Synthesis of 5-Methoxy-4-benzyloxazoles from Tyrosine and *m*-Tyrosine under Bischler-Napieralski Conditions*

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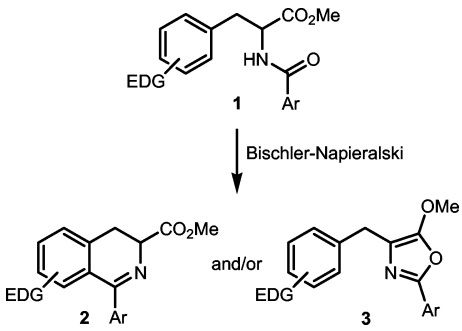
Various 2-substituted 5-methoxy-4-benzyloxazoles **6** and **9** were obtained from tyrosine and *m*-tyrosine derived amides **5** and **8** by treatment with phosphoryl chloride. A mechanism is proposed in order to explain the observed steric effects of the substituents in 2-position.

Key words: Amides, Bischler-Napieralski Reaction, 3,4-Dihydroisoquinolines, Oxazoles, Tyrosine

Introduction

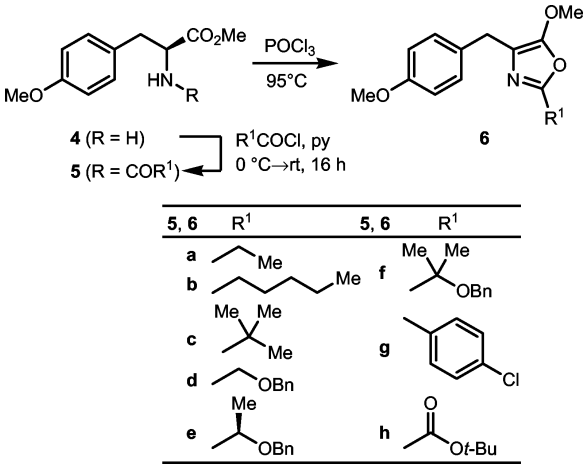
Oxazoles are interesting from both a pharmacological and a chemical point of view. For example, they are known to interact with various proteins such as sodium-dependent excitatory amino acid transporters [1] or DNA repair protein OG-alkylguanine DNA-alkyl-transferase [2], and furthermore, they display bacteriostatic [3] and antiinflammatory activity [4]. Additionally, oxazoles provide useful entries into the synthesis of other heterocyclic compounds such as pyridines [5], α-amido oximes [6], and azlactones [7]. Since the seminal finding by Reeve and Paré [8] that acylamidophenylalanine esters **1** can undergo a cyclization to the oxazole **3** instead of the desired dihydroisoquinolines **2** under Bischler-Napieralski conditions [9] (Scheme 1), this reaction was observed by several groups [6, 10]. The electronic influence of substituents at the phenyl moiety has been explored to some extent [10b, 10c], however, substituent effects at the amide function remained unclear. Herein we wish to disclose our studies on this reaction in more detail.



Scheme 1. Possible products from acylamidophenylalanine esters **1** under Bischler-Napieralski conditions. EDG = electron donating group.

Results and Discussion

As shown in Scheme 2, methyl L-*O*-methyl-tyrosinate (**4**) was first *N*-acylated with 1.1 equivalents of the respective acid chloride in pyridine at 0 °C. The mixture was then kept at r. t. for 16 h and after workup, the amides **5a** – **h** were obtained in 65 – 93% yield



Scheme 2. Bischler-Napieralski reaction of methyl L-*O*-methyl-tyrosinate (**4**) to oxazoles **6**.

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Table 1. Formation of amides **5** and oxazoles **6**.

Entry	R	Amide	Yield [%]	Time [min]	Oxazole	Yield [%][a]
1	Et	**5a**	82	25	**6a**	49
2	*n*-C_5H_{11}	**5b**	86	10	**6b**	50
3	*t*-Bu	**5c**	91	150	**6c**	28
4	CH_2OBn	**5d**	75	90	**6d**	40
5	(*R*)-$CHCH_3OBn$	**5e**	93	10	**6e**	–[b]
6	$C(CH_3)_2OBn$	**5f**	65	5	**6f**	–[b]
7	*p*-ClC_6H_4	**5g**	74	20	**6g**	76
8	CO_2*t*-Bu	**5h**	76	6 h	**6h**	–[b]

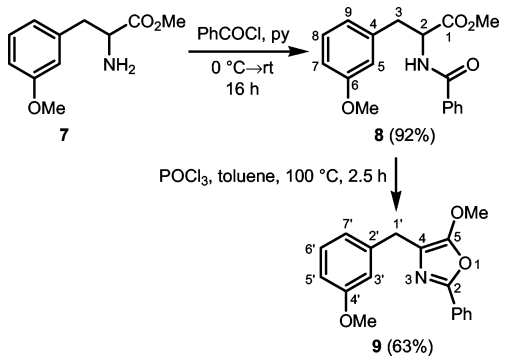
[a] Isolated yields are given; [b] only decomposition was observed.

(Table 1). Subsequent treatment of **5** with an excess of phosphoryl chloride at 95 °C following the procedure by Saxena [11] yielded the 5-methoxy-4-benzyloxazoles **6**. The course of reaction was followed by GC, and the reaction mixture was worked up immediately after the starting material could not be detected any more. In the cases of aliphatic acid chlorides, the yields of the oxazoles **6a – c** decreased with steric bulkiness of the alkyl substituent from 50% for 2-ethyl and 2-pentyl-substituted oxazoles **6a, b** (entry 1, 2) to only 28% for 2-*tert*-butyloxazole **6c** (entry 3).

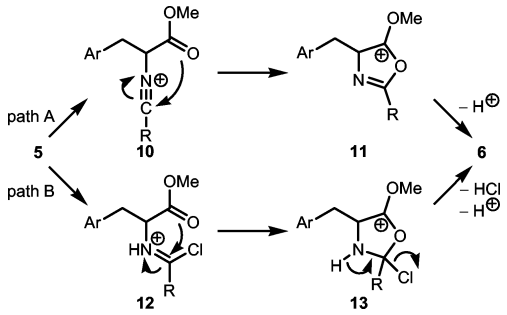
Benzyloxymethyl-substituted oxazole **6d** was also isolated in 40% yield without any problems (entry 4). We were therefore curious whether the cyclization of chiral amide **5e** derived from *O*-benzyl (*R*)-lactate would retain its stereochemistry during oxazole formation. As a further derivative with a quaternary carbon atom the benzyloxymethyl-substituted amide **5f** was tested in the Bischler-Napieralski reaction. However, not even a trace of the desired oxazoles **6e** and **6f** could be detected (entries 5, 6). In contrast, the *p*-chlorophenyl-substituted amide **5g** reacted smoothly to afford the oxazole **6g** (entry 7), while the *tert*-butyl glyoxylate-derived amide **5h** did not give the target oxazole **6h** (entry 8).

Under similar conditions *rac* methyl 3-methoxyphenylalaninate (**7**) was converted with benzoyl chloride to the corresponding benzamide **8** in 92% yield (Scheme 3). Subsequent treatment with an excess of phosphoryl chloride in toluene at 100 °C in analogy to conditions by Chakravorti [12] yielded the oxazole **9** in 63% yield. It should be noted that we did not detect any trace of the corresponding 3,4-dihydroisoquinolinecarboxylate. This finding is in clear contrast to observations by Saxena [11], who found exclusively the 3,4-dihydroisoquinolinecarboxylate under similar reaction conditions.

As shown in Scheme 4, two mechanistic proposals may be drawn for the oxazole formation. According



Scheme 3. Bischler-Napieralski reaction of *m*-tyrosine derivative **7**.



Scheme 4. Mechanistic proposal for the oxazole formation.

to Fodor [13] nitrilium cations such as **10** are intermediates in Bischler-Napieralski reactions. Thus, *via* path A, amide **5** is converted to **10**, which is intramolecularly attacked by the carbonyl group of the ester moiety to give intermediate **11**. The latter is deprotonated to yield oxazole **6**. In path B, initial formation of the chloroiminium ion **12** analogous to the Vilsmeier-Haack reaction [14] is proposed. Intramolecular nucleophilic attack of the ester moiety should lead to the tetrahedral intermediate **13**. Further elimination of HCl and deprotonation should give the oxazole **6**. The sensitivity of the oxazole formation towards steric effects may be taken as evidence for mechanism B rather than A. The linear nitrilium cation **10** should be less prone to steric hindrance by the substituent R as compared to the tetrahedral intermediate **13**.

In conclusion, we found some steric influence of the amide substituent in the phosphoryl chloride-mediated cyclization of tyrosine derivatives **5** and **8** to the oxazoles **6** and **9**. While linear substituents like ethyl, *n*-pentyl or benzyloxymethyl (**5a**, **b**, **d**) react without difficulty, a branch at the α-C atom as in amides **5c**, **e**, **f** either clearly diminished the yield of the corresponding oxazole **6** or led to decomposition.

Experimental Section

General information

The following compounds were prepared according to literature procedures: benzyloxyacetyl chloride [15], (*R*)-2-D-benzyllactic acid chloride [16], 2-benzyloxy-2,2-dimethylacetyl chloride [17, 18], and *tert*-butyl-chloroglyoxylate [19]. Commercial reagents were used without further purification unless otherwise indicated. Phosphoryl chloride was distilled, pyridine and toluene were distilled from CaH_2 prior to use. Reactions were performed in oven-dried glassware under N_2 atmosphere. Flash chromatography was performed on silica gel Fluka 60 (230 – 400 mesh) or Merck aluminium oxide 90 active neutral or aluminium oxide 90 active basic (0.063 – 0.200 mm). The following spectroscopic and analytical instruments were used. IR: Bruker Vector 22 FTIR. – NMR: Bruker AC 250 and Avance 500 (^{1}H: 250.13 MHz, 500.15 MHz, ^{13}C: 62.90 MHz, 125.76 MHz). For ^{1}H spectra, TMS was used as internal standard. Signal assignments are based on DEPT and COSY experiments. – Melting points: Büchi SMP 20, m. p. are uncorrected. – Mass spectrometry: Finnigan MAT 95 and Varian MAT 711. – GC: Hewlett-Packard HP 6890, column HP 5TA (30 m × 0.32 mm), temperature program: 16 °C min^{-1} gradient from 80 °C to 300 °C.

*General procedure for the preparation of amides **5**, **8**, as described for methyl O-methyl-N-propionyltyrosinate (**5a**):* In a Schlenk flask methyl (*S*)-*O*-methyltyrosinate (**4**) (499 mg, 2.38 mmol) was dissolved in pyridine (7 ml). After cooling with an ice bath, propionyl chloride (0.23 ml, 242 mg, 2.62 mmol) was added *via* syringe. The resulting slurry was allowed to warm to r. t. (16 h) and concentrated to give a colorless, waxy solid. The solid was purified by filtration through 25 g neutral aluminium oxide with ethyl acetate (EtOAc) to give **5a** as colorless crystals (515 mg, 1.94 mmol, 82%). $R_f = 0.14$ (hexanes/EtOAc = 3 : 1). – $[\alpha]^{22}_D = +84.3°$ ($c = 1.0$, CH_2Cl_2). – M. p. 53 °C. – IR (ATR): ν = 3305 (C-H), 2946, 2189, 1969, 1730 (C=O), 1643 (C=O), 1538 (N-H), 1512, 1434, 1282, 1238 (C-O), 1219, 1174, 1031, 1012, 829 (C-H), 685 cm^{-1}. – ^{1}H NMR (500.15 MHz, $CDCl_3$): $\delta = 1.13$ (t, $J = 7.6$ Hz, 3 H, CH_2CH_3), 2.21 (q, $J = 7.7$ Hz, 2 H, CH_2CH_3), 3.04 (dd, $^2J = 14.0$ Hz, $^3J = 5.6$ Hz, 1 H, $MeOC_6H_4CH_2$), 3.09 (dd, $^2J = 13.8$ Hz, $^3J = 5.9$ Hz, 1 H, $MeOC_6H_4CH_2$), 3.73 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 4.82 (dt, $^3J = 7.6$ Hz, $^3J = 5.6$ Hz, 1 H, MeO_2CCH), 5.92 (br. d, $J = 7.4$ Hz, 1 H, N*H*), 6.82 (d, $J = 8.6$ Hz, 2 H, *o*-$C_6H_4OCH_3$), 7.00 (d, $J = 8.7$ Hz, 2 H, *m*-$C_6H_4OCH_3$). – ^{13}C NMR (125.76 MHz, $CDCl_3$): $\delta = 9.7$ (CH_2CH_3), 29.6 (CH_2CH_3), 37.0 ($MeOC_6H_4CH_2$), 52.2 (OCH_3), 53.1 (MeO_2CCH), 55.2 (OCH_3), 114.0 (*o*-$C_6H_4OCH_3$), 127.8 (*p*-$C_6H_4OCH_3$), 130.3 (*m*-$C_6H_4OCH_3$), 158.7 (*i*-$C_6H_4OCH_3$), 172.3, 173.4 (*C*(O)NH, *C*(O)OMe). – MS (EI, 70 eV): *m/z* (%) 265 [M$^+$] (7), 193 [M$^+$ – NHC(O)C_2H_5] (11), 192 [M$^+$ – H – NHC(O)C_2H_5] (37), 161 (14), 122 (9), 121 [$H_3COC_6H_4CH_2^+$] (100), 91 [$C_7H_7^+$] (4), 77 (5), 57 [C(O)$C_2H_5^+$] (10), 29 (12). – $C_{14}H_{19}NO_4$ (265.3): calcd. C 63.38, H 7.22, N 5.28; found C 63.16, H 7.15, N 5.18.

*Methyl (S)-N-hexanoyl-O-methyltyrosinate (**5b**):* Yield: 479 mg, 1.56 mmol, 86%, colorless crystals. – M. p. 38 °C. – $R_f = 0.34$ (hexanes/EtOAc = 3 : 1). – $[\alpha]^{22}_D = +72.0°$ ($c = 1.0$, CH_2Cl_2). – IR (ATR): ν = 3286 (C-H), 2936, 2191, 1970, 1735 (C=O), 1645 (C=O), 1541 (N-H), 1512, 1435, 1244 (C-O), 1175, 1039, 1015, 812 (C-H), 727, 688 cm^{-1}. – ^{1}H NMR (500.15 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 7.0$ Hz, 3 H, $(CH_2)_4CH_3$), 1.23 – 1.33 (m, 4 H, $CH_2CH_2CH_2CH_2CH_3$), 1.59 (quint, $J = 7.5$ Hz, 2 H, $CH_2CH_2CH_2CH_2CH_3$), 2.18 (t, $J = 7.3$ Hz, 2 H, $CH_2CH_2CH_2CH_2CH_3$), 3.03 (dd, $^2J = 14.0$ Hz, $^3J = 5.7$ Hz, 1 H, $MeOC_6H_4CH_2$), 3.09 (dd, $^2J = 14.0$ Hz, $^3J = 5.8$ Hz, 1 H, $MeOC_6H_4CH_2$), 3.73 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 4.86 (dt, $^3J = 7.9$ Hz, $^3J = 5.8$ Hz, 1 H, MeO_2CCH), 5.89 (br. d, $J = 7.6$ Hz, 1 H, N*H*), 6.82 (d, $J = 8.7$ Hz, 2 H, *o*-$C_6H_4OCH_3$), 7.00 (d, $J = 8.6$ Hz, 2 H, *m*-$C_6H_4OCH_3$). – ^{13}C NMR (125.76 MHz, $CDCl_3$): $\delta = 13.9$ ($(CH_2)_4CH_3$), 22.4 ($CH_2CH_2CH_2CH_2CH_3$), 25.3 ($CH_2CH_2CH_2CH_2CH_3$), 31.4 ($CH_2CH_2CH_2CH_2CH_3$), 36.5 ($CH_2CH_2CH_2CH_2CH_3$), 37.1 ($MeOC_6H_4CH_2$), 52.3 (OCH_3), 53.04 (MeO_2CCH), 55.2 (OCH_3), 114.0 (*o*-$C_6H_4OCH_3$), 127.8 (*p*-$C_6H_4OCH_3$), 130.3 (*m*-$C_6H_4OCH_3$), 158.7 (*i*-$C_6H_4OCH_3$), 172.3, 172.7 (*C*(O)NH, *C*(O)OMe). – MS (EI, 70 eV): *m/z* (%) 307 [M$^+$] (5), 193 [M$^+$ – C(O)C_5H_{11}] (12), 192 [M$^+$ – H – NHC(O)C_5H_{11}] (100), 161 (9), 122 (7), 121 [$H_3COC_6H_4CH_2^+$] (64), 91 [$C_7H_7^+$] (3), 71 [$C_5H_{11}^+$] (3), 43 (11), 28 (16), 18 (17). – $C_{17}H_{25}NO_4$ (307.4): calcd. C 66.43, H 8.20, N 4.56; found C 66.29, H 8.13, N 4.50.

*Methyl (S)-N-(2,2-dimethylpropanoyl)-O-methyltyrosinate (**5c**):* Yield: 446 mg, 1.52 mmol, 91%, colorless crystals. – M. p. 63 °C. – $R_f = 0.28$ (hexanes/EtOAc = 8:1). – $[\alpha]^{22}_D = +66.1°$ ($c = 1.0$, CH_2Cl_2). – IR (ATR): ν = 3327 (C-H), 2958, 2192, 1968, 1752 (C=O), 1730, 1628 (C=O), 1513 (N-H), 1438, 1245 (C-O), 1200, 1180, 1120, 1034, 1003, 841 (C-H), 785, 633 cm^{-1}. – ^{1}H NMR (250.13 MHz, $CDCl_3$): $\delta = 1.16$ (s, 9 H, $C(CH_3)_3$), 3.04 (dd, $^2J = 13.9$ Hz, $^3J = 5.6$ Hz, 1 H, $MeOC_6H_4CH_2$), 3.11 (dd, $^2J = 13.9$ Hz, $^3J = 5.6$ Hz, 1 H, $MeOC_6H_4CH_2$), 3.74 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 4.82 (dt, $^3J = 7.6$ Hz, $^3J = 5.6$ Hz, 1 H, MeO_2CCH), 6.05 (br. d, $J = 7.4$ Hz, 1 H, N*H*), 6.82 (d, $J = 8.7$ Hz, 2 H, *o*-$C_6H_4OCH_3$), 6.99 (d, $J = 8.7$ Hz, 2 H, *m*-$C_6H_4OCH_3$). – ^{13}C NMR (62.90 MHz, $CDCl_3$): $\delta = 27.4$ ($C(CH_3)_3$), 36.9 ($MeOC_6H_4CH_2$), 38.7 ($C(CH_3)_3$), 52.3 (OCH_3), 53.0 (MeO_2CCH), 55.2 (OCH_3), 113.9 (*o*-$C_6H_4OCH_3$), 127.9 (*p*-$C_6H_4OCH_3$), 130.3 (*m*-$C_6H_4OCH_3$), 158.7 (*i*-$C_6H_4OCH_3$), 172.4, 177.8 (*C*(O)NH, *C*(O)OMe). – MS (EI, 70 eV): *m/z* (%) 293 [M$^+$] (5), 193 [M$^+$ – NHC(O)C_4H_9] (8), 192 [M$^+$ – H – NHC(O)C_4H_9]

(100), 161 (10), 122 (7), 121 (65), 57 [$C_4H_9^+$] (20), 41 (7), 29 (4). – $C_{16}H_{23}NO_4$ (293.4): calcd. C 65.51, H 7.90, N 4.77; found C 65.34, H 7.90, N 4.69.

*Methyl (S)-N-[(benzyloxy)acetyl]-O-methyltyrosinate (**5d**):* Yield: 349 mg, 0.98 mmol, 75%, colorless oil. – $R_f = 0.15$ (hexanes/EtOAc = 2 : 1). – $[\alpha]_D^{22} + 35.3°$ ($c = 1.0$, CH_2Cl_2). – IR (ATR): $\nu = 3401$ (C-H), 2951, 1741 (C=O), 1677 (C=O), 1611, 1510 (N-H), 1439, 1343, 1246 (C-O), 1205, 1176, 1099, 1029, 839 (C-H), 738, 698 cm^{-1}. – ^{1}H NMR (500.15 MHz, $CDCl_3$): $\delta = 3.08$ (dd, $^3J = 2.8$ Hz, $^2J = 5.9$ Hz, 2 H, $MeOC_6H_4CH_2$), 3.73 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.98 (s, 2 H, $HNC(O)CH_2$), 4.52 (dd, $^3J = 11.7$ Hz, $^2J = 28.5$ Hz, 2 H, $PhCH_2O$), 4.87 (dt, $^3J = 8.4$ Hz, $^3J = 6.0$ Hz, 1 H, MeO_2CCH), 6.79 (d, $J = 8.6$ Hz, 2 H, *o*-$C_6H_4OCH_3$), 7.02 (d, $J = 8.6$ Hz, 2 H, *m*-$C_6H_4OCH_3$, N*H*), 7.25 – 7.27 (m, 2 H, *o*-$PhCH_2O$), 7.32 – 7.38 (m, 3 H, *m*-, *p*-$PhCH_2O$). – ^{13}C NMR (125.76 MHz, $CDCl_3$): $\delta = 37.1$ ($MeOC_6H_4CH_2$), 52.4 (OCH_3), 52.5 (MeO_2CCH), 55.2 (OCH_3), 69.3 ($HNC(O)CH_2$), 73.4 ($PhCH_2O$), 114.0 (*o*-$C_6H_4OCH_3$), 127.6 (*p*-$C_6H_4OCH_3$), 127.8 (*o*-$PhCH_2O$), 128.1 (*p*-$PhCH_2O$), 128.6 (*m*-$PhCH_2O$), 130.2 (*m*-$C_6H_4OCH_3$), 136.8 (*i*-$PhCH_2O$), 158.7 (*i*-$C_6H_4OCH_3$), 169.3, 171.8 (*C*(O)NH, *C*(O)OMe). – MS (CI, CH_4): *m/z* (%) 386 [$M^+ + C_2H_4$] (11), 358 [M^+ + H], 326 [$M^+ - OCH_3$] (7), 298 [$M^+ - CO_2CH_3$] (34), 280 (3), 251 (5), 223 (3), 192 [M^+ – H – $NHC(O)CH_2OCH_2Ph$] (100), 161 (5), 121 [$H_3COC_6H_4CH_2^+$] (40), 107 [$PhCH_2O$] (2), 91 [$C_7H_7^+$] (24), 77 (1). – $C_{20}H_{23}NO_5$ (357.4): calcd. C 67.21, H 6.49, N 3.92; found C 67.12, H 6.52, N 3.82.

*Methyl (S)-N-[(2S)-2-(benzyloxy)propanoyl]-O-methyltyrosinate (**5e**):* Yield: 816 mg, 2.20 mmol, 93%, colorless oil. – $R_f = 0.32$ (hexanes/EtOAc = 3 : 1). – $[\alpha]_D^{22} = +48.0°$ ($c = 1.0$, CH_2Cl_2). – IR (ATR): $\nu = 3413$ (C-H), 2935, 2191, 1971, 1740 (C=O), 1672 (C=O), 1510 (N-H), 1442, 1337, 1246 (C-O), 1106, 1029, 839 (C-H), 738, 698 cm^{-1}. – ^{1}H NMR (250.13 MHz, $CDCl_3$): $\delta = 1.40$ (d, $J = 6.8$ Hz, 3 H, OCH_3), 3.03 (dd, $^2J = 14.1$ Hz, $^3J = 6.7$ Hz, 1 H, $MeOC_6H_4CH_2$), 3.11 (dd, $^2J = 14.1$ Hz, $^3J = 5.6$ Hz, 1 H, $MeOC_6H_4CH_2$), 3.73 (s, 6 H, OCH_3), 3.90 (q, $J = 6.8$ Hz, 1 H, $CHCH_3$), 4.41 (s, 2 H, $PhCH_2O$), 4.83 (dt, $^3J = 6.1$ Hz, $^3J = 8.2$ Hz, 1 H, MeO_2CCH), 6.74 (d, $J = 8.7$ Hz, 2 H, *o*-$C_6H_4OCH_3$), 7.00 (d, $J = 8.7$ Hz, 2 H, *m*-$C_6H_4OCH_3$), 7.18 – 7.24 (m, 2 H, *o*-, *m*-, *p*-$PhCH_2O$), 7.27 – 7.39 (m, 3 H, *o*-, *m*-, *p*-$PhCH_2O$). – ^{13}C NMR (62.90 MHz, $CDCl_3$): $\delta = 18.4$ (CH_3), 36.9 ($MeOC_6H_4CH_2$), 52.3 (OCH_3), 52.6 (MeO_2CCH), 55.2 (OCH_3), 71.7 ($PhCH_2$), 76.0 ($CHCH_3$), 114.1 (*o*-$C_6H_4OCH_3$), 127.6 (*o*-, *m*-, *p*-$PhCH_2O$), 127.7 (*i*-$PhCH_2O$), 128.0, 128.5 (*o*-, *m*-, *p*-$PhCH_2O$), 130.2 (*m*-$C_6H_4OCH_3$), 137.4 (*i*-$PhCH_2O$), 158.7 (*i*-$C_6H_4OCH_3$), 171.8, 173.0 (*C*(O)NH, *C*(O)OMe). – MS (EI, 70 eV): *m/z* (%) 371 [M^+] (3), 265 [M^+ + H – $PhCH_2O$] (5), 193 [M^+ – $NHC(O)CH(CH_3)OCH_2Ph$] (12), 192 [M^+ – H – $NHC(O)CH(CH_3)OCH_2Ph$] (100), 122 (6), 121 [$H_3COC_6H_4CH_2^+$] (55), 91 [$C_7H_7^+$] (36), 43 (6), 28 (7). – $C_{21}H_{25}NO_5$ (371.4): calcd. C 67.91, H 6.78, N 3.77; found C 67.88, H 6.84, N 3.69.

*Methyl (S)-N-[2-(benzyloxy)-2-methylpropanoyl]-O-methyltyrosinate (**5f**):* Yield: 769 mg, 2.00 mmol, 65%, colorless oil. – $R_f = 0.50$ (hexanes/EtOAc = 3 : 1). – $[\alpha]_D^{22} = +83.9°$ ($c = 1.0$, CH_2Cl_2). – IR (ATR): $\nu = 3416$ (C-H), 2951, 1741 (C=O), 1675 (C=O), 1612, 1510 (N-H), 1441, 1359, 1246 (C-O), 1175, 1029, 837 (C-H), 736, 697 cm^{-1}. – ^{1}H NMR (500.15 MHz, $CDCl_3$): $\delta = 1.41$ (s, 3 H, CH_3), 1.47 (s, 3 H, CH_3), 3.02 (dd, $^2J = 14.1$ Hz, $^3J = 6.5$ Hz, 1 H, $MeOC_6H_4CH_2$), 3.09 (dd, $^2J = 14.1$ Hz, $^3J = 5.6$ Hz, 1 H, $MeOC_6H_4CH_2$), 3.71 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 4.42 (dd, $^2J = 22.3$ Hz, $^3J = 11.0$ Hz, 1 H, $PhCH_2O$), 4.82 (dt, $J = 8.2$ Hz, $J = 6.1$ Hz, 1 H, MeO_2CCH), 6.72 (d, $J = 8.6$ Hz, 2 H, *o*-$MeOC_6H_4$), 6.97 (d, $J = 6.7$ Hz, 2 H, *m*-$MeOC_6H_4$), 7.09 (d, $J = 8.2$ Hz, 1 H, N*H*), 7.23 (d, $J = 7.0$ Hz, 2 H, *o*-$PhCH_2O$), 7.27 – 7.36 (m, 3 H, *m*-, *p*-$PhCH_2O$). – ^{13}C NMR (125.76 MHz, $CDCl_3$): $\delta = 23.5$ (CH_3), 24.5 (CH_3), 36.9 ($MeOC_6H_4CH_2$), 52.3 (OCH_3), 52.8 (MeO_2CCH), 55.2 (OCH_3), 65.7 ($(CH_3)_2COCH_2Ph$), 78.8 ($PhCH_2O$), 114.0 (*o*-$MeOC_6H_4$), 127.4 (*o*-$PhCH_2O$), 127.6 (*m*-, *p*-$PhCH_2O$), 127.7 (*p*-$MeOC_6H_4$), 128.4 (*m*-, *p*-$PhCH_2O$), 130.2 (*m*-$MeOC_6H_4$), 138.2 (*i*-$PhCH_2O$), 158.7 (*i*-$MeOC_6H_4$), 172.0, 175.1 (CO_2Me, *C*(O)NH). – MS (EI, 70 eV): *m/z* (%) 385 [M^+] (3), 354 [$M^+ - OCH_3$] (1), 326 [$M^+ - CO_2CH_3$] (2), 279 [M^+ + H – OCH_2Ph] (25), 262 (1), 236 [$M^+ - C(CH_3)_2OCH_2Ph$] (12), 208 (7), 192 [M^+ – H – $NHC(O)C(CH_3)_2OCH_2Ph$] (100), 176 [M^+ + H – $C(O)C(CH_3)_2OCH_2Ph$] (10), 149 (8), 121 [$H_3COC_6H_4CH_2^+$] (59), 91 [$C_7H_7^+$] (76), 59 [$CO_2CH_3^+$] (2). – $C_{22}H_{27}NO_5$ (385.5): calcd. C 68.55, H 7.06, N 3.63; found C 68.59, H 7.16, N 3.51.

*Methyl (S)-N-(4-chlorobenzoyl)-O-methyltyrosinate (**5g**):* Yield: 526 mg, 1.51 mmol, 74%, colorless crystals. – M. p. 111 °C. – $R_f = 0.32$ (hexanes/EtOAc = 3 : 1). – $[\alpha]_D^{22} = +14.9°$ ($c = 1.0$, CH_2Cl_2). – IR (ATR): $\nu = 3288$ (C-H), 2949, 1736 (C=O), 1635 (C=O), 1536 (N-H), 1513, 1485, 1436, 1247 (C-O), 1224, 1174, 1089, 1028, 1013, 848 (C-H), 834 (C-H), 765, 658 cm^{-1}. – ^{1}H NMR (500.15 MHz, $CDCl_3$): $\delta = 3.16$ (dd, $^2J = 14.0$ Hz, $^3J = 5.3$ Hz, 1 H, $MeOC_6H_4CH_2$), 3.23 (dd, $^2J = 14.0$ Hz, $^3J = 5.7$ Hz, 1 H, $MeOC_6H_4CH_2$), 3.78 (s, 6 H, OCH_3), 5.03 (dt, $^3J = 7.6$ Hz, $^3J = 5.5$ Hz, 1 H, MeO_2CCH) 6.56 (d, $J = 7.5$ Hz, 1 H, N*H*), 6.82 (d, $J = 8.5$ Hz, 2 H, *o*-$MeOC_6H_4$), 7.03 (d, $J = 8.7$ Hz, 2 H, *m*-$MeOC_6H_4$), 7.39 (d, $J = 8.4$ Hz, 2 H, *o*-ClC_6H_4), 7.66 (d, $J = 8.6$ Hz, 2 H, *m*-ClC_6H_4). – ^{13}C NMR (125.76 MHz, $CDCl_3$): $\delta = 36.9$ ($MeOC_6H_4CH_2$), 52.5 (OCH_3), 53.7 (MeO_2CCH), 55.2 (OCH_3), 114.0 (*o*-$MeOC_6H_4$), 127.6 (*p*-$MeOC_6H_4$), 128.5 (*m*-ClC_6H_4), 128.9 (*o*-ClC_6H_4), 130.3 (*m*-$MeOC_6H_4$), 132.3 (*i*-ClC_6H_4), 138.1 (*p*-ClC_6H_4), 158.8

(*i*-$MeOC_6H_4$), 165.7 (*C*(O)NH), 172.1 (*C*(O)OMe). – GC-MS (EI, 70 eV): *m/z* (%) 347 [M^+] (4), 288 (2), 192 [M^+ – H – NHC(O)C_6H_4Cl] (100), 161 (9), 139 [C(O)$C_6H_4Cl^+$] (20), 121 [$H_3COC_6H_4CH_2^+$] (73), 111 [$C_6H_4Cl^+$] (9), 81 (2), 77 (3), 28 (1). – $C_{18}H_{18}ClNO_4$ (347.8): calcd. C 62.16, H 5.22, N 4.03 Cl 10.19; found C 62.19, H 5.35, N 3.86, Cl 10.32.

*Methyl (S)-O-methyl-N-pyruvoyltyrosinate (**5h**):* Yield: 74 mg, 0.22 mmol, 76%, colorless oil. – R_f = 0.44 (hexanes/EtOAc = 2 : 1). – $[\alpha]_D^{22}$ = +61.8° (*c* = 0.5, CH_2Cl_2). – IR (ATR): ν = 3341 (C-H), 2954, 1744 (C=O), 1698 (C=O), 1612, 1511 (N-H), 1441, 1369, 1298, 1246 (C-O), 1152, 1032, 837 (C-H) cm^{-1}. – ^1H NMR (500.15 MHz, $CDCl_3$): δ = 1.55 (s, 9 H, C(CH_3)$_3$), 3.10 (d, *J* = 5.8 Hz, 2 H, $MeOC_6H_4CH_2$), 3.73 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 4.80 (dt, *J* = 5.8 Hz, *J* = 8.2 Hz, 1 H, MeO_2CCH), 6.83 (d, *J* = 8.7 Hz, 2 H, *o*-$C_6H_4OCH_3$), 7.03 (d, *J* = 8.7 Hz, 2 H, *m*-$C_6H_4OCH_3$), 7.41 (d, *J* = 7.9 Hz, 1 H, N*H*). – ^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 27.7 (C(CH_3)$_3$), 36.9 ($MeOC_6H_4CH_2$), 52.5 (OCH_3), 53.7 (MeO_2CCH), 55.2 (OCH_3), 84.8 (*C*(CH_3)$_3$), 114.2 (*o*-$C_6H_4OCH_3$), 127.2 (*p*-$C_6H_4OCH_3$), 130.2 (*m*-$C_6H_4OCH_3$), 157.0, 158.88, 158.92 (*m*-$C_6H_4OCH_3$, NH*C*(O)*C*(O)O*t*-Bu), 171.0 (CO_2Me). – GC-MS (CI, CH_4): *m/z* (%) 338 [M^+ + H] (45), 322 (2), 310 (9), 296 (3), 282 (100), 250 (7), 236 [M^+ – CO_2*t*-Bu] (11), 222 (10), 208 [M^+ – C(O)CO_2*t*-Bu] (2), 192 [M^+ – H – NHC(O)CO_2*t*-Bu] (72), 176 (4), 161 (3), 121 [$H_3COC_6H_4CH_2^+$] (44), 57 [$C_4H_9^+$] (12). – $C_{17}H_{23}NO_6$ (337.4): calcd. C 60.52, H 6.87, N 4.15; found C 60.77, H 6.93, N 4.08.

*Methyl N-benzoyl-3-(methoxyphenyl)alaninate (**8**):* Yield: 131 mg, 0.42 mmol, 92%, colorless oil. – R_f = 0.24 (hexanes/EtOAc = 3 : 1). – IR (ATR): ν = 3315 (C-H), 2950, 1975, 1739 (C=O), 1639 (C=O), 1601, 1526 (N-H), 1487, 1435, 1256 (C-O), 1213, 1152, 1039, 875 (C-H), 775, 691 cm^{-1}. – ^1H NMR (500.15 MHz, $CDCl_3$): δ = 3.21 (dd, ^2J = 13.8 Hz, ^3J = 5.3 Hz, 1 H, $MeOC_6H_4CH_2$), 3.28 (dd, ^2J = 13.8 Hz, ^3J = 5.8 Hz, 1 H, $MeOC_6H_4CH_2$), 3.74 (s, 3 H, $C_6H_4OCH_3$), 3.78 (s, 3 H, CO_2CH_3), 5.09 (dt, *J* = 7.5 Hz, *J* = 5.6 Hz, 1 H, MeO_2CCH), 6.59 (d, *J* = 7.3 Hz, 1 H, N*H*), 6.66 – 6.68 (m, 1 H, 5-H), 6.72 (d, *J* = 13.8 Hz, 1 H, 9-H), 6.80 (dd, *J* = 8.1 Hz, *J* = 2.4 Hz, 1 H, 7-H), 7.20 (t, *J* = 7.9 Hz, 1 H, 8-H), 7.42 – 7.45 (m, 2 H, *m*-C(O)Ph), 7.50 – 7.53 (m, 1 H, *p*-C(O)Ph), 7.72 – 7.74 (m, 2H, *o*-C(O)Ph). – ^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 37.9 ($MeOC_6H_4CH_2$), 52.5 (CO_2CH_3), 53.5 (MeO_2CCH), 55.1 ($C_6H_4OCH_3$), 112.8 (C-7), 114.9 (C-5), 121.7 (C-9), 127.0 (*o*-C(O)Ph), 128.6 (*m*-C(O)Ph), 129.6 (C-6), 131.8 (*p*-C(O)Ph), 133.9, 137.3 (C-4, *i*-C(O)Ph), 159.7 (C-6), 166.8 (*C*(O)Ph), 172.0 (CO_2Me). – GC-MS (EI, 70 eV): *m/z* (%) 314 [M^+ + H] (2), 313 [M^+] (12), 282 (1), 254 [M^+ – CO_2CH_3] (3), 193 [M^+ – NHC(O)Ph] (12), 192 [M^+ – H – NHC(O)Ph] (100), 161 (9), 121 [$H_3COC_6H_4CH_2^+$] (3), 105 (51), 91 [$C_7H_7^+$] (2), 77 [$C_6H_5^+$] (16), 51 (1). – $C_{18}H_{19}NO_4$ (313.3): calcd. C 68.99, H 6.11, N 4.47; found C 69.15, H 6.21, N 4.24.

*General procedure for the preparation of oxazoles **6**, as described for 2-ethyl-5-methoxy-4-(4-methoxybenzyl)-1,3-oxazole (**6a**):* In a Schlenk flask **5a** (100 mg, 0.38 mmol) was dissolved in phosphoryl chloride (2.5 ml, 27 mmol). The reaction mixture was heated at 95 °C for 25 min, cooled to r. t. and poured into an ice-cold saturated $NaHCO_3$ solution (50 ml), and further $NaHCO_3$ was carefully added to adjust pH 8. After warming to r. t., the mixture was stirred for 15 min and was then extracted with dichloromethane (3 × 30 ml). The combined organic layers were washed with brine (2 × 50 ml), dried (Na_2SO_4), and concentrated. The pale yellow liquid was purified by chromatography on basic aluminium oxide (10 g) with hexanes/EtOAc (4 : 1, R_f = 0.58) to give **6a** as a colorless liquid (46 mg, 0.19 mmol, 49%). – IR (ATR): ν = 2942, 1668 (N=C), 1612, 1579, 1511 (C=C), 1461, 1353, 1241 (C-O), 1175, 1141, 1108, 1063, 1034, 974, 795 cm^{-1}. – ^1H NMR (500.15 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.6 Hz, 3 H, CH_2CH_3), 2.64 (q, *J* = 7.6 Hz, 2 H, CH_2CH_3), 3.66 (s, 2 H, $MeOC_6H_4CH_2$), 3.77 (s, 3 H, $C_6H_4OCH_3$), 3.83 (s, 3 H, OCH_3), 6.82 (d, *J* = 8.7 Hz, 2 H, *o*-$C_6H_4OCH_3$), 7.18 (d, *J* = 8.7 Hz, 2 H, *m*-$C_6H_4OCH_3$). – ^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 11.1 (CH_2CH_3), 22.0 (CH_2CH_3), 30.1 ($MeOC_6H_4CH_2$), 55.3 ($C_6H_4OCH_3$), 61.2 (OCH_3), 113.9 (*o*-$MeOC_6H_4$), 114.9 (C-4), 129.5 (*m*-$MeOC_6H_4$), 131.7 (*p*-$MeOC_6H_4$), 154.7, 156.5 (C-2, C-5), 158.05 (*i*-$MeOC_6H_4$). – MS (EI, 70 eV): *m/z* (%) 247 [M^+] (67), 219 (6), 218 [M^+ – C_2H_5] (25), 204 [M^+ – $COCH_3$] (11), 190 [M^+ – C(O)C_2H_5] (9), 188 (20), 186 (9), 161 (5), 147 (8), 133 (26), 121 [$H_3COC_6H_4CH_2^+$] (26), 89 (5), 77 (9), 57 (100), 29 [C_2H_5] (19), 28 (14). – HRMS (EI, 70 eV): calcd. for $C_{14}H_{17}NO_3$ 247.1208, found 247.1210 [M^+]. – $C_{14}H_{17}NO_3$ (247.3): calcd. C 68.00, H 6.93, N 5.66; found C 67.62, H 6.88, N 5.62.

*5-Methoxy-4-(4-methoxybenzyl)-2-pentyl-1,3-oxazole (**6b**):* Yield: 47 mg, 0.16 mmol, 50%, pale yellow liquid. – R_f = 0.37 (hexanes/EtOAc = 20 : 1). – IR (ATR): ν = 2932, 2860, 1668 (N=C), 1611, 1578, 1511 (C=C), 1463, 1354, 1242 (C-O), 1175, 1142, 1084, 1034, 990, 804 cm^{-1}. – ^1H NMR (500.15 MHz, $CDCl_3$): δ = 0.88 – 0.90 (m, 3 H, $(CH_2)_4CH_3$), 1.29 – 1.35 (m, 4 H, $(CH_2)_2CH_2CH_2CH_3$), 1.67 – 1.73 (m, 2 H, $CH_2CH_2(CH_2)_2CH_3$), 2.59 (t, *J* = 8.7 Hz, 2 H, $CH_2(CH_2)_3CH_3$), 3.66 (s, 2 H, $MeOC_6H_4CH_2$), 3.77 (s, 3 H, $C_6H_4OCH_3$), 3.83 (s, 3 H, OCH_3), 6.82 (d, *J* = 8.7 Hz, 2 H, *o*-$MeOC_6H_4$), 7.16 (d, *J* = 8.6 Hz, 2 H, *m*-$MeOC_6H_4$). – ^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 13.9 ($(CH_2)_4CH_3$), 22.3 ($(CH_2)_2CH_2CH_2CH_3$), 26.7 ($CH_2CH_2(CH_2)_2CH_3$), 28.6 ($CH_2(CH_2)_3CH_3$), 30.1 ($MeOC_6H_4CH_2$), 31.3 ($(CH_2)_2CH_2CH_2CH_3$), 55.3 ($C_6H_4OCH_3$), 61.2 (OCH_3),

113.8 (*o*-$MeOC_6H_4$), 114.8 (C-4), 129.5 (*m*-$MeOC_6H_4$), 131.7 (*p*-$MeOC_6H_4$), 154.7, 155.8 (C-2, C-5), 158.1 (*i*-$MeOC_6H_4$). – GC-MS (EI, 70 eV): *m/z* (%) 289 [M^+] (100), 274 (11), 260 (4), 246 [M^+ – $COCH_3$] (4), 230 (11), 218 (7), 201 (9), 186 (9), 173 (16), 159 (7), 147 [M^+ – $COCH_3$ – $C(O)C_5H_{11}$] (32), 140 (31), 133 (18), 121 [$H_3COC_6H_4CH_2{}^+$] (61), 103 (10), 91 (15), 83 (33), 71 [$C_5H_{11}{}^+$] (26), 63 (10), 55 (38). – $C_{17}H_{23}NO_3$ (289.4): calcd. C 70.56, H 8.01, N 4.84; found C 70.47, H 8.07, N 4.87.

*2-tert-Butyl-5-methoxy-4-(4-methoxybenzyl)-1,3-oxazole (**6c**):* Yield: 26 mg, 0.094 mmol, 28%, colorless liquid. – $R_f = 0.35$ (hexanes/EtOAc = 20 : 1). – IR (ATR): $\nu = 2971$, 1669 (N=C), 1612, 1566, 1511 (C=C), 1461, 1368, 1299, 1241 (C-O), 1174, 1136, 1078, 1035, 987, 819, 782 cm^{-1}. – ^1H NMR (500.15 MHz, $CDCl_3$): $\delta = 1.32$ (s, 9 H, $C(CH_3)_3$), 3.69 (s, 2 H, $MeOC_6H_4CH_2$), 3.79 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 6.82 (d, $J = 8.7$ Hz, 2 H, *o*-$MeOC_6H_4$), 7.16 (d, $J = 8.6$ Hz, 2 H, *m*-$MeOC_6H_4$). – ^{13}C NMR (125.76 MHz, $CDCl_3$): $\delta = 28.4$ ($C(CH_3)_3$), 30.2 ($C(CH_3)_3$), 33.7 ($MeOC_6H_4CH_2$), 55.3 ($C_6H_4OCH_3$), 61.0 (OCH_3), 113.7 (*o*-$MeOC_6H_4$), 114.5 (C-4), 129.5 (*m*-$MeOC_6H_4$), 131.8 (*p*-$MeOC_6H_4$), 154.6, 158.0, 161.6 (C-2, C-5, *i*-$MeOC_6H_4$). – GC-MS (EI, 70 eV): *m/z* (%) 275 [M^+] (50), 260 (5), 232 [M^+ – $COCH_3$] (5), 218 (23), 204 (6), 190 [M^+ – $C(O)C_4H_9{}^+$] (7), 186 (6), 160 (7), 158 (6), 146 (5), 133 (9), 126 (17), 121 [$H_3COC_6H_4CH_2{}^+$] (21), 108 (5), 91 (7), 89 (7), 77 (13), 63 (7), 57 [$C_4H_9{}^+$] (100). – $C_{16}H_{21}NO_3$ (275.3): calcd. C 69.79, H 7.69, N 5.09; found C 69.76, H 7.78, N 5.04.

*2-[(Benzyloxy)methyl]-5-methoxy-4-(4-methoxybenzyl)-1,3-oxazole (**6d**):* Yield: 16 mg, 0.047 mmol, 40%, pale yellow liquid. – $R_f = 0.48$ (hexanes/EtOAc = 3 : 1). – IR (ATR): $\nu = 2938$, 1964, 1661 (N=C), 1511 (C=C), 1454, 1360, 1244 (C-O), 1176, 1072, 1029, 983, 807 (C-H), 738, 698 cm^{-1}. – ^1H NMR (500.15 MHz, $CDCl_3$): $\delta = 3.68$ (s, 2 H, $MeOC_6H_4CH_2$), 3.77 (s, 3 H, $C_6H_4OCH_3$), 3.85 (s, 3 H, OCH_3), 4.44 (s, 2 H, CH_2OCH_2Ph), 4.58 (s, 2 H, CH_2OCH_2Ph), 6.82 (d, $J = 8.7$ Hz, 2 H, *o*-$MeOC_6H_4$), 7.17 (d, $J = 8.5$ Hz, 2 H, *m*-$MeOC_6H_4$) 7.28 – 7.30 (m, 1 H, *p*-$PhCH_2O$), 7.33 (d, $J = 8.1$ Hz, 4 H, *o*-, *m*-$PhCH_2O$). – ^{13}C NMR (125.76 MHz, $CDCl_3$): $\delta = 30.0$ ($MeOC_6H_4CH_2$), 55.3 ($C_6H_4OCH_3$), 60.9 (OCH_3), 64.4 (CH_2OCH_2Ph), 72.8 (CH_2OCH_2Ph), 113.9 (*o*-$MeOC_6H_4$), 115.3 (C-4), 127.9 (*p*-$PhCH_2O$), 128.0, 128.5 (*o*-$PhCH_2O$, *m*-$PhCH_2O$), 129.5 (*o*-$MeOC_6H_4$), 131.4 (*p*-$MeOC_6H_4$), 137.3 (*i*-$PhCH_2O$), 151.2, 155.5 (C-2, C-5), 158.1 (*i*-$MeOC_6H_4$). – MS (CI, CH_4): *m/z* (%) 679 (5) $[2M + H]^+$, 571 (3), 460 (9), 430 (13), 355 [M^+ + CH_4] (7), 340 [M^+ + H] (100), 298 (6), 232 [M^+ – OCH_2Ph] (40), 218 [M^+ – CH_2OCH_2Ph] (26), 201 (8), 148 (8), 132 (9), 121 [$H_3COC_6H_4CH_2{}^+$] (21), 91 [$C_7H_7{}^+$] (42). – HRMS (DCI): calcd. for $C_{20}H_{21}NO_4$ 339.1471, found 339.1454 [M^+]. – $C_{20}H_{21}NO_4$ (339.4): calcd. C 70.78, H 6.24, N 4.13; found C 71.33, H 6.48, N 3.59.

*2-(4-Chlorophenyl)-5-methoxy-4-(4-methoxybenzyl)-1,3-oxazole (**6g**):* Yield: 74 mg, 0.22 mmol, 76 %, yellow solid. – M. p. 78 – 79 °C. – $R_f = 0.36$ (hexanes/EtOAc = 15 : 1). – IR (ATR): $\nu = 2943$, 2832, 1657 (N=C), 1612, 1510 (C=C), 1479, 1449, 1355, 1290, 1241 (C-O), 1178, 1087, 1037, 970, 822 (C-H), 768, 727 (C-Cl), 694, 620, 560 cm^{-1}. – ^1H NMR (500.15 MHz, $CDCl_3$): $\delta = 3.76$ (s, 2 H, $MeOC_6H_4CH_2$), 3.79 (s, 3 H, $C_6H_4OCH_3$), 3.94 (s, 3 H, OCH_3), 6.84 (d, $J = 8.7$ Hz, 2 H, *o*-$MeOC_6H_4$), 7.23 (d, $J = 8.6$ Hz, 2 H, *m*-$MeOC_6H_4$), 7.37 (d, $J = 8.7$ Hz, 2 H, *o*-ClC_6H_4), 7.84 (d, $J = 8.5$ Hz, 2 H, *m*-ClC_6H_4). – ^{13}C NMR (125.76 MHz, $CDCl_3$): $\delta = 30.2$ ($MeOC_6H_4CH_2$), 55.3 ($C_6H_4OCH_3$), 61.2 (CO_2CH_3), 113.9 (*m*-$MeOC_6H_4$), 117.1 (C-4), 126.2 (*m*-$MeOC_6H_4$), 126.7 (*m*-ClC_6H_4), 128.9 (*o*-ClC_6H_4), 129.5 (*m*-$MeOC_6H_4$), 131.3 (*p*-ClC_6H_4), 135.5 (*i*-ClC_6H_4), 151.3, 155.3 (C-2, C-5), 158.1 (*i*-$MeOC_6H_4$). – MS (EI, 70 eV): *m/z* (%) 329 [M^+] (96), 314 (6), 287 (4), 270 [M^+ – CO_2CH_3] (14), 254 (2), 209 (5), 191 (1), 164 (2), 147 (3), 139 [$C(O)C_6H_5Cl^+$] (100), 111 [$C_6H_5Cl^+$] (13), 77 (4), 59 [$CO_2CH_3{}^+$] (2), 43 [$COCH_3{}^+$] (1). – $C_{18}H_{16}ClNO_3$ (329.8): calcd. C 65.56, H 4.89, N 4.25, Cl 10.75; found C 65.39, H 5.01, N 4.14, Cl 10.66.

*5-Methoxy-4-(3-methoxybenzyl)-2-phenyl-1,3-oxazole (**9**):* In a Schlenk flask **8** (45 mg, 0.14 mmol) was dissolved in toluene (2.5 ml). Then phosphoryl chloride (0.45 ml, 0.74 g, 4.83 mmol) was added *via* syringe and the reaction mixture was heated at 100 °C for 2.5 h. After cooling to r. t., the mixture was poured into an ice-cold saturated $NaHCO_3$ solution (35 ml). The reaction mixture was warmed to r. t., stirred for a further 10 min and was then extracted with toluene (1 × 15 ml) and dichloromethane (3 × 30 ml). The combined organic layers were washed with brine (2 × 40 ml), dried (Na_2SO_4), and concentrated. The residual yellow oil was purified by chromatography on silica gel with hexanes/EtOAc (3 : 1, $R_f = 0.62$) to give **9** as a colorless oil (27 mg, 0.091 mmol, 63%). – IR (ATR): $\nu = 2941$, 1654 (N=C), 1599 (C=C), 1487, 1450, 1358, 1260 (C-O), 1147, 1047, 982, 769, 689 cm^{-1}. – ^1H NMR (500.15 MHz, $CDCl_3$): $\delta = 3.79$ (s, 3 H, $C_6H_4OCH_3$), 3.81 (s, 2 H, $MeOC_6H_4CH_2$), 3.95 (s, 3 H, OCH_3), 6.75 (dd, $J = 8.2$ Hz, $J = 2.5$ Hz, 1 H, 3'-H), 6.89 – 6.91 (m, 2 H, 7'-H, 5'-H), 7.21 (t, $J = 7.9$ Hz, 1 H, 6'-H), 7.37 – 7.42 (m, 3 H, *m*-, *p*-Ph), 7.84 (d, $J = 8.5$ Hz, 2 H, *o*-Ph), 7.91 – 7.93 (dd, $J = 7.9$ Hz, $J = 1.6$ Hz, 2 H, *o*-Ph). – ^{13}C NMR (125.76 MHz, $CDCl_3$): $\delta = 31.0$ ($MeOC_6H_4CH_2$), 55.2 ($C_6H_4OCH_3$), 61.1 (OCH_3), 111.6 (C-3'), 114.3 (C-7', C-5'), 116.3 (C-4), 120.9 (C-7', C-5'), 125.5 (*o*-Ph), 127.7 (*i*-Ph), 128.6 (*m*-, *p*-Ph), 129.4 (C-6'), 129.6 (*m*-, *p*-Ph), 141.0 (C-2'), 152.2, 155.4, 159.7 (C-2, C-4, C-4'). – MS (EI, 70 eV): *m/z* (%) 295 [M^+] (100), 294 (24), 252 [M^+ –

$COCH_3$] (11), 236 [M^+ – CO_2CH_3] (32), 234 (8), 209 (9), 192 (3), 179 (5), 147 (5), 133 (5), 121 [$H_3COC_6H_4CH_2^+$] (4), 105 [$C(O)Ph^+$] (95), 103 (8), 91 [$C_7H_7^+$] (3), 77 (10), 51 (2). – HRMS (EI, 70 eV): calcd. for $C_{18}H_{17}NO_3$ 295.1208, found 295.1207 [M^+]. – $C_{18}H_{17}NO_3$ (295.3): calcd. C 73.20, H 5.80, N 4.74; found C 73.00, H 5.96, N 4.60.

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