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# An Efficient Asymmetric Synthesis of A Potent COX-2 Inhibitor L-784,512

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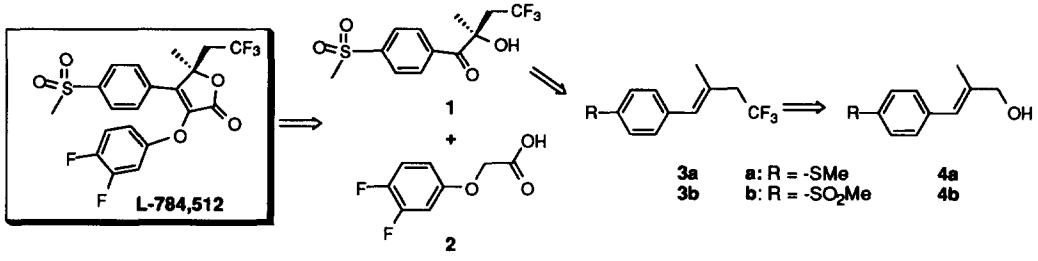
**Abstract:** *An efficient enantioselective synthesis of L-784,512 featuring a Horner-Emmons reaction, a new one-pot trifluoromethylation, and the Sharpless asymmetric dihydroxylation is described.*


Cyclooxygenase (COX) catalyzes the first step in arachidonic acid metabolism.[1] Two isoforms of the membrane protein COX are known:[2] COX-1 is responsible for the physiological production of prostaglandins; COX-2 is responsible for the elevated production of prostaglandins during inflammation. Most traditional non-steroidal anti-inflammatory drugs (NSAID's) inhibit both COX-1 and COX-2 with little specificity, leading to serious side effects such as gastric lesions and renal toxicity.[3] The identification of a COX-2-selective inhibitor, therefore, should offer potent anti-inflammatory activity *in vivo* with minimal side effects.[4] L-784,512 displays high selectivity and potency against COX-2.[5] In this paper we wish to describe a highly efficient asymmetric synthesis of L-784,512, which employs the Sharpless asymmetric dihydroxylation of a trisubstituted olefin as a key step. A novel and general trifluoromethylation procedure was developed, allowing for direct conversion of allylic alcohols into the trifluoroethyl substituted alkenes.

The retro-synthetic analysis of L-784,512 is shown in Scheme 1. We anticipated the introduction of the chiral quaternary carbon center via the Sharpless asymmetric dihydroxylation of a trisubstituted olefin, such as **3a** or **3b**. This approach takes advantage of the quaternary alcohol in the selective oxidation of the benzyl alcohol to prepare the α-hydroxyketone **1**. The olefins, in turn, could be prepared from the allylic alcohols **4a** and **4b** using a trifluoromethylation reaction.

**Scheme 1**

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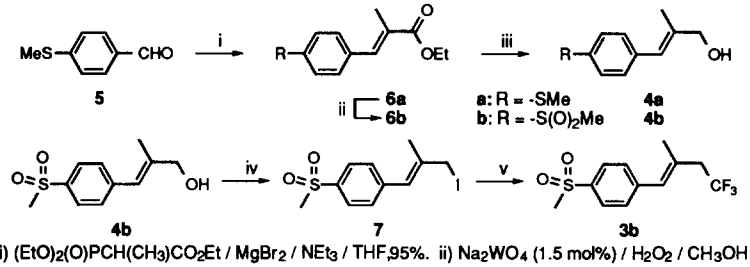
Alcohols **4a**[6] and **4b**[6] were prepared from 4-(methylthio)benzaldehyde in 92% and 84% overall yield, respectively, using a Horner-Emmons olefination, which established the stereochemistry of the olefins (Scheme 2), followed by reduction of the ester. The initial effort to convert allylic alcohol **4b** into compound **3b** followed the protocol developed by Duan and co-workers.[7] The procedure requires the intermediacy of iodide **7**. Thus, alcohol **4b** was converted to **7**[6] in 85% yield after flash chromatography. Unfortunately, the coupling reaction of **7** with trifluoromethylcuprate at 110-120 °C only afforded **3b**[6] in 43% yield.

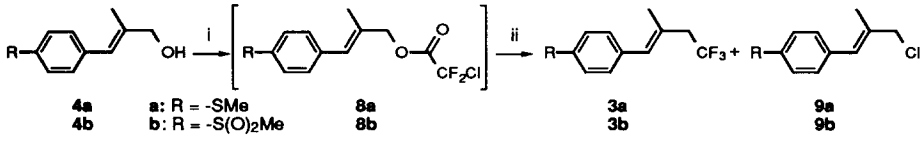
**Scheme 2**




i) $(EtO)_2(O)PCH(CH_3)CO_2Et$ / $MgBr_2$ / $NEt_3$ / THF,95%. ii) $Na_2WO_4$ (1.5 mol%) / $H_2O_2$ / $CH_3OH$ / 45 °C, 90%. iii) DIBAL-H (2.5 equiv) / $CH_2Cl_2$, -78 °C, 97% for **6a-4a** and 98% for **6b-4b**. iv) $I_2$ / $PPh_3$ / ImH / acetonitrile, 85%. v) $ClCF_2CO_2Me$ / KF / CuI / DMF / 90 °C, 43%.

Subsequently ester **8b** was identified to be an intermediate in the reaction by HPLC/NMR analysis. Perhaps, trifluoromethylation of **8b** would lead to **3b** and obviate the iodide. Treatment of **4b** with chlorodifluoroacetic anhydride in DMF generated **8b** quantitatively, and the trifluoromethylated product **3b** was isolated when the DMF solution of **8b** was directly treated with 1.1 equiv of KF and 1 equiv of CuI at 90 °C for 1 h. The major by-product of this reaction was the chloride **9b**[6]. One equiv of CuI was required to minimize the formation of **9b** (Table 1, entry 4-7). The reaction is also highly dependent on base; the hindered base diisopropylethylamine gave the best result (entry 8). With the optimized conditions[8] **3b** was isolated in 74% yield. Similarly, **4a** was converted to **3a**[6] in 61% yield. This process provides a convenient one-pot preparation of trifluoromethylated compounds from alcohols.

**Scheme 3**




i) $(CF_2ClCO)_2O$ / DMF / base. ii) KF, CuI, 90 °C

**Table 1 Trifluoromethylation of Alcohol 4b**

| entry | Base (equiv) | CuI (mol%) | **3b** HPLC yield (%) | **9b** HPLC yield (%) |
|---|---|---|---|---|
| 1 | no base | 100 | 15 | 0 |
| 2 | pyridine (2.0) | 100 | 18 | 51 |
| 3 | $K_2CO_3$ (2.0) | 100 | 49 | 6 |
| 4 | TEA (2.0) | 100 | 56 | 0 |
| 5 | TEA (2.0) | 50 | 54 | 5.5 |
| 6 | TEA (2.0) | 20 | 31 | 12 |
| 7 | TEA (2.0) | 0 | 0 | 81 |
| 8 | DIEA (2.3) | 100 | 83 | 0 |

The Sharpless asymmetric dihydroxylation of **3b** using commercially available AD-mix-β only afforded diol **10b**[6,9] in 63% ee. Since the chiral ligand plays a crucial role in the asymmetric dihydroxylation[9], other ligands were also explored (Table 2). With $(DHQD)_2PHAL$ as the ligand increased enantioselectivity was observed (Scheme 4). The reaction went to completion in 5-6 h at 18-20 °C to give **10b** in 90% yield and 79% ee. At 0 °C no selectivity enhancement was observed and the reaction took more than 24 hours. Unlike most AD reactions reported in the literature, the reaction rate was not accelerated by the addition of methanesulfonamide. Under the same reaction conditions the asymmetric dihydroxylation of the sulfide **3a** gave a mixture of **10a**, **10b**, and **10c** in a ratio of 74:10:6 after 22 h. The mixture, after a simple extraction and solvent switch, was converted to **10b** in 88% yield by treatment with $H_2O_2$ in methanol in the presence of a catalytic amount of $Na_2WO_4$. The dihydroxylation of the sulfide intermediate increased the enantioselectivity to 82% ee. Diol **10b** was upgraded to >98% ee by a single recrystallization from a mixture of isopropyl acetate and hexane.[10]

**Scheme 4**

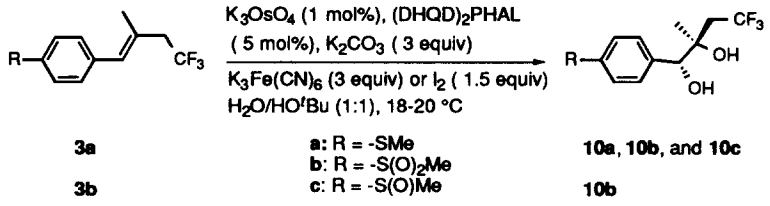
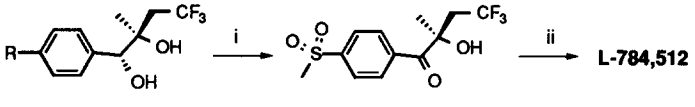



**Table 2 Asymmetric Dihydroxylation of Olefin 3**

| Entry | Ligand | Product **10b** (% ee) |
|---|---|---|
| 1 | $(DHQD)_2PHAL$ | 79 |
| 2 | $(DHQD)_2$-DP-PHAL | 70 |
| 3 | $(DHQD)_2PYR$ | 69 |
| 4 | (DHQD)-PHN | 67 |
| 5 | $(DHQD)_2AQN$ | 64 |
| 6 | $(DHQD)_2DPP$ | 61 |
| 7 | (DHQD)-CLB | 41 |

Swern oxidation of **10b** provided the α-hydroxy ketone **1** in 94% isolated yield. The product was crystallized from toluene to afford analytically pure **1**[6]. Conversion of **1** and 3,4-difluorophenoxylacetic acid **2**[11] to L-784,512 was accomplished in one pot *via* an esterification using CMC and a catalytic amount of DMAP. The subsequent Dieckman condensation was initiated with DBU (Scheme 5). In order to obtain complete conversion isopropyl trifluoroacetate (1.2 equiv) was used as a water scavenger. Recrystallization of the crude product in ethanol gave optically pure L-784,512 in 95% overall yield from **1**.

**Scheme 5**




i) DMSO (4.2 equiv) / ClCOCOCl (2.1 equiv) / $CH_2Cl_2$/ -78 °C, 30 min then $NEt_3$ (9 equiv) / -78 °C to rt.
ii) **2** / CMC / $CH_2Cl_2$ / DMAP (10 mol%), 4 h then DBU (1.2 equiv) / $CF_3CO_2CH(CH_3)_2$ (1.2 equiv)

In conclusion, we have developed a highly practical asymmetric synthesis of COX-2 inhibitor L-784,512 in 32-36% overall yield with no chromatography. In addition, the one-step transformation of allylic alcohols to the trifluoromethylated compound should be of general use.

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## References and Notes

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5 Belley, M. Y.; Leblanc, J.Y.; Gauthier, E.; Grimm, M.; Therien, C. B.; Prasit, P.; Lau, C. K.; Roy, P. World Patent Application, WO 9714691.

6 All new compounds were completely characterized by appropriate spectroscopic methods. All gave satisfactory elemental analyses.

7 Duan, J.-X., Su, D.-B., Chen, Q.-Y. *J. Fluorine Chem.* **1993**, *61*, 279.

8 (a) Procedure for the preparation of **3b** from **4b**: To a solution of **4b** (11.30 g) and diisopropylethylamine (21 mL) in DMF (50 mL) was added dropwise chlorodifluoroacetic anhydride (11 mL) with an external cooling bath. Potassium fluoride (3.5 g) and cuprous iodide (9.5 g) were added after 5 min. The mixture was heated at 90 °C for 1 h , poured into 100 g of ice, extracted with ethyl acetate (2 x 100 mL), and concentrated. The residue was transferred into a funnel containing ~ 250 g of silica gel and eluted with 15% ethyl acetate in hexane. Concentration of the eluent gave 10.3 g (74%) of **3b** as a white solid. (b) Trifluoromethylation of allylic alcohols with methyl chlorodifluoroacetate has been reported. See, Duan, J.-X., Chen, Q.-Y. *J. Chem. Soc. Perkin Trans 1*, **1994**, *6*, 725.

9 Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

10 Experimentally, crude **10b** (10.5 g, 82% ee) was dissolved in hot IPAc (90 mL) and then cooled to 23 °C. The crystal (12% ee, 14.3% recovery) was collected by filtration. The filtrate was diluted with hexane (final ratio of IPAc/hexane: 4/5) and the crystal was collected by filtration to give pure **10b** (>98% ee, 72.4% recovery).

11 Compound **2** was prepared in 72% yield by heating a mixture of 3,4-difluorophenol and bromoacetic acid in THF in the presence of 2 N NaOH.