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Asymmetric Synthesis of (-)-(4R, 5R)-4-[5-(Benzo[1, 3]dioxol-5-yl)-4-hydroxyl-1-(pyridin-2-yl)-4, 5-dihydro-1H-pyrazol-3-yl]benzamide

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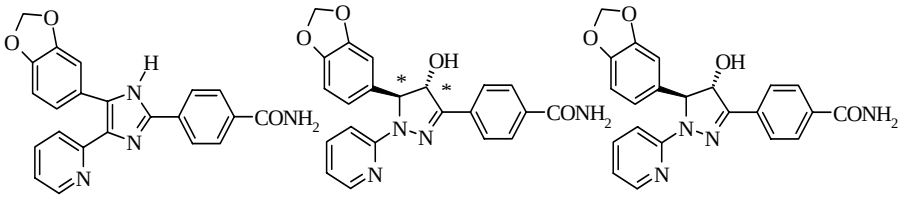
Abstract: The asymmetric synthesis of (-)-(4R, 5R)-4-[5-(benzo[1, 3]dioxol-5-yl)-4-hydroxyl-1-(pyridin-2-yl)-4,5-dihydro-1H-pyrazol-3-yl]-benzamide with improved Juliá-Colonna asymmetric epoxidation procedure as key step was described.

Keywords: Asymmetric synthesis, Juliá-Colonna epoxidation, 1,3,5-triaryl-4-hydroxyl-4,5-dihydro-1H-pyrazole.

For discovering novel small molecule inhibitors of transforming growth factor-β1 (TGF-β1) type-I receptor (ALK5), we designed 1,3,5-triaryl-4-hydroxyl-4,5-dihydro-1H-pyrazole (**1**) as target compound, mimic the structure of SB-431542 which is a 2-pyridyl substituted triarylimiazole inhibitor of ALK5[1]. Racemic compound **1** showed moderate ALK5 inhibitory activity in luciferase reporter assays [inhibition (%control): 0.1 umol/L 8.79%; 1umol/L 19.05%]. To investigate the influence of the absolute configuration of compound **1** on its bioactivity, to get valuable SAR information for further design and synthesis of inhibitors of ALK5, the asymmetric synthesis of compound **1** had been carried out.

Herein we describe the successful asymmetric synthesis of (-) **1** using improved Juliá-Colonna asymmetric epoxidation procedure as key step (as shown in **Scheme 1**).



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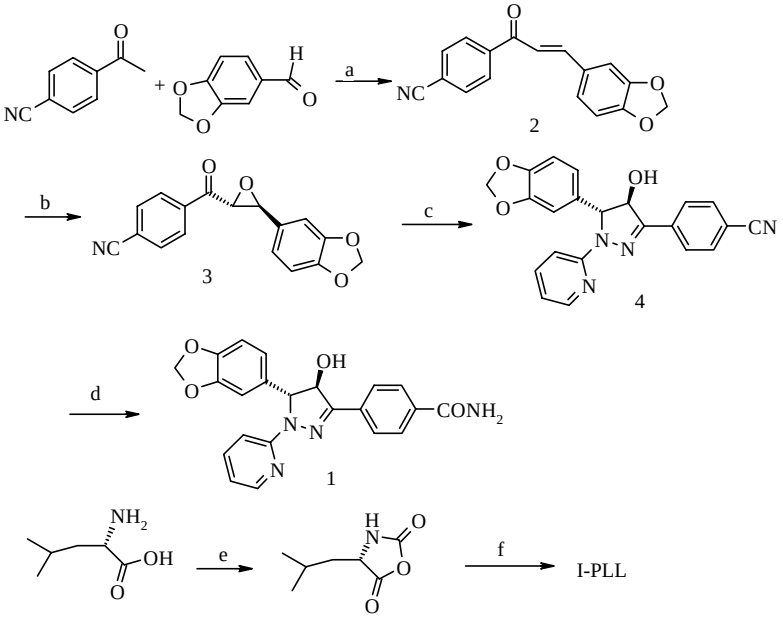
Scheme 1



Reagents and Conditions: a: MeONa/MeOH b: I-PLL/UHP/DBU/THF c: 2-hydrazinpyridine /EtOH/reflux, d: KOH/*t*-BuOH/ heat, e: bis(trichloromethyl)carbonate/THF, f: aminomethyl polystyrene resin/ THF

The use of polyamino acids as catalysts in asymmetric epoxidation of chalcones was discovered by Julić and Colonna[2]. B.M.Adger improved the procedure by replacing H_2O_2 /NaOH with urea hydrogen peroxide (UHP) /1,8-diazabicyclo [5, 5, 0] undec-7-ene (DBU) and using immobilized polyamino acids as catalyst in stead of polyamino acids, so as to facilitate the recover of the catalyst and work-up[3].

The substituted chalcone *trans*-**2** can be prepared by condensation of 4-cyanoacetophenone and piperonal under the catalysis of NaOH in ethanol[4]. Asymmetric epoxidation of **2** under the conditions recommended by B.M. Adger[3], using UHP in THF containing DBU with immobilized poly-L-leucine(I-PLL) as the insoluble catalyst, furnished epoxide (-)**3** in high yield (70%) and excellent enantioselecitive (>99.5% ee determined by chiral capillary electrophoresis). The absolute configuration of **3** was conclude to be (2R, 3S), because chalcone and chalcone derivatives produced (2R, 3S) epoxide under the same condition, and no exception had been reported. The high enantioselecitive may partially owe to the cyano and/or the methylenedioxy group. They may offer additional binding energy, which can consolidate the coordination between the substrate and the catalyst. The epoxide (-)-**3** on condensation with 2-hydrazinopyridine in ethanol gave (-)-**4**[7]. Its absolute configurtion must be (4S, 5S) from (-)-(2R, 3S)-**3**. Conversion of the nitrile group of (-)-**4** to carboxamide was accomplished by treatment with KOH power in *t*-BuOH under reflux to give (-)-(4S, 5S)-**1**[5, 8]. The racemic and optically active **1**, **2**, **3**, **4** are all novel compounds to our knowledge.

Table Physical properties and yield of compounds

compound	mp°C	$[\alpha]_D^{20}$	Yield(%)
2	173-176	----------	85
3	157-159	-75.5, (C, 1.1, $CHCl_3$)	75
4	212-215	-113, (C, 0.495, $CDCl_3$)	71
1	134-136	-163, (C, 0.405, EtOH)	45

Chiral catalyst I-PLL was prepared through following procedure. Firstly, L-leucine of N-carboxyanhydride(NCA) was synthesized using L-leucine and bis(trichloromethyl)carbonate according to the literature[5] then L-leucine-NCA was polymerized in THF at room temperature utilizing 1% cross-linked microporous polystyrene resin (purchased from Shanghai Jier Biochemisry Co.) as initiator to give the immobile-PLL[3](as shown in **Scheme 1**).

Unfortunately the ALK5 inhibitory activity of (-)-(4R, 5R)-**1**[inhibition (%control): 0.1 μmol/L 3.71%; 1 μmol/L 8.80%] was lower than its racemic. The (+)-(4S, 5S)-**1** has not been synthesized due to D-leucine was too expensive and will be synthesized through other route.

Acknowledgment

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References and Notes

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7. Selected spectroscopic data for compound **4**
   ^{1}H-NMR($CDCl_3$, δ ppm) 5.07(s, 1H,), 5.21(brs, 1H, D_2O exchangeable), 5.75(s, 1H), 5.87(s, 2H), 6.54(d,1H, J=1.4Hz), 6.58(dd(t), 1H, J=5.64, 6.52Hz), 6.65(dd, 1H, J=8.0, 1.4Hz), 6.67(d, 1H, J=8.0Hz), 7.22(d, 1H, J=8.6Hz), 7.53(dd,1H, J=8.0, 8.0Hz), 7.66(d, 3H, J=8.4Hz), 7.94(d, 2H, J=8.4Hz). ^{13}C-NMR 153.5, 148.3, 148.1, 147.2, 138.0, 135.6, 132.4, 131.4, 126.5, 119.1, 118.8, 115.8, 111.8, 109.5, 108.7, 105.8, 101.1, 81.6, 71.3; FAB-Ms (*m/z*), 385(MH^+), 367(MH^+-H_2O).
8. Selected spectroscopic data for compound **1**:
   ^{1}H-NMR(DMSO-D_6, δ ppm), 5.03(dd, 1H, J=7.28, 2.24Hz), 5.37(d, 1H, J=2.24Hz, D_2O exchangeable), 6.43(d, 1H, J=7.28Hz), 6.61(dd, 1H, J=7.84, 1.6Hz), 6.67 (dd, 1H, J=5.04, 5.04Hz), 6.82(d, 1H, J=1.6Hz), 7.41(brs, 1H, D_2O exchangeable), 7.53(d, 1H, J=8.00Hz), 7.67(dd, 1H, J=8.00, 5.04Hz), 7.92(AB system, 4H, J=9.00Hz), 8.04(brs 1H, D_2O exchangeable), 8.05(d, 1H, J=5.04Hz); ^{13}C-NMR 167.2, 154.3, 149.7, 147.6, 147.4, 146.2, 137.6, 133.9, 133.7,133.3,127.7, 125.8, 118.4, 115.2, 108.5, 108.4, 108.3, 105.8, 100.9, 80.7, 70.6, 64.8; FAB-Ms(*m/z*), 403(MH^+), 385(MH^+-H_2O).

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