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Zr-mediated synthesis of chiral cyclic imines and their application in Betti reactions

Elena Speich[1], Luca Banfi[1], Lisa Moni[1], Renata Riva[1], Valeria Rocca[1], Andrea Basso[1]*

[1] *Università degli Studi di Genova, Dipartimento di Chimica e Chimica Industriale, 31 Via Dodecaneso, 16146 Genova, Italy; e-mail: andrea.basso@unige.it*

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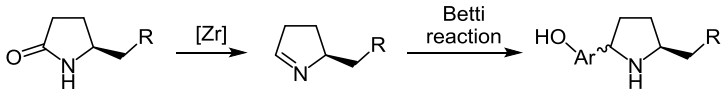


A novel synthetic strategy has been outlined to assemble enantiomerically pure Betti bases with unprecedented structures. This involves the Zr-mediated reduction of pyrrolidin-2-ones to cyclic imines and their subsequent reaction with phenolic derivatives.

Keywords: cyclic imines, Schwartz reagent, Betti reaction.

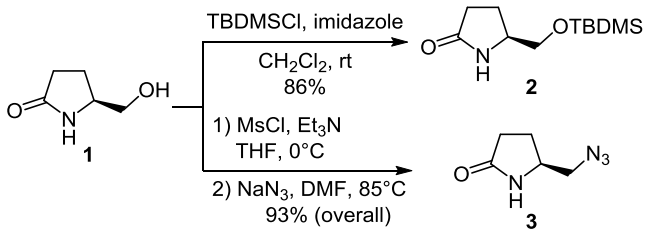
The Betti reaction, discovered by the Italian chemist Mario Betti at the beginning of the 20th century, takes place between imines and phenolic derivatives to give aminoalkylphenols and naphthols.[1] The products of this reaction known as Betti bases, if obtained as individual enantiomers, can find application in asymmetric synthesis. For example, Betti bases are useful as chiral ligands in the enantioselective addition of diethylzinc to aldehydes,[2] they can be used for the synthesis of chiral aminophosphonic acids,[3] iminophosphines and aminophosphinoxides,[4] and as chiral shift reagents for carboxylic acids.[5] The use of chiral imines, as well as of cyclic imines,[4a,6] has only rarely been reported in the literature. Therefore, we would like to present our preliminary results on the use of chiral cyclic imines in Betti reactions.

Bis(cyclopentadienyl)zirconium(IV) chloride hydride, known as the Schwartz reagent,[7] is a reducing agent that can be employed, for example, to reduce amides and lactams into the corresponding imines.

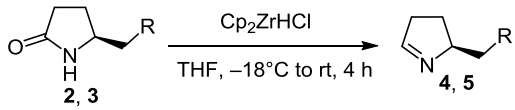
In this article, we report for the first time the Zr-mediated synthesis of chiral cyclic imines and their transformation into optically pure Betti bases through a straightforward two-step procedure. Our studies started with the preparation of suitable lactam substrates from commercially available (*S*)-5-(hydroxymethyl)pyrrolidin-2-one (**1**). This was converted into silyl-protected alcohol **2** and azido derivative **3** (Scheme 1), as free hydroxy and amine functionalities are not inert toward the Schwartz reagent.

The conversion of compounds **2** and **3** into the corresponding cyclic imines **4** and **5** (Scheme 2) was investigated under various conditions, and the best results were obtained by modification of the procedure previously reported in the literature.[8] Specifically, the reaction required 2.1 equiv of Cp_2ZrHCl, which suggests that a dinuclear complex similar to those observed in carbonylation reactions[9] is probably involved. The substrate dissolved in anhydrous THF was transferred by syringe to a suspension of Cp_2ZrHCl at –18°C under inert atmosphere (argon). The temperature was slowly raised to room temperature, and upon completion the reaction mixture became homogeneous. The solution was then concentrated, cooled to 0°C, and diluted with hexane. The white solid

Scheme 1. Conversion of (*S*)-5-(hydroxymethyl)pyrrolidin-2-one (**1**) into silyl-protected alcohol **2** and azido derivative **3**



Scheme 2. Conversion of lactams **2** and **3** into the corresponding cyclic imines **4** and **5**



2, **4** R = OTBDMS; **3**, **5** R = N_3

was filtered and the mother liquor concentrated to afford the desired products.

Under these conditions, the imines were isolated in pure form with a yield ranging between 50 and 70%. The relatively low recovery was attributed to the purification procedure required to remove traces of Zr derivatives, the presence of which was found to be deleterious for the subsequent Betti reactions. The partial instability of the imines, in fact, prevented their purification through flash chromatography. Noteworthy, precipitation of Zr adducts in hexane was fast and almost quantitative. It is worth noting that the enantiomer of compound **4** had already been prepared in our group starting from (*S*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)propan-1-ol through a seven-step procedure in comparable yield.[10]

With the imines in hand, the optimization of the Betti reaction was carried out on compound **4**, which was reacted with naphthol **6** under various conditions reported in Table 1. The desired product **8** (Scheme 3) was isolated as a mixture of diastereoisomers. The reaction proceeded better with chloroform as the solvent under MW heating. The diastereomeric ratio apparently was not affected by the reaction conditions. Yields were referred to the two-step procedure starting from lactam **2**. Under the conditions of entry 6, therefore, the Betti reaction afforded the product almost quantitatively, considering the yield of the first step.

Under optimized conditions, Betti bases **8**–**11** were synthesized combining imines **4**–**5** with phenols **6**–**7** (Scheme 3, Table 2). The two-step procedure afforded the desired products in moderate yields as variable mixtures of diastereoisomers. The structures of these compounds are unprecedented and, thanks to the additional functional groups, they could find application, for example, in fragment-based drug discovery.[11] Recently, compound **8** was prepared by Koley and Jana through a multistep synthesis.[12]

Compounds **8a**,**b** were subjected to a detailed NOE experiment in order to determine the relative configuration of the stereocenters. The presence of a NOE signal between H_A and H_B in compound **8a**, absent in diastereoisomer **8b**, was in accordance with the *cis* configuration, as confirmed by analysis of the 3D models. The NMR pattern observed for compounds **8a**,**b** could be exploited to establish the relative configuration of compounds **9a**,**b** by analogy of chemical shifts and coupling constants (Fig. 1).

Table 1. Optimization of the Betti reaction between imine **4** and naphthol **6**

Entry	Solvent	*T*, °C	Time, h	Yield*, %	*dr*** (*cis:trans*)
1	EtOH	Δ	18	38	55:45
2	MeOH	Δ	18	n.d.*[4]	n.d.
3	MeCN	Δ	18	n.d.	n.d.
4	EtOH	100***	5	36	55:45
5	$CHCl_3$	Δ	18	53	57:43
6	$CHCl_3$	120***	2	62	55:45

* The total yield of diastereomers **8** calculated with respect to the precursor amide **2**.
** The *dr* was determined by integration of ^{1}H NMR signals of the crude product. See text for assignment of *cis/trans* configuration.
*** The reaction was carried out in pressure vial with MW heating.
*[4] Not determined.

Scheme 3. Synthesis of Betti bases **8–11** under optimized conditions

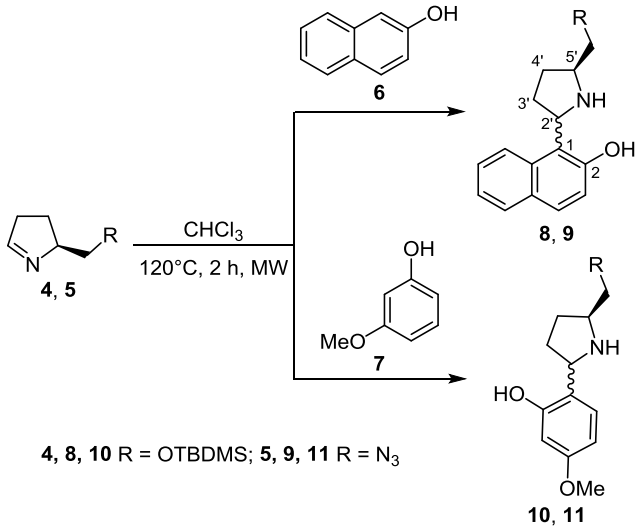


Table 2. Synthesis of Betti bases **8**–**11**

Imine	ArOH	Products	Time, h	Yield*, %	*dr*** (*cis:trans*)
4	**6**	**8a** + **8b**	2	62	55:45
5	**6**	**9a** + **9b**	2	53	54:46
4	**7**	**10a** + **10b**	2	64	68:32
5	**7**	**11a** + **11b**	2	41	60:40

* The total yield calculated with respect to the precursor amides **2** and **3.**
** The *dr* was determined by integration of ^{1}H NMR signals of the crude product. See text for assignment of *cis/trans* configuration.

However, the same did not apply to compounds **10a**,**b** and **11a**,**b**, therefore, their relative configuration was determined by transforming compounds **10a**,**b** into the corresponding Boc-protected derivatives **12a**,**b** (Scheme 4). NOE experiments on compounds **12a**,**b** allowed to establish, similarly to naphthol derivatives **8**, that derivative **12a** was the *cis*-diastereomer. In this case the diagnostic NOE signal was observed between H_B and H_E in compound **12b**, and was absent in compound **12a**. Therefore, in accordance with the 3D models, compound **12a** was assigned a *cis* configuration. The configuration of diastereoisomers **11a**,**b** was established by analogy with compounds **10a**,**b**.

It was interesting to notice that compounds **10** and **11** were characterized by configurational instability. In fact,

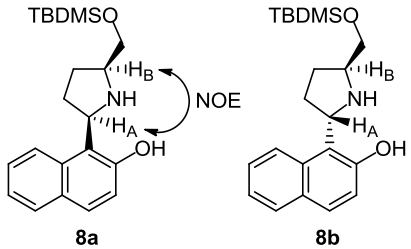
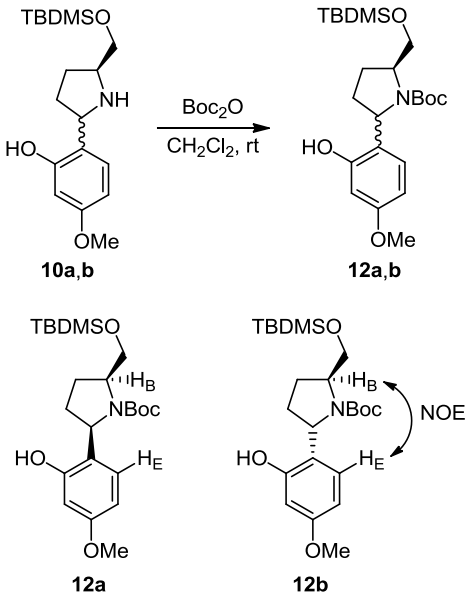


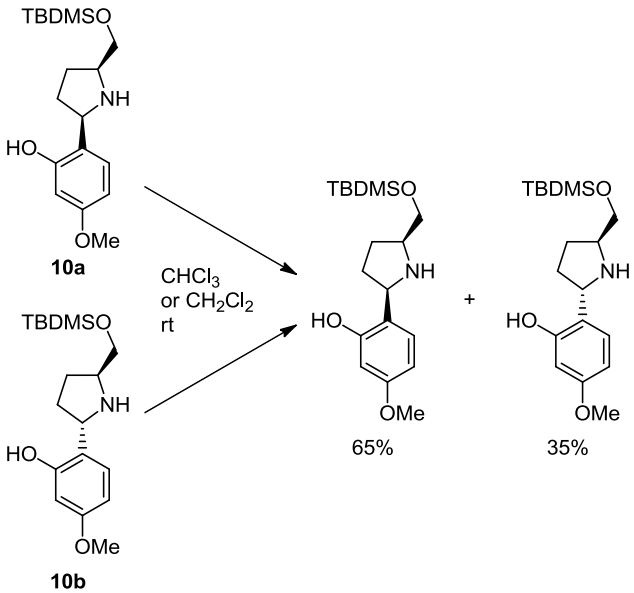
Figure 1. Diastereoisomers **8a**,**b**.

Scheme 4. Synthesis of Boc-protected derivatives **12a**,**b**



leaving the pure isolated diastereoisomers **10a**, **10b**, **11a**, or **11b** in CH_2Cl_2 or $CHCl_3$ at room temperature for several days we could notice a slow epimerization with formation of a 65:35 mixture in favor of the *cis*-isomer (Scheme 5). On the contrary, compounds **8** and **9** as well as the Boc-protected compounds were configurationally stable.

Scheme 5. Epimerization of compounds **10a**,**b**



In conclusion, we have demonstrated that chiral imines obtained through a Zr-mediated reduction of optically pure lactams can be employed in the preparation of Betti bases with unprecedented structures. The presence of additional functional groups can be in principle exploited to further modify these scaffolds and prepare densely functionalized pyrrolidines, that can find application, for example, in the fragment-based drug discovery process. More results will be reported in due course.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Varian 300 instrument (300 and 75 MHz, respectively) in $CDCl_3$ at 295 K; internal standard TMS. High-resolution mass spectra were obtained on a Synapt G2 QToF mass spectrometer. MS signals were acquired from *m*/*z* 50 to 1200 in ESI positive ionization mode. Reactions were monitored by TLC on silica gel plates (thickness 0.25 mm), viewed at UV (λ 254 nm) and developed with Hanessian stain (dipping into a solution of $(NH_4)_4MoO_4 \cdot 4H_2O$ (21 g) and $Ce(SO_4)_2 \cdot 4H_2O$ (1 g) in H_2SO_4 (31 ml) and H_2O (469 ml) and warming). Flash column chromatography was performed using 220–400 mesh silica. Solvents employed as eluents and for all other routine operations, as well as anhydrous solvents and all reagents used were purchased from commercial suppliers and employed without any further purification.

(*S*)-5-{[(*tert*-Butyldimethylsilyl)oxy]methyl}pyrrolidin-2-one (2).[13] A solution of compound **1** (1.0 g, 8.7 mmol) in dry dichloromethane (25 ml) was treated with *tert*-butyldimethylsilyl chloride (2.0 g, 13.0 mmol) and imidazole (1.8 g, 26.1 mmol) under N_2 atmosphere. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated, and the crude residue was purified by chromatography with ethyl acetate as eluent. Yield 1.8 g (86%). R_f 0.40 (AcOEt). Pale-yellow transparent oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.80 (1H, br. s, NH); 3.81–3.67 (1H, m, CH); 3.62 (1H, dd, *J* = 10.0, *J* = 3.9) and 3.43 (1H, dd, *J* = 10.0, *J* = 7.8, CH_2O); 2.39–2.29 (2H, m, CH_2); 2.22–2.10 (1H, m, CH_2); 1.78–1.66 (1H, m, CH_2); 0.86 (9H, s, $C(CH_3)_3$); 0.05 (6H, s, $2SiCH_3$).

(*S*)-5-(Azidomethyl)pyrrolidin-2-one (3).[14] A solution of compound **1** (0.77 g, 6.7 mmol) in dry THF (22 ml) was treated with Et_3N (1.9 ml, 13.4 mmol) and methanesulfonyl chloride (0.77 ml, 10.0 mmol) at 0°C, under N_2 atmosphere. The reaction mixture was stirred at 0°C for 3 h. The crude product was purified by chromatography with AcOEt–MeOH, 9:1, to give a brown-orange oil (1.24 g, 96%). The mesylate product was solubilized into anhydrous DMF (22 ml), and NaN_3 (0.87 g, 13.4 mmol) was added to the solution. The solution was stirred at 85°C for 15 h. The crude product was purified by chromatography with petroleum ether – AcOEt, 8:2, 7:3, 1:1, 3:7; AcOEt; AcOEt–MeOH, 9:1. Yield 0.86 g (96%). R_f 0.67 (AcOEt–MeOH, 9:1). Pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.89 (1H, br. s, NH); 3.86–3.75 (1H, m, CH); 3.46 (1H, dd, *J* = 12.3, *J* = 4.6) and 3.29 (1H, dd, *J* = 12.3, *J* = 6.9, CH_2N_3); 2.48–2.17 (3H, m, CH_2); 1.91–1.73 (1H, m, CH_2).

Synthesis of chiral cyclic imines 4 and 5 with Schwartz reagent (General method). A solution of the appropriate chiral lactam **2** or **3** in dry THF under Ar atmosphere was added dropwise to a suspension of Cp_2ZrHCl (2.1 equiv) in dry THF at –18°C. The final concentration of the lactam in the solution was 0.14 M. The reaction mixture was gradually warmed to room temperature. After 4 h, the reaction mixture was concentrated *in vacuo*, hexane was added to the residue at 0°C with vigorous stirring. The heterogeneous mixture was filtered

twice through a Celite pad. The filtrate was concentrated on a rotary evaporator to afford the desired imine.

(*S*)-2-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-3,4-dihydro-2*H*-pyrrole (4). Analytical data are in accordance with the literature.[10] R_f 0.48 (petroleum ether – AcOEt, 3:7). Pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.60 (1H, s, 5-CH); 4.26–4.05 (1H, m, 2-CH); 3.84 (1H, dd, *J* = 10.1, *J* = 4.1) and 3.66 (1H, dd, *J* = 10.1, *J* = 5.3, CH_2O); 2.67–2.30 (2H, m), 1.93–1.80 (1H, m), and 1.76–1.55 (1H, m, 3,4-CH_2); 0.87 (9H, s, $C(CH_3)_3$); 0.07 (3H, s, $SiCH_3$); 0.05 (3H, s, $SiCH_3$).

(*S*)-2-(Azidomethyl)-3,4-dihydro-2*H*-pyrrole (5). R_f 0.27 (petroleum ether – AcOEt, 1:1). Yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.63 (1H, s, 5-CH); 4.27–4.12 (1H, m, 2-CH); 3.50 (1H, dd, *J* = 12.3, *J* = 5.2) and 3.41 (1H, dd, *J* = 12.3, *J* = 5.4, CH_2N_3); 2.75–2.57 (1H, m), 2.57–2.45 (1H, m), 2.03–1.90 (1H, m), and 1.63–1.45 (1H, m, 3,4-CH_2). ^{13}C NMR spectrum, δ, ppm: 168.4; 72.4; 55.2; 37.2; 23.9.

Synthesis of Betti bases 8–11 a,b (General method). To a solution of imine **4** or **5** (1.0 equiv) in dry $CHCl_3$ (*c* 0.2 M), phenolic compound **6** or **7** (1.0 equiv) was added. The reaction mixture was heated under MW at 120°C for 2 h. The solvent was evaporated, and the crude residue was purified by flash chromatography.

1-((2*R*,5*S*)-5-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-pyrrolidin-2-yl)naphthalen-2-ol (8a).[12] R_f 0.80 (petroleum ether – Et_2O – AcOEt, 7.5:1.5:1.0). Pale-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 13.36 (1H, br. s, OH); 7.76 (1H, d, *J* = 8.4, H Ar); 7.73 (1H, d, *J* = 7.6, H Ar); 7.64 (1H, d, *J* = 8.9, H Ar); 7.42 (1H, ddd, *J* = 8.5, *J* = 6.8, *J* = 1.5, H Ar); 7.27 (1H, ddd, *J* = 7.9, *J* = 6.7, *J* = 1.1, H Ar); 7.06 (1H, d, *J* = 8.8, H Ar); 5.14 (1H, t, *J* = 8.1, 2'-CH); 3.78 (1H, dd, *J* = 9.9, *J* = 4.9) and 3.68 (1H, dd, *J* = 9.9, *J* = 7.3, CH_2O); 3.56–3.45 (1H, m, 5'-CH); 2.94–2.72 (1H, m, NH); 2.53–2.32 (1H, m), 2.09–1.96 (1H, m), 1.94–1.82 (1H, m), and 1.80–1.63 (1H, m, 3',4'-CH_2); 0.93 (9H, s, $C(CH_3)_3$); 0.12 (6H, s, $2SiCH_3$). ^{13}C NMR spectrum, δ, ppm: 156.3; 132.2; 128.8 (2C); 128.2; 126.2; 122.2; 121.0; 120.2; 115.5; 67.1; 60.0; 58.4; 31.7; 26.8; 26.0; 18.3; –5.3; –5.4. Found, *m*/*z*: 358.2201. $C_{21}H_{32}NO_2Si$. Calculated, *m*/*z*: 358.2197.

1-((2*S*,5*S*)-5-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-pyrrolidin-2-yl)naphthalen-2-ol (8b). R_f 0.48 (petroleum ether – Et_2O – AcOEt, 7.5:1.5:1.0). Pale yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.75 (1H, d, *J* = 8.5, H Ar); 7.74 (1H, d, *J* = 8.0, H Ar); 7.64 (1H, d, *J* = 8.9, H Ar); 7.42 (1H, ddd, *J* = 8.4, *J* = 6.8, *J* = 1.4, H Ar); 7.30–7.23 (1H, m, H Ar); 7.07 (1H, d, *J* = 8.9, H Ar); 5.17 (1H, dd, *J* = 9.8, *J* = 6.9, 2'-CH); 3.78–3.69 (1H, m) and 3.68–3.56 (2H, m, CH_2O, 5'-CH); 3.02–2.78 (1H, m, NH); 2.58–2.43 (1H, m), 2.14–2.00 (1H, m), 1.99–1.82 (1H, m), and 1.80–1.65 (1H, m, 3',4'-CH_2); 0.93 (9H, s, $C(CH_3)_3$); 0.11 (6H, s, $2SiCH_3$). OH was not observed. ^{13}C NMR spectrum, δ, ppm: 156.6; 132.2; 128.8 (2C); 128.2; 126.2; 122.1; 121.0; 120.4; 115.2; 64.3; 58.6; 57.7; 33.2; 27.1; 25.9; 18.3; –5.3; –5.4. Found, *m*/*z*: 358.2201. $C_{21}H_{32}NO_2Si$. Calculated, *m*/*z*: 358.2197.

1-[(2*R*,5*S*)-5-(Azidomethyl)pyrrolidin-2-yl]naphthalen-2-ol (9a). R_f 0.42 (petroleum ether – Et_2O – AcOEt, 7.5:1.5:1.0). Dark-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.81 (1H, s, OH); 7.75 (1H, d, *J* = 4.5, H Ar); 7.72 (1H, d, *J* = 4.9, H Ar); 7.65 (1H, d, *J* = 8.9, H Ar); 7.42 (1H, ddd, *J* = 8.5, *J* = 6.8, *J* = 1.4, H Ar); 7.28 (1H, ddd, *J* = 7.9, *J* = 6.9, *J* = 1.0, H Ar); 7.07 (1H, d, *J* = 8.8, H Ar); 5.13 (1H, t, *J* = 8.2, 2'-CH); 3.61–3.42 (3H, m, CH_2N_3, 5'-CH); 2.80 (1H, s, NH); 2.52–2.35 (1H, m), 2.20–2.05 (1H, m), 2.00–1.87 (1H, m), and 1.85–1.71 (1H, m, 3',4'-CH_2). ^{13}C NMR spectrum, δ, ppm: 156.0; 132.0; 129.1; 128.9; 128.4; 126.4; 122.4; 120.9; 120.1; 114.8; 58.8; 57.2; 56.4; 31.6; 28.2. Found, *m*/*z*: 269.1390. $C_{15}H_{17}N_4O$. Calculated, *m*/*z*: 269.1397.

1-[(2*S*,5*S*)-5-(Azidomethyl)pyrrolidin-2-yl]naphthalen-2-ol (9b). R_f 0.24 (petroleum ether – Et_2O – AcOEt, 7.5:1.5:1.0). Dark-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.74 (2H, d, *J* = 9.1, H Ar); 7.64 (1H, d, *J* = 8.8, H Ar); 7.46–7.39 (1H, m, H Ar); 7.27 (1H, t, *J* = 7.7, H Ar); 7.06 (1H, d, *J* = 8.9, H Ar); 5.20 (1H, dd, *J* = 9.7, *J* = 6.8, 2'-CH); 3.78–3.68 (1H, m, 5'-CH); 3.63 (1H, dd, *J* = 12.4, *J* = 4.3) and 3.48 (1H, dd, *J* = 12.4, *J* = 7.1, CH_2N_3); 2.58–2.46 (1H, m), 2.24–2.12 (1H, m), 2.00–1.84 (1H, m), and 1.82–1.68 (1H, m, 3',4'-CH_2). OH and NH were not observed. ^{13}C NMR spectrum, δ, ppm: 156.2; 132.1; 129.0; 128.9; 128.3; 126.3; 122.3; 121.0; 120.3; 114.7; 57.7; 56.2; 54.7; 32.9; 28.8. Found, *m*/*z*: 269.1395. $C_{15}H_{17}N_4O$. Calculated, *m*/*z*: 269.1397.

2-[(2*R*,5*S*)-5-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-pyrrolidin-2-yl)-5-methoxyphenol (10a). R_f 0.46 (petroleum ether – AcOEt, 7:3). Dark-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.85 (1H, d, *J* = 8.3, H Ar); 6.40 (1H, d, *J* = 2.6, H Ar); 6.33 (1H, dd, *J* = 8.3, *J* = 2.6, H Ar); 4.25 (1H, dd, *J* = 9.1, *J* = 7.1, 2'-CH); 3.75 (3H, s, OCH_3); 3.70 (1H, dd, *J* = 9.9, *J* = 4.6) and 3.57 (1H, dd, *J* = 9.9, *J* = 7.2, CH_2O); 3.45–3.34 (1H, m, 5'-CH); 2.13–2.02 (1H, m), 1.97–1.82 (2H, m), and 1.71–1.53 (1H, m, CH_2); 0.90 (9H, s, $C(CH_3)_3$); 0.08 (6H, s, $2SiCH_3$). OH and NH were not observed. ^{13}C NMR spectrum, δ, ppm: 159.9; 158.6; 128.3; 118.0; 104.8; 102.3; 67.1; 62.7; 59.7; 55.2; 32.5; 26.5; 25.9; 18.3; –5.4 (2C). Found, *m*/*z*: 338.2154. $C_{18}H_{32}NO_3Si$. Calculated, *m*/*z*: 338.2146.

2-((2*S*,5*S*)-5-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-pyrrolidin-2-yl)-5-methoxyphenol (10b). R_f 0.35 (petroleum ether – AcOEt, 7:3). Dark-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.84 (1H, dd, *J* = 8.3, *J* = 2.2, H Ar); 6.39 (1H, d, *J* = 2.6, H Ar); 6.32 (1H, dd, *J* = 8.3, *J* = 2.6, H Ar); 4.34 (1H, dd, *J* = 9.2, *J* = 6.4, 2'-CH); 3.75 (3H, s, OCH_3); 3.70–3.58 (1H, m) and 3.55–3.43 (2H, m, CH_2O, 5'-CH); 2.19–2.05 (1H, m), 2.02–1.83 (2H, m), and 1.63–1.46 (1H, m, 3',4'-CH_2); 0.90 (9H, s, $C(CH_3)_3$); 0.07 (6H, s, $2SiCH_3$). OH and NH were not observed. ^{13}C NMR spectrum, δ, ppm: 159.9; 159.2; 128.2; 117.6; 104.7; 102.3; 64.4; 61.0; 58.4; 55.2; 34.0; 26.8; 25.9; 18.2; –5.4 (2C). Found, *m*/*z*: 338.2154. $C_{18}H_{32}NO_3Si$. Calculated, *m*/*z*: 338.2151.

2-[(2*R*,5*S*)-5-(Azidomethyl)pyrrolidin-2-yl]-5-methoxyphenol (11a). R_f 0.58 (petroleum ether – AcOEt, 1:1). Dark-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.84 (1H, d, *J* = 8.3, H Ar); 6.40 (1H, d, *J* = 2.6, H Ar); 6.33 (1H, dd, *J* = 8.3, *J* = 2.5, H Ar); 4.27 (1H, dd, *J* = 9.4, *J* = 6.5, 2'-CH); 3.76 (3H, s, OCH_3); 3.51–3.35 (3H, m, CH_2N_3,

5'-CH); 2.16–1.86 (3H, m) and 1.74–1.62 (1H, m, 3',4'-CH_2). OH and NH were not observed ^{13}C NMR spectrum, δ, ppm: 160.2; 158.5; 128.4; 117.2; 105.2; 102.5; 63.1; 61.0; 56.6; 55.1; 32.4; 27.9. Found, *m*/*z*: 249.1342. $C_{12}H_{17}N_4O_2$. Calculated, *m*/*z*: 249.1346.

2-[(2*S*,5*S*)-5-(Azidomethyl)pyrrolidin-2-yl]-5-methoxyphenol (11b). R_f 0.34 (petroleum ether – AcOEt, 1:1). Dark-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.84 (1H, d, *J* = 8.3, H Ar); 6.39 (1H, d, *J* = 2.6, H Ar); 6.33 (1H, dd, *J* = 8.3, *J* = 2.6, H Ar); 4.35 (1H, dd, *J* = 9.6, *J* = 6.3, 2'-CH); 3.76 (3H, s, OCH_3); 3.60 (1H, ddd, *J* = 13.7, *J* = 7.1, *J* = 4.4, 5'-CH); 3.51 (1H, dd, *J* = 12.3, *J* = 4.3) and 3.37 (1H, dd, *J* = 12.4, *J* = 7.4, CH_2N_3); 2.23–2.06 (2H, m), 2.01–1.86 (1H, m), and 1.66–1.52 (1H, m, 3',4'-CH_2). OH and NH were not observed. ^{13}C NMR spectrum, δ, ppm: 160.1; 158.8; 128.3; 117.1; 105.0; 102.4; 61.1; 56.2; 55.2; 54.9; 33.6; 28.5. Found, *m*/*z*: 249.1348. $C_{12}H_{17}N_4O_2$. Calculated, *m*/*z*: 249.1346.

Boc-protection of Betti bases 10a,b (General method). Boc_2O (1.0 equiv) was added to a solution of Betti base **10a**,**b** in dry CH_2Cl_2 at room temperature under N_2 atmosphere. The reaction mixture was stirred overnight. The crude product was purified by chromatography with petroleum ether – Et_2O – AcOEt, 8:1:1, then 7.5:1.5:1.0, affording compounds **12a**,**b** in quantitative yield.

***tert*-Butyl (2*S*,5*R*)-2-{[(*tert*-butyldimethylsilyl)oxy]-methyl}-5-(2-hydroxy-4-methoxyphenyl)pyrrolidine-1-carboxylate (12a)**. R_f 0.38 (petroleum ether – AcOEt, 95:5). White solid. Mp 162.4–167.0°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.06 (1H, d, *J* = 8.5, H Ar); 6.44 (1H, d, *J* = 2.4, H Ar); 6.40 (1H, dd, *J* = 8.5, *J* = 2.5, H Ar); 4.97 (1H, s, 2'-CH); 4.00–3.87 (1H, m, 5'-CH); 3.80–3.68 (4H, m) and 3.66–4.48 (1H, m, CH_3O, CH_2O); 2.28–2.11 (4H, m, 3',4'-CH_2); 1.39 (9H, s, $C(CH_3)_3$); 0.88 (9H, s, $C(CH_3)_3$); 0.07 (6H, s, $2SiCH_3$). OH was not observed. ^{13}C NMR spectrum, δ, ppm: 160.1; 157.0 (2C); 128.0; 120.3; 106.2; 102.8; 81.0; 65.4; 60.2; 56.3; 55.2; 30.1; 28.7; 28.4; 26.0; 18.4; –5.3 (2C). Found, *m*/*z*: 438.2681. $C_{23}H_{40}NO_5Si$. Calculated, *m*/*z*: 438.2670.

***tert*-Butyl (2*S*,5*S*)-2-{[(*tert*-butyldimethylsilyl)oxy]-methyl}-5-(2-hydroxy-4-methoxyphenyl)pyrrolidine-1-carboxylate (12b)**. R_f 0.25 (petroleum ether – AcOEt, 95:5). Dark-yellow oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.82 (1H, d, *J* = 8.5, H Ar); 6.29 (1H, d, *J* = 7.9, H Ar); 6.07–5.92 (1H, m, H Ar); 5.18 (1H, d, *J* = 7.7, 2'-CH); 4.07–3.87 (1H, m, 5'-CH); 3.83–3.71 (1H, m) and 3.60–3.45 (4H, m, OCH_3, CH_2O); 2.53–2.23 (1H, m), 2.23–1.95 (2H, m), and 1.87–1.68 (1H, m, 3',4'-CH_2); 1.51 (9H, s, $C(CH_3)_3$); 0.91 (9H, s, $C(CH_3)_3$); 0.08 (6H, s, $2SiCH_3$). OH was not observed. ^{13}C NMR spectrum, δ, ppm: 159.5; 155.9; 155.3; 125.4; 121.6; 105.7; 101.7; 80.7; 63.2; 59.7; 55.9; 54.7; 30.5; 28.7; 26.4; 26.1; 18.4; –5.12 (2C). Found, *m*/*z*: 438.2671. $C_{23}H_{40}NO_5Si$. Calculated, *m*/*z*: 438.2670.

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