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A convenient synthesis of 2-fluoro- and 6-fluoro-(2*S*,3*R*)-*threo*-(3,4-dihydroxyphenyl)serine using Sharpless asymmetric aminohydroxylation

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Abstract—Ring-fluorinated β-hydroxy α-amino methyl esters **3b**,**c** were synthesized enantioselectively using Sharpless asymmetric aminohydroxylation. These were converted to 2-fluoro- and 6-fluoro-(2*S*,3*R*)-*threo*-(3,4-dihydroxyphenyl)serine **1b**,**c** using our previously published procedure.

There is substantial evidence that administered (2*S*,3*R*)-*threo*-(3,4-dihydroxyphenyl)serine (L-*threo*-DOPS) **1a** crosses the blood–brain barrier and is subsequently decarboxylated to produce norepinephrine in the central nervous system (CNS).[1,2] Norepinephrine is an important neurotransmitter in the CNS and is the principal neurotransmitter of the sympathetic nervous system. We have found that 2-fluoro- and 6-fluoronorepinephrine are selective agonists for β- and α-adrenergic receptors, respectively.[3] These combined observations suggest that 2- and 6-fluoro-L-*threo*-DOPS **1b**,**c** may possess interesting biological properties and therapeutic potential. In recognition of this, we recently completed multi-step syntheses of these analogues based on initial aldol condensations using a chiral glycine synthon.[4] In addition, we continued our on-going attempts to apply the Sharpless asymmetric aminohydroxylation to this synthetic problem, since we recognized this as providing a more direct route with potential for scale-up. Despite initial and repeated disappointing results, we now report that, under carefully defined conditions, this procedure indeed offers a convenient and efficient route to these analogues (Scheme 1). Moreover, this demonstrates that normal regiochemical bias can be overcome to provide access to the important class of phenyl serines from readily available cinnamates in a highly enantioselective manner.

Asymmetric aminohydroxylation of cinnamates normally produces β-amino α-hydroxy esters as the major product. This reaction has been used effectively to prepare such compounds.[5] However, Sharpless recently reported that, in certain cases, reversal of this regioselectivity can be achieved by using the anthraquinone ligands $(DHQ)_2AQN$ and $(DHQD)_2AQN$.[6] This observation provided the basis for our work.

Initially, we used benzylcarbamate as the amine source. An advantage of this reagent would be that the tris-*O*,*N*,*N*-benzyl protecting groups of the product could be removed in one step. Unfortunately, the reaction of the 6-fluoro-cinnamate methyl ester **2c** with benzylcarbamate in the presence of $(DHQD)_2AQN$ ligand afforded the amino alcohols in only low yield (4%). However, the desired regioisomer **3c** was formed with good regioselectivity (5:1). The reaction of **2c** with *t*-butylcarbamate as the amine source in CH_3CN/H_2O (1:1) gave the desired regioisomer **3c** in increased yield (22%), in good regioselectivity (3.7:1) and good enantioselectivity (88% ee). Although the chemical yield was less than satisfactory, the fact that the product **3c** is identical to the intermediate prepared in our previous synthesis facilitated structural determination of regioisomers and enantiomers. Encouraged by these results, we next examined the behavior of 2-fluoro-cinnamate methyl ester **2b** in the same system. In this case, the desired regioisomer **3b** was formed with only moderate regioselectivity (2.7:1) but with good enantioselectivity (84%) and reasonable yield (33%).

From these results, we chose to retain the *t*-butylcabamate as the amine source and to examine effects of

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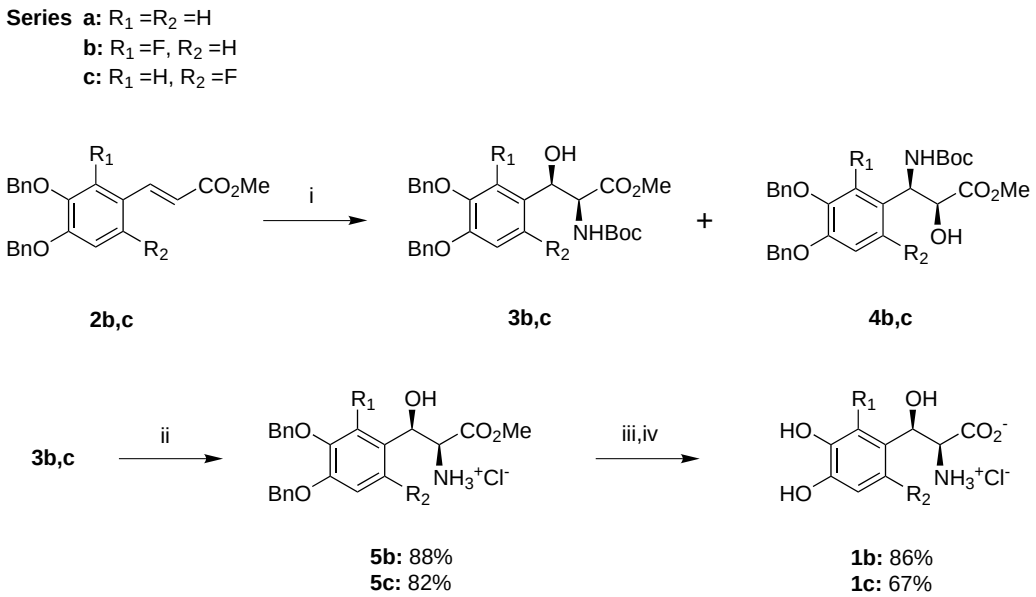

Scheme 1. *Reagents and conditions*: (i) $K_2OsO_2(OH)_4$, *t*-BuOCl, 1N NaOH, $BocNH_2$, $(DHQD)_2AQN$, organic solvent/H_2O (1:1), rt, 2 h; (ii) HCl, EtOAc, rt, 4 h; (iii) 2N NaOH, MeOH, rt, 1 day; (iv) 10% Pd-C, H_2, 3N HCl/MeOH (1:4), rt, 2 h for **1b**; 10% Pd-C, H_2, MeOH, rt, 2 h for **1c**.

changes in other reaction parameters. Because asymmetric aminohydroxylation reactions are known to be sensitive to solvent,[7] we studied the effect of solvent variation on the reaction of **2b** with *t*-butylcarbamate. From this, we determined that the reaction in PrOH/H_2O (1:1) gave greatly improved results. The desired regioisomer **3b** was obtained as the major isomer with good regioselectivity (4.5:1), good enantioselectivity (86%) and good yield (76%). At this point **3b** was separated readily from the regioisomer **3c** by silica gel column chromatography. Treatment of **3b** with gaseous HCl in ethyl acetate, as described in our previous work, gave amino acid methyl ester **5b**.[8] Recrystallization of **5b** from methanol, ethyl acetate, and ether led to selective crystallization of the racemate, and the (2*S*,3*R*)-**5b** recovered from the mother liquor had increased in enantiomeric purity from 66 to 93% ee.[9] We followed our previous procedure with the resulting enantiomerically purified amino acid methyl ester **5b** to obtain L-*threo*-2FDOPS **1b**,[4] identical, except for magnitude of optical rotation, with our previously prepared material:[4] ($[\alpha]_D^{25} = -18.0$ (*c* 0.14, MeOH) from asymmetric aminohydroxylation; $[\alpha]_D^{25} = -15.1$ (*c* 0.65, MeOH) from asymmetric aldol condensation).

With this success we concentrated on the optimization of the asymmetric aminohydroxylation reaction of 6-fluoro methyl cinnamate **2c**. Unfortunately, the conditions that were effective for the reaction with **2b** gave unsatisfactory results with **2c**. The lower solubility of **2c** relative to **2b** and extensive formation of the diol byproduct (11–29%), a complication frequently encountered with this reaction, were apparent contributing factors to the low yield of **2c**. To improve solubility, we added CH_2Cl_2 to the reaction mixture. As shown in Table 1 (entries 8–10), this resulted in increased yields but somewhat lower enantioselectivities. A 10:1 mixture of *n*-PrOH and CH_3CN gave a more modest yield compared to CH_2Cl_2 mixtures, but the enantioselectivity was significantly improved to 78% (entry 11). Doubling the amount of each reagent relative to that used in the previous entries gave an increased yield (36%) but a decreased enantioselectivity (68% ee). However, if this increased portion of reagents was introduced as a second addition after a 1 h interval, the desired regioisomer **3c** was formed with much improved enantioselectivity (82% ee) and increased yield (38%). Because of the inconvenience that two separate generations of *N*-chloro-*N*-sodio *t*-butylcarbamate entails, we elected to use the conditions described in entry 12 condition for scale-up because of the good yield (54%) based on recovery of starting material. Since the enantiomeric purity can be increased by subsequent recrystallization, we also felt the enantioselectivity (68% ee) was acceptable. After carrying out the aminohydroxylation according to the conditions in entry 12, **3c** was separated readily from its regioisomer **4c**. This was treated with gaseous HCl in ethyl acetate to give free amino acid methyl ester **5c** in 82% yield. Recrystallization of the resulting amino acid methyl ester **5c** increased the enantiomeric purity (95% ee).[9] Using our previous procedure, **5c** was converted to L-*threo*-6FDOPS **1c**, identical to our previously prepared sample,[4] except for magnitude of optical rotation. ($[\alpha]_D^{25} = -20.5$ (*c* 0.073, MeOH) from asymmetric aminohydroxylation; $[\alpha]_D^{25} = -22.6$ (*c* 0.073, MeOH) from asymmetric aldol condensation).

In conclusion, we have made both L-*threo*-2FDOPS **1b** and L-*threo*-6FDOPS **1c** using the Sharpless asymmetric aminohydroxylation.[6] Although the conversion in the case of **2c** is only modest, the short reaction sequence makes this the method of choice for the synthesis of both **1b** and **1c**.

Table 1. Optimization of Sharpless asymmetric aminohydroxylation

Entry	Substrate	Solvent[a]	Yield (%)	**3b**:**4b** or **3c**:**4c**[b]	ee of **3b**,**c** (%)[c]
1	**2b**	*n*-PrOH	76	4.5:1	86
2	**2b**	CH_3CN	33	2.7:1	84
3	**2b**	*t*-BuOH	22 (29)[d]	4.8:1	60
4	**2c**	*n*-PrOH	24 (56)[d]	3.9:1	68
5	**2c**	CH_3CN	22	3.7:1	87.6
6	**2c**	*n*-BuOH	35	4.3:1	44.4
7	**2c**	*t*-BuOH	6 (25)[d]	3.9:1	73
8	**2c**	*n*-PrOH:CH_2Cl_2 (10:1)	38	4.6:1	60
9	**2c**	*n*-PrOH:CH_2Cl_2 (1:1)	28	4.1:1	66
10	**2c**	*n*-PrOH:CH_2Cl_2 (1:10)	40 (42)[d]	6.1:1	65.6
11	**2c**	*n*-PrOH:CH_3CN (10:1)	24 (61)[d]	4.3:1	77.8
12	**2c**	*n*-PrOH:CH_3CN (10:1)[e]	36 (54)[d]	3.7:1	67.8
13	**2c**	*n*-PrOH:CH_3CN (10:1)[f]	38 (66)[d]	4.1:1	82.4
14	**2c**	*n*-PrOH:CH_3CN (1:1)	11 (26)[d]	4.0:1	57.4
15	**2c**	*n*-PrOH:CH_3CN (1:10)	9 (29)[d]	4.4:1	84

[a] The actual experimental solvent system is this solvent/H_2O (1:1).
[b] This regioselectivity was determined by 300 MHz ^1H NMR analysis.
[c] This enantioselectivity was determined by HPLC [Chiralcel OD; *n*-hexane/*i*-PrOH (70:30); flow rate 0.15 mL/min; retention time (2*S*,3*R*)-enantiomer of **3b** = 43.02, (2*R*,3*S*)-enantiomer of **3b** = 38.88, (2*S*,3*R*)-enantiomer of **3c** = 50.40, (2*R*,3*S*)-enantiomer of **3c** = 42.68].
[d] Yield based on recovered starting material.
[e] Amounts of regent used in entry 11 were doubled.
[f] Reagent quantities used in entry 12 were added in two portions at a 1 h interval.

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9. This enantiomeric purity was determined by HPLC [Chiralpak AD; 1:1 *n*-hexane/EtOH+0.2% diethylamine; flow rate 1 mL/min; retention time (2*S*,3*R*)-enantiomer of **5b** = 16.14 min, (2*R*,3*S*)-enantiomer of **5b** = 10.38 min, (2*S*,3*R*)-enantiomer of **5c** = 16.22 min, (2*R*,3*S*)-enantiomer of **5c** = 11.86 min].