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Enantioselective synthesis of constrained phenylalanine analogues

Prasad V. Chaturvedula *, Stephen E. Mercer, Leatte Guernon, John E. Macor, Gene M. Dubowchik

Neuroscience Discovery Chemistry, Bristol-Myers Squibb Research and Development, 5 Research Parkway, Wallingford, CT, USA

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ABSTRACT

Constrained phenylalanine derivatives containing hydrophobic groups and hydrogen bond acceptor and/or donor functionalities were synthesized through a tandem palladium-mediated Heck reaction followed by a rhodium(II)-catalyzed asymmetric hydrogenation. Aryl bromides were found to be better substrates in providing products with higher purity and in good yield. The cesium carbonate-mediated cyclization proceeded smoothly in good yield and optical purity. Aryl iodides reacted selectively over bromides under Jeffery-type conditions ($Pd(OAc)_2$, Bu_4NCl, Et_3N) providing an opportunity for further metal-mediated functionalization.

The development of new therapeutic agents based on peptides and proteins is of fundamental importance in biomedical research.[1] A major effort in many research laboratories has been devoted to the development of methodologies to design peptide surrogates or mimetics for peptides of biological interest. Many of these mimetics are based on conformationally constrained organic replacements that contribute a favorable entropic component to their binding relative to the flexible peptide ligand.[2] 1,2,3,4-Tetrahydroisoquinoline 3-carboxylic acid (Tic) is a cyclic constrained analogue of phenylalanine in which a covalent bond is inserted between the α-nitrogen and 2′-carbon of the aromatic ring. Tic has been incorporated as a phenylalanine replacement in many biologically active peptides (e.g., opioid, Bradykinin, Neurokinin A, substance P, Kallikrein, etc.).[3] Using solution and crystal-state conformational analysis, Hruby and his co-workers showed (Fig. 1) that Tic could be part of a β-turn and/or α-helix, and that the preferred conformations were g(−) (for the D-Tic enantiomer) or g(+) (for the L-Tic enantiomer).[4] New Tic derivatives substituted on the aromatic ring with basic guanidine,[5]

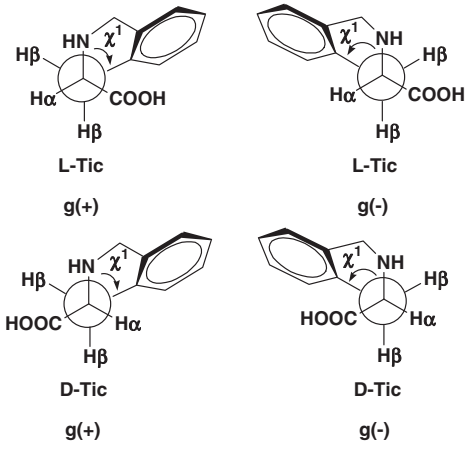

Figure 1. χ^1 rotamers of L- and D-Tic.[4]

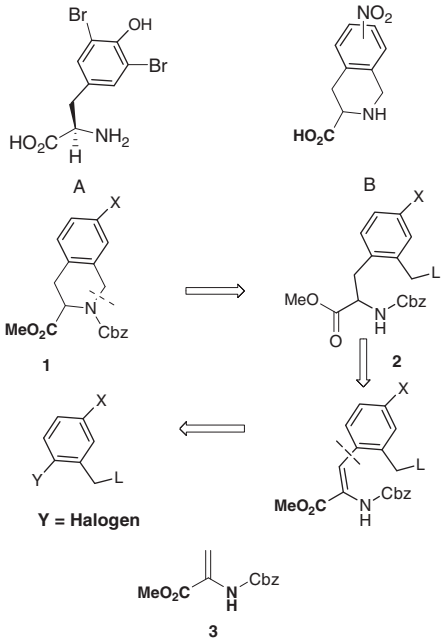

Figure 2. Retrosynthesis of Tic derivatives.

* Corresponding author. Tel.: +1 230 677 6699; fax: +1 203 677 7702.
E-mail address: prasad.chaturvedula@bms.com (P.V. Chaturvedula).

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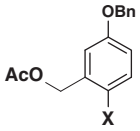
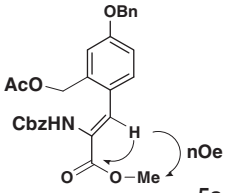
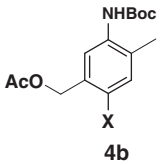
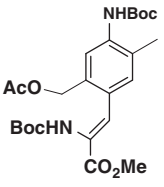
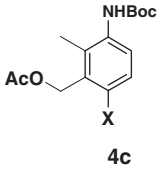
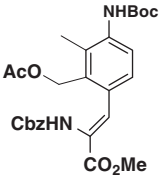
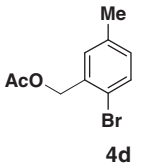
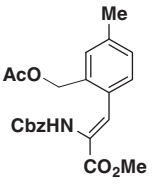
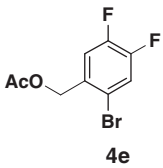
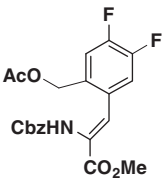
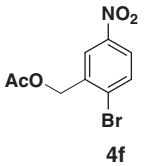
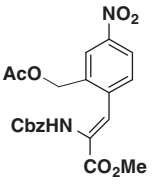
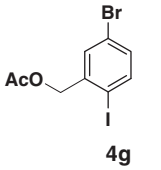
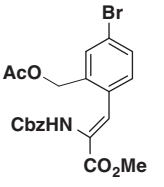
acidic phosphonoethyl, hydroxyl,[6] etc. have been used to modulate receptor or enzyme function. Most of the classical methods for the synthesis of Tic derivatives (e.g., Pictet–Spengler, Bischler–Napieralski, and Pomeranz–Fritsch reactions) involve the participation of aromatic ring π electrons in the cyclization step accompanied by partial racemization under the acidic reaction conditions.[7] In order to synthesize constrained tyrosine analogues, diiodo- or dibromo tyrosine (structure A, Fig. 2) was used to suppress a phenol-formaldehyde polymerization reaction.[8] In the synthesis of Tic derivatives carrying electron-withdrawing groups on the aromatic ring, electrophilic substitution reactions have been used often giving regio isomers (structure B, Fig. 2).[9]

In connection with our CGRP (calcitonin gene-related peptide) antagonist medicinal chemistry program,[10] we were interested in the synthesis of Tic derivatives in enantiomerically pure form represented by **1** (Fig. 2) with a diverse array of substituents carrying lipophilic groups and hydrogen bond acceptors and donors (R = alkyl, aryl, heteroaryl or basic moieties).

Our retrosynthetic bond disconnection is shown in Figure 2. A leaving group at the benzylic position could easily be displaced with α-nitrogen. The synthesis of key intermediate **2** with a leaving group (L) would follow via a tandem palladium-mediated Heck coupling[11,12] of an aryl halide with a dehydroamino acid, followed by asymmetric hydrogenation mediated by rhodium(II)-based chiral catalysts.[13] We and others have previously disclosed an efficient approach to the synthesis of **2** using a Heck coupling followed by asymmetric hydrogenation.[14] The halogen functionality Y needed for a Heck coupling could easily be introduced regioselectively under the directing influence of functional group X. Successful implementation of this approach under mild conditions is described below.

Aryl halides **4a–c** (Table 1) were synthesized regioselectively with either iodine monochloride or *N*-bromosuccinimide in 62–85% yield.[15] Aryl halides **4d–g** (Table 1) were synthesized from the corresponding carboxylic acids by (i) activation with 1,1′-carbonyldiimidazole followed by reduction ($NaBH_4$), and then (ii) acetylation under standard conditions (Ac_2O, DMAP). The aryl halides were coupled to dehydroamino acid **3** (Fig. 2) under different sets of Heck reaction conditions, depending on the halide. Aryl iodides were coupled in the presence of tetrabutylammonium chloride and a base such as Et_3N (Condition A) or $NaHCO_3$ (Condition C), mediated by 5–10 mol % of palladium(II) acetate in refluxing THF (Table 1). The aryl bromides **4a–f** (X = Br) were coupled to dehydroamino acid in the presence of *N*-methyldicyclohexylamine (Condition B), mediated by bis (tri-*tert*-butylphosphine) palladium(0) (0.05 mol %) under Fu's reaction conditions (dioxane, 100 °C).[12] Aryl bromides were found to be superior substrates as they provided cleaner products (**5a, 5b, 5c and 5f**) in good yields and higher purities (>95% purities), from quaternary ammonium salt (*N*-methyldicyclohexylammonium bromide) contamination. Simple dilution of the reaction mixture with diethyl ether followed by filtration was the purification method used to accomplish this. This easy purification was found to have significant impact in the subsequent hydrogenation step since the quaternary ammonium salts were detrimental, even in trace quantities, to the asymmetric rhodium(II) catalysts. As observed earlier,[14] the coupled products **5a–g** (Table 1) were obtained as single isomers with (*Z*)-stereochemistry in 38–96% yield, except **5f**, which was obtained as a mixture of (*Z*) and (*E*) isomers [(*Z*)/(*E*) = 10/1)]. The geometry of the double bond for Heck coupled products was determined by proton coupled ^{13}C NMR experiments using a gated decoupled pulse sequence. The observed H-C three-bond coupling constant (^3J H_{vinyl}, $C_{methyl\ acetate\ carbonyl}$ = 6.9 Hz) is consistent with the *cis*-$^3J_{COOR,\ H}$ coupling.16 The (*Z*)-configuration was further supported by the observed NOE between the vinyl proton and the methyl protons on the acetate group. As shown in Table 1, alkoxy, alkyl, amine, nitro and bromo functionalities on the aryl halide were compatible with the Jeffery-type reaction conditions. Asymmetric

Table 1
Heck reaction of aryl halides with dehydroamino acids[a]

Substrate	Product	Conditions	Yield[b]
 **4a**	 $^3J(H_{vinyl}, C_{carbonyl})$ = 6.7 Hz **5a**	A B	74 92
 **4b**	 **5b**	A (X = I) B (X = Br) C (X = I)	62 96 56
 **4c**	 **5c**	A (X = I) B (X = Br) C(X = I)	71 97 54
 **4d**	 **5d**	B	66
 **4e**	 **5e**	C	38
 **4f**	 **5f**	A B	57 89[c]
 **4g**	 **5g**	A	45

[a] Reaction conditions: 70 °C for 4.5 h, 1.1 equiv Bu_4NCl, 0.05 mol % $Pd(OAc)_2$, 1.3 equiv dehydroamino acid, 3.0 equiv Et_3N, in THF (Condition A); 100 °C for 12 h, 1.1 equiv *N,N*-dicyclohexylmethyamine, 1.2 equiv dehydroamino acid, 0.05 equiv bis(tri-*t*-butylphosphine)palladium(0) in dioxane (Condition B); 70 °C for 6 h, 1.1 equiv Bu_4NCl, 0.05 mol % $Pd(OAc)_2$, 1.3 equiv dehydroamino acid, 2.7 equiv $NaHCO_3$, in THF (Condition C).

[b] Yields refer to weight of product obtained after flash chromatography. All the examples in the table were >95% pure as determined by ^1H NMR.

[c] Yield refers to combined yield of (*E*) and (*Z*)-isomers.

hydrogenations of (*Z*)-alkyl-substituted enamides were carried out either with (+)-1,2-bis((2*S*,5*S*)-2,5-diethylphospholano)benzene(cyclooctadiene)rhodium (II) tetrafluoroborate[13] (or its (*R*,*R*)-enantiomer) in dichloromethane or in 1:1 dichloromethane–methanol to give the reduced chiral product in >95% yield. Chiral HPLC analysis of amino acid esters **7a, 8a, 9a, 11a**, and **12a** (Table 2) and their enantiomers suggested that reduction proceeded in >99% ee.[17] The absolute configuration of hydrogenation products **7a–13a** were tentatively assigned based on reported chiral preference of cationic rhodium catalysts. Cleavage of the acetate group proceeded with catalytic K_2CO_3 in MeOH or NaOMe in $CHCl_3$–MeOH in good yield, but the obtained alcohol had a compromised chiral purity (80–95% ee). However, magnesium methoxide[18] in a 2:1 mixture of chloroform and methanol provided the alcohols **7b, 8b**, and **9b** with >98% ee and in quantitative yield. Treatment of alcohol with excess methanesulfonyl chloride and *N*,*N*′-diisopropylethyl amine in dichloromethane provided chlorides **7c–13c**.

Cyclization of benzylic chlorides to the desired Tic derivatives was examined using different bases (NaH, $CsCO_3$–DMF). Alternatively, cyclization of benzylic alcohol **12b** under Mitsunobu conditions (DEAD, PPh_3) was also explored. Substrates **7–9** were carefully examined by measuring the enantiomeric excess at each step from acetate hydrolysis through cyclization. As shown in Table 2, cesium carbonate in DMF provided optimal conditions for providing Tic derivatives in high optical purities.[19] Partial racemization was observed with substrates **11** and **12** where electron-withdrawing groups have been attached to the aromatic ring (88–91% ee). Under milder Mitsunobu conditions (PPh_3, DEAD, CH_2Cl_2, 0 °C, 12 h) **12b** was obtained in improved optical purity but in lower yield. Substrate **13c** also provided desired cyclized product **20** in good yield where the bromo functionality should facilitate further derivatization under standard metal-catalyzed conditions.[20]

In summary, an efficient enantioselective approach to constrained phenylalanine derivatives has been developed using a palladium-mediated Heck reaction followed by asymmetric reduction with cationic rhodium catalysts. Functional group manipulation and cyclization proceeded with a minimal amount of racemization. Application of this methodology in our CGRP antagonist drug discovery program will be reported in due course.

Table 2
Functionalization and formation of Tic derivatives[a,b]

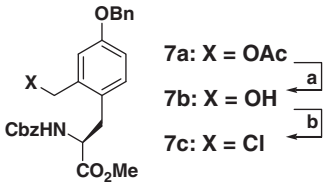
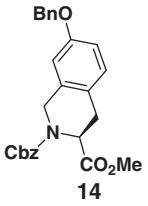
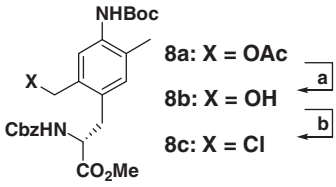
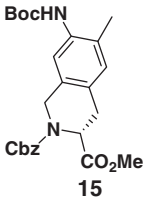
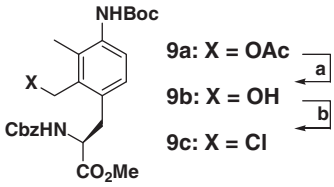
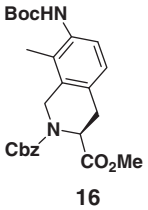
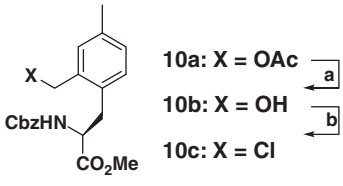
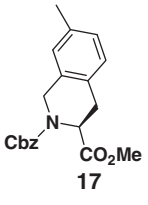
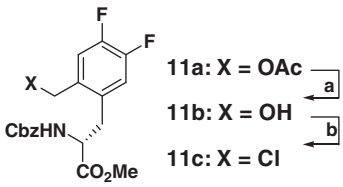
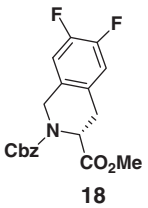
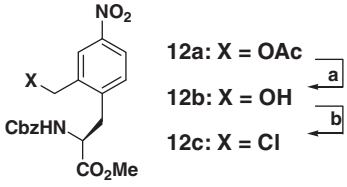
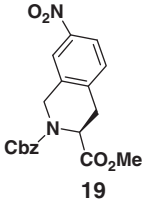
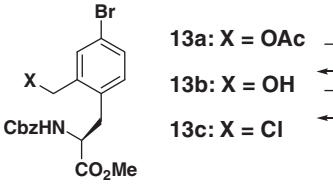
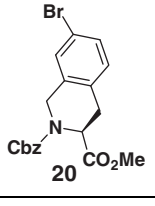
Substrate	Yield (ee)	Product yield (ee)[c,f]
 **7a: X = OAc** (a) **7b: X = OH** (b) **7c: X = Cl**	95 (99.4)	 **14** 93 (97)
 **8a: X = OAc** (a) **8b: X = OH** (b) **8c: X = Cl**	96 (99.8)	 **15** 98 (98)
 **9a: X = OAc** (a) **9b: X = OH** (b) **9c: X = Cl**	97(99.4)	 **16** 98 (99)
 **10a: X = OAc** (a) **10b: X = OH** (b) **10c: X = Cl**	76	 **17** 78 (nd)[d]
 **11a: X = OAc** (a) **11b: X = OH** (b) **11c: X = Cl**	75 (99.9)	 **18** 65 (91)[e]
 **12a: X = OAc** (a) **12b: X = OH** (b) **12c: X = Cl**	96 (98.8)	 **19** 84 (88)[d]
	98	36 (95)[g]

Table 2 (*continued*)

Substrate	Yield (ee)	Product yield (ee)[c,f]
 **13a: X = OAc** (a) **13b: X = OH** (b) **13c: X = Cl**	99 (98.8)	 **20** 88 (nd)[d]

[a] Reaction conditions: (a) 1.3 equiv of $Mg(OMe)_2$ in $CHCl_3$–methanol (2:1) at rt 4–6 h; (b) 1.2 equiv CH_3SO_2Cl, 1.2 equiv Hunig's base in CH_2Cl_2; (c) 1.05 equiv $CsCO_3$ in DMF; (d) combined yield for two steps (chloride formation and cyclization); (e) combined yield for three steps (hydrolysis, chloride formation and cyclization); (f) ee refers to enantiomeric excess determined by chiral column.[17,19] nd: not determined; (g) combined yield for hydrolysis and cyclization under DEAD/PPh_3.

[b] Yields refer to weight of product obtained after flash chromatography. All the examples in the Table were >95% pure as determined by ^1H NMR.

Acknowledgments

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16. (a) James L. Marshall, 'Carbon–Carbon and Carbon–Proton NMR Couplings: Application to Organic Stereochemistry and Conformational Analysis' by Veriag Chemie International, 1983. (b) NMR experiments were performed on a Bruker 500 MHz spectrometer equipped with a TXI cryo probe. (c) The observed H–C three-bond coupling constant (^3J $H_{vinyl,}$ $C_{methyl\ acetate\ carbonyl}$ = 10.9 Hz) for the (*E*) isomer of **5f** is consistent with the *trans*-$^3J_{COOR,\ H}$ coupling.
17. Chiral HPLC analysis was performed to determine the enantiomeric excess of **7a–c**, **8a–c**, **9a–c**, **11a–b**, **12a–b** and their enantiomers. The analysis was performed on a Chiralcel OD-H analytical column (4.6 × 250 mm, 5 mm) using 15% isopropanol in CO_2 at 150 Bar and at 35 °C as mobile phase at a flow rate of 2.0 mL/min. Absorbance was measured at 220 nm and 5 μL of 1 mg/mL of **7a–c** or their enantiomers in ethanol was injected. Compound **7a** had a retention time of 11.91 min (its enantiomer had a retention time of 14.2 min) and an enantiomeric excess of **7a** was determined to be 99.4%. The retention times for the other compounds are: **8a** has a retention time of 4.51 min (Chiracel AD-H column, 15% methanol in CO_2 as mobile phase, 8.63 min for its enantiomer), **8b** has a retention time of 9.99 min (Chiracel OD-H column, 15% isopropanol in CO_2 as mobile phase, 8.43 min for its enantiomer), **8c** has a retention time of 13.27 min (Chiracel AD-H column, 15% isopropanol in CO_2 as mobile phase, 14.25 min for its enantiomer), **9a** has a retention time of 18.36 min (Chiracel OJ-H column, 8% isopropanol in CO_2 as mobile phase, 20.81 min for its enantiomer), **9b** has a retention time of 33.15 min (Chiracel OJ-H column, 8% isopropanol in CO_2 as mobile phase, , 29.97 min for its enantiomer), **9c** has 30.60 min (Chiracel OJ-H column, 7% isopropanol in CO_2 as mobile phase, 27.50 min for its enantiomer), **11a** has a retention time of 10.6 min (Chiracel AS column, 90% heptane—10% methanol as mobile phase, 13.0 min for its enantiomer), **12a** has a retention time of 12.65 min (Chiracel OJ-H column, 10% methanol in CO_2 as mobile phase, 11.2 min for its enantiomer).
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19. Chiral HPLC analysis was performed to determine the enantiomeric excess of **14**, **15**, **16**, **18** and **19** and their enantiomers. The analysis was performed on a Chiralcel analytical column (4.6 × 250 mm, 5 mm) using 15% isopropanol in CO_2 at 150 Bar and at 35 °C as mobile phase at a flow rate of 2.0 mL/min. Absorbance was measured at 220 nm and 5 μL of 1 mg/mL of compound in ethanol was injected. The retention times are: **15** has a retention time of 5.01 min (Chiracel OD-H column, 20% isopropanol in CO_2 as mobile phase, 4.30 min for its enantiomer), **16** has a retention time of 4.37 min (Chiracel OD-H column, 20% isopropanol in CO_2 as mobile phase, 4.96 min for its enantiomer), **18** has a retention time of 9.60 min (Chiracel AD column, 8% ethanol in CO_2 as mobile phase, 10.7 min for its enantiomer) and **19** has a retention time of 20.6 min (Chiracel AD-H column, 10% ethanol in CO_2 as mobile phase, 25.5 min for its enantiomer).
20. Yields were not optimized. All compounds gave satisfactory spectroscopic data consistent with the proposed structures. Data for selected compounds **14**: ^{1}H NMR (500 MHz, DMSO-d_6) showed a mixture of rotamers doubling most signals δ ppm 3.02–3.16 (m, 2H) 3.50 and 3.55 (2s, 3H, OCH_3, rotamers) 4.40–4.63 (2 d, J = 16.50 Hz, 1H, rotamers) 4.66–4.75 (2 d, J = 16.50 Hz, 1H, rotamers) 4.85–5.19 (m, 5H), 6.80–6.86 (m, 1H), 6.90–6.97 (m, 1H), 7.08–7.15 (m, 1H), 7.25–7.52 (m, 10 H); MS (ES), 454 $(M+Na)^+$ **15**: ^{1}H NMR (500 MHz, chloroform-*d*) showed a mixture of rotamers doubling most signals δ ppm 1.50 (s, 9H), 2.09 and 2.17 (s, 3H,) 3.08–3.28 (m, 2H) 3.52 and 3.59 (2s, 3H, OCH_3, rotamers) 4.48–4.57 (2 d, J = 17.20 Hz, 1H, rotamers) 4.79–4.95 (2 d, J = 17.20 Hz, 1H, rotamers) 5.14–5.33 (m, 3H) 6.25 and 6.26 (2s, 1H, rotamers), 6.90 (s, 1H) 7.28–7.46 (m, 5H), 7.62 (s, 1H); MS (ES), 477 $(M+Na)^+$ **16**: ^{1}H NMR (500 MHz, chloroform-*d*) showed a mixture of rotamers doubling most signals δ ppm 1.53 (s, 9H), 2.09 and 2.14 (2s, 3H, rotamers) 3.06–3.31 (m, 2H) 3.57 and 3.63 (2s, 3H, OCH_3, rotamers) 4.38–4.56 (2 d, J = 16.94 Hz, 1H, rotamers) 4.78 (2 d, J = 16.94 Hz, 1H, rotamers) 4.97–5.07 (m, 1H) 5.14–5.35 (m, 2H) 6.28 (d, J = 10.99 Hz, 1H) 6.99 (dd, J = 8.24, 3.97 Hz, 1H) 7.29–7.56 (m, 5H); MS (ES), 453 $(M-H)^-$ **18**: ^{1}H NMR (300 MHz, chloroform-*d*) showed a mixture of rotamers doubling most signals δ ppm 3.04–3.27 (m, 2H) 3.57 and 3.61 (2s, 3H, OCH_3, rotamers) 4.40–4.56 (2 d, J = 16.94 Hz, 1H, rotamers) 4.65–4.75 (2 d, J = 16.94 Hz, 1H, rotamers) 4.97–5.21 (m, 3H) 6.77–7.01 (m, 2H), 7.25–7.43 (m, 5H); **19**: ^{1}H NMR (500 MHz, chloroform-*d*) showed a mixture of rotamers doubling most signals δ ppm 3.22–3.44 (m, 2H), 3.57 and 3.64 (2s, 3H, OCH_3, rotamers) 4.70 (d, J = 17.0 Hz, 1H) 4.93 (d, J = 17.0 Hz, 1H) 5.09–5.30 (m, 3H), 7.30–7.45 (m, 6H), 7.93–8.11 (m, 2H); MS (ES), 393 $(M+Na)^+$.