key intermediate for brefeldin A, was achieved using this reaction.

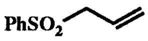
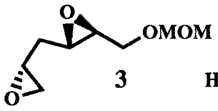
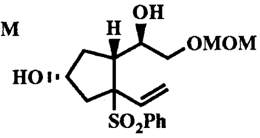
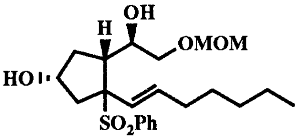
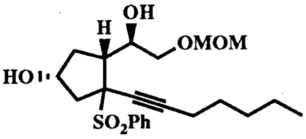
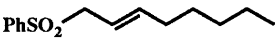
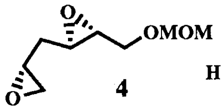
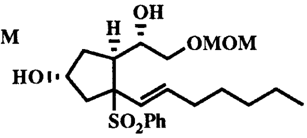
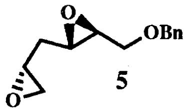
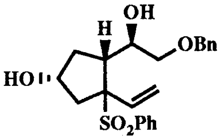
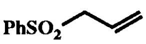
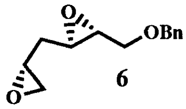
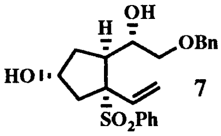
KEYWORDS one-pot synthesis; dihydroxycyclopentane derivative; allyl phenyl sulfone; chiral diepoxide; brefeldin A

Sulfone compounds are useful in carbon-carbon bond-forming reactions, particularly in cyclization.[1-4] For example, Eisch and co-workers reported the conversion of 4-bromo-1,2-epoxybutane and [(phenylsulfonyl)methylene] dilithium to 3-(phenylsulfonyl)-cyclopentanol in 84% yield.[3] But simultaneous formation of two new carbon-carbon bonds has not yet been reported. We wish to report a new reaction of phenylsulfonyl compounds with chiral diepoxides for the formation of optically active cyclopentane derivatives. This reaction was applied to a synthesis of the aldehyde **2**,[5c] which is a key synthetic intermediate of (+)-brefeldin A (**1**).[5]


brefeldin A (1)


2

The lithio derivatives of sulfone compounds were prepared from the sulfone [6](2.5 eq) and *n*-butyllithium (2.4 eq) in tetrahydrofuran (THF) at -78°C for 1 h. The diepoxide (1.0 eq) in THF was then added dropwise at -78°C. The reaction mixture was stirred at -78°C for 1 h. and then kept at room temperature with stirring for 1 h. The reaction of two allyl phenyl sulfones gave the dihydroxycyclopentane derivatives as diastereomeric mixtures in the ratio of 1:1 via selective *exo* cyclization in 78% and 95% yields based on the diepoxide **3** [7,8](entries 1, 2). The reaction of phenyl propargyl sulfone gave the cyclopentane derivative as a diastereomeric mixture in the ratio of 6:1 in 84% yield (entry 3). The diepoxide **4**,[9] a diastereomer of **3**, reacted with allyl phenyl sulfone to form the cyclopentane as a sole product in 71% yield (entry 4). The diepoxide **5**,[9] which was protected with benzylether, gave the cyclopentane derivative in the ratio of 1:1 in 95% yield (entry 5). The diepoxide

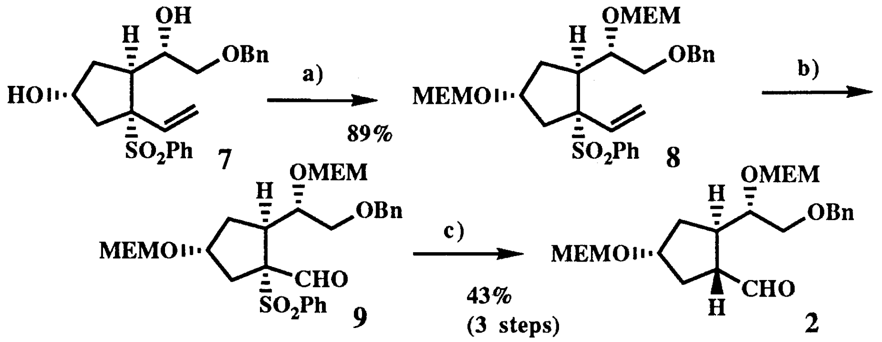
Entry	Sulfone	Diepoxide	Products	Yield,[a] %
1		 3		78[b]
2		3		95[b]
3		3		84[c]
4		 4		71[d]
5		 5		95[b]
6		 6	 7	95[e]

a) Isolated yield based on the diepoxide.
b) A 1:1 mixture of diastereomer was generated.
c) A 6:1 mixture of diastereomer was generated.
d) A single compound, whose stereochemistry was not determined.
e) A single compound.

6 [9]) reacted with allyl phenyl sulfone to form the cyclopentane **7** as a single product, whose stereochemistry was determined by NOE experiment, in 95% yield (entry 6).

Based on this approach to constructing dihydroxycyclopentane derivatives, a synthetic study for brefeldin A was carried out. The hydroxy group of **7** was protected with 2-methoxyethoxymethyl chloride to give **8.** The terminal olefin of **8** was converted to an aldehyde **9**. The phenylsulfonyl group of **9** was removed by treatment with SmI_2 in the presence of HMPA. The isomerization of the formyl group was carried out by treatment with K_2CO_3 in methanol to give the aldehyde **2**.[10]) The aldehyde **2** has already been synthesized by Taber's group in their synthesis of (+)-brefeldin A.

The present results clearly demonstrate the potential of this method for syntheses of not only brefeldin A but also other natural products.



a) MEM-Cl, ${}^iPr_2NEt$, CH_2ClCH_2Cl, 50°C, b) O_3, CH_2Cl_2-MeOH, -78°C, then Me_2S, r.t.,
c) i) SmI_2, THF-HMPA, r.t., ii) K_2CO_3, MeOH, r.t.,

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2) a) Y. Gaoni, *Tetrahedron Lett.*, 503 (1976); b) Y. Gaoni, *Tetrahedron Lett.*, 4339 (1981); c) Y. Gaoni, *J. Org. Chem.*, **47**, 2564 (1982).
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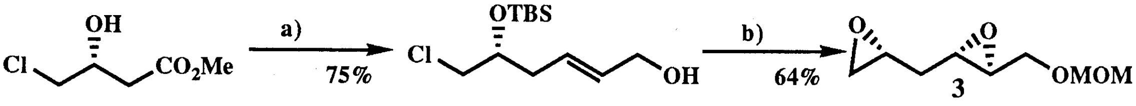
5) Recent synthetic studies on (+)-brefeldin A: a) E. J. Corey, and P. Carpino, *Tetrahedron Lett.*, **31**, 7555 (1990); b) J. Nokami, M. Ohkura, Y. Dan-oh, and Y. Sakamoto, *Tetrahedron Lett.*, **32**, 2409 (1991); c) D. F. Taber, L. J. Silverberg, and E. D. Robinson, *J. Am. Chem. Soc.*, **113**, 6639 (1991) and references cited therein.
6) Phenylsulfonyl compounds were prepared by treating the corresponding halides with sodium benzenesulfinate in DMF (80-95% yield).

7) Diepoxides **3** was synthesized as follows from (R)-methyl 4-chloro-3-hydroxybutyrate(96.6% ee):



a) i) TBS-Cl, ii) DIBAL-H, toluene, -78°C, iii) $Ph_3P{=}CHCO_2Et$, iv) DIBAL-H, CH_2Cl_2, -78°C, b) i) TBHP, $Ti(O^iPr)_4$, L-(+)-DET, ii) MOM-Cl, iii) ${}^nBu_4NF$, iv) K_2CO_3, MeOH

8) Data for **3** : ${}^1H$-NMR (400 MHz, $CDCl_3$) δ ppm: 1.79 (1H, dt, J=15.0, 5.9 Hz), 2.07 (1H, dt, J=15.0, 4.2 Hz), 2.60 (1H, dd, J=4.9, 2.8 Hz), 2.99 (1H, m), 3.04 (1H, m), 3.07 (1H, m), 3.38 (3H, s), 3.57 (1H, dd, J=11.7, 5.5 Hz), 3.77 (1H, dd, J=11.7, 3.3Hz), 4.66 (2H, s); $[\alpha]_D$-13.8° (c=4.37, $CHCl_3$).
9) Diepoxides **4**, **5** and **6** were synthesized by a similar method to that described for **3**.
10) Data for **2** : ${}^1H$-NMR (400 MHz, $CDCl_3$) δ ppm: 1.71 (1H, ddd, J=13.6, 10.3, 4.9 Hz), 1.96 (1H, m), 2.0 - 2.1 (2H, m), 2.68 (1H, m), 2.78 (1H, m), 3.37 (3H, s), 3.38 (3H, s), 3.5-3.8 (10H, m), 3.80 (1H, m), 4.25 (1H, m), 4.46 (1H, d, J=11.8 Hz), 4.50 (1H, d, J=11.8 Hz), 4.67 (1H, d, J=7.0 Hz), 4.67 (1H, d, J=7.0 Hz), 4.75 (1H, d, J=6.9 Hz), 4.88 (1H, d, J=6.9 Hz), 7.25 - 7.4 (5H, m), 9.60 (1H, d, J=2.3 Hz); IR (neat) : 1720 cm^{-1}; $[\alpha]_D$ -27.3° (c= 0.66, $CHCl_3$).

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