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# A highly efficient stereocontrolled synthesis of (*S*)-2′,6′-dimethyltyrosine [(*S*)-DMT]

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ABSTRACT

A new, practical and very convenient stereocontrolled synthesis of (*S*)-2′,6′-dimethyltyrosine [(*S*)-Dmt] **4** was accomplished in a good yield, starting from the chiral synthon 1,4-*N*,*N*-[(*S*)-phenylethyl]-piperazine-2,5-dione **1**. The procedure, which is an extension of our original strategy and occurs with a high level of stereoselectivity (>98%), is simple and inexpensive allowing us to prepare the unnatural α-aminoacid (*S*)-Dmt also on a multi-gram scale.



## 1. Introduction

Continuing our project directed towards the preparation of natural and unnatural α-aminoacids, we undertook the asymmetric synthesis of (*S*)-2′,6′-dimethyltyrosine [(*S*)-Dmt] **4** because this unnatural α-aminoacid is a component of the δ-opioid antagonist Dmt-Tic pharmacophore present in many biologically active compounds (δ antagonists, δ agonists and δ antagonists/μ agonists).[1] Besides, to the best of our knowledge, only two enantioselective syntheses of Dmt have been reported in the literature. One method is based on the asymmetric hydrogenation of (*Z*)-2-acetamido-3-(4-acetoxy-2,6-dimethylphenyl)-2-propenoate in the presence of [Rh(1,5-COD)(*R*,*R*-DIPAMP)]$BF_4$,[2] a very expensive chiral catalyst. The key step of the synthesis, the hydrogenation, occurs in good ee by performing the reaction in the absence of the oxygen (oxygen level <5 ppm). Another approach involves the alkylation of a Ni(II) complex of the chiral Schiff base obtained from glycine and (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone.[3] In addition, an enzymatic hydrolysis of α-*N*-acetyl-DL-2′,6′-dimethyltyrosine methyl ester in the presence of α-chymotrypsin has also been reported.[4]

Herein we report a more convenient and economical asymmetric synthesis of (*S*)-Dmt which is an extension of our original strategy accomplished for the stereocontrolled approach to natural and unnatural α-aminoacids.[5] The procedure reported herein is a useful and practical application of our experience,[5a] in the use of the 2,5-diketopiperazine derivative **1**, a chiral synthon easily obtained in two steps from chloroacetyl chloride and (*S*)-phenylethylamine by using a modified procedure[6] and is more practical than that previously employed.[5c] The success of our method resides mostly in the stereocontrolled alkylation of synthon **1**, which occurs with practically total diastereoselectivity to furnish the *cis*-derivative (3*S*,6*S*)-**3**.[5] A further interesting feature of this procedure is the total conversion of (*S*)-phenylethylamine to (*S*)-Dmt: two units of the target α-aminoacid are obtained from one unit of the chiral synthon **1** (Scheme 1).

## 2. Results and discussion

Previously,[5a–h] we demonstrated that the monoalkylation of the chiral synthon **1** occurred with a satisfactory diastereoselectivity, induced by the chiral substituent at both (N-1) and (N-4), to give the (3*S*) monoalkylated diastereomer in about 50% de, while the second alkylation takes place with complete 1,4-*cis*-induction furnishing only the (3*S*,6*S*)-dialkylderivative. This diastereoselectivity results from steric interactions as the monoalkyl derivative intermediate is thermodynamically more stable in the (*S*)- than in the (*R*)-configuration due to the presence of the chiral substituents at both (N-1) and (N-4).[5] In this case, by using iododerivative **2** (obtained as summarized in Scheme 2) as the electrophile, the first alkylation of **1** also occurs with very good diastereoselectivity (>98%) yielding only the (3*S*)-diastereomer, while the (3*R*)-diastereomer is not detectable by $^1$H NMR. This result can be explained in terms of the greater size of the iododerivative **2** with respect to the previously used haloderivatives, in relation to the chiral substituents on the synthon **1**. It is our opinion that the *trans*-isomer does not form because of the strong steric interactions between the alkyl substituents at (C-3) and (C-6) and the adjacent phenyl ring of the chiral inductor bonded at (N-1) and (N-4). Most probably, the total *cis*-diastereoselectivity obtained during alkylation of the synthon **1** is due to the "steric chiral relay" suggested by Davies et al. to explain the diastereofacial selection observed in the case of different chiral 2,5-diketopiperazine derivatives.[7] In fact, as shown by the X-ray structure, intermediate **3** adopts a boat conformation:

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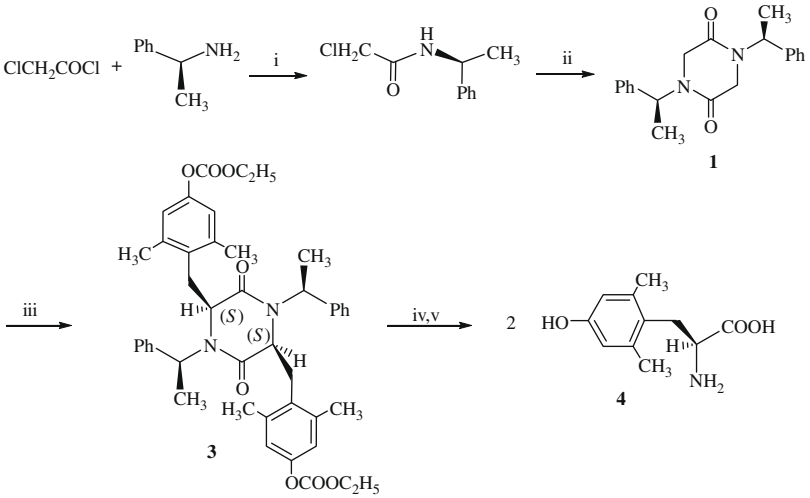
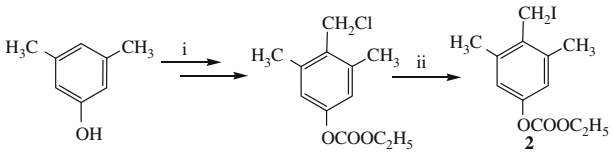


**Scheme 1.** Reagents and conditions: (i) $Na_2CO_3 \cdot 10H_2O$, in water/acetone (Ref. 5a); (ii) NaOH in $CH_3CN$ (Ref. 6); (iii) LHMDS in THF at −78 °C, then **2** (see Scheme 2); (iv) 57% HI at reflux for 3 h; (v) treatment with Dowex 50 WX 8 (20–50 mesh) ion-exchange resin.



**Scheme 2.** Reagents and conditions: (i) see Ref. 4; (ii) NaI in acetone at rt for 50 h.

the large alkyl substituents at (C-3) and (C-6) assume a diaxial arrangement (the aryl rings carrying the carbonate chains oriented as far away as possible to reduce the steric strain) and the two phenylethyl groups assume a diequatorial position (see Fig. 1). Consequently, the vicinal phenyl rings lie on the opposite side of the diketopiperazine ring.

Such an excellent stereochemical result prompted us to perform the double alkylation of **1** in a one-pot procedure directly obtaining the intermediate **3** in good chemical yield and total diastereocontrol. The one-pot reaction offers an evident and remarkable advantage in making the experiment simpler and the procedure more reliable for preparing the title unnatural α-aminoacid. Intermediate **3** was successively cleaved by refluxing in 57% HI for 3 h after which the target (*S*)-Dmt **4** was then recovered in practically quantitative yield after adsorption on Dowex 50 WX 8 (20–50 mesh) ion-exchange resin and removal of ammonia solution (Scheme 1).

The absolute configuration of intermediate **3** was assigned through the shielding effects induced on (C-3)-H and (C-6)-H by the phenyl ring of the chiral inductor bound to each of the N-atoms, as previously observed for similar compounds.[5a–c] In fact, these protons absorb as a pseudotriplet at 4.08 ppm in accordance with that previously reported by us for a very similar derivative in an (*S*)-configuration.[5c] In addition, in the $^1H$ NMR and $^{13}C$ NMR spectra of the intermediate **3** half signals appear, showing the existence of a $C_2$ symmetry axis, as we have already observed in similar substrates.[5a,c] This symmetry element is evident by the overlap of the signals for the chiral groups at (N-1) and (N-4) and the same behaviour can be observed for the methyl and ethyl groups as well as for the (C-3)–H and (C-6)–H, these nuclei being equivalent by chemical shift. However, the absolute configurations of the two new stereocentres in **3** were confirmed by X-ray crystallographic analysis (see later) and by the specific rotation value of **4** which is in agreement with that reported in the literature.[3]

## 3. X-ray crystal structure

The asymmetric unit contains two slightly different conformers of **3**. The molecular structure of one of them is shown in Figure 1 and consists of a diketopiperazine ring (DKP) whose nitrogen atoms are connected to two (*S*)-phenylethyl groups. In addition two dimethylphenyl ethylcarbonate groups are bound to the carbons adjacent to the amide CO group.

The molecule as a whole has an idealized $C_2$ symmetry and the DKP ring adopts a boat conformation. The two ethylcarbonate groups lie on the same side while the phenylethyl moieties lie on the opposite side of the DKP ring.

Interestingly, the phenyl rings of the two phenylethyl groups are not parallel to each other but are bent towards the centre of the DKP ring, while the carbonate chains point to the peripheral part of the molecule (Fig. 2). Moreover, the two carbonate planes are differently

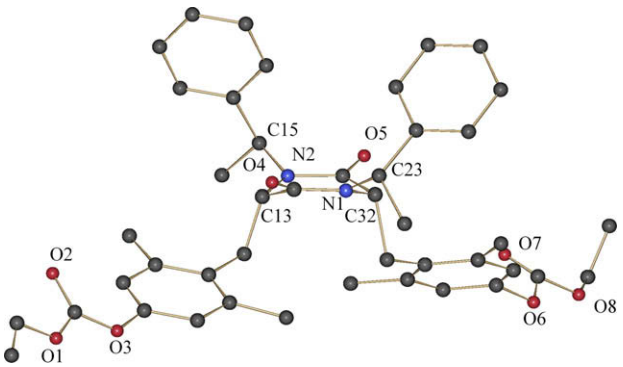



**Figure 1.**

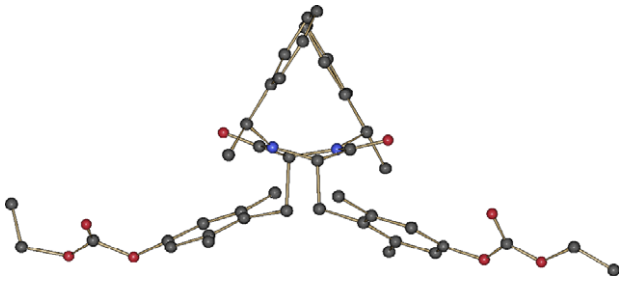


**Figure 2.**

twisted with respect to the plane of the dimethylphenyl ring [dihedral angles: 28.0(8)° and 51.1(4)° for one conformer and 32.9(6)° and 51.1(5)° for the second one].

The absolute configuration of the stereogenic centres at C(13), C(15), C(23) and C(32) is (*S*). Comparison with other cyclic dipeptide structures of DKP derivatives[8,9] shows that the presence of two conformers is common and, depending on the nature of the substituents, the DKP ring can adopt a boat, flattened boat or planar conformation.

## 4. Conclusion

In conclusion we can assume that the synthesis reported herein offers some advantages: a total stereoselectivity, a good overall yield [about 50% estimated on the starting (*S*)-phenylethylamine], low to moderate cost of reagents, simplicity of experimental procedures and product isolation. Therefore, we believe that this approach, which is an application of our previous procedure, is an efficient improvement in the asymmetric synthesis of (*S*)-DMT with respect to the methodologies reported in the literature. It is also noteworthy that this approach is reliable to prepare the enantiomerically pure target product on a multi-gram scale.

Finally, since the diastereoselectivity of the alkylation of synthon **1** is controlled by the chiral group bound at both (N-1) and (N-4), the enantiomerically pure (*R*)-Dmt can be easily obtained by using the (*R*)-phenylethylamine instead of the (*S*)-enantiomer.

Further work is currently underway to extend the methodology to other unnatural α-aminoacids present in biologically active compounds. The procedure described herein was patented on 2008, deposition number RM2008A000118.

## 5. Experimental

### 5.1. General

$^1$H- and $^{13}$C NMR spectra were recorded on a Gemini spectrometer at 300 MHz using $CDCl_3$, unless otherwise stated. Chemical shifts are reported in ppm relative to $CDCl_3$ and the coupling constants (*J*) are in hertz. Optical rotation values were measured at 25 °C on a Perkin–Elmer 343 polarimeter. IR data were recorded on a Perkin–Elmer spectrum 100. Melting points are uncorrected. Dry tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Chromatographic separations were performed with Silica gel 60 (230–400 mesh).

The spectroscopic and physical data of the chiral synthon **1** are reported in Ref. 5c.

### 5.2. 4-Iodomethyl-3,5-dimethylphenyl ethylcarbonate 2

Compound **2** was prepared by treatment of 4-chloromethyl-3,5-dimethylphenyl ethylcarbonate[4] (5.8 g, 23.9 mmol) with NaI (7.2 g, 48 mmol) in 60 mL of acetone and the reaction mixture was stirred at rt. After about 50 h the organic solvent was evaporated under reduced pressure. Water was added to the residue and the reaction product extracted with ethyl acetate. The organic phase was dried and the title product isolated as oil in 90% yield after total evaporation of organic solvent under vacuum. $^1$H NMR $\delta$: 1.39 (t, 3H, $J$ = 7), 2.35 (s, 6H), 4.31 (q, 2H, $J$ = 7), 4.41 (s, 2H), 6.84 (s, 2H). $^{13}$C NMR $\delta$: 2.1, 14.2, 19.4, 64.8, 120.9, 132.7, 138.6, 150.2, 153.5.

### 5.3. 1,4-*N*,*N*-[(*S*)-Phenylethyl]-3,6-bis[4-*O*-carbethoxy-2,6-dimethyl-benzyl]-piperazine-2,5-dione 3

The chiral synthon **1** (4.1 g, 12.7 mmol) in dry THF (60 mL) was metalled with 1 M solution of LHMDS (12.7 mL) at −78 °C under an inert atmosphere. After 1 h the iodo derivative **2** (4.25 g, 12.7 mmol) was added and the reaction mixture, under stirring, was monitored by TLC. When the starting reagent **1** was consumed, the second aliquot of LHMDS (12.7 mL) was added and the reaction mixture was stirred for 1 h. Then, the second aliquot of **2** (4.25 g, 12.7 mmol) was added and the reaction was stirred for about 4 h, monitoring by TLC. The reaction was then quenched with water, extracted with ethyl acetate and the organic solution was evaporated under vacuum to dryness. From the residue the pure reaction product **3** was isolated in 50% yield after crystallization from methanol (mp 171.5–173.5 °C). The mother liquor was evaporated to dryness under reduced pressure and the residue submitted to silica gel chromatographic separation eluting with hexane/ethyl acetate to recover an additional 25% of the pure title product. $^1$H NMR $\delta$: 1.30 (d, 6H, $J$ = 7, CH–$CH_3$), 1.40 (t, 6H, $J$ = 7, $CH_2$–$CH_3$), 2.33 (s, 12H, $CH_3$–Ph), 3.43 (m, 4H, CH–$CH_2$), 4.08 (m,2H, $CH$–$CH_2$), 4.32 (q, 4H, $J$ = 7,$CH_2$–$CH_3$), 5.68 (q, 2H, $J$ = 7,$CH$–$CH_3$), 6.90 (s, 4ArH), 7.00 (m, 4ArH), 7.30 (m, 6ArH). $^{13}$C NMR $\delta$: 14.1, 16.8, 21.3, 35.5, 53.1, 57.7, 64.7, 120.9, 127.2, 128.1, 128.7, 131.5, 138.5, 139.0, 149.4, 153.6, 167.7. IR (solid state) $\nu$ 2984.4, 1755.3, 1660.8, 1598.7, 1231.7, 1186.4. $[\alpha]_D$ = −61.1 (*c* 0.9, $CHCl_3$). Anal. Calcd for $C_{44}H_{50}N_2O_8$: C, 71.91; H, 6.86; N, 3.81. Found: C, 72.25; H, 6.84; N, 3.81.

### 5.4. (*S*)-2′,6′-Dimethyltyrosine [(*S*)-Dmt] 4

Intermediate **3** (1.2 g, 1.6 mmol) was refluxed in 57% HI (12 mL) for 3 h. The reaction solution was then evaporated under vacuum, the residue dissolved in water (15 mL) and extracted with ethyl acetate. The aqueous solution was eluted more than once on a column filled with the acid ion-exchange resin Dowex 50 WX 8 (20–50 mesh) carefully washed with distilled water. The resin was again washed with distilled water until neutral pH of eluent and then the title product was eluted with 5 M $NH_4OH$. The aqueous solution was evaporated under vacuum to dryness and the pure (*S*)-Dmt was obtained practically in quantitative yield as a white solid which decomposes at 239–240 °C. $^1$H NMR ($D_2O$) $\delta$: 2.09 (s, 6H), 2.83 (dd, 1H, $J_{AX}$ = 8, $J_{AB}$ = 14.5), 3.05 (dd, 1H, $J_{BX}$ = 8, $J_{AB}$ = 14.5), 3.62 (t, 1H, $J_{AX}$ = 8, $J_{BX}$ = 8), 6.45 (s, 2H). $^{13}$C NMR ($D_2O$ vs 1,4-dioxane) $\delta$: 20.0, 30.8, 55.1, 115.7, 125.1, 140.0, 154.6, 174.7. $[\alpha]_D$ = +72.9 (*c* 0.5, 0.5 M HCl).

(*S*)-Dmt **4** was dissolved in diluted HCl and after evaporation under vacuum to dryness the (*S*)-Dmt.HCl was recovered as a white solid. $^1$H NMR ($CD_3OD$) $\delta$: 2.29 (s,2H), 3.14 (dd, 1H, $J_{AX}$ = 8, $J_{AB}$ = 14.5), 3.30 (dd, 1H, $J_{BX}$ = 8, $J_{AB}$ = 14.5), 4.0 (t, 1H, $J$ = 8), 6.53 (s, 2H). $^{13}$C NMR ($CD_3OD$) $\delta$: 20.5, 31.4, 54.0, 116.5, 123.9, 139.9, 157.0, 172.1. $[\alpha]_D$ = +39.8 (*c* 1.1, $CH_3OH$) [lit.[3] +39.4 (*c* 1, $CH_3OH$)].

### 5.5. X-ray crystallography

Single crystals of **3** suitable for an X-ray diffraction study were grown from a methanolic solution by slow evaporation. The X-ray intensity data were measured on a Bruker Apex II CCD area detector diffractometer. Cell dimensions and the orientation matrix were initially determined from a least-squares refinement on reflections measured in three sets of 20 exposures, collected in three different ω regions, and eventually refined against all data. For the crystal, a full sphere of reciprocal space was scanned by 0.3° ω steps. The software SMART[10] was used for collecting frames of data, indexing reflections and determination of lattice parameters. The collected frames were then processed for integration by the SAINT program,[10] and an empirical absorption correction was applied using SADABS.[11] The structure was solved by direct methods (SIR 97)[12] and subsequent Fourier syntheses and refined by full-matrix least-squares on $F^2$ (SHELXTL),[13] using anisotropic thermal parameters for all non-hydrogen atoms. Two independent molecules were found in the asymmetric unit. All hydrogen atoms were added in calculated

positions, included in the final stage of refinement with isotropic thermal parameters, $U(H) = 1.2\ U_{eq}(C)$ [$U(H) = 1.5\ U_{eq}$(C–Me)], and allowed to ride on their carrier carbons.

Crystal data for **3** [$C_{44}H_{50}N_2O_8$], colourless prism, $M = 734.86$, monoclinic, space group $P2_1$, $a = 17.420(6)$ Å, $b = 8.722(3)$ Å, $c = 27.174(9)$ Å, $\beta = 100.763(5)$, $U = 4056(2)$ Å$^3$, $Z = 4$, $\mu = 0.08$ mm$^{-1}$, $\theta$ range 1.29–24.10°, a total of 12603 total reflections were measured, and 4618 of them have $I > 2\sigma(I)$.

The crystal structure of **3** has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 670741.

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