Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

ARTICLE TYPE www.rsc.org/xxxxxx | XXXXXXXX

Consecutive three-component synthesis of (hetero)arylated propargyl amides by chemoenzymatic aminolysis-Sonogashira coupling sequence†

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Received (in XXX, XXX) Xth XXXXXXXXX 200X, Accepted Xth XXXXXXXXX 200X
First published on the web Xth XXXXXXXXX 200X
DOI: 10.1039/b000000x

A novel chemoenzymatic three-component synthesis of (hetero)arylated propargyl amides in good yields based upon Novozyme® 435 (*Candida antarctica* lipase B (CAL-B)) catalyzed aminolysis of methyl carboxylates followed by Sonogashira coupling with (hetero)aryliodides in a consecutive one-pot fashion has been disclosed. This efficient methodology can be readily concatenated with a CuAAC (Cu catalyzed alkyne azide cycloaddition) as a third consecutive step to furnish 1,4-disubstituted 1,2,3-triazole ligated arylated propargyl amides. This one-pot process can be regarded as a sequentially transition metal catalyzed sequence taking advantage of the copper source still present from the cross-coupling step.

Introduction

Propargyl amides are particularly interesting as biologically active functionalities and as synthetic building blocks. Protein derived propargyl amides have been studied to irreversibly inhibit cysteine proteases[1] while systems containing rigid propargylated aryl cores have been demonstrated to be active as structurally modified homodimeric gonadotropin releasing hormone receptor (GnRHR) antagonist dimers with rigid functionalities such as bistriazole with hydrophilic polyethylene glycol (PEG) spacer[2] or a propargylated aryl system as a spacer.[3] Synthetically theses compound were prepared by coupling propargylated amino acid derivatives with the aryliodides.[3] Likewise, deoxynucleoside derivatives of *N*-trifluoroacetyl propargyl amides were synthesized.[4]

As synthetic building blocks propargyl amides have been employed as monomers for the synthesis of chromophore labeled poly (*N*-propargyl amides) as stimuli responsive conjugated polymers.[5] Optically active *N*-propargyl amides bearing hydroxyl groups have been synthesized and polymerized for studying their secondary structure and chiral-recognition.[6] Furthermore, propargyl amides are excellent substrates in coupling-cycloisomerization sequences[7] that can be expanded to three-component syntheses of blue-luminescent 5-(3-indolyl)oxazoles[8] and $PtCl_2$ induced intramolecular cyclizations of *N*-propargyl indole-2-carboxamides to give azepino[3,4-*b*]indol-1-ones.[9]

The combination of chemical and enzymatic transformations offers numerous opportunities for designing new syntheses. Therefore, these chemoenzymatic transformations have recently received considerable attention and many applications have been founded on chiral resolution of racemic or *meso* substrates to furnish enantiomerically enriched chiral building blocks for organic syntheses in a catalytic fashion.[10] In contrast to a chemoenzymatic continuous flow processes[11] the concatenation of enzymatic and chemical catalyzed steps in a one-pot fashion thus furnishing novel types of chemoenzymatic sequences remains a major challenge. While the one-pot combination of enzymes and transition metal catalysis is dominated by dynamic kinetic resolution as an important tool in asymmetric synthesis,[12] chemoenzymatic one-pot sequences involving Pd-catalyzed coupling[13] or Cu-catalyzed alkyne-azide cycloaddition (CuAAC)[14,15] are still in their infancy. Recently, we have disclosed a consecutive three-component sequence consisting of CAL-B (*Candida antarctica* lipase B) catalyzed aminolysis of methyl esters with propargyl amine furnishing propargyl amides and CuAAC to give amide ligated 1,4-disubstitued 1,2,3-triazoles in good to excellent yields. Here we communicate first consecutive three-component syntheses of (hetero)arylated propargyl amides by chemoenzymatic aminolysis-Sonogashira coupling sequence.

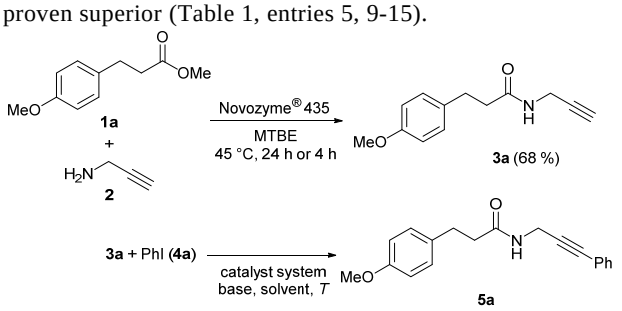
Results and discussion

We have previously reported the efficient CAL-B catalyzed aminolysis for the synthesis of propargyl amides as milder alternative to the base catalyzed process that occurs with remarkable chemoselectivity with α-heteroatom substituted methyl carboxylates.[15] Encouraged by the excellent compatibility of CAL-B catalyzed aminolysis with copper catalysis in a single reaction vessel we set out to concatenate this aminolysis step with Sonogashira coupling to access (hetero)arylated propargyl amides in a diversity-oriented one-pot sequence.

First the Sonogashira coupling of propargyl amide **3a**, formed by CAL-B aminolysis of methyl ester **1a** with propargylamine (**2**),[15] and iodo benzene (**4a**) to furnish 3-phenylpropargyl amide **5a** was optimized as a model reaction with respect to a suitable catalyst system, base, solvent and temperature (Scheme 1, Table 1).

In comparison to standard Sonogashira conditions, propargyl amides are apparently peculiar since all Pd(II) catalyst precursors failed to give reasonable yields (Table 1, entries 1-4). Even novel carbene ligands that have been efficiently established for Sonogashira coupling,[16,17] were not successful in the model reaction (Table 1, entries 7 and

8). However, $Pd(PPh_3)_4$ as Pd(0) catalyst precursor was proven superior (Table 1, entries 5, 9-15).



Scheme 1 Formation of propargyl amide **3a** by CAL-B catalyzed aminolysis of methyl ester **1a** and optimization of the Sonogashira coupling of propargyl amide **3a** and iodo benzene (**4a**).

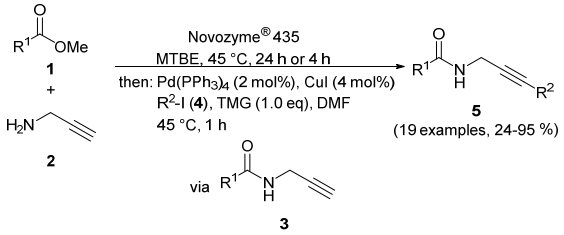
The choice of the base was equally important. It turned out that 1,1,3,3-tetramethyl guanidine (TMG), successfully employed in Pd-catalyzed coupling-cyclization syntheses of indoles from *ortho*-iodo anilines[18,19] and in domino sequences involving *N*-propargyl sulfoximines,[20] as the most favorable amidine base that not only gave good yields of propargyl amide **5a** but also drastically reduced reaction times at 45 °C (Table 1, entry 15). Moreover, it was sufficient to employ an equimolar amount of TMG to achieve full conversion. Therefore, with these conditions for the coupling step in hand the stage was set to combine the CAL-B catalyzed aminolysis with the Sonogashira coupling in a consecutive one-pot fashion.

Table 1 Optimization of Sonogashira reaction of propargyl amide **3a** and iodo benzene (**4a**) giving rise to 3-phenylpropargyl amide **5a**

Entry	Catalyst system	Solvent	Base/additive	*T*, *t*	Yield of **5a** (%)[a]
1	2 mol% $PdCl_2(PPh_3)_2$, 4 mol% CuI	THF	NEt_3 (1.0 equiv)	rt to 50 °C, 24 h	-[b]
2	2 mol% $PdCl_2(PPh_3)_2$, 4 mol% CuI	1,4-dioxane	NEt_3 (1.0 equiv)	rt to 70 °C, 24 h	13
3	2 mol% $PdCl_2(PPh_3)_2$, 4 mol% CuI	1,4-dioxane	pyrrolidine (1.0 equiv)	rt to 70 °C, 24 h	25
4	2 mol% $PdCl_2(PPh_3)_2$, 4 mol% CuI	1,4-dioxane	pyrrolidine (1.5 equiv)	rt to 70 °C, 24 h	33
5	5 mol% $Pd(PPh_3)_4$, 1 mol% CuI	DMF	pyrrolidine/DMF (1:4 v/v)	45 °C, 6 h	75
6	2.5 mol% $Pd_2(dba)_3 \cdot CHCl_3$, 10 mol% P(2-furyl)$_3$	MeCN	NaO*t*-Bu (2.0 equiv)	45 °C, 24 h	-[b]
7	2.5 mol% $Pd_2(dba)_3 \cdot CHCl_3$, 10 mol% IPr · HCl[c]	MeCN	NaO*t*-Bu (2.0 equiv)	45 °C, 24 h	-[b]
8	5 mol% $Pd(OAc)_2$, 10 mol% IPr · HCl[c]	MeCN	K_2CO_3 (2.0 equiv), TBAC (2.0 equiv)	45 °C, 24 h	-[b]
9	2 mol% $Pd(PPh_3)_4$, CuI	DMF	NEt_3 (1.0 equiv)	rt, 24 h	53
10	2 mol% $Pd(PPh_3)_4$, 4 mol% CuI	DMF	DIPEA[d] (1.5 equiv)	45 °C, 6 h	67
11	2 mol% $Pd(PPh_3)_4$, 4 mol% CuI	DMF	pyrrolidine (1.0 equiv)	45 °C, 8 h	56
12	2 mol% $Pd(PPh_3)_4$, 4 mol% CuI	DMF	pyrrolidine (1.5 equiv)	45 °C, 4 h	**85**
13	2 mol% $Pd(PPh_3)_4$, 4 mol% CuI	DMF	DABCO[e] (1.0 equiv)	45 °C, 8 h	**57**
14	2 mol% $Pd(PPh_3)_4$, 4 mol% CuI	DMF	DBU[f] (1.0 equiv)	45 °C, 8 h	69
15	**2 mol% $Pd(PPh_3)_4$, 4 mol% CuI**	**DMF**	**TMG[g] (1.0 equiv)**	**45 °C, 1 h**	**83**

[a] Isolated yield after chromatography on silica gel. [b] No product formation. [c] IPr · HCl: 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride. [d] DIPEA: diisopropylethylamine. [e] DABCO: 1,4-diazabicyclo[2.2.2]octane. [f] DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene. [g] TMG: 1,1,3,3-tetramethyl guanidine.

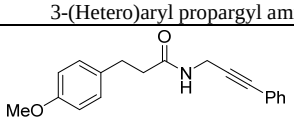
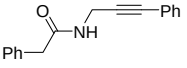
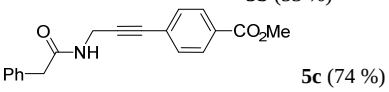
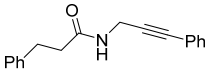
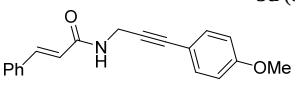
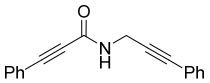
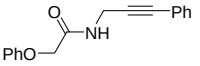
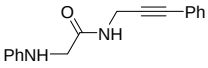
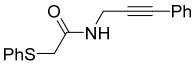
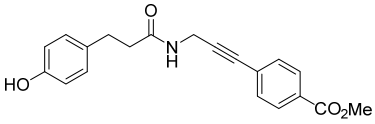
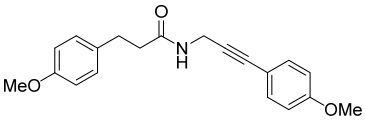
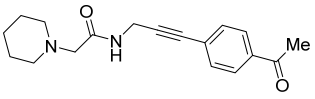
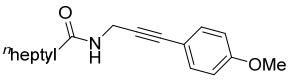
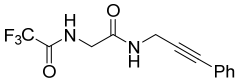
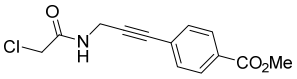
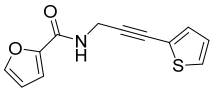
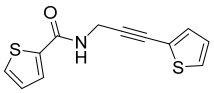
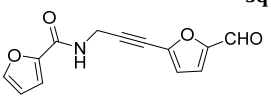
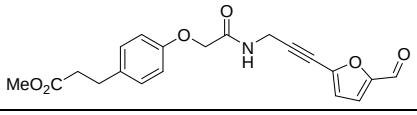
Upon Novozyme® 435 catalyzed aminolysis of methyl carboxylates **1** with propargyl amine (**2**) in MTBE (methyl *tert*-butylether) at 45 °C, the formed propargyl amide **3** was subsequently reacted with (hetero)aryl iodides **4** in the presence of DMF as a cosolvent, TMG as a base and catalytic amounts of $Pd(PPh_3)_4$ and CuI at 45 °C to give 3-(hetero)arylpropargyl amides **5** in a three-component one-pot fashion in moderate to excellent yields (Scheme 2, Table 2).



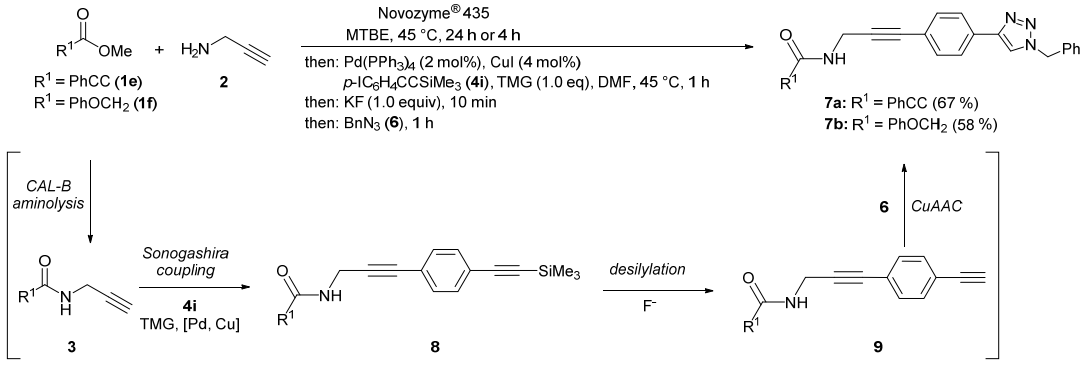
Scheme 2 Consecutive three-component synthesis of 3-(hetero)arylpropargyl amides **5** by CAL-B catalyzed aminolysis-Sonogashira coupling sequence.

Taking into account the already established substrate scope of the Novozyme® 435 catalyzed aminolysis[15] the general substitution pattern is equally well accepted in this chemoenzymatic sequence. Moreover, also a free phenol moiety in substrate **1i** is well tolerated furnishing the propargyl amide **5j** in remarkably high yield (Table 2, entry 10). The same holds true for methyl chloro acetate (**1m**), which is transformed to give the corresponding propargyl amide **5o** in excellent yield (Table 2, entry 15). Most importantly, the chemoselectivity of the aminolysis of the more electrophilic methyl carboxylate in substrate **1p** underlines the superiority of applying CAL-B as a catalyst in the sequence. However, it should be noted that 2-iodopyridine and 1,3-diiodobenzene failed to undergo the Sonogashira step under the optimized conditions.

Table 2 Chemoenzymatic three-component synthesis of 3-(hetero)arylpropargyl amides **5**

Entry	Methyl ester **1**	(Hetero)aryl iodide **4**	3-(Hetero)aryl propargyl amide **5**
1[a]	R^1 = *p*-$MeOC_6H_4CH_2CH_2$ (**1a**)	R^2 = Ph (**4a**)	 **5a** (58 %)
2[a]	R^1 = $C_6H_5CH_2$ (**1b**)	**4a**	 **5b** (53 %)
3[a]	**1b**	R^2 = *p*-$MeO_2CC_6H_4$ (**4b**)	 **5c** (74 %)
4[a]	R^1 = $C_6H_5CH_2CH_2$ (**1c**)	**4a**	 **5d** (54 %)
5[a]	R^1 = *E*-C_6H_5CH=CH (**1d**)	R^2 = *p*-$MeOC_6H_4$ (**4c**)	 **5e** (26 %)
6[a]	R^1 = $C_6H_5C{\equiv}C$ (**1e**)	**4a**	 **5f** (51 %)
7[b]	R^1 = $C_6H_5OCH_2$ (**1f**)	**4a**	 **5g** (24 %)
8[b]	R^1 = $C_6H_5NHCH_2$ (**1g**)	**4a**	 **5h** (77 %)
9[b]	R^1 = $C_6H_5SCH_2$ (**1h**)	**4a**	 **5i** (77 %)
10[a]	R^1 = *p*-$HOC_6H_4CH_2CH_2$ (**1i**)	**4b**	 **5j** (85 %)
11[a]	**1h**	**4c**	 **5k** (62 %)
12[b]	R^1 = $(CH_2)_5NCH_2$ (**1j**)	R^2 = *p*-$H_3CCOC_6H_4$ (**4d**)	 **5l** (64 %)
13[a]	R^1 = $Me(CH_2)_5CH_2$ (**1k**)	**4c**	 **5m** (59 %)
14[a]	R^1 = $F_3CCONHCH_2$ (**1l**)	**4a**	 **5n** (71 %)
15[b]	R^1 = $ClCH_2$ (**1m**)	**4b**	 **5o** (95 %)
16[a]	R^1 = 2-furyl (**1n**)	R^2 = 2-thienyl (**4e**)	 **5p** (71 %)
17[a]	R^1 = 2-thienyl (**1o**)	**4e**	 **5q** (44 %)
18[a]	**1n**	R^2 = 5-OHC-2-furyl (**4f**)	 **5r** (62 %)
19[b]	R^1 = *p*-$(MeO_2CCH_2CH_2)C_6H_4OCH_2$ (**1p**)	**4f**	 **5s** (61 %)

Finally, we have combined the chemoenzymatic aminolysis-Sonogashira coupling with a terminal CuAAC step furnishing propargyl amide functionalized 1-aryl 4-benzyl 1,2,3-triazoles **7** in good yields (Scheme 3). Commencing with the CAL-B catalyzed aminolysis, the propargyl amides **3** are reacted with *p*-iodo[(trimethylsilyl)ethynyl)benzene (**4i**) to give the TMS-protected 3(*p*-ethynyl)phenyl propargyl amides **8**, which are rapidly desilylated by potassium fluoride furnishing the ethynyl derivatives **9**. The presence of the Sonogashira cocatalyst CuI and benzyl azide (**6**) terminates the sequence by a CuAAC giving rise to the formation of functionalized 1,2,3-triazoles **7** in the sense of a sequentially transition metal catalyzed one-pot sequence.[21]



Scheme 3 Consecutive four-component synthesis of 3-(4-1,2,3-triazolyl)phenyl propargyl amides **7** by CAL-B catalyzed aminolysis-Sonogashira coupling-CuAAC sequence.

Conclusions

In conclusion, we have disclosed a novel chemoenzymatic one-pot synthesis of 3-(hetero)arylpropargyl amides **5** by CAL-B catalyzed aminolysis-Sonogashira coupling sequence. This combination of enzyme-metal catalyzed methodology is well suited for application to more sophisticated peptides and aryl halides as a bioorganic tool for the efficient generation of peptidomimetics in a one-pot fashion. Furthermore, the potential to concatenate CuAAC as a third step opens new avenues for the rapid alignment of various functionalities in the sense of diversity-oriented synthesis of complex chromophores.[22] Studies directed to further expand and develop this chemoenzymatic sequence are currently underway.

Acknowledgments

The authors cordially thank CLIB Graduate Cluster for the financial support (scholarship of S. H.), and the Fonds der Chemischen Industrie.

Experimental

Chemoenzymatic three-component synthesis of methyl 4-(3-(3-(4-hydroxyphenyl)propanamido)prop-1-yn-1-yl) benzoate (5j) (typical procedure)

To a solution of propargylamine (**2**) (55 mg, 1.00 mmol) in dry MTBE (2.0 mL) in a screw-cap Schlenk vessel, methyl *p*-hydroxy dihydrocinnamate (**1i**) (216 mg, 1.20 mmol) and Novozyme® 435 (108 mg, 50 % w/w of substrate **1i**) were successively added and reaction was allowed to shake in an incubating shaker at 45 °C for 24 h. After the complete conversion (monitored by TLC) DMF (2.0 mL) was added to the reaction mixture which was then flushed with argon for 15 min. Then methyl *p*-iodobenzoate (**4b**) (262 mg, 1.00 mmol), TMG (115 mg, 1.00 mmol), $Pd(PPh_3)_4$ (23 mg, 0.02 mmol), and CuI (8 mg,0.04 mmol) were successively added to the reaction mixture under argon and the reaction was allowed to shake at 45 °C for 1 h. The reaction mixture was filtered to remove the enzyme beads. Then, brine (5.0 mL) was added to the filterate, followed by extraction with ethylacetate (3 x 10.0 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and after column chromatography on silica gel (*n*-hexane/ethyl acetate) 288 mg (85 %) of analytically pure compound **5j** was obtained as a colorless solid, Mp 151 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.35 (t, ^3J= 7.9 Hz, 2 H), 2.72 (t, ^3J= 7.9 Hz, 2 H), 3.85 (s, 3 H), 4.13 (d, ^3J= 5.5 Hz, 2 H), 6.64 (d, ^3J= 8.4 Hz, 2 H), 6.99 (d, $^3J_{4,3}$= 8.4 Hz, 2 H), 7.54 (d, ^3J= 8.5 Hz, 2 H), 7.94 (d, ^3J= 8.5 Hz, 2 H), 8.38 (t, ^3J= 5.5 Hz, 1 H), 9.14 (s, 1 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 28.5 (CH_2), 30.1 (CH_2), 37.2 (CH_2), 52.3 (CH_3), 80.7 (C_{quat}), 90.6 (C_{quat}), 115.0 (CH), 127.1 (C_{quat}), 129.0 (CH), 129.1 (C_{quat}), 129.3 (CH), 131.2 (C_{quat}), 131.6 (CH), 155.4 (C_{quat}), 165.6 (C_{quat}), 171.3 (C_{quat}). EI-MS (*m/z* (%)): 337 (M^+, 13), 336 ($[M-H]^+$, 22), 230 ($C_{13}H_{12}NO_3^+$, 100), 188 ($C_{11}H_{10}NO_2^+$, 19), 120 ($C_8H_8O^+$, 20), 107 ($C_7H_7O^+$, 52). IR (ATR) $\tilde{\nu}$[cm^{-1}] = 3385 (m), 3291 (m), 2966 (m), 2951 (w), 2924 (w), 2845 (w),1705 (s), 1632 (s), 1601 (w), 1533 (m), 1516 (s), 1435 (m), 1362 (w), 1344 (m), 1288 (m), 1279 (s), 1259 (m), 1225 (s), 1198 (m), 1175 (m), 1103 (m), 1011 (w), 966 (w), 862 (m), 831 (w), 816 (m), 766 (s), 684 (m), 640 (w). Anal. calcd. for $C_{20}H_{19}NO_4$ (337.4): C 71.20, H 5.68, N 4.15; Found: C 70.96, H 5.38, N 4.07.

Chemoenzymatic four-component synthesis of *N*-(3-(4-(1-benzyl-1H-1,2,3-triazol-4-yl)phenyl)prop-2-yn-1-yl)-2-phenoxy acetamide (7b) (typical procedure)

To a solution of propargylamine (**2**) (55 mg, 1.00 mmol) in dry MTBE (2.0 mL) in a screw-cap Schlenk vessel, methyl 2-phenoxyacetate (**1f**) (199 mg, 1.20 mmol) and Novozyme® 435 (100 mg, 50 % w/w of substrate **1f**) were successively added and reaction was allowed to shake in an incubating shaker at 45 °C for 4 h. After the complete conversion (monitored by TLC), DMF (2.0 mL) was added to the reaction mixture, which was then flushed with argon for 15 min. Then (4-iodophenyl)ethynyl trimethylsilane (**4i**) ((300 mg, 1.00 mmol), TMG (115 mg, 1.00 mmol), $Pd(PPh_3)_4$ (23 mg, 0.02 mmol), and CuI (8 mg,0.04 mmol) were successively added to the reaction mixture under argon and the reaction was allowed to shake at 45 °C for 1 h. Then potassium fluoride (58 mg, 1.00 mmol) was added to the reaction mixture and after 10 min benzyl azide (**6**) (133 mg, 1.00 mmol) was added. After 1 h of shaking in the incubating shaker the reaction mixture was filtered to remove the enzyme beads. Then, brine (5.0 mL) was added to the filtrate followed by extraction with ethyl acetate (3 x 10.0 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and after column chromatography on silica gel (*n*-hexane/ethyl acetate) 245mg (58 %) of analytically pure compound **7b** was obtained as a yellow solid, Mp 147 °C.

Yellow solid. Mp 147 °C. ^{1}H NMR (300 MHz, d_6-DMSO): δ = 4.21 (d, ^3J = 5.6 Hz, 2 H), 4.54 (s, 2 H), 5.65 (s, 2 H), 6.97-7.00 (m, 3 H), 7.28-7.39 (br m, 7 H), 7.45 (d, ^3J = 8.4 Hz, 2 H), 7.59-7.62 (m, 1 H), 7.86 (d, ^3J = 8.4 Hz, 2 H), 8.69 (s, 1 H).^{13}C NMR (75 MHz, d_6-DMSO): δ = 28.5 (CH_2), 53.1 (CH_2), 66.8 (CH_2), 81.3 (C_{quat}), 87.7 (C_{quat}), 114.7 (CH), 121.2 (CH), 121.5 (C_{quat}), 122.1 (CH), 125.3 (CH), 127.9 (CH), 128.2 (CH), 129.5 (CH), 130.7 (C_{quat}), 132.0 (CH), 135.9 (C_{quat}), 145.9 (C_{quat}), 157.6 (C_{quat}), 167.7 (C_{quat}). MALDI-MS: *m/z* = 423 ([M + H]$^+$). IR (ATR) $\tilde{\nu}$ [cm^{-1}] = 3034 (w), 2922 (w), 2910 (w), 2856 (w), 1662 (s), 1598 (w), 1587 (w), 1519 (m), 1489 (s), 1456 (w), 1435 (w), 1409 (w), 1350 (w), 1286 (w), 1242 (s), 1226 (s), 1170 (w), 1080 (w), 1060 (w), 1047 (w), 1028 (w), 1018 (w), 1001 (w), 835 (m), 798 (m), 756 (s), 721 (s), 657 (w), 603 (w). Anal. calcd. for $C_{26}H_{22}N_4O_2$ (422.5): C 73.92, H 5.25, N 13.26; Found: C 74.06, N 5.32, H 13.47.

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization, and ^{1}H and ^{13}C NMR spectra of compounds **5** and **7**. See DOI: 10.1039/b000000x/

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