CONCISE ENANTIOSELECTIVE SYNTHESIS OF (+)-ASPERLIN BY APPLICATION OF THE SHARPLESS KINETIC RESOLUTION TO 2-FURYLMETHANOL DERIVATIVES BEARING ALKENYL MOIETY ON THE SIDE CHAIN

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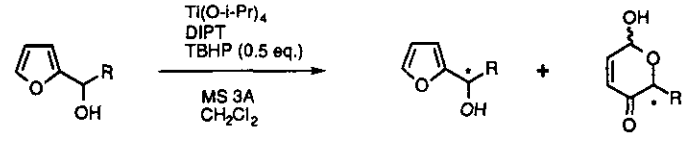
Abstract —— A reaction of (±)-(*E*)-1-(2-furyl)but-2-en-1-ol (**1**) under the Sharpless asymmetric oxidation condition using 30 mol% of D-(-)-diisopropyl tartrate (DIPT), 25 mol% of titanium tetraisopropoxide and 120 mol% of *tert*-butyl hydroperoxide (TBHP) afforded the (*S*)-epoxide (**3**), in 42% yield with high optical purity, which was further converted into an antitumour antibiotic, asperlin (**10**).

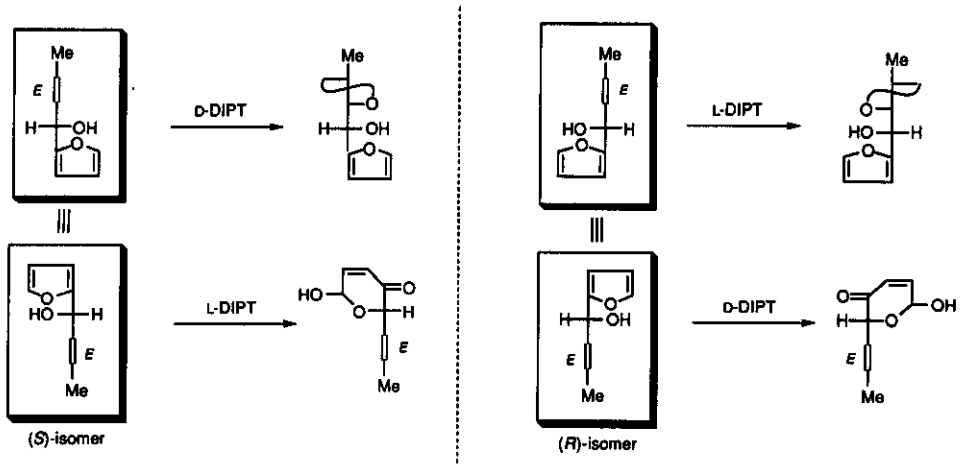
Recently both this group[1] and Sato *et al.*[2] independently developed a novel procedure for the chiral synthesis of secondary 2-furylmethanol derivatives in high enantiomeric excess. The key step involved a *kinetic resolution of the corresponding racemates* by the Sharpless epoxidation[3] (Scheme 1). This methodology has been employed in the chiral synthesis of physiologically active natural products.[4] Here we report an enantioselective synthesis of an antibiotic, (+)-asperlin, by further application of the Sharpless epoxidation to 2-furylmethanol derivative bearing alkenyl moiety on the side chain.



Scheme 1

We have previously reported[1] that the treatment of (±)-(*E*)-1-(2-furyl)but-2-en-1-ol (**1**) with 10 mol% of L-(+)-DIPT, 15 mol% of titanium tetraisopropoxide and 70 mol% of TBHP resulted in the recovery of (*R*)-(*E*)-1-(2-furyl)but-2-en-1-ol (**1**) in 32% yield with 82% ee together with the (*S*)-pyranone (**2**). With D-(-)-DIPT, as expected, the (*S*)-alcohol (**1**) was recovered in 32% yield with 88% ee. When this product was subjected to a further kinetic resolution using 35 mol% of TBHP, 20 mol% of titanium tetraisopropoxide and 24 mol% of D-(-)-DIPT, the optical purity of the recovered (*S*)-alcohol (**1**) was increased to 97% ee in 60% yield.

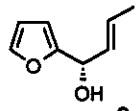
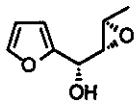
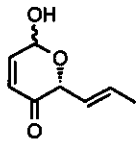
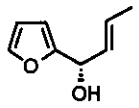
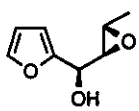
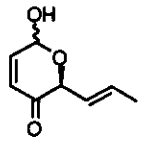
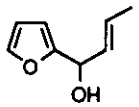
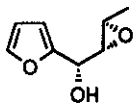
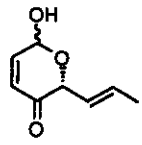
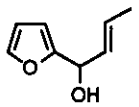
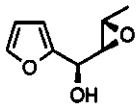
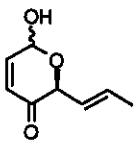
The enantioselective Sharpless epoxidation of allyl alcohols containing two double bonds typically results in the preferential epoxidation of the more electron rich double bond.[3] The results obtained in the kinetic resolution of alcohol (**1**) reflected the relative reactivities of both double bonds presented in the molecule. However, we found that the reactivity of the double bonds of alcohol (**1**) varied with the chirality of DIPT employed in the reaction (Scheme 2). Although the investigation on the Sharpless epoxidation of symmetrical divinyl carbinol have been reported by several groups,[5] none of the systematic studies on the Sharpless epoxidation for unsymmetrical divinyl carbinol derivatives seems to have been described.



Scheme 2. The Fischer projection for the Sharpless epoxidation of (*E*)-(2-furyl)but-2-en-1-ol.

When the epoxidation of the (*S*)-alcohol (**1**) (97% ee) was carried out with 1.2 equivalents of TBHP in the presence of L-(-)-DIPT the (*S*)-pyranone (**2**), arising from the oxidation of the more reactive furan double bond, was isolated in 85% yield, as expected, together with a trace of the (*R*)-epoxide (**3**) (Table, Entry 2). However oxidation of the (*S*)-alcohol (**1**) using D-(+)-DIPT resulted in the (*S*)-epoxide (**3**) in 89% yield with 97% ee (based on the optical purity of the starting material employed) accompanied by a small amount of the (*R*)-pyranone (**2**) (Table, Entry 1). The furan double bond of the (*S*)-alcohol (**1**) formed a matched pair with the titanium-L-(+)-DIPT complex resulting in the formation of the (*S*)-pyranone (**2**). However use of D-(-)-DIPT resulted in the almost exclusive epoxidation of the alkenyl double bond indicating the alkenyl double bond of (*S*)-alcohol (**1**) formed a matched pair with the titanium-D-(-)-DIPT complex. The Sharpless kinetic resolution of the racemate (**1**), with 1.2 equivalents of TBHP in the presence of D-(-)-DIPT, gave the (*S*)-epoxide (**3**) and the (*R*)-pyranone (**2**) in 42 and 43% yields respectively (Table, Entry 3). Comparison of the optical rotation of the (*S*)-epoxide (**3**) with that of the epoxide derived from the (*S*)-2-furylmethanol derivative (**1**) (97% ee) indicated an ee of >97%. Conversely oxidation of racemate (**1**) using L-(+)-DIPT gave the optically pure (*R*)-epoxide (**3**) and the (*S*)-pyranone (**2**) in 41 and 41% yields respectively (Table, Entry 4). It is noteworthy that none of the epoxide diastereoisomers was isolated indicating that the epoxidation proceeded in entirely diastereofacial-selective manner.

Table.[a] The Sharpless oxidation of (*E*)-(2-furyl)but-2-en-1-ol

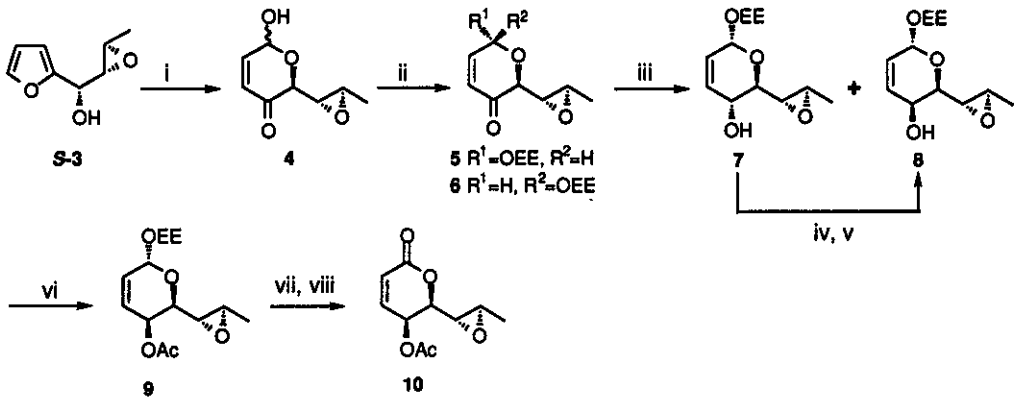
Entry	Starting Material	DIPT	Products (Yield)	
1		D		
	***S*-1** (97%ee)[c]		***S*-3** (89%)	***R*-2** (1.4%)
	$[\alpha]_D$ +56° ($CHCl_3$)		$[\alpha]_D$ -42.7° ($CHCl_3$)	
2[b]		L		
	***S*-1** (97%ee)[c]		***R*-3** (0.4%)	***S*-2** (85%)
3		D		
	1 (racemate)		***S*-3** (42%)	***R*-2** (43%)
			$[\alpha]_D$ -43° ($CHCl_3$)	
4		L		
	1 (racemate)		***R*-3** (41%)	***S*-2** (41%)
			$[\alpha]_D$ +43.4° ($CHCl_3$)	

[a] All reactions were carried out at -20°C with 25 mol % of $Ti(O\text{-}i\text{-}Pr)_4$, 30 mol % of DIPT, and 120 mol % of TBHP in the presence of CaH_2 and 3A molecular sieves, except for the Entry 2. [b] 150 mol % of TBHP were employed. [c] Determined based on hplc analysis using the chiral column CHIRALCEL OB (Daicel Chemical Industries LTD.).

By application of this methodology to the natural product synthesis and also as a means to determine the stereochemistry at C-2 and C-3 positions of the (*S*)-epoxide (**3**), a facile synthesis of antitumour antibiotic asperlin,[6] isolated from *Aspergillus nidulans* ,[7] was investigated (Scheme 3).

Oxidation of the optically pure (*S*)-epoxide (**3**) with aqueous *N*-bromosuccinimide[8] gave the pyranone derivative (**4**), which was converted into the ethoxyethyl ethers (**5**) and (**6**) in 60 and 27% yields from epoxide (**3**), respectively. Reduction of the major isomer (**5**) with sodium borohydride in the presence of cerium(III) chloride afforded the alcohols (**7**) and (**8**) in 90 and 9% yields, respectively. The minor alcohol (**8**) having the correct configuration for the natural product was derived from the major alcohol (**7**) by Mitsunobu reaction[9] using benzoic acid, followed by hydrolysis of the benzoate in 87% yield. After acetylation of (**8**) with acetic anhydride, the acetate (**9**) was transformed to asperlin (**10**), mp 71.5-72.0°C (hexene-Et_2O) (lit.,[6] 71-73°C), by removal of the ethoxyethyl protecting group, and subsequent oxidation

with pyridinium chlorochromate. The spectroscopic data including its specific optical rotation, {$[\alpha]_D$ +342.4° (c 1, EtOH), lit.,[6] $[\alpha]_D$ +345° (c 0.9, EtOH)}, of the synthetic compound were identical with those of natural product.



Scheme 3. *Reagents and conditions*: i, NBS, *aq*. THF (66%); ii, ethyl vinyl ether, PPTS, CH_2Cl_2 (**5**; 60%, **6**; 27%); iii, $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH (**7**; 90%, **8**; 9%); iv, $PhCO_2H$, DEAD, Ph_3P, THF (87%); v, K_2CO_3, MeOH (100%); vi, Ac_2O, Py, DMAP, CH_2Cl_2 (100%); vii, *aq*. AcOH, THF (96%); viii, PCC, Celite, AcONa,CH_2Cl_2 (91%).

To our knowledge this is the first example of the Sharpless epoxidation of the unsymmetrical divinyl carbinol leading to the formation of the epoxide on the less reactive double bond in regio- and diastereofacial-selective manner. By the use of this strategy, a practical synthesis of (+)-asperlin was achieved. Further investigation of this methodology for the other types of divinyl carbinols are still in progress.

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