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The Betti base: absolute configuration and routes to a family of related chiral nonracemic bases

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Abstract

A detailed protocol for the resolution of the Betti base [i.e. 1-(α-aminobenzyl)-2-naphthol] was investigated and the absolute configuration of the two isomers was established by means of an X-ray diffractometric study. A series of optically active derivatives was also prepared. The list includes the *N*-benzyl- and the *N*,*N*,*O*-trimethyl derivatives. The *N*,*N*-dimethyl derivative was prepared in racemic form by means of the Betti reaction and was resolved into the two enantiomers with an extremely easy and efficient procedure. The *O*-methyl derivative was prepared in a racemic form and subjected to resolution. The configuration of each base was determined by correlation with the configuration of the Betti amine.

1. Introduction

At the beginning of this century, Betti, a pioneer of asymmetric synthesis,[1] reported a straightforward condensation of 2-naphthol, ammonia and 2 equivalents of benzaldehyde.[2–5] A product **1** is easily obtained from these reagents. The so-called Betti base **2** is produced by acid treatment of this intermediate, followed by the addition of KOH to the ammonium salt to yield the amine **2**[6–11] (Scheme 1).

On the basis of IR data,[12] the structure **1a** is considered valid for the solid material, whereas an equilibrium between **1a** and **1b** is established in solution.[12]

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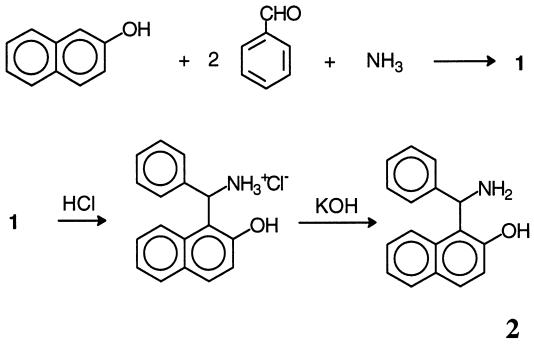
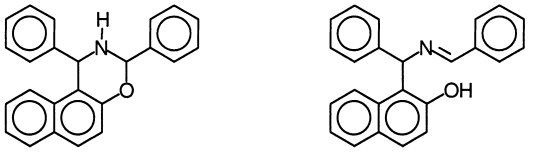


Scheme 1.



1 a **1 b**

A similar reaction can be performed using other naphthols[13–16] or quinolinols[17–20] or replacing ammonia with amines.[21] The enantiomers of the base **2** were resolved by Betti[22,23] and used by the same author to resolve 2-(p-anisyl)propanaldehyde[24] and glyceraldehyde[25] and to discriminate between aldohexoses and ketohexoses.[26] However, in spite of both availability and low cost of the base **2**, no further application was reported for the optically active compound. In recent times, the racemic Betti base was used only for the transformation into products showing antibacterial activity.[27] In addition, a variety of racemic structures related to the Betti base have been prepared recently by preformed iminium salts.[28]

In our opinion, the long silence over this optically active material was in sharp contrast with the high popularity enjoyed by the chirality theme in recent decades. This appeared to us still more surprising considering the bifunctionality of the base which is reminiscent of well recognized members of the chirality pool (e.g. ephedrine derivatives, cinchona alkaloids), and can be considered a good requisite for further elaborations.

With this background, an investigation aimed at re-evaluation of the Betti base seemed warranted. In the present contribution, we report the determination of the absolute configuration of the two enantiomers of **2**, the synthesis of various derivatives of the base and the correlation of their configuration with the configuration of the prototype **2**.

2. Results and discussion

The synthesis of the base **2** was performed in a similar manner to that described by Betti.[11] However, some small but significant variations were introduced by us in the resolution of the base, since the Betti original protocol was vague and fragmentary, expecially as far as the procedure to obtain (−)-**2** is concerned. The crystalline material which was subjected to X-ray diffraction analysis was represented by the hydrobromide **2**·HBr·H_2O, obtained by treating (+)-**1**[2,3,11] with aqueous hydrogen bromide.

As shown in Fig. 1, the absolute configuration of (+)-**2** was found to be (*S*).

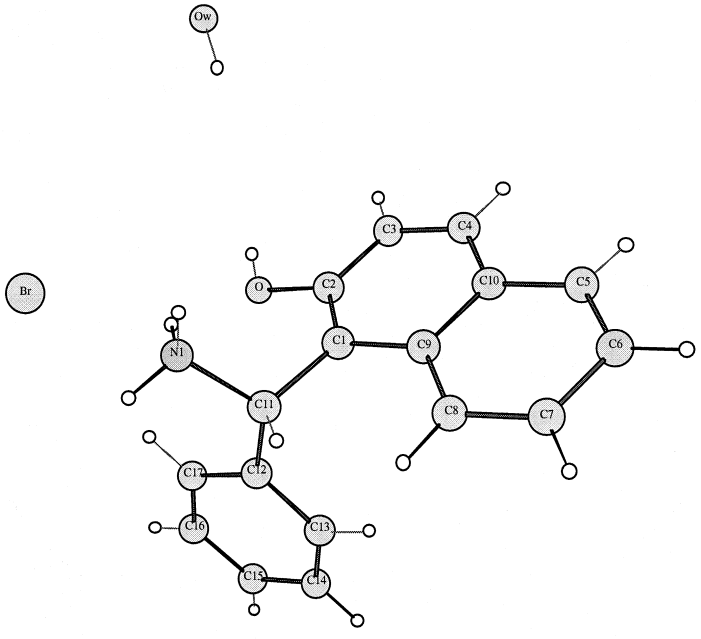
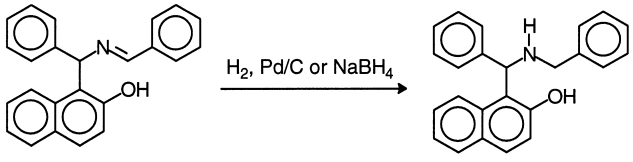


Fig. 1. Projection down the *a*-axis of the structure of the hydrobromide **2**·HBr·H_2O, obtained by treating (+)-**1** with aqueous hydrogen bromide

3. Synthesis of derivatives of the Betti base

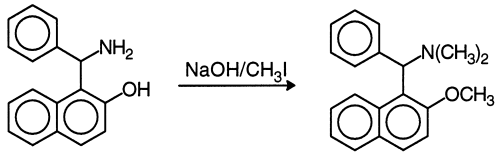
The *N*-benzyl derivative **3** was easily obtained by reducing (*S*)-(+)-**1** with hydrogen in the presence of Pd/C, or with $NaBH_4$ (Scheme 2).



(*S*)-(+)-**1** (*S*)-(+)-**3**

Scheme 2.

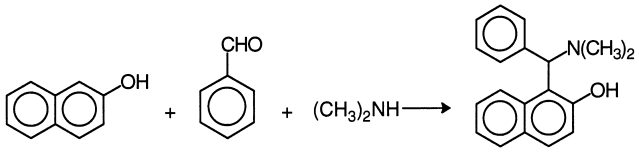
In an equally straightforward manner, treatment of the (*S*)-(+)-**2** base with $NaOH/CH_3I$ led to the trimethyl derivative (*S*)-(−)-**4** (Scheme 3).



(*S*)-(+)-**2** (*S*)-(−)-**4**

Scheme 3.

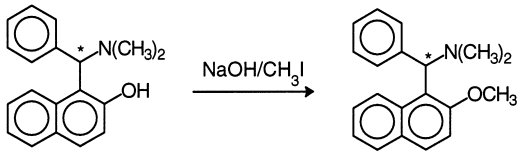
In order to obtain the *N*,*N*-dimethylamino derivative **5**, in principle a chemoselective alkylation of the amino group should be required. However, we found that the problem of chemoselection could be skipped by adopting a variation of the synthetic strategy. Indeed, the *N*,*N*-dimethylamino derivative **5** can be easily obtained by Betti reaction replacing ammonia with dimethylamine[21] (Scheme 4).



5

Scheme 4.

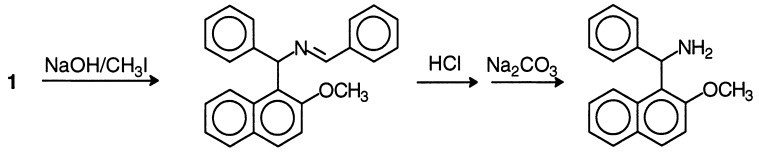
Furthermore, resolution of the enantiomers of **5** was achieved in an extremely easy manner by separation of the diastereoisomeric tartaric acid salts in acetone. The less soluble salt was found to precipitate in an almost pure form. As a consequence, the more soluble salt was obtained, also almost pure, by evaporation of the solvent. After the hydrolysis of the less soluble salt, the *N*,*N*-dimethylamino derivative (+)-**5** was treated with NaOH/CH_3I to give (*S*)-(−)-**4**, thus allowing us to attribute the (*S*) configuration to the compound (+)-**5** (Scheme 5).



(+)-**5** (*S*)-(−)-**4**

Scheme 5.

Finally, it was considered convenient to obtain the *O*-methyl derivative of **2**. Difficulties in preparing such a derivative were described by Ray and coworkers,[29,30] who eventually synthesized the same product by a multistep procedure.[29] We found that methylation of the oxygen was possible by treatment of **1** with NaOH/CH_3I followed by hydrolysis of the intermediate **6** (Scheme 6).

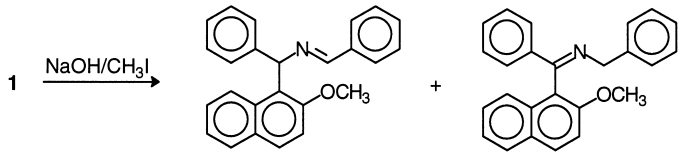


6 **7**

Scheme 6.

Unfortunately, the procedure could be applied only to the synthesis of the racemic *O*-methyl derivative. The extension of the method to the optically active material was plagued with the complete loss of optical activity, very likely the result of an aza-allylic tautomerism.[31] Indeed, compound **8** was found as a side product in the methylation of **1** (Scheme 7).

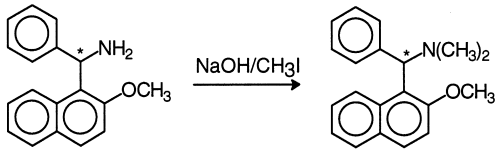
However, this pitfall did not represent a special problem, since it is known that the *O*-methyl derivative **7** can be resolved by using malic acid.[29] As a consequence, the optimized procedure could be represented by the synthesis of the racemic compound, starting with **1**, followed by resolution with this acid.



6 **8**

Scheme 7.

Careful methylation of the nitrogen atom of (+)-**7** was found to give (*S*)-(−)-**4**. Thus, both compounds must present the (*S*) configuration (Scheme 8).



(+)-**7** (*S*)-(−)-**4**

Scheme 8.

4. Conclusion

Our work has shown that a family of interesting chiral nonracemic bases with a known configuration can be obtained by using the Betti reaction and performing simple operations. Taking into account that a scale-up can be easily envisaged,[32] the obtained bases, in particular the base **5**, appear very convenient from an economical point of view. In addition, the products of our investigation are likely candidates for a variety of applications dealing with enantioselective processes. Our contributions in this field will appear in forthcoming papers.

5. Experimental section

The purified reaction products were characterized by their ^{1}H- and ^{13}C-NMR spectra, recorded at 500 and 125 MHz, respectively, and their mass spectra determined, when possible, by GC–MS analysis (SE30, 30 m, capillary columns and mass selective detector, 70 eV).

*5.1. Improved synthesis of **2***

Crude 1,3-diphenyl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazine **1a** and **2**·HCl were obtained according to the Betti procedure[11] and used in the preparation of **2** without further purification.

80 ml of 2 M Na_2CO_3 was added to a suspension of **2**·HCl in water (15 ml). The mixture was stirred for 1 h at rt and then extracted with diethyl ether and dried (anhydrous Na_2SO_4). The organic solvent was evaporated under reduced pressure, producing a residue, 1-(α-aminobenzyl)-2-naphthol **2** (5.7 g, yield 85%), which can be further purified by washing with a small amount of diethyl ether. Mp 124–125°C (lit.[11] mp 124–125°C).

5.2. Resolution of **2**

A solution of (2*R*,3*R*)-tartaric acid (4.51 g, 30.0 mmol) in an ethanol 95%:methanol mixture (20:10 ml) was added dropwise to a solution of racemic **2** (7.49 g, 30.0 mmol) in ethanol 95% (240 ml). After the addition, the mixture was stirred for 6 h at rt and then filtered. Methanol (30 ml) was added to the less soluble salt and the suspension was stirred for 3 h at rt. The salt was filtered and collected (5.4 g, 13.5 mmol, 45%). The mother solution was evaporated to dryness under reduced pressure, producing an orange residue, which was washed with methylene chloride, yielding a white crystalline powder (3.01 g, 7.54 mmol, 25%).

Each diastereomeric salt was suspended in water (10 ml/g salt) and a 2 M Na_2CO_3 solution was added (10 ml/g salt) to this suspension. After 45 min, the mixture was extracted with diethyl ether and dried (Na_2SO_4). The solvent was evaporated under reduced pressure (yield 95%) to give resolved **2** which was further purified by washing with a small amount of diethyl ether.

The less soluble salt originated (+)-**2**, mp 136–137°C, $[\alpha]_D$ +56 (*c* 4.4, benzene) (lit.[22] $[\alpha]_D$ +58.84 (*c* 5, benzene)). The salt recovered from the evaporation of the mother liquors originated (−)-**2**, mp 136–137°C, $[\alpha]_D$ −56 (*c* 4.4, benzene) (lit.[22] $[\alpha]_D$ −58.9 (*c* 5, benzene)). The enantiomeric purity was measured by ^{1}H-NMR experiments with the addition of (*R*)-(−)-3,5-dinitro-*N*-(1-phenylethyl)benzamide and was found to be >98%.

5.3. Synthesis of (+)-**1**

A solution of benzaldeyde (0.132 g, 1.24 mmol) in 2 ml of ethanol 95% was added dropwise to a solution of (+) **2** (0.310 g, 1.24 mmol) in 14 ml of ethanol 95%. The mixture was stirred overnight at rt. The solid was recovered by filtration (0.393 g, 1.16 mmol, yield 94%). (+)-**1**: mp 163–164°C, lit.[33] mp 158°C, $[\alpha]_D$ +169 (*c* 1; $CHCl_3$), lit.[33] $[\alpha]_D$ +110.72 (*c* 4.734; benzene).

5.4. Absolute configuration of **2**·*HBr*·*H*$_2$*O*

2·HBr·H_2O was obtained from (+)-**1** as described for the racemic **2**·HCl. The crystalline compound was dissolved in ethanol and the solution was slowly evaporated to dryness. The crystalline salt was subjected to a single crystal X-ray diffraction analysis. The data collection was carried out on a Nonius CAD4 diffractometer at room temperature using MoKα radiation (λ=0.71067 Å). Relevant crystal data are: crystal dimensions 0.16×0.17×0.55 mm; formula $C_{17}H_{16}BrNO\cdot H_2O$, M_r=348.24, orthorhombic, space group $P2_12_12_1$; *a*=5.198(1), *b*=16.474(2), *c*=17.999(3) Å, *V*=1541.3 Å^3; *Z*=4, d_x=1.48 g/cm^3.

The cell constants were obtained from a least squares fit of the setting angle on 25 reflections in the range $7\leq\theta\leq13°$. The intensity measurements were performed with the $\omega/2\theta$ scan mode in the range $2\leq\theta\leq28°$, $0\leq h\leq6$, $0\leq k\leq21$, $0\leq l\leq23$ for a total of 2162 reflections (1710 unique) and subsequently corrected for Lorentz and polarization effects. An empirical absorption correction (ψ-scan) was also applied.[34]

The structure was solved using direct methods (SIR92)[35] and refined with the full matrix least squares procedure (CRYSTALS'96).[36] Atomic positions with isotropic equivalent temperature factors, bond distances and bond angles are submitted separately. A sketch of the molecule with the Br^- ion and a water solvent molecule is shown in Fig. 1. The anisotropic refinement of 1179 reflections with $I>2\sigma(I)$ converged at R=0.053, R_w=0.038. All hydrogen atoms were located in calculated positions with the exception of H and H_w, bound to the oxygen atoms O and O_w, respectively. These hydrogen atoms were located by difference Fourier and then refined isotropically. Attempts to locate the second hydrogen atom

of the solvent molecule by difference Fourier were unsuccessful. Minimum and maximum map densities of the difference Fourier after the last refinement step were −0.474 and 0.558 $e^-/Å^3$, respectively.

The refinement of the centrosymmetric structure led to R=0.070, R_w=0.050, implying that the molecule illustrated in Fig. 1 is of the correct configuration. The absolute configuration of the molecule was also determined according to the method proposed by Flack.[37] The value of the refined Flack's parameter, using the coordinate data set calculated, is −0.06(4) (and 0.04(6) for all reflections), thus confirming that Fig. 1 refers to the actual atomic coordinates for the studied compound. The determination of the absolute configuration for **2**·HBr·H_2O yielded the (*S*) configuration for the (+)-**2** enantiomer, and consequently for the (+)-**1** enantiomer, and the (*R*) configuration for the (−)-**2** isomer.

5.5. *1-(α-N-Benzylaminobenzyl)-2-naphthol **3***

Racemic **1** or (+)-**1** in toluene were reduced by hydrogen in the presence of Pd/C (90% yield) or by $NaBH_4$ in THF (95% yield). Racemic **3**, mp 136–137°C (lit.[30] mp 143°C). (+)-**3**, mp 124–125°C, $[\alpha]_D$ +208 (*c*=1; benzene). ^{1}H-NMR (CD_3OD) δ 7.66–7.64 (m, 2H), 7.57–7.55 (m, 1H), 7.29–7.10 (m, 13H), 7.04–7.02 (m, 1H), 5.66 (s, 1H), 3.90 (d, *J*=13.3 Hz, 1H), 3.72 (d, *J*=13.3 Hz, 1H), 2.08 ppm (m, 1H). ^{13}C-NMR ($CDCl_3$) δ 156.71, 141.17, 137.82, 132.61, 129.76, 128.97, 128.80, 128.68, 128.66, 128.50, 127.99, 127.66, 126.43, 122.41, 121.07, 120.05, 112.91, 62.67, 52.62 ppm. The enantiomeric purity was determined by chiral HPLC (Chiralcel OD, hexane:isopropanol=90:10, flow rate 1 ml/min, separation factors for the racemic compound α=1.39) and was found to be >98%.

5.6. *[(2-Methoxynaphth-1-yl)benzyl]dimethylamine **4***

Powdered NaOH (1.8 g, 45.0 mmol) was added to a solution of **2** (2.50 g, 10,0 mmol) in THF (30 ml). After 10 min CH_3I (6 ml) was dropped into the slurry. The mixture was stirred for 6 h and then a solution of saturated NH_4Cl was added. After extraction with diethyl ether, the organic extracts were dried with anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was crystallized from ethanol 95% yielding 2.62 g (90%) of racemic **4**, mp 117–118°C. (−)-**4**, mp 98–99°C, $[\alpha]_D$ −26 (*c* 1.09; $CHCl_3$). MS 70 eV m/e (relative intensity) 291 (M^+, 17), 247 (59), 215 (26), 134 (34), 91 (100). ^{1}H-NMR ($CDCl_3$) δ 9.23 (d-like, *J*=8.7 Hz, 1H), 7.69–7.66 (m, 2H), 7.63–7.61 (m, 2H), 7.44–7.40 (m, 1H), 7.29–7.17 (m, 4H), 7.08–7.04 (m, 1H), 5.40 (s, 1H), 3.97 (s, 3H), 2.28 ppm (broad s, 6H). ^{13}C-NMR ($CDCl_3$) δ 154.57, 143.34, 132.61, 129.51, 129.14, 128.18, 127.96, 127.80, 126.16, 125.97, 125.86, 124.33, 123.40, 113.87, 68.15, 56.75, 45.2 ppm. Anal. calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found C, 82.60; H, 7.41; N, 4.71.

5.7. *Resolution of 1-(α-N,N-dimethylaminobenzyl)-2-naphthol **5***

Racemic **5**, mp 165–166°C (lit.[21] mp 164–164.5°C) was prepared by the Betti reaction, as previously shown for compound **2**. Spectral data agreed with those reported.[28] (2*R*,3*R*)-Tartaric acid (3.5 g, 23.44 mmol) in 100 ml of acetone was added to racemic **5** (6.5 g, 23.44 mmol) in acetone (150 ml). Upon addition of the acid, the solution became pale yellow. After 5 h, the mixture was filtered and the less soluble salt was washed with acetone (4.5 g, 10.5 mmol, 45%). The mother solution was evaporated to dryness under reduced pressure, yielding a yellow residue which was crystallized from ethyl ether:ethyl acetate 80:20 to a white powder (4.1 g, 9.6 mmol, 41%).

Each diastereomeric salt was suspended in water (10 ml/g salt) and a 2 M Na_2CO_3 solution was added (10 ml/g salt) to the suspension. After 15 min, the mixture was extracted with ethyl acetate and

dried (Na_2SO_4). The solvent was evaporated under reduced pressure (yield 95%). The less soluble salt originated (+)-**5**, mp 158°C, $[\alpha]_D$ +238 (*c* 0.5; ethanol). The salt recovered from the evaporation of the mother liquors originated (−)-**5**, $[\alpha]_D$ −238 (*c* 0.5; ethanol). The enantiomeric purity was determined by chiral HPLC (Chiralcel OD, hexane:isopropanol=99.5:0.5, flow rate 1 ml/min, separation factors for the racemic compound α=1.311) and was found to be >98%.

*5.8. (2-Methoxynaphth-1-yl)benzylamine **7***

Powdered NaOH (1.8 g, 45 mmol) was added to a solution of **1** (10.12 g, 30 mmol) in 60 ml of THF and 80 ml of acetone at 0°C. After 10 min, 5 ml of methyl iodide was added and the mixture was stirred at rt for 6 h. The reaction mixture was concentrated under reduced pressure, and then extracted with ethyl acetate. The organic phase was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure, yielding a pale yellow mixture of **6** and **8**.

The crude mixture was treated with 100 ml of HCl 2 N, heating with vigorous stirring at 70–80°C for 1 h. After cooling to room temperature, the solid phase was filtered, washed first with cold water and then in a Soxhlet apparatus with acetone for 3 h. The salt was treated with a solution of Na_2CO_3 2 M for 1 h at rt, and the mixture was extracted with diethyl ether. The organic phase was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to yield 5.093 g (64%) of **7**, mp 98–101°C (lit.[29] mp 102°C). MS 70 eV m/e (relative intensity) 263 (M^+, 36), 232 (16), 186 (100), 170 (38). ^{1}H-NMR ($CDCl_3$) δ 8.03 (d-like, *J*=8.6 Hz, 1H), 7.78–7.75 (m, 2H), 7.41–7.35 (m, 3H), 7.31–7.22 (m, 4H), 7.16–7.13 (m, 1H), 6.14 (s, 1H), 3.72 (s, 3H), 2.27 ppm (broad s, 2H). ^{13}C-NMR ($CDCl_3$) δ 154.64, 146.50, 131.86, 129.52, 129.00, 128.56, 127.75, 126.96, 126.35, 125.85, 125.65, 123.45, 123.23, 114.07, 56.27, 50.72 ppm. **7** was resolved by malic acid, according to a reported procedure.[29] (+)-**7**: $[\alpha]_D$ +196 (*c* 1.6; $CHCl_3$) (lit.[29] $[\alpha]_D$ +197 (*c* 1.55; diethyl ether)). The enantiomeric purity was measured by ^{1}H-NMR experiments with the addition of (*R*)-(−)-3,5-dinitro-*N*-(1-phenylethyl)benzamide and was found to be >98%.

5.9. Correlations of configuration

*5.9.1. Synthesis of (S)-(−)-**4** from (+)-**5***

(+)-**5** ($[\alpha]_D$ +238 (*c* 0.5; ethanol)) was methylated according to the methylation procedure described for (*S*)-**2**, yielding (*S*)-(−)-**4**, $[\alpha]_D$ −26.2 (*c* 1.1; $CHCl_3$).

*5.9.2. Synthesis of (S)-(−)-**4** from (+)-**9***

(+)-**9** ($[\alpha]_D$ +196 (*c* 1.6; $CHCl_3$)) was methylated according to the methylation procedure described for (*S*)-**2**, yielding (*S*)-(−)-**4**, $[\alpha]_D$ −26.8 (*c* 1.1; $CHCl_3$).

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