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Stereoselection in the Betti reaction of valine methyl esters

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Dedicated to Prof. Francesco Naso on the occasion of his 80th birthday

ABSTRACT

The multi-component Betti reaction of 2-naphthol, benzaldehyde and (*S*)-amines, that usually provides highly valuable aminobenzylnaphthol bearing two stereogenic centers, yielded a completely racemic product, when (*S*)-valine methyl ester was employed as the amine in the usual reaction protocol. The cause of this drawback, that appears to be overlooked in the literature, was investigated. As a result, new reaction conditions were set up, that were able to yield the expected useful product, having two fully resolved stereogenic centers. Furthermore, when the effect of substituents on the phenyl ring was preliminarily studied, we found that 4-fluoro- and 4-chlorobenzaldeyde gave stereoisomerically pure compounds also in the original reaction protocol.

1. Introduction

The Betti reaction is a straightforward multi-component condensation between 2-naphthol, aryl aldehydes and amines, that are assembled to yield aminobenzylnaphthols.[1,2] The Betti reaction had been seldom applied for almost a century until our early papers,[3] that stimulated a great deal of interest.[1,2] The most interesting feature of this process is the access to chiral nonracemic materials, that were employed in asymmetric synthesis.[1,2] An interesting extension, provided independently by three different research groups,[4–6] was the reactions of 2-naphthol, aryl aldehydes and a chiral amine, such as (*R*)- or (*S*)-1-phenylethylamine (Scheme 1) to yield the corresponding (*R*,*R*)- or (*S*,*S*)-aminobenzylnaphthols.

Among them, the groups of Palmieri[4] and Forlani[5] also reported mechanistic investigations. In particular, Palmieri et al. observed a decisive improvement when the reaction was performed at 60 °C without any solvent (Scheme 1, X = H).[4] Under these reaction conditions, a large predominance of the (*R*,*R*)-aminobenzylnaphthols is obtained[4] (or the (*S*,*S*)-aminobenzylnaphthols, when the (*S*)-1-arylethylamine is employed).[7] Palmieri et al. hypothesized a conversion between the predominant (*R*,*R*)- and the minor (*S*,*R*)-diastereoisomers at 60 °C, followed by the separation of the most stable species from the equilibrium, in a process that was described as an "asymmetric transformation of the second kind".[4]

From a practical point of view, it must be underlined that the addition of small amounts of ethanol to the crude reaction mixture causes the precipitation of only the (*R*,*R*)-aminobenzylnaphthol, free from the (*S*,*R*)-stereoisomer, that remains in the mother liquor with a complex mixture of by-products.[4] This reactivity was also confirmed by Szatmari et al. in the reaction in which (*R*)-1-(1-naphthyl)ethylamine or (*R*)-1-(2-naphthyl)ethylamine were employed,[8] and by us in the reaction involving three different (*S*)-1-arylethylamines.[7] Our protocol was shown to be a straightforward route to the (*S*,*S*)-aminobenzylnaphthol in satisfactory yields (51–68%) without resorting to chromatography (Scheme 1).[7] Our subsequent analysis of the crystal structures, revealed that these (*S*,*S*)-aminobenzylnaphthols are stabilized with respect to the (*R*,*S*)-stereoisomers, according to the Palmieri hypothesis,[4] by many and cooperating CH···π interactions.[9]

The naphthol derivatives synthesized so far were tested for their bio-activity, or used as building blocks in drug discovery.[1,2] To select only some significant and recent results, some (*S*,*S*)-aminobenzylnaphthols were transformed into (*S*,*S*,*S*)-cyclophosphonamides, interesting structures related to anti-tumor agents.[10] Racemic glycine derivatives were obtained by the condensation of 1- or 2-naphthols with glyoxylic acid and benzyl carbamate; chiral HPLC allowed the separation of the enantiomers.[11] The (*S*,*S*)-aminobenzylnaphthols obtained by the Betti reaction of 2-naphthol, aryl aldehydes and (*S*)-prolinol[12] were tested as anti-yeast agents inhibiting *Candida albicans*.

At this stage, we decided to extend the Betti reaction to other aminoacid derivatives to obtain molecules bearing the valuable aminoacid moiety, that could lead to other bioactive species. However, this investigation soon showed unexpected features.

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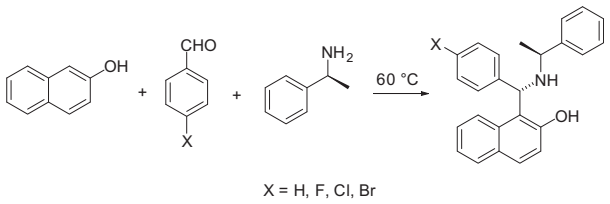


Scheme 1. Betti reaction between 2-naphthol, aryl aldehydes and (*S*)-1-phenylethylamine.

2. Results and discussion

2-Naphthol, benzaldehyde and (*S*)-valine methyl ester, chosen as a representative aminoacid derivative, were reacted at 60 °C without any solvent for two days, according to the cited procedure[4,7,12] (Table 1, entry 1).

We observed the presence of one main product in the crude reaction mixture. We believed that it was the aminobenzylnaphthol **1** having the (*S*,*S*)-configuration (see later for a discussion on the assignment of configuration), as always occurs in these reaction when an (*S*)-amine was employed. The intermediate **1** was accompanied by minor amounts of a product, that we believed to be the (*R*,*S*)-stereoisomer, together with tiny amounts of other unidentified by-products. The crude reaction mixture was purified by chromatography and we found that the isolated yield of the main product was 58% (Table 1, Entry 1), a value that is in the range of other similar reactions. NMR spectra and elemental analysis were consistent with the structure of the desired aminobenzylnaphthol-**1**. However, when we measured its optical rotatory power, we obtained values close to 0° (using many repeated reactions, the recorded values were in the 1°–2° range). Usually,[4–7] these aminobenzylnaphthols have specific rotations in the hundreds. Apparently, the stereogenic center of the valine methyl ester was completely scrambled; thus, the synthesized compound-**1** should have been a mixture of (*R*,*R*)- and (*S*,*S*)-enantiomers (Table 1, entry 1), separated in the purification steps from the minor (*R*,*S*)- and (*S*,*R*)-pair.

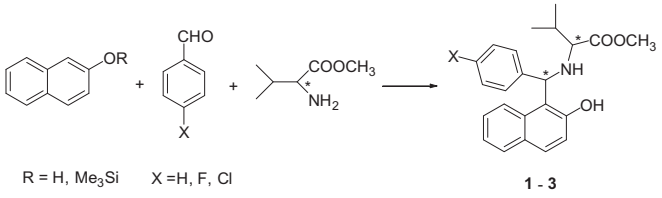
The reaction was repeated with the (*R*)-valine methyl ester, and the same result was obtained (Table 1, entry 2), *i.e.* the predominant product was a mixture of (*R*,*R*)- and (*S*,*S*)-enantiomers, isolated in a similar yield (55%, Table 1, entry 2). As a final check, a mixture of products of the reactions of Entries 1 and 2 was used first to set up the HPLC separation on a chiral column (Whelk O2 column, see Supplementary data, Table S1). The consequent HPLC analysis showed unequivocally that both reactions of entries 1 and 2 yielded an almost equimolar mixture of (*R*,*R*)- and (*S*,*S*)-**1**.

This result was unexpected, because the configurational stability of various (*R*,*R*)-stereoisomers synthesized with the Betti procedure was also tested at 60 °C for many days, without detecting loss of chirality.[4] The (*S*)-stereocenter of the valine methyl ester looked to be completely scrambled, even if, formally, it should not be involved into the reaction. In fact, the Betti procedure is believed to proceed through the formation of a chiral aldimine, deriving from the benzaldehyde and the amine, that subsequently reacts with 2-naphthol.[1] From a literature survey, we found many reports of the employment of chiral aldimine deriving from aminoacid esters in asymmetric synthesis. To limit only to the aldimines deriving from (*S*)-valine methyl ester and aryl aldehydes, silylated nucleophiles were reported to react smoothly with these compounds, with the aminoacid stereocenter acting as a chiral inducer.[13–15]

On the other hand, we found also that α-amino acid derivatives can be racemised in the presence of aldehydes, and in particular of salicylaldehyde.[16] In fact, the imine, obtained with the reaction between the ester of the aminoacid and the aldehyde, can undergo an aza-allyl tautomerism. If this process occurs, the chirality of the ester of the aminoacid would be completely scrambled.[16] The aza-allyl tautomerism that could be active in our process is drawn in Scheme 2.

The tautomerism was reported to be favored by the hydroxyl group of the salicyl aldehyde, close to the reaction center.[16] We reasoned that the disappointing results of Entries 1 and 2 can be similar to the racemization of chiral aldimines in the presence of salicyl aldehyde, occurring in our case with the anchimeric assistance of the naphthol hydroxyl group. In fact, in their work, Forlani et al. stressed the role of the anchimeric assistance of the naphthol hydroxyl group in this reaction.[5] Moreover, the 60 °C temperature could have been detrimental, since it was reported that higher temperature favored the loss of chirality.[16] Along the same lines, previous reports in asymmetric synthesis of chiral aldimines deriving from (*S*)-valine methyl ester were performed always at far lower temperatures.[13–15]

Table 1
Betti reaction of 2-naphthol, aryl aldehydes and valine methyl ester



Entry	R	X	VAL Config[a]	*T* (°C)	Solvent	Product	Yield[b]
1	H	H	(*S*)	60	No	(*S*,*S*) + (*R*, *R*)-**1**	58
2	H	H	(*R*)	60	No	(*S*,*S*) + (*R*, *R*)-**1**	55
3	Me_3Si	H	(*S*)	40	CH_2Cl_2	(*S*,*S*)-**1**[c]	40[d]
4	H	H	(*S*)	35	Et_2O	(*S*,*S*)-**1**[c]	35[(e)]
5	H	F	(*S*) + (*R*)	60	No	(*S*,*S*) + (*R*,*R*)-**2**	68
6	H	F	(*S*)	60	No	(*S*,*S*)-**2**[c]	62
7	H	Cl	(*S*) + (*R*)	60	No	(*S*,*S*) + (*R*,*R*)-**3**	58
8	H	Cl	(*S*)	60	No	(*S*,*S*)-**3**[c]	62

[a] Configuration of the employed valine methyl ester.
[b] Isolated yields.
[c] Configuration attributed by NMR analysis (see text).
[d] Addition of ytterbium triflate and sodium sulfate. (e) Addition of chlorotrimethylsilane and lithium perchlorate.

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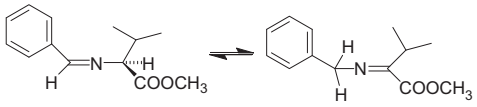

Scheme 2. Aza-allyl tautomerism in an aldimine deriving from (*S*)-valine methyl ester.

At this stage, we decided to follow the reaction between 2-naphthol, benzaldehyde and (*S*)-valine methyl ester over time, analyzing samples of the crude reaction mixture with the chiral HPLC. After 12 hours at room temperature, chiral HPLC analysis showed the early formation of only (*S*,*S*)-aminobenzylnaphthol (see Supplementary data, Fig. S1). After this time, the temperature of the Betti reaction was raised to 60 °C. After 8 h at 60 °C, chiral HPLC analysis showed that traces of (*R*,*R*)-aminobenzylnaphthol appeared (see Supplementary data, Fig. S2; the arrow points towards these traces). After two days at 60 °C, both (*S*,*S*)- and (*R*,*R*)-aminobenzylnaphthol were present (see Supplementary data, Fig. S3). The detrimental effect of the higher temperature, necessary to ensure good yields, is evident from this test. Moreover, this experiment is in agreement with the reaction pathway depicted by Palmieri et al., in which the Betti reaction at 60 °C was described as an equilibrium between the reactants and the product.[4] Part of the product dissociates to yield the reactants; thus, even an enantioenriched aminobenzylnaphthols, synthesized in the early moments, can scramble its chirality due to this equilibrium.

At this point, we sought different and milder conditions to accomplish the Betti reaction. Our project was both to reduce the reaction temperature and to block the action of the naphthol hydroxyl group. In this context, we tested a series of different protocols that had been previously reported for the Betti reaction.[1,2] After some tests, we found that the stereopure (*S*,*S*)-aminobenzylnaphthol-**1** can be obtained by reacting 2-naphthyl trimethylsilyl ether (instead of the 2-naphthol) with benzaldehyde and (*S*)-valine methyl ester in methylene chloride at 40 °C, in the presence of catalytic amounts of ytterbium triflate[17] (Table 1, entry 3). In a more straightforward route, the reaction was performed with 2-naphthol, benzaldehyde and (*S*)-valine methyl ester in diethyl ether, in the presence of chlorotrimethylsilane and lithium perchlorate[18] (Table 1, entry 4). The enantiomeric purity of the products of the reactions of entries 3 and 4 was thoroughly checked by chiral HPLC analysis, thus confirming that only one enantiomer was obtained under these reaction conditions. However, the enantiopure (*S*,*S*)-**1** was obtained with lower yields (entries 3 and 4), as a consequence of the lower reaction temperature, but also because greater amounts of (*R*,*S*)-**1** were obtained, according to the general mechanistic pathway of the Betti procedure reported by Palmieri et al.[4] and by Forlani et al.[5] (*R*,*S*)-**1** is elusive, because it decomposes on standing. However, in its lifetime, it was possible to record its NMR spectra (see Supplementary data), that were used to attribute the configuration of these products, according to a procedure already reported.[4,12] The procedure, that has been confirmed when compared with the X-ray diffraction experiments, hinges on the presence of a strong intramolecular hydrogen bonding between the naphthol hydrogen and the nitrogen atom.[1,4,7,12]This tight interaction yields an almost rigid six member ring, that is able to dictate the arrangement of the other groups in the molecule,[4,12] according to the Figures 1 and 2.

In the case of the (*R*,*S*)-**1** stereoisomer, the arrangement of the groups causes the contemporary interaction of the H_a-hydrogen atom with the phenyl group, and of the H_b-hydrogen atom with the oxygen of the carbonyl moiety (Fig. 1). These possibilities are precluded for the (*S*,*S*)-**1** stereoisomer (Fig. 2).

If the H_a interacts with the phenyl group, it should move upfield, due to the shielding by the aryl group, a well known effect

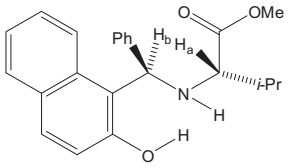

Figure 1. Steric arrangement of groups in (*R*,*S*)-aminobenzylnaphthols **1**.

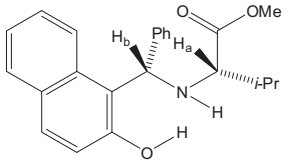

Figure 2. Steric arrangement of groups in (*S*,*S*)-aminobenzylnaphthols **1**.

used in several attribution of configuration with NMR methodologies.[19] If H_b interacts with the oxygen atom in an hydrogen bonding fashion, it is deshielded, and thus it should move downfield.[20] The ^{1}H NMR chemical shifts of the H_b are 5.58 ppm for the (*S*,*S*)-**1** and 5.82 ppm for the (*R*,*S*)-**1** (actually, a downfield shift due to the hydrogen bonding[20]). The ^{1}H NMR chemical shifts of the H_a are 3.35 ppm for the (*S*,*S*)-**1** and a multiplet centered at 3.11 ppm for the (*R*,*S*)-**1** (actually, an upfield shift, due to the phenyl group shielding[19]). According to both these considerations, the (*S*,*S*)-configuration can be attributed to the predominant stereoisomer of the reaction, as always occurs in every reported Betti reaction starting from (*S*)-amines.[1,2,4–7,12]

Contemporary to the NMR analysis, crystallographic experiments were undertaken, but it was difficult to find a crystal of the aminobenzylnaphthol**1** suitable for the X-ray diffraction analysis. However, preliminary results seem to confirm the (*S*,*S*)-configuration, and the complete analysis will be reported in due course.

(*S*,*S*)-Aminobenzylnaphthol **1** had a specific rotation of +125.9, actually similar to the values of other aminobenzylnaphthols.[4–7,12] and a melting point of 88–90 °C. On the other hand, we measured a 157–159 °C melting point for the mixture (*S*,*S*)-**1** + (*R*,*R*)-**1** (Table 1, Entries 1 and 2).

While these reactions were investigated, Bedekar et al. published a paper,[21] in which some aminobenzylnaphthols were synthesized by the Betti reaction with the previously outlined protocol (*i.e.* mixing of the reagents without solvents at 80 °C). The intermediates obtained were tested as chiral solvating agents (CSA) in the NMR separation of a sample of racemic mandelic acid.[21] Among other molecules, the aminobenzylnaphthol **1** deriving from the (*S*)-valine methyl ester was synthesized. The authors reported the spectral properties of this compound, together with a melting point of 146–148 °C and a specific rotation of +428°. When mixed with racemic mandelic acid, this aminobenzylnaphthol caused a 0.02 ppm shift of the ^{1}H NMR chemical shift, but no splitting.

The ^{1}H NMR spectra of the aminobenzylnaphthol **1** synthesized by us and by Bedekar et al. were similar, but we do not agree about the enantiomeric purity that they reported. In fact, in our hands, we observed the total loss of the original stereochemical integrity, when similar reaction conditions were used.

To settle this point, the (*S*,*S*)-aminobenzylnaphthol **1** produced by us was used as a chiral solvating agent in the cited NMR experiment with the racemic mandelic acid. We observed the shift of the chemical shift, as reported,[21] but also a clear splitting of the signal at 5.22 ppm (3.3 Hz at 500 MHz), that had not been observed by the other authors (Fig. 3).[21]

This is a convincing proof that their sample was racemic, because the lack of splitting has to be attributed to the complete

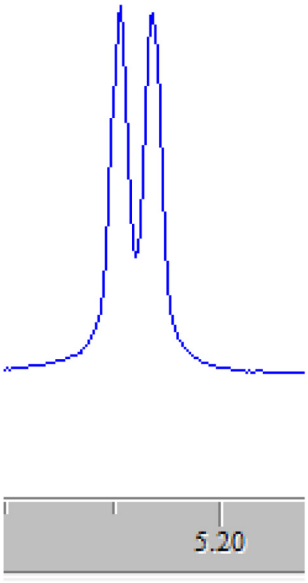

Figure 3. Splitting of the 5.22 ppm signal of racemic mandelic acid as a consequence of the addition of the (*S*,*S*)-**1**, synthesized according to our reaction conditions.

scrambling of chirality that occurs during the reaction at a higher temperature. The comparison of the melting points is also consistent with our conclusions. In fact, we found a large difference between the mp of the (*S*,*S*)-**1** (88–90 °C) and the value of its racemic counterpart (157–159 °C). The report of a mp of 146–148 °C[21] is close to the mp found by us for the racemic mixture. Summing up, it remains obscure to us the origin of the specific rotation of +428[21] measured by Bedekar et al.

At this stage, along the lines of our previous wok,[7,10,12] we extended the Betti reaction of 2-naphthol and (*S*)-valine methyl ester to haloaryl aldehydes, such as 4-fluorobenzaldehyde and 4-chlorobenzaldehyde (Table 1, entries 5–8). We observed a behavior similar to the reaction with benzaldehyde, with the formation of one predominant product, accompanied by some other side products in lower amounts. The isolation of this product by chromatography, and the following analysis, revealed that the expected aminobenzylnaphthols **2** and **3** were obtained.

The reaction with a 1:1 mixture of (*S*)- and (*R*)-valine methyl ester, in order to have a sample of the couple of the (*S*,*S*) + (*R*,*R*)-aminobenzylnaphthol **2** and **3** (Table 1, entries 5 and 7) was performed first. These racemic compounds were needed to establish the chiral HPLC separation conditions (see Supplementary data, Table 1).

Later, the reaction was repeated with the (*S*)-valine methyl ester under the usual reaction conditions (60 °C temperature, no solvent) as a first test. We obtained the desired aminobenzylnaphthols **2** and **3** both in 62% isolated yields (Table 1, entries 6 and 8), a satisfactory value for these reactions. Then, and more importantly, the corresponding (*S*,*S*)-aminobenzylnaphthols **2** and **3** were obtained without any loss of stereochemical integrity, even under these less smooth reaction conditions (*T* = 60 °C, no solvent, 2 days reaction time). The (*S*,*S*)-absolute configuration can be attributed also in these cases by inspection of the ^{1}H NMR spectra of the crude reaction mixture, in which signals referring to minor amounts of the (*R*,*S*)-stereoisomers can be observed. These signals behave as the resonances of the (*R*,*S*)-**1** stereoisomers; thus, the same considerations developed for the attribution of the configuration of (*S*,*S*)-**1** hold also in the cases of **2** and **3**. In conclusion, in the usual H/F/Cl sequence[7,10,12] substituents variation of the aryl aldehydes, it was only in the case of benzaldehyde that racemisation occurred, when the reaction was performed with the usual reaction protocol.

Within this reactivity framework, it is not easy to draw mechanistic conclusions about the stereochemistry of the extension of this reaction to haloaryl aldehydes. It would be safer to wait for a systematic screening of aryl aldehydes, bearing substituents having different electronic properties.

3. Conclusions

In conclusion, the Betti reaction with 2-naphthol, (*S*)-valine methyl ester and the investigated aryl aldehydes shows one peculiar case of loss of stereochemical integrity under the usual reaction conditions, when benzaldehyde was employed, a fact that has been overlooked in the literature. In the present work, this single unusual case was recognized, and new and smooth reaction conditions were set up to overcome this undesired process. A warning emerges from this paper, and careful checks should be always carried out when a derivative of aminoacids is used as a chirality inducer, even when the stereogenic center appears not to be involved in the reaction.

Three new chiral aminobenzylnaphthols, bearing the aminoacid residue, were synthesized. These compounds, that are potentially useful in asymmetric synthesis, enlarge the family of chiral pool of intermediates synthesized using the Betti procedure. Furthermore, according to the original spirit of our research, we have synthesized three new compounds bearing the aminoacid fragment, that makes them of interest in the wide field of bioactive compounds.

4. Experimental procedures

(*S*)- and (*R*)-Valine methyl ester were obtained from the commercial valine methyl ester hydrochloride. The Betti reaction was performed according to the standard protocol, with or without the additives listed in Table 1.

Procedure 1 (Standard and solvent-less procedure). (*S*)-Valine methyl ester (0.35 g, 2.67 mmol) was added to 4-fluorobenzaldehyde (0.25 mL, 2.32 mmol) and stirred for 10 minutes at room temperature. 2-Naphthol (0.32 g, 2.22 mmol) was added and the mixture was heated to 60 °C for two days. The crude reaction mixture was purified first by chromatography (silica gel, eluent *n*-hexane/ethyl acetate 9:1), followed by crystallization (ethanol) to yield 0.53 g (62%). The same procedure can be applied to the Betti reaction with *p*-chlorobenzaldehyde.

Procedure 2 (with a solvent and additives). (*S*)-Valine methyl ester (0.5 g, 3.81 mmol), benzaldehyde (0.39 mL, 3.83 mmol) and lithium perchlorate (0.041 g, 0.381 mmol) were mixed in 2 ml of diethyl ether. After 10 minutes, chlorotrimethylsilane (0.24 mL, 1.91 mmol) and 2-naphthol (0.55 g, 3.81 mmol) were added and the mixture was reacted for two days at 35 °C. The crude reaction mixture was purified first by chromatography (silica gel; eluent: *n*-hexane/ethyl acetate 9:1), followed by crystallization to yield 0.48 g (35%).

4.1. (*S*,*S*)-2-((Hydroxynaphth-1-yl)benzylamino)-3-methylbutanoic acid methyl ester 1.[21]

$[\alpha]_D^{25}$ = +125.9 (*c* 1.2, $CHCl_3$). (*RS*,*RS*)-**1**: mp 157–159 °C. The stereoisomeric purity was checked with chiral HPLC (column (*R*, *R*)-Whelk O2, eluent *n*-hexane/*i*-propanol 95:5).

4.2. (*S*,*S*)-2-(((Hydroxynaphth-1-yl)(4′-fluorophenyl)methyl) amino)-3-methylbutanoic acid methyl ester 2

Mp 156–158 °C (ethanol), $[\alpha]_D^{25}$ = +136.7 (*c* 0.5, $CHCl_3$). The stereoisomeric purity was checked with chiral HPLC (column

Chiralcel OD-H, eluent *n*-hexane/*i*-propanol 95:5). Anal. Calcd for $C_{23}H_{24}FNO_3$: C 72.42; H 6.34; N 3.67. Found C 72.44; H 6.23; N 3.96. ^{1}H NMR ($CDCl_3$, 500 MHz) ^{1}H NMR ($CDCl_3$, 500 MHz) δ 12.49–12.46 (broad, 1H, OH), 7.77–7.73 (m, 2H, H_{Ar}), 7.57–7.54 (m, 1H, H_{Ar}), 7.43–7.39 (m, 2H, H_{Ar}), 7.35–7.31 (m, 1H, H_{Ar}), 7.28–7.24 (m, 1H, H_{Ar}), 7.19–7.15 (m, 1H, H_{Ar}), 7.02–6.96 (m, 2H, H_{Ar}), 5.55 (1H, $HCAr_2$), 3.79 (s, 3H, OMe), 3.33 (dd, J = 5.2, J = 12.8 Hz, 1H, HCC=O), 2.63 (d, J = 12.8 Hz, 1H, NH), 2.13–2.05 (m, 1H, $CHMe_2$), 0.99 (d, J = 6.8 Hz, 3H, Me), 0.97 (d, J = 6.8 Hz, 3H, Me). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.5 (C=O), 162.4 (d, J = 247 Hz, C_{Ar}-F), 156.5 (C_{Ar}-OH), 136.3 (d, J = 3.5 Hz, C_{Ar}), 132.7 (C_{Ar}), 130.1 (C_{Ar}), 129.8 (d, J = 8.3 Hz, C_{Ar}), 128.9 (C_{Ar}), 128.7 (C_{Ar}), 126.7 (C_{Ar}), 122.7 (C_{Ar}), 120.7 (C_{Ar}), 120.0 (C_{Ar}), 115.9 (d, J = 21.5 Hz, C_{Ar}), 112.4 (C_{Ar}), 65.3 (C–C=O), 60.8 ($HCAr_2$), 51.9 (OCH_3), 31.6 ($CHMe_2$), 18.9 (Me), 18.8 (Me).

4.3. (*S*,*S*)-2-(((Hydroxynaphth-1-yl)(4′-chlorophenyl)methyl) amino)-3-methylbutanoic acid methyl ester 3

Mp 119–121 °C (ethanol). $[\alpha]_D^{25}$ = +105 (*c* 0.9, $CHCl_3$). $C_{23}H_{24}ClNO_3$ HRMS 396.1349 (predicted 396.1372). The stereoisomeric purity was checked with chiral HPLC (column Chiralcel OD-H, eluent *n*-hexane/*i*-propanol 95:5). ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 12.41–12.38 (broad, 1H, OH), 7.77–7.74 (m, 2H, H_{Ar}), 7.61–7.57 (m, 1H, H_{Ar}), 7.41–7.38 (m, 2H, H_{Ar}), 7.37–7.33 (m, 1H, H_{Ar}), 7.32–7.29 (m, 2H, H_{Ar}), 7.28–7.24 (m, 1H, H_{Ar}), 7.15 (d, J = 9.0 Hz, 1H, H_{Ar}), 5.56 (s, 1H, $HCAr_2$), 3.79 (s, 3H, OCH_3), 3.32 (dd, J = 13.0, J = 5.5 Hz, 1H, HCC=O), 2.68–2.64 (broad, 1H, NH), 2.13–2.04 (m, 1H, $CHMe_2$), 0.99 (d, J = 6.8 Hz, 3H, Me), 0.97 (d, J = 6.8 Hz, 3H, Me). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.4 (C=O), 156.5 (C-OH), 139.0 (C_{Ar}), 134.0 (C_{Ar}), 132.7 (C_{Ar}), 130.2 (C_{Ar}), 129.4 (C_{Ar}), 129.2 (C_{Ar}), 128.9 (C_{Ar}), 128.7 (C_{Ar}), 126.7 (C_{Ar}), 122.7 (C_{Ar}), 120.7 (C_{Ar}), 120.0 (C_{Ar}), 112.1 (C_{Ar}), 65.3 (C–C=O), 60.8 ($HCAr_2$), 51.9 (OCH_3), 31.6 ($CHMe_2$), 18.9 (Me), 18.8 (Me).

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A. Supplementary data

Supplementary data (HPLC separations of the enantiomers of aminobenzylnaphthols **1**–**3**. Chiral HPLC sampling during time of the Betti reaction leading to **1**. NMR spectra of already reported compounds.) associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetasy.2017.10.026.

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