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Synthesis of 2- and 6-fluoro analogues of *threo*-3-(3,4-dihydroxyphenyl)serine (2- and 6-fluoro-*threo*-DOPS)

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Abstract

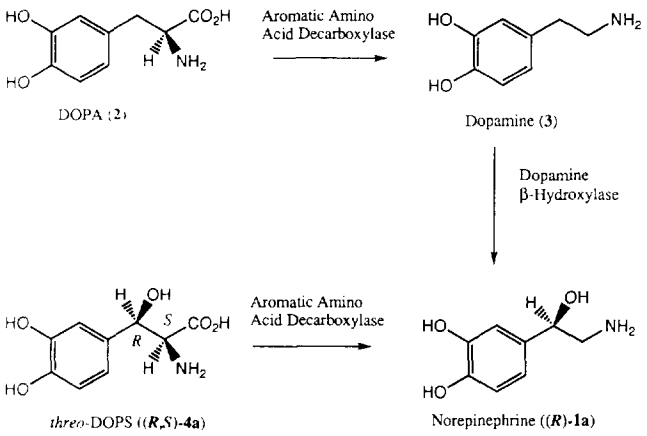
2-Fluoro- and 6-fluoro-*threo*-dihydroxyphenylserine (2-*F*- and 6-*F*-*threo*-DOPS) have the potential, after crossing the blood–brain barrier, of functioning in the central nervous system as biological precursors of 2- and 6-fluoronorepinephrine (2- and 6-*F*-NE). Since 2-*F*-NE is a selective β-adrenergic agonist and 6-*F*-NE is a selective α-adrenergic agonist, subsequent selective actions at β- and α-adrenergic receptors could be beneficial for both clinical and pharmacological studies. We have prepared 2- and 6-*F*-*threo*-DOPS by the $ZnCl_2$-catalyzed reaction of a protected glycine trimethylsilylketene acetal with benzyl-protected 2- and 6-fluoroprocatechuealdehyde. Other enantio- and diastereoselective approaches to these analogues either gave no product or produced predominantly the *erythro* diastereomer, apparently formed during work-up by acid-promoted racemization of the benzylic OH group in compounds possessing an unprotected catechol.

Keywords: Synthesis; Fluoro-*threo*-DOPS; NMR spectroscopy; Mass spectrometry

1. Introduction

Norepinephrine (NE) (**1a**) is an important neurotransmitter in both the central and peripheral nervous systems and serves as the principal neurotransmitter of the sympathetic nervous system. The biosynthesis of NE involves ring-hydroxylation of tyrosine to produce L-(3,4-dihydroxyphenyl)alanine (L-DOPA) (**2**), decarboxylation of L-DOPA to give dopamine (DA) (**3**) and dopamine β-hydroxylase-catalyzed hydroxylation of DA to give NE (Scheme 1). One strategy for modulation of adrenergic and dopaminergic function in vivo has been to intervene in the biosynthesis of DA and/or NE, for example, through enzyme inhibition or through providing increased levels of enzyme substrate. For example, administration of DOPA to provide increased levels of DA has been used extensively for the alleviation of Parkinsonian symptoms caused by low levels of DA in the brain [1].

Recently, attention has been given to the pharmacological properties and therapeutic potential of L-*threo*-(3,4-dihydroxyphenyl)serine (L-*threo*-DOPS) (**4a**), enzymatic decarboxylation of which produces NE directly, bypassing



Scheme 1.

DA as an intermediate. There is evidence that administered L-*threo*-DOPS crosses the blood–brain carrier and is subsequently decarboxylated to produce NE in the central nervous system, particularly in situations wherein catecholamine deficiencies are indicated. Several clinical trials suggest that L-*threo*-DOPS may be beneficial in treating disorders of both the central and sympathetic nervous systems that are characterized by NE deficiencies. For example, Tohgi and coworkers found a dose-dependent increase in cerebrospinal

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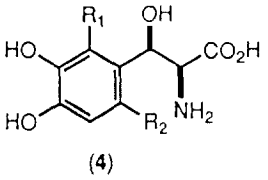
fluid NE concentrations in six advanced Parkinsonian patients. In three or six patients, the 'freezing phenomenon' in gait and speech improved [2]. Such symptoms, in advanced cases, become unresponsive to L-DOPA treatment.



(4)

Series **a**: $R_1 = R_2 = H$
b: $R_1 = F$, $R_2 = H$
c: $R_1 = H$, $R_2 = F$

The hypothesis has been made that these symptoms may be caused by NE deficiency [1] [3]. Other case studies wherein the therapeutic potential of *threo*-DOPS has been indicated include the improvement of certain memory functions in patients with Korsakoff's disease (amnesia induced by chronic alcoholism) [5], and the treatment of orthostatic hypertension in Shy–Drager syndrome [6] and in familial amyloid neuropathy [7]. These and other pharmacological properties of L-*threo*-DOPS assure interest in the biological properties of this NE precursor.

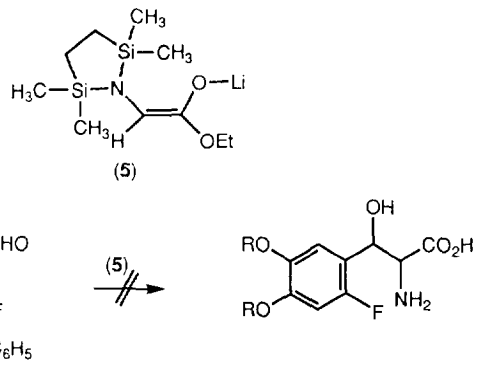
Our previous research has demonstrated that 2-*F*-NE is a selective β-adrenergic agonist and 6-*F*-NE is a selective α-adrenergic agonist [8]. If 2- and 6-*F*-*threo*-DOPS serve as precursors for biosynthesis of the corresponding fluorinated norepinephrines (*F*-NE), this would provide a pro-drug strategy to deliver the selective α- and β-adrenergic agonists, 2-*F*-NE and 6-*F*-NE, to the central nervous system. In vivo studies with these analogues of DOPS should provide insights into the pharmacological effects of activating only α-adrenergic pathways or β-adrenergic pathways, systems that DOPS-derived NE would activate concomitantly. It is possible that 2- or 6-*F*-*threo*-DOPS could be more potent and/or more selective than *threo*-DOPS in clinical applications. In addition to their pharmacological and therapeutic potential, fluorinated analogues of *threo*-DOPS labelled with positron-emitting ^{18}F ($t_{1/2} = 109.7$ min) may have potential as PET-scanning agents for central adrenergic activity [9].

In this report, we describe the syntheses of 2- and 6-*F*-*threo*-DOPS (**4b,c**). In addition, we describe the extreme acid lability of the benzylic hydroxy group of compounds in this series having an unprotected catechol system. This lability has led to a serendipitous synthesis of *erythro* isomers.

2. Chemistry

Aldol condensation of a glycine equivalent with a suitably protected fluoroprocatechualdehyde provides a strategy to construct the phenylethanolamino acid moiety having the proper functionality. The stereochemistry of this condensation becomes important for the efficient synthesis of the

[1] For a review of L-*threo*-DOPS in advanced Parkinsonism, see Ref. [4].



(5)

6c: R = $CH_2C_6H_5$
7c: R = CH_3

Scheme 2.

desired *threo*-(2*SR*, 3*RS*) diastereomeric mixture or *threo*-(2*S*, 3*R*) enantiomer. We have carried out both diastereoselective and enantioselective aldol condensations to produce protected fluorinated *threo*-DOPS analogues. However, the sensitivity of the benzylic carbon centre towards racemization has complicated the removal of protecting groups and, to date, has limited the application of certain promising routes. This chemistry will be discussed, and the successful synthesis of racemic 2- and 4-*F*-*threo*-DOPS will be described.

2.1. Attempted syntheses of 2- and 6-F-threo-DOPS using base-promoted aldol condensations

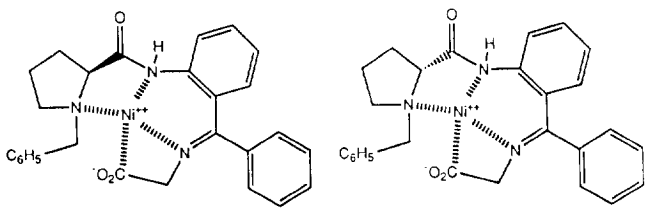
Our initial attempt to carry out this strategy was based on the efficient condensation of the lithium salt of the stabase-protected glycine ethyl ester (**5**) with a series of aldehydes to produce good yields of protected serine derivatives, as reported by Magnus and coworkers [10]. However, all attempts to condense this glycine equivalent with 4,5-dibenzyloxy- or 4,5-dimethoxy-2-fluorobenzaldehyde (**6c, 7c**) produced no isolable condensation product (Scheme 2). We attribute this lack of reactivity to the back-donation of fluorine π-electrons into the aromatic π-system which apparently reduces the electrophilicity of the carbonyl carbon.

We next considered the enantioselective approach to serine derivatives described in a series of papers by Belokon' and coworkers, based on chiral glycine equivalents. A series of *threo*-*R*-serine analogues were prepared by sodium methoxide-mediated condensation of a Ni^{2+} complex *S*-**8** of the Schiff base derived from (*S*)-2-[*N*-(benzylprolyl)-amino]acetophenone or (*S*)-2-[benzylprolyl)-amino]-benzophenone with aldehydes, including, for example, 3,4-(methylenedioxy)benzaldehyde [11]. We were encouraged by the clean reaction of **7c** with the Ni^{2+} complex *R*-**8** derived from (*R*)-2-[*N*-(benzylprolyl)-amino]benzophenone to give, after hydrolytic decomposition of the Ni^{2+} complex, 3-(4,5-dimethoxy-2-fluorophenyl)serine (**9**) as one predominant diastereomer, tentatively assigned the desired 2*S*, 3*R*-*threo* configuration (Scheme 3). We recognized that demethylation would be problematic, particularly with respect to the expected acid lability of the benzylic hydroxy group. Unfortunately, the catechol methyl ethers remained

Scheme 3.

intact during all attempts at BBr_3 cleavage under a variety of conditions. We have no explanation for this unexpected inertness. We were thwarted in our attempts to circumvent this problem by the use of benzyl protecting groups in that we were unable to effect the condensation of 4,5-dibenzyloxy-2-fluorobenzaldehyde (**6c**) with the Ni^{2+} complex (Scheme 3). The use of a more acid-labile catechol protecting group, and the unexpected results obtained, will be discussed below.

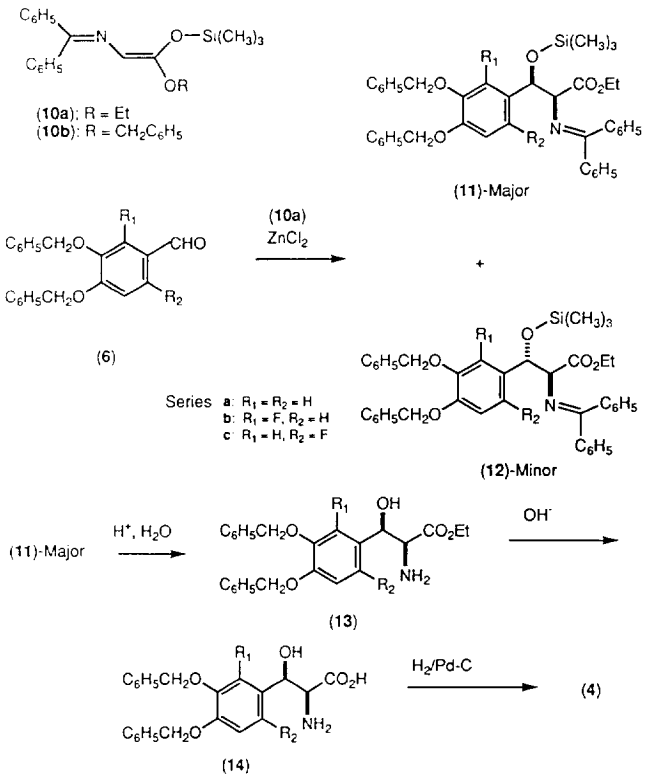
2.2. Synthesis of 2- and 6-F-threo-DOPS



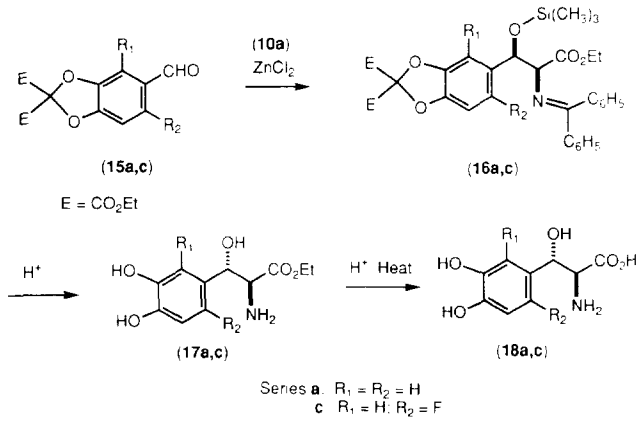
The lack of reactivity of aldehyde **6c** in base-promoted aldol reactions with the lithium enolate **5** or the Ni^{2+} complex **8**, and the lack of reactivity of aldehyde **7c** with **5**, are consistent with previous observations regarding the apparent low electrophilicity of the carbonyl carbon in these catechol-protected fluoroprocatechuealdehydes. For example, we were unable to effect direct cyanohydrin formation by reaction of **7c** with HCN, and relied on the ZnI_2-catalyzed condensation of trimethylsilyl cyanide with this and other fluoroaldehydes in our previous syntheses of the fluorinated phenethanolamines, such as the *F*-NEs [12]. With this in mind, we next considered a similar Lewis acid approach for the preparation of the *threo*-DOPS. We were particularly encouraged by the recent report of Kellogg and coworkers on the $ZnCl_2$-catalyzed stereoselective syntheses of 3-substituted serine derivatives [13]. Indeed, condensation of aldehyde **6c** in the presence of 5 mol% of $ZnCl_2$ with the trimethylsilyl ketene acetal **10a** derived from the benzophenone imine of glycine ethyl ester gave a 6:1 mixture of *threo* and *erythro* condensation products (**11c** and **12c**, respectively) (Scheme 4). A similar 7:1 mixture of *threo* and *erythro* products (**11b, 12b**) was obtained from 3,4-dibenzyloxy-2-fluorobenzaldehyde (**6b**). After separation of the major diastereomer in each series, the imine and silyl ether functionalities were removed with dilute acid to give the esters **13b,c**. Saponification of the ester to give the acid **14b,c** followed by hydrogenolysis produced 2- and 6-*F-threo*-DOPS (**4b,c**). As verification of the final stereochemical assignments, a similar sequence starting with 3,4-dihydroxybenzaldehyde (**6a**) produced *threo*-DOPS **4a**, whose NMR spectrum was identical in all respects to that of authentic *threo*-DOPS.

2.3. As serendipitous synthesis of erythro-DOPS and 6-fluoro-erythro-DOPS

Catechol protection and deprotection are critical steps in catecholamine and amino acid syntheses. A dicarboethoxymethylenedioxyphenyl moiety has recently been described as a synthetic intermediate in the synthesis of a β_3-selective adrenergic agonist [14]. We felt the dicarboethoxymethylene (DCEM) functionality might be stable to the conditions of the Lewis acid-catalyzed aldol reaction, but should be readily removed under mild protonic acid conditions. As a first step to explore this possibility, we prepared DCEM-protected-6-fluoroprocatechualdehyde (**15c**). Condensation of **15c** with the ketene acetal **10a** in the presence of $ZnCl_2$ cleanly produced the DCEM aldol product **16c** as a major diastereomer, accompanied by a minor diastereoisomer (Scheme 5). Mild acid treatment indeed hydrolyzed the silyl ether, the imine and the DCEM group to give 6-*F*-DOPS ethyl ester (**17c**). Mindful of the ready oxidation of catechols under basic conditions, we used more strenuous acid conditions to hydrolyze the ethyl ester. This produced predominantly one diastereomer of *F*-DOPS. However, comparison of the NMR spectrum with that of 6-*F-threo*-DOPS (**4c**), including the use of



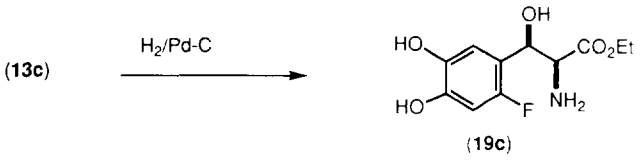
Scheme 4.



Scheme 5.

Table 1
Comparison of ^{1}H NMR (CD_3OD) chemical shifts (δ, ppm) and coupling constants (J, Hz) of methine protons and of aromatic protons of 6-*F*-DOPS (**18c**) prepared from DCEM-protected 6-fluoroprocatechualdehyde (**15c**) (Scheme 5) with those of 6-*F*-DOPS (**4c**) prepared from benzyl-protected procatechualdehyde (**6c**) (Scheme 4)

	NC*H*	OC*H*	Ar-H_5	Ar-H_2
18c	4.10–4.11	5.50–5.51	6.87–6.90	7.21–7.22
	J = 3.6	J = 3.8	J^o_{HF} = 9.4	J^m_{HF} = 5.9
4c	4.03–4.05	5.42–5.44	6.55–6.59	7.00–7.02
	J = 3.6	J = 3.5	J^o_{HF} = 11.5	J^m_{HF} = 7.3



Scheme 6.

Table 2
Comparison of ^{1}H NMR (CD_3OD) chemical shifts (δ, ppm) and coupling constants (J, Hz) of methine protons and of aromatic protons of 6-*F*-DOPS ethyl ester (**19c**) prepared by hydrogenolysis of 3-(4,5-dihydroxy-2-fluorophenyl)serine ethyl ester (**13c**) (Scheme 6) and 6-*F*-DOPS ethyl ester (**17c**) prepared by mild acid-catalyzed hydrolysis of aldol product **16c** (Scheme 5)

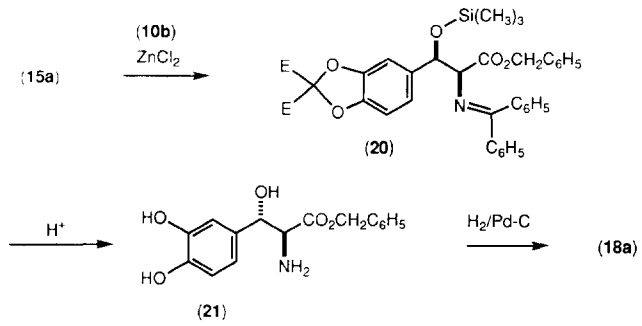
	NC*H*	OC*H*	Ar-H_5	Ar-H_2
19c	4.08–4.10	5.30–5.31	6.56–6.60	6.99–7.01
	J = 5.4	J = 5.1	J^o_{HF} = 11.3	J^m_{HF} = 7.2
17c	4.14–4.16	5.40–5.41	6.87–6.90	7.18–7.20
	J = 4.8	J = 4.8	J = 9.7	J = 5.8

'mixed' NMR spiking experiments, revealed that we had produced the *erythro* diastereomer **18c** as the major product (Table 1). We thus assumed that the more strenuous acid conditions used to hydrolyze the ethyl ester had resulted in epimerization of the benzylic OH group.

For a direct comparison of configurations before the hydrolysis of **17c**, dibenzyl-6-*F*-*threo*-DOPS ethyl ester (**13c**), prepared as discussed above, was converted to 6-*F*-*threo*-DOPS ethyl ester (**19c**) by debenzylation (Scheme 6). By comparison of the NMR spectra (Table 2), this product was shown to be, in fact, the diastereomer of the 6-*F*-DOPS ethyl ester (**17c**), that now can be assigned the *erythro* configuration, derived from DCEM-protected 6-fluoroprocatechualdehyde.

To put these stereochemical assignments on a more secure footing, a similar reaction of DCEM-protected procatechualdehyde (**15a**) with ketene acetal **10a** was carried out and found to give predominantly one aldol product diastereomer (> 10:1) (**16a**) (Scheme 7). Hydrolysis, as above, in hot 3 N HCl gave one major diastereoisomer of DOPS, **18a**, shown by NMR to be an isomer of authentic *threo*-DOPS and thus assigned to *erythro* configuration (Table 3). In order to obviate the final, more strenuous acid-catalyzed ethyl ester hydrolysis, we condensed aldehyde **15a** with the trimethylsilyl ketene acetal **10b** prepared from the benzophenone imine of glycine benzyl ester. Mild hydrolysis of the initial condensation product (**20**) removed the silyl and DCEM groups to give the benzyl ester **21**. Hydrogenolysis again gave predominantly *erythro*-DOPS (**18a**) (Table 4).

Examination of the NMR spectra of the initial condensation products (**11b,c, 16a,c** and **20**) reveals that, in every



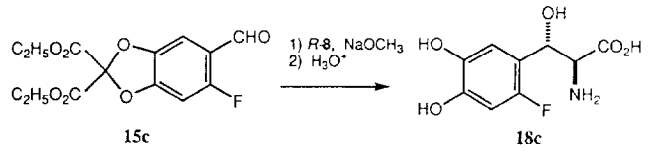
Scheme 7.

Table 3
Comparison of ^{1}H NMR (CD_3OD) chemical shifts (δ, ppm) and coupling constants (J, Hz) of methine protons of DOPS (**18a**) prepared by acid hydrolysis of DCEM-protected aldol product **16a** (Scheme 5) with those of authentic *threo*-DOPS (**4a**)

	NC*H*	OC*H*
18a (from **16a**)	4.14–4.15, J = 3.7	5.27–5.29, J = 3.7
4a (*threo*-DOPS)	4.04–4.05, J = 3.8	5.16–5.17, J = 3.9

Table 4
Comparison of ^{1}H NMR (D_2O, DCl) chemical shifts (δ, ppm) and coupling constants (J, Hz) of methine protons of DOPS (**18a**) prepared by hydrogenolysis of benzyl ester **21** (Scheme 7) with those of authentic *threo*-DOPS (**4a**)

	NC*H*	OC*H*
18a (from **21**)	4.16–4.19, J = 3.8	5.28–5.30, J = 3.7
4a (*threo*-DOPS)	4.06–4.08, J = 4.0	5.15–5.17, J = 4.0



Scheme 8.

case, predominantly the *threo* product was formed [2]. Thus, it is apparent that during acid-catalyzed hydrolysis of the DCEM group, the silyl ether and benzophenone imine of intermediates (**16a,c** and **20**), acid-catalyzed racemization of the benzylic OH also occurs. The driving force for the predominant formation of the *erythro* diastereomers during this process presumably reflects the greater thermodynamic stability of this isomer. Rapid removal of the DCEM group to give the strongly electron-donating free catechol system must be a requirement for this racemization, since racemization occurs only to a limited extent during the acid-catalyzed conversion of the aldol product **11c** to the benzyl-protected ester **14**.

Included in our plans for DCEM catechol protection was the investigation of the compatibility of this group with the conditions used in the aldol condensation with the Belokon' Ni^{2+} complexes. We expected that, following condensation, the acid treatment used to hydrolyze the complex should also cleave the DCEM group. This would constitute an enantioselective two-step synthesis of *F*-DOPS whose efficiency would be particularly advantageous for preparing ^{18}F-labelled material. Condensation of the aldehyde **15c** with the glycine Schiff base Ni^{2+} complex **8** derived from (*R*)-2-[*N*-(benzylprolyl)-amino]benzophenone proceeded well (Scheme 8). However, all attempts to hydrolyze the Ni^{2+} complex of the aldol product produced the *erythro*-amino acid **18a**, based on comparison of the NMR spectra with the spectrum of **4c**. We attribute this, again, to the extreme sensitivity of the benzylic OH group towards racemization when the free catechol group is present. A similar propensity of *R*-6-fluoronorepinephrine to racemize has been reported [15].

3. Experimental details

3.1. General

D,L-*threo*-DOPS was purchased from the Aldrich Chemical Co., Milwaukee, WI. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. All moisture-sensitive reactions were carried out using anhydrous solvents in an inert atmosphere of dry nitrogen or argon. NMR spectra were obtained on a Varian Gemini 300 MHz spectrometer. CI mass spectra were performed on a Finnigan 1015 mass spectrometer by the staff of the Laboratory of Analytical Chemistry, NIDDK.

3.2. Reaction of 6-fluoroveratraldehyde with Ni^{2+} complex 8. Preparation of 3-(4,5-dimethoxy-2-fluorophenyl)serine (9)

Sodium (500 mg, 22 mmol) was added in portions to 15 ml of methanol. To the resulting solution of sodium methoxide was added 500 mg of Ni^{2+} complex **8** in 2 ml of THF. After 10 min, 184 mg (1.0 mmol) of 6-fluoroveratraldehyde (**7c**) [16] in 2 ml of THF was added to the resulting red–brown solution and the mixture was stirred for 3 h at room temperature. The reaction mixture was then quenched with 15 ml of 5.5 N HCl and stirred for 3 h at 60 °C. The THF and MeOH were evaporated, the white solid was removed by filtration and the aqueous solution was adjusted to pH 9 with 10% NH_4OH. After being washed with $CHCl_3$, the aqueous solution was added to a column of Dowex HCR5 (H^+ form). The column was washed with water and then eluted with 10% NH_4OH. Evaporation of the eluant gave 386 mg of a white solid. This was triturated with warm (60 °C) isopropanol and filtered. The filtrate was evaporated to give 47 mg of a white solid. ^1H NMR (D_2O/DCl) δ: 3.86–3.87 (d, 6H, J = 8.7 Hz, CH_3O); 4.40–4.42 (d, 1H, J = 4.6 Hz, NC*H*); 6.92–6.95 (d, 1H, J = 11.8 Hz, Ar*H*); 7.13–7.16 (d, 1H, J = 7.0 Hz, Ar*H*) ppm. (The OC*H* peak was obscured by the solvent peak.)

3.3. Preparation of aldol products 11a–c and 12a–c

To a solution of 735 mg (2.75 mmol) of *N*-(diphenylmethylene)glycine ethyl ester in 30 ml of THF was added 2.5 ml (5 mmol, 2 M in heptane/THF/ethyl benzene) of LDA dropwise under N_2 at −78 °C (Dry Ice/acetone bath) and the mixture stirred for 1 h at the same temperature. To this was added 1.6 ml (13 mmol) of trimethylchlorosilane, the bath removed and 17 mg (0.13 mmol) of $ZnCl_2$ added. After 5 min, 840 mg (1 mmol) of 3,4-dibenzyloxy-2- [17] or -6-fluorobenzaldehyde [12] (**6b** or **6c**) was added and the resulting pale brown solution was stirred at room temperature under N_2 overnight. After addition of 20 ml of hexane, the solution was washed with water and dried over Na_2SO_4. After filtration and evaporation, a pale yellow oil was obtained as a crude product which was purified with preparative TLC plate (silica gel) using petroleum ether/ethyl acetate (9:1) as the solvent system.

3.3.1. 6-F derivative

D,L-*threo*-(**11c**): From the TLC separation of 1.5 g of crude product from **6c**, 1.29 g (2.5 mmol, 76%) was obtained as an oil. MS (CI NH_3) m/z: 676 ($M^+ + 1$). ^1H NMR ($CDCl_3$) δ: 0.01 [s, 9H, $Si(CH_3)_3$]; 1.17–1.22 (m, 3H, CH_3); 4.05–4.18 (2H, m, CH_2); 4.18–4.21 (d, 1H, J = 4.9 Hz, C*H*N); 4.95–5.21 (m, 4H, 2 $CH_2C_6H_5$); 5.55–5.59 (d, 1H, J = 4.9 Hz, OC*H*); 6.50–7.81 (m, 12H, Ar*H*) ppm.

[2] In this intermediate, the methine protons of the *threo* isomer have significantly smaller (by ca. 2–4 Hz) coupling constants than those of the *erythro* isomer, unlike the situation with later intermediates and final products wherein coupling constants are quite similar (see also Ref. [13]).

D,L-*erythro*-(**12c**): 59 mg (3.5%) was obtained as an oil. MS (CI NH_3) *m/z*: 676 ($M^+ + 1$). ^1H NMR ($CDCl_3$) δ: 0.01 [s, 9H, $Si(CH_3)_3$]; 1.25–1.45 (m, 3H, CH_3); 4.20–4.31 (m, 2H, CH_2); 4.38–4.40 (d, 1H, $J = 8.69$ Hz, CHN); 4.88, 5.14 (2s, 4H, 2 $CH_2C_6H_5$); 5.68–5.69 (1H, d, $J = 8.7$ Hz, OCH); 6.50–7.61 (m, 22H, ArH) ppm.

3.3.2. 2-F derivative

D,L-*threo*-(**11b**): From the mixture, 708 mg (1.05 mmol, 42%) of **11b** was obtained as an oil. MS (CI NH_3) *m/z*: 676 ($M^+ + 1$). ^1H NMR ($CDCl_3$) δ: 0.01 [s, 9H, $Si(CH_3)_3$]; 1.17–1.22 (t, 3H, $J = 6.9$–7.3 Hz, CH_2CH_3); 4.02–4.18 (m, 2H, CH_2); 4.16–4.33 (d, 1H, $J = 5.8$ Hz, CHN); 5.01–5.02 (m, 4H, 2 $CH_2C_6H_5$); 5.53–5.55 (d, 1H, $J = 5.6$ Hz, OCH); 6.66–7.61 (22H, m, ArH) ppm.

D,L-*erythro*-(**12b**): 50 mg (3%) was obtained as an oil. MS (CI NH_3) *m/z*: 676 ($M^+ + 1$). ^1H NMR ($CDCl_3$) δ: 0.01 [s, 9H, $Si(CH_3)_3$]: 1.30–1.40 (t, 3H, $J = 7.1$–7.2 Hz, CH_3); 4.22–4.29 (m, 2H, CH_2); 4.30–4.33 (d, 1H, $J = 8.8$ Hz, CHN); 4.92–5.18 (m, 4H, 2 $CH_2C_6H_5$); 5.68–5.71 (d, 1H, $J = 8.8$ Hz, OCH); 6.55–7.65 (m, 22H, ArH) ppm.

3.3.3. Non-fluorinated derivative

D,L-*threo*-(**11a**): Using the above procedure, from 795 mg of aldehyde **6a** there was obtained after purification by TLC (10% ethyl acetate in petroleum ether) 1.04 g (63%) of **11a** as a yellow oil. MS (CI NH_3) *m/z*: 658 ($M^+ + 1$). ^1H NMR ($CDCl_3$) δ: 0.00 [s, 9H, $Si(CH_3)_3$]; 1.11–1.34 (m, 3H, CH_2CH_3); 4.05–4.20 (m, 2H, CH_2); 4.23–4.25 (d, 1H, $J = 5.9$ Hz, CHN); 5.06, 5.17 (2s, 4H, 2 $CH_2C_6H_5$); 5.23–5.25 (d, 1H, $J = 5.8$ Hz, OCH); 6.75–7.71 (m, 23H, ArH) ppm.

D,L-*erythro*-(**12a**): From the mixture there was obtained 27 mg (2%) of **12a.** ^1H NMR ($CDCl_3$) δ: 0.00 [s, 9H, $(CH_3)_3Si$]; 1.36–1.40 (t, 3H, CH_3CH_3); 4.23–4.26 (d, 1H, $J = 8.8$ Hz, CHN); 4.30–4.70 (q, 2H, CH_2CH_3); 5.17 (s, 4H, 2 $CH_2C_6H_5$); 5.28–5.31 (d, 1H, $J = 8.9$ Hz, OCH); 6.8–7.88 (m, 23H, ArH) ppm.

3.4. O,O-Dibenzyl-6-F-threo-DOPS ethyl ester (13c)

A solution of aldol product **11c** (1.0 g, 1.48 mmol) in 5 ml of ethanol was added to 30 ml of 3 N HCl and the resulting milky white mixture stirred at ambient temperature under nitrogen overnight. After evaporation of the ethanol, the aqueous solution was washed with ether and evaporated to afford 606 mg (1.4 mmol, 93%) of a white solid (**13c**). MS (CI NH_3) *m/z*: 440 ($M^+ + 1$). ^1H NMR (D_2O) δ: 0.91–1.00 (t, 3H, $J = 7.1$–7.3 Hz, CH_3); 4.02–4.10 (q, 2H, $J = 7.0$–7.3 Hz, CH_2); 4.22–4.26 (d, 1H, $J = 6.6$ Hz, CHN); 5.15–5.24 (m, 4H, 2 $CH_2C_6H_5$); 5.26–5.30 (d, 1H, $J = 6.5$ Hz, OCH); 6.92–6.98 (d, 1H, $J^o_{HF} = 11.8$ Hz, ArH); 7.12–7.18 (d, 1H, $J^m_{HF} = 6.8$ Hz, ArH); 7.35–7.46 (m, 10H, ArH) ppm. A sample was recrystallized for analysis from ethyl acetate/petroleum ether, m.p. 110–111 °C. Analysis: Calc. for $C_{25}H_{26}NFO_5 \cdot H_2O$: C, 67.63; H, 6.02; N, 3.15%. Found: C, 67.75; H, 6.06; N, 3.20%.

3.5. O,O-Dibenzyl-2-F-threo-DOPS ethyl ester (13b)

A solution of aldol product **11b** (693 mg, 1.03 mmol) in 4 ml of ethanol was added to 50 ml of 3 N HCl. The resulting milky white mixture was stirred at room temperature under N_2 overnight. After evaporation to remove the ethanol, the aqueous solution was washed with ether and extracted with ethyl acetate. The ethyl acetate solution was dried over Na_2SO_4 and evaporated to afford 400 mg (1.0 mmol, 95%) of a white solid (**13b**·HCl) which was recrystallized from methanol/ethyl acetate to give 353 mg of a white solid, m.p. 90–99 °C. MS (CI NH_3) *m/z*: 440 ($M^+ + 1$). ^1H NMR (CD_3OD) δ: 1.19–1.24 (t, 3H, $J = 7.3$ Hz, CH_3); 4.11–4.13 (d, 1H, $J = 5.3$ Hz, CHN); 4.20–4.27 (q, 2H, $J = 7.0$–7.3 Hz, CH_2); 5.08–5.18 (m, 4H, 2 $CH_2C_6H_5$); 5.33–5.35 (d, 1H, $J = 5.1$ Hz, OCH); 6.98–7.47 (m, 12H, ArH) ppm. Analysis: Calc. for $C_{25}H_{27}O_5NFCl \cdot H_2O$: C, 61.92; H, 5.82; N, 2.89%. Found: C, 61.65; H, 5.66; N, 2.89%.

3.6. O,O-Dibenzyl-threo-DOPS ethyl ester (13a)

A similar procedure produced **13a** in 63% yield, m.p. 119–124 °C. MS (CI NH_3) *m/z*: 422 ($M^+ + 1$). ^1H NMR ($CDCl_3$) δ: 0.67–0.72 (t, 3H, $J = 6.7$ Hz, CH_2CH_3); 3.76–3.78 (q, 2H, $J = 6.7$ Hz, CH_2CH_3); 4.50–4.51 (d, 1H, $J = 7.6$ Hz, CHN); 4.95, 4.98 (2s, 4H, $CH_2C_6H_5$); 5.10–5.12 (d, 1H, $J = 7.6$ Hz, OCH); 6.70–7.80 (m, 13H, ArH) ppm.

3.7. O,O-Dibenzyl-6-F-threo-DOPS (14c)

A solution of ester **13c** (492 mg, 1.12 mmol) in 5 ml of methanol was added to 30 ml of aqueous 2 N NaOH. The resulting milky mixture was stirred at room temperature overnight. After evaporation, the residual white solid was dissolved in 10 ml of water and adjusted to pH < 2 with concentrated HCl. Filtration of the resulting white solid gave 410 mg (1.0 mmol, 89%) of amino acid **14c**. Recrystallization from methanol/ethyl acetate gave 340 mg, m.p. 148–151 °C. MS (CI NH_3) *m/z*: 412 ($M^+ + 1$). ^1H NMR (CD_3OD) δ: 3.72–3.73 (d, 1H, $J = 3.2$ Hz, CHN); 5.11, 5.12 (2s, 4H, 2 $CH_2C_6H_5$); 5.49–5.50 (d, 1H, $J = 3.0$ Hz, OCH); 6.85–6.89 (d, 1H, $J^o_{HF} = 11.6$ Hz, ArH); 7.30–7.46 (m, 11H, ArH) ppm. Analysis: Calc. for $C_{23}H_{24}NFO_6 \cdot H_2O$: C, 64.33; H, 5.63; N, 3.26%. Found: C, 64.27; H, 5.70; N, 3.26%.

3.8. O,O-Dibenzyl-2-F-threo-DOPS (14b)

To a solution of amino ester **13b** (292 mg, 0.67 mmol) in 5 ml of 2 N NaOH was added 5 ml of methanol. The resulting milky mixture was stirred at ambient temperature overnight. After evaporation, the residual white solid was suspended in 10 ml of water and the pH adjusted to < 2 with concentrated HCl. After filtration and washing with water, 192 mg of a

white solid (**14b**) was obtained which recrystallized from methanol/ether, m.p. 176–180 °C. MS (CI NH_3) *m/z*: 412 ($M^+ + 1$); 429 ($M^+ + 18$). ^1H NMR (CD_3OD) δ: 4.05–4.07 (d, 1H, *J* = 3.9 Hz, C*H*N); 5.08, 5.17 (2s, 4H, 2 $CH_2C_6H_5$); 5.45–5.46 (d, 1H, *J* = 3.9 Hz, OC*H*); 6.96–7.46 (m, 12H, Ar*H*) ppm. Analysis: Calc. for $C_{23}H_{22}NFO_5$: C, 65.71; H, 5.51; N, 3.33%. Found: C, 65.75; H, 5.70; N, 3.26%.

3.9. O,O-Dibenzyl-threo-DOPS (14a)

Similar conditions were used to hydrolyze amino ester **13a** to give amino acid **14a** in 98% yield. ^1H NMR (CD_3OD) δ: 3.95–3.96 (d, 1H, *J* = 3.8 Hz, C*H*N); 5.05, 5.07 (2s, 4H, 2 $CH_2C_6H_5$); 5.15–5.16 (d, 1H, *J* = 3.9 Hz, OC*H*); 6.94–7.39 (m, 13H, Ar*H*) ppm.

3.10. Preparation of threo-F-DOPS (4)

3.10.1. 6-F-threo-DOPS (4c)

To a solution of 340 mg (0.77 mmol) of **14c**·HCl (prepared from **14c**) in 30 ml of methanol was added 200 mg of 10% Pd–C. The flask was connected to a balloon filled with H_2 and the solution was stirred at room temperature for 5 h. After filtration and evaporation, the resulting pale off-white solid was washed to give **4c**·HCl, 95 mg (0.36 mmol, 96%). ^1H NMR (CD_3OD) δ: 4.03–4.05 (d, 1H, *J* = 3.6 Hz, C*H*N); 5.42–5.33 (d, 1H, *J* = 3.5 Hz, OC*H*); 6.55–6.59 (d, 1H, J^o_{HF} = 11.3 Hz, Ar*H*); 7.00–7.02 (d, 1H, J^m_{HF} = 7.5 Hz, Ar*H*) ppm.

3.10.2 2-F-threo-DOPS (4b)

To a solution of 165 mg (0.37 mmol) of **14b** in 20 ml of methanol and 1 ml of 5 N HCl in methanol was added 120 mg of 10% Pd–C. The flask was connected to a balloon filled with H_2 and was stirred at room temperature for 5 h. After filtration and evaporation, the resulting solid was washed with ethyl acetate to give **4b** as the HCl salt, 95 mg (0.36 mmol, 96%). ^1H NMR (CD_3OD) δ: 4.00–4.01 (d, 1H, *J* = 3.8 Hz, C*H*N); 5.38–5.39 (d, 1H, *J* = 3.7 Hz, OC*H*); 6.58–6.61 (q, 1H, J_{HH} = 8.8 Hz, J^o_{HF} = 1.9 Hz, Ar-H_5); 6.80–6.85 (t, 1H, J_1 = 8.1 Hz, J_2 = 8.3 Hz, Ar-H_6) ppm.

3.10.3. threo-DOPS (4a)

Debenzylation of **14a** as above gave **4a** as the hydrochloride. ^1H NMR (CD_3OH) δ: 3.91–3.92 (d, 1H, *J* = 3.8 Hz, C*H*N); 5.04–5.05 (d, 1H, *J* = 3.9 Hz, OC*H*); 6.68 (s, 2H, Ar*H*); 6.78 (s, 1H, Ar*H*) ppm. This NMR spectrum was identical to that of authentic *threo*-DOPS, an observation confirmed by the absence of additional NMR peaks when authentic material was added to an NMR tube containing **4a**.

3.11. 2-Fluoro-4,5-dicarboethoxymethylenedioxybenzaldehyde (15c)

To a solution of 1.78 g (11.4 mmol) of 6-fluoroprocatechuealdehyde [12] in 100 ml of acetone was added 7.25 g (22.8 mmol) of diethyl dibromomalonate and 3.15 g (22.8 mmol) of potassium carbonate. After the mixture was stirred for 24 h at room temperature, the reaction mixture was added to 20 ml of water. After removal of acetone, the aqueous solution was extracted three times with ether. The ether extracts were washed with water, brine, dried over anhydrous Na_2SO_4 and evaporated to give, after purification by preparative TLC (15% ethyl acetate in petroleum ether), 1.23 g (3.94 mmol, 35%) of DCEM-protected aldehyde **15c** as an oil. MS (CI NH_3) *m/z*: 349 ($M^+ + 35$, $N_2H_7^+$); 330 ($M^+ + 18$, NH_4^+); 312 (M^+). ^1H NMR ($CDCl_3$) δ: 1.36–1.38 (t, 6H, $J_1 = J_2 = 7.3$ Hz, CH_3); 4.40–4.43 (q, 4H, J_1 = 7.0 Hz, J_2 = 7.4 Hz, J_3 = 7.2 Hz, CH_2); 6.78–6.81 (d, 1H, *J* = 8.9 Hz, Ar*H*); 7.36–7.38 (d, 1H, *J* = 5.1 Hz, Ar*H*); 10.21 (s, 1H, C*H*O) ppm.

3.12. 3,4-Dicarboethoxymethylenedioxybenzaldehyde (15a)

DCEM-protected procatechualdehyde was prepared as described above for the synthesis of **15c**. From 2.48 g (18 mmol) of 3,4-dihydroxybenzaldehyde there was obtained 2.70 g (9.2 mmol, 51%) of DCEM-protected procatechualdehyde after purification by preparative TLC (15% ethyl acetate in petroleum ether). MS (EI) *m/z*: 294 (M^+). ^1H NMR ($CDCl_3$) δ: 1.33–1.38 (t, 6H, J_1 = 7.0 Hz, J_2 = 7.2 Hz, CH_3); 4.36–4.43 (q, 2H, J_1 = 7.4 Hz, J_2 = 7.0 Hz, J_3 = 7.1 Hz, CH_2); 7.07–7.10 (d, 1H, *J* = 8.2 Hz, Ar*H*); 7.47–7.53 (m, 2H, 2 Ar*H*); 9.86 (s, 1H, C*H*O) ppm.

3.13. Aldol product 16c

The $ZnCl_2$-catalyzed aldol condensation between aldehyde **15c** and ketene acetal **10a** was carried out as described for the reaction with aldehydes **6b** and **6c**. Reaction of 324 mg (1.04 mmol) of **15c** with **10a** gave 797 mg of crude product. Preparative TLC (15% ethyl acetate in petroleum ether) gave a major diastereomer (310 mg, 0.50 mmol, 48%) as a pale oil. MS (CI NH_3) *m/z*: 652 (M^+). ^1H NMR ($CDCl_3$) δ: 0.00 [s, 9H, $Si(CH_3)_3$]; 1.11–1.33 (m, 9H, 3 CH_2CH_3); 4.03–4.23 (m, 4H, 2 CH_2); 4.24–4.26 (d, 1H, *J* = 5.7 Hz, NC*H*); 4.32–4.37 (q, 2H, J_1 = 7.4 Hz, J_2 = 7.2 Hz, J_3 = 6.8 Hz, CH_2); 5.53–5.55 (d, 1H, *J* = 5.8 Hz, OC*H*); 6.53–7.58 (m, 12H, Ar*H*) ppm. A minor isomer was obtained (< 20 mg), albeit in impure form. ^1H NMR ($CDCl_3$) δ: 4.22–4.24 (d, 1H, *J* = 7.7 Hz, NC*H*); 5.65–5.67 (d, 1H, *J* = 8.6 Hz, OC*H*) ppm. Based on the relative sizes of the coupling constants, the minor isomer was assigned the *erythro* configuration and the major isomer the *threo* configuration, consistent with the previous results.

3.14. Aldol product 16a

Using the same procedure, from 0.98 g (3.3 mmol) of aldehyde **15a** there was obtained 1.50 g (2.37 mmol, 71%) of the D,L-*threo*-aldol product **16a**. MS (CI NH_3) *m/z*: 635 ($M^+ + 1$). ^1H NMR ($CDCl_3$) δ: 0.0–0.1 [s, 9H, $Si(CH_3)_3$];

1.06–1.11 (t, 3H, $J_1 = 7.2$ Hz, $J_2 = 7.3$ Hz, CH_2CH_3); 1.24–1.34 (m, 6H, 2 CH_2CH_3); 3.99–4.03 (q, 2H, $J_1 = J_2 = 7.2$ Hz, $J_3 = 7.1$ Hz, CH_2); 4.17–4.19 (d, 1H, $J = 6.3$ Hz, NCH); 4.26–4.36 (m, 4H, 2 CH_2); 5.20–5.23 (d, 1H, $J = 6.4$ Hz, OCH); 6.80–7.64 (m, 13H, ArH) ppm.

3.15. Hydrolysis of aldol product **16c**. Preparation of erythro-6-F-DOPS ethyl ester (**17c** · HCl)

To 100 mg of **16c** dissolved in 3 ml of EtOH was added 10 ml of 3 N HCl. The white milky mixture was stirred under nitrogen overnight at room temperature. The ethanol was removed by evaporation and the aqueous solution washed with ether to remove benzophenone and evaporated to give 6-*F*-DOPS ethyl ester · HCl (**17c** · HCl) as a colourless semi-crystalline solid. ^{1}H NMR (CD_3OD) δ: 1.01–1.14 (t, 3H, $J_1 = 6.9$ Hz, $J_2 = 7.2$ Hz, CH_3); 4.01–4.03 (d, 1H, $J = 4.8$ Hz, NCH); 4.10–4.17 (q, 2H, $J_1 = 7.1$ Hz, $J_2 = 7.1$ Hz, $J_3 = 7.3$ Hz, CH_2); 5.27–5.28 (d, 1H, $J = 4.8$ Hz, OCH); 6.7–6.8 (d, 1H, $J = 9.7$ Hz, ArH); 7.05–7.07 (d, 1H, $J = 5.8$ Hz, ArH) ppm.

3.16. Preparation of erythro-6-F-DOPS hydrochloride (**18c** · HCl)

A 52 mg sample of **17c** · HCl in 15 ml of 3 N HCl was refluxed for 2.5 h. After being cooled at room temperature, the solution was washed with ethyl acetate and evaporated to give 32 mg of **18a** · HCl as a white solid. ^{1}H NMR (CD_3OD) δ: 4.10–4.11 (d, 1H, $J = 3.6$ Hz, NCH); 5.50–5.51 (d, 1H, $J = 3.5$ Hz, OCH); 6.87–6.90 (d, 1H, $J = 10.0$ Hz, ArH); 7.20–7.22 (d, 1H, $J = 5.86$ Hz, ArH) ppm. Comparison of the NMR spectra of **18c** · HCl and **4c** · HCl prepared as above (assigned the *threo* configuration), both separately in CD_3OD (Table 1) and as a mixture in DCl/D_2O, revealed that the two amino acids were diastereomeric. From this, **18c** was provisionally assigned the *erythro* configuration.

3.17. Preparation of threo-DOPS ethyl ester hydrochloride (**19c**)

To a solution of 28 mg of dibenzyl-*threo*-DOPS ethyl ester (**13c**) in methanol was added 10 mg of 10% Pd–C. The flask was attached to a balloon filled with H_2 and the solution was stirred overnight. Filtration and evaporation gave **19c** as a solid. Comparison of the ^{1}H NMR spectra (DCl/D_2O) of **19c** and **17c**, including a spectrum of a mixture of the two compounds, revealed that the two esters were diastereomeric (Table 2).

3.18. Preparation of erythro-DOPS (**18a**)

A sample of aldol product **16a** was hydrolyzed by heating at reflux in 3 N HCl for 2.5 h. Removal of the benzophenone and evaporation gave an amino acid diastereomeric with authentic *threo*-DOPS, as determined by comparison of the NMR spectra (Table 3). From this, **18a** was assigned the *erythro* configuration.

3.19. Aldol condensation of **15a** and **10b**. Synthesis of threo-(**20**)

Condensation of DCEM-protected procatechualdehyde (**15a**) with the trimethylketene acetal **10b** was performed as above. From 315 mg (1.07 mmol) of **15a** and 388 mg of **10b** (1.18 mmol) there was obtained 580 mg (0.83 mmol, 78%) of aldol product **20** as a yellow oil. ^{1}H NMR δ; 1.27–1.35 (q, 6H, $J_1 = 7.27$ Hz, $J_2 = 7.68$ Hz, $J_3 = 7.06$ Hz, 2 CH_2CH_3); 4.24–4.27 (d, 1H, $J = 6.52$ Hz, NCH); 4.28–4.39 (m, 4H, 2 CH_2CH_3); 5.23–5.25 (d, $J = 6.62$ Hz, 1H, OCH); 7.17–7.65 (m, 18H, ArH) ppm.

3.20. Hydrolysis of **20**

Room temperature hydrolysis of 450 mg of **20** with 20 ml of 3 N HCl for 3 h gave 279 mg of DOPS benzyl ester hydrochloride **21** as a tan solid. ^{1}H NMR (CD_3OD/DCl) δ: 4.23–4.24 (d, 1H, $J = 5.5$ Hz, NCH); 5.12–5.14 (d, 1H, $J = 5.6$ Hz, OCH); 5.19 (s, 2H, CH_2); 6.89–7.33 (m, 8H, ArH) ppm.

Hydrolysis of **20** was also carried out in 5 N acetic acid overnight. NMR analysis (DCl/D_2O) of the product showed that the same diastereomer of DOPS benzyl ester was obtained as above.

3.21. Hydrogenolysis of **21**. Synthesis of erythro-DOPS · HCl (**18a**)

To a solution of 192 mg (0.56 mmol) of **21** in 10 ml of ethanol was added 89 mg of 10% Pd–C. The flask was connected to a balloon filled with H_2. The solution was stirred overnight at room temperature, then filtered and evaporated to give a clean, glassy product. Comparison of the NMR spectrum (D_2O/DCl) of this product and authentic *threo*-DOPS (Aldrich Chemical Corp.), including a spectrum of the mixture (D_2O/DCl), revealed that the product from the hydrogenolysis of **21** is the diastereomer (**18a**) of *threo*-DOPS (**4a**) (Table 4).

3.22. Aldol condensation of **15c** with the Ni^{2+} complex **8**

Sodium (315 mg, 15 mmol) was added slowly in portions to 15 ml of anhydrous methanol with stirring under nitrogen. To the resulting solution of sodium methoxide was added a solution of 494 mg (0.99 mmol) of the Ni^{2+} complex **8** in 6 ml of THF. To the resulting red solution was added 310 mg (0.99 mmol) of **15c** in 3 ml of THF and the mixture was stirred overnight. To decompose the complex, 40 ml of 5.5 N HCl [11b] was added and the mixture stirred for 3 h at 55–60 °C. The organic solvent was removed by evaporation to give a yellow solution and a white precipitate. This mixture was washed twice with $CHCl_3$, then adjusted to pH 2 with

10% NH_4OH and washed once again with $CHCl_3$. The solution was evaporated to give a yellow solid. This was treated with 20 ml of methanol and filtered. The filtrate was concentrated to 10 ml, the mixture filtered and the filtrate evaporated to give 470 mg of crude product. NMR spectral analysis confirmed the presence of *erythro-F*-DOPS by comparison with the spectra of **4c** and **18c**.

*3.23. Aldol condensation of **15a** with the Ni^{2+} complex **8***

The above procedure was used to effect the condensation of aldehyde **15a** with the Ni^{2+} complex **8**. For the acid-catalyzed decomposition of the intermediate complexed condensation product, 0.5 N HCl was used. Comparison of the ^1H NMR spectra of authentic *threo*-DOPS (**4a**) and *erythro*-DOPS (**18a**) in DCl/D_2O revealed that the product of this procedure was the *erythro* isomer.

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