A Modified Synthesis of ($\pm$)-β-Aryllactic acids[1]

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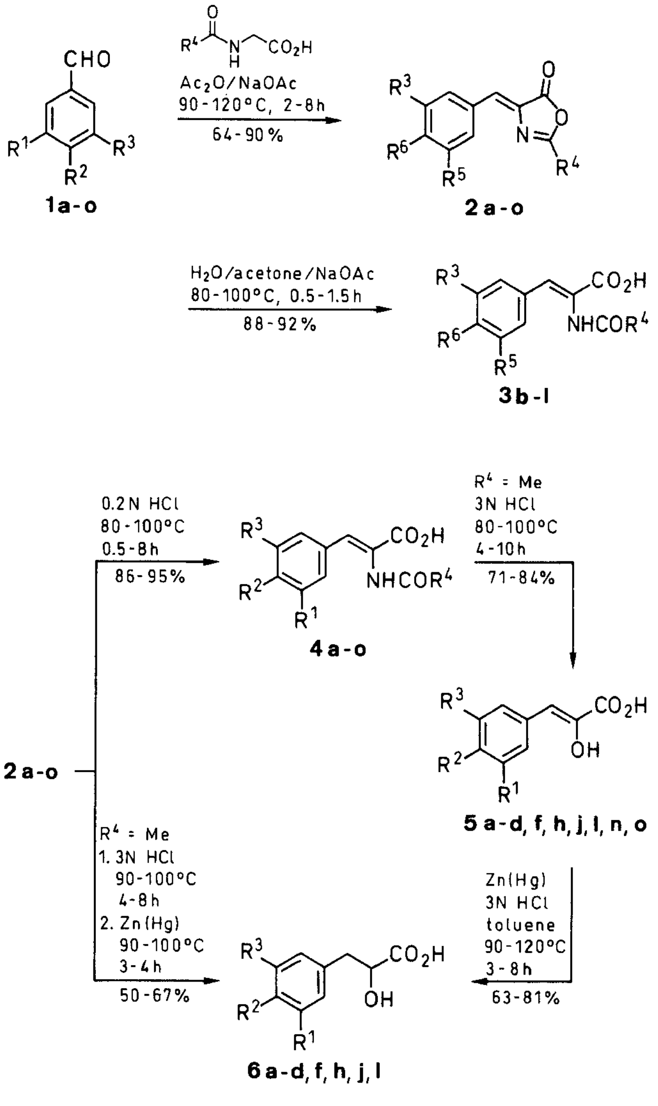
The synthesis of racemic forms of the reportedly active principle of Danshen, namely ($\pm$)-β-(3,4-dihydroxyphenyl)lactic acid [($\pm$)-3-(3,4-dihydroxyphenyl)-2-hydroxypropanoic acid] and its seven racemic derivatives is reported.

In our effort[1,2] to explore the structure–activity relationships and to identify biologically active compounds from *Salvia miltiorrhiza* Bunge (Danshen),[3] considerable interest has been devoted of late to the synthesis of substituted ($\pm$)-β-aryllactic acids. Accordingly, the synthetic plan initially called for the construction of the racemic form of an active ingredient from Danshen, namely D-(+)-β-(3,4-dihydroxyphenyl)lactic acid.[4–7] Notwithstanding the synthesis of ($\pm$)-β-(3,4-dihydroxyphenyl)lactic acid has been recorded,[8,9] we found it difficult to repeat these procedures[8,9] because the intermediates involved in these programs have not been unequivocally identified.[10] Based on the known literature procedures for the preparation of **2**,[8,9,11–13] we report herein a modified synthesis of ($\pm$)-β-(3,4-dihydroxyphenyl)lactic acid as well as seven of its derivatives.[14] We have also identified all the intermediates in these experiments and provided spectral evidence for the 3-aryl-2-hydroxy-2-propenoic acid intermediates **5**.

As can be seen in the following Scheme, the Erlenmeyer synthesis of 4-benzylideneoxazol-5(4*H*)-ones **2** from benzaldehydes **1** and *N*-acetylglycine or *N*-benzoylglycine was employed as the first step.[11,12] In practice, it was found that a small amount of sodium acetate exhibited remarkable enhancement effect in hydrolyzing **2** to α-(aroylamino)cinnamic acids **3**,[13] whose acetyl protecting groups remained intact. The yields of these reactions ranged from 88 to 92%. Alternatively, **2** were also cleaved by 0.2 N hydrochloric acid to generate the α-(aroylamino)cinnamic acids **4**, with concomitant deprotection. Further treatment with 3 N hydrochloric acid converted **4** (R^4 = Me) into α-hydroxycinnamic acids **5**, whose enol structures were supported by ^{1}H NMR spectra (see Table). The formation of α-hydroxycinnamic acids **5** is in marked contrast to the previous report,[8] which favored α-oxoacid structures. Eventually, Clemmensen reduction of **5** with zinc amalgam in boiling 3 N hydrochloric acid gave the desired ($\pm$)-β-aryllactic acids **6** in fair yields (see Table). However, acids **6** are rather unstable and must be handled under inert atmosphere. 4-Benzylidene-4-methyloxazol-5-one (**2a**) was reportedly transformed in one step to the ($\pm$)-β-phenyllactic acid (**6a**) by Clemmensen reduction, although the yield was not disclosed.[14] In light of this fact, a modified "one-pot" procedure was derived, in which 4-benzylidene-2-methyloxazol-5-ones **2** (R^4 = Me) were first refluxed with 3 N hydrochloric acid until complete conversion to α-hydroxycinnamic acids **5** which was monitored by thin layer



1–6	R^1	R^2	R^3	R^4	R^5	R^6
a	H	H	H	Me	H	H
b	H	OH	H	Me	H	OAc
c	OH	H	H	Me	OAc	H
d	OH	OH	H	Me	OAc	OAc
e	OH	OH	H	Ph	OAc	OAc
f	OMe	OH	H	Me	OMe	OAc
g	OMe	OH	H	Ph	OMe	OAc
h	OMe	OMe	H	Me	OMe	OMe
i	OMe	OMe	H	Ph	OMe	OMe
j	OCH_2O		H	Me	OCH_2O	
k	OCH_2O		H	Ph	OCH_2O	
l	OMe	OMe	OMe	Me	OMe	OMe
m	OMe	OMe	OMe	Ph	OMe	OMe
n	NO_2	H	H	Me	NO_2	H
o	H	NO_2	H	Me	H	NO_2

Table. Compounds **1**–**7** Prepared

Starting Material	Product	Conditions		Yield (%)	mp (°C)	Molecular Formula or Lit. mp (°C)[a]	^{1}H NMR (DMSO-d_6/TMS)[b] δ, J (Hz)	MS (m/z)
		Time (h)	Temp. (°C)					
1a	**2a**	5	90	67	151–152	148–150[11]	2.40 (s, 3H), 7.22 (s, 1H), 7.47–7.54 (m, 3H), 8.15–8.20 (m, 2H)	187 (M$^+$, 44), 117 (100)
1b	**2b**	5	120	90	134–136	138–139[15]	2.30 (s, 3H), 2.39 (s, 3H), 7.25 (s, 1H), 7.28, 8.23 (2d, 4H, J = 8.8)	245 (M$^+$, 9), 133 (95)
1c	**2c**	5	120	80	124–125	$C_{13}H_{11}NO_4$ (245.2)	2.31 (s, 3H), 2.40 (s, 3H), 7.24 (s, 1H), 7.27 (dd, 1H, J = 8.1, 2.1), 7.54 (t, 1H, J = 8.1, 8.1), 8.00 (dd, 2H, J = 8.0, 1.9)	245 (M$^+$, 15), 133 (80)
1d	**2d**	5	120	64	162–163	$C_{15}H_{13}NO_6$ (303.3)	2.31 (s, 3H), 2.33 (s, 3H), 2.40 (s, 3H), 7.24 (d, 1H, J = 1.8), 7.42 (d, 1H, J = 8.3), 8.07 (dd, 1H, J = 8.3, 1.8), 8.13 (s, 1H)	303 (M$^+$, 2), 261 (10)
1e	**2e**	5	120	80	137–138	$C_{20}H_{15}NO_6$ (365.3)	2.33 (s, 3H), 2.36 (s, 3H), 7.38 (s, 1H), 7.46 (d, 1H, J = 8.2), 7.65 (t, 2H, J = 8.5, 8.5), 7.75 (t, 1H, J = 8.5, 8.5), 8.13–8.24 (m, 4H)	365 (M$^+$, 8), 105 (100)
1f	**2f**	4	120	74	146–147	144–148[16]	2.29 (s, 3H), 2.40 (s, 3H), 3.82 (s, 3H), 7.23 (s, 1H), 7.24, 7.86 (2d, 2H, J = 8.3), 7.97 (s, 1H)	275 (M$^+$, 10), 163 (100)
1g	**2g**	4	120	84	191–192	$C_{19}H_{15}NO_5$ (337.3)	2.30 (s, 3H), 3.70 (s, 3H), 7.65 (s, 1H), 7.27 (d, 1H, J = 8.2), 7.91 (dd, 1H, J = 8.2, 1.4), 7.62–7.77 (m, 3H), 8.14 (d, 2H, J = 7.1)	337 (M$^+$, 4), 105 (100)
1h	**2h**	8	120	65	166–167	167[17]	2.38 (s, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 7.10 (s, 1H), 7.02, 7.67 (2d, 2H, J = 7.7), 7.93 (s, 1H)	247 (M$^+$, 88), 177 (100)
1i	**2i**	5	120	75	147–148	151–152[12]	3.88 (s, 3H), 3.90 (s, 3H), 7.05 (d, 1H, J = 8.5), 7.24 (s, 1H), 7.56–7.68 (m, 3H), 7.73 (dd, 1H, J = 8.5, 1.8), 8.07 (d, 2H, J = 8.2), 8.11 (d, 1H, J = 1.8)	309 (M$^+$, 7), 105 (100)
1j	**2j**	3.5	120	71	178–179	181[17] 178–180[18]	2.38 (s, 3H), 6.13 (s, 2H), 7.03, 7.63 (2d, 2H, J = 8.2), 7.14 (s, 1H), 7.90 (s, 1H)	231 (M$^+$, 68), 161 (100)
1k	**2k**	2	120	87	188–189	$C_{17}H_{11}NO_4$ (293.3)	6.16 (s, 2H), 7.06 (d, 1H, J = 8.2), 7.72 (dd, 1H, J = 8.2, 1.3), 7.60–7.70 (m, 3H), 8.07 (d, 1H, J = 1.3), 8.10 (s, 1H), 8.13 (s, 1H)	293 (M$^+$, 26), 105 (100)
1l	**2l**	8	120	71	157–158.5	$C_{14}H_{15}NO_5$ (277.3)	($CDCl_3$) 2.40 (s, 3H), 3.92 (2s, 9H), 7.05 (s, 1H), 7.41 (s, 2H)	277 (M$^+$, 81), 207 (100)
1m	**2m**	6	120	69	191–192	$C_{19}H_{17}NO_5$ (339.3)	3.78 (s, 3H), 3.89 (s, 6H), 7.31 (s, 1H), 7.61–7.70 (m, 3H), 7.75 (s, 2H), 8.11 (d, 2H, J = 7.0)	339 (M$^+$, 73), 105 (100)
1n	**2n**	5	120	80	156–157	$C_{11}H_8N_2O_4$ (232.2)	2.45 (s, 3H), 7.39 (s, 1H), 7.76 (t, 1H, J = 8.0, 8.0), 8.29, 8.52 (2dd, 2H, J = 8.0, 1.8), 9.09 (t, 1H, J = 1.8, 1.8)	232 (M$^+$, 6), 204 (2)
1o	**2o**	5	120	81	182–183	$C_{11}H_8N_2O_4$ (232.2)	2.44 (s, 3H), 7.35 (s, 1H), 8.33 (d, 2H, J = 9.0), 8.41 (d, 2H, J = 9.0)	232 (M$^+$, 70), 143 (27)
2b	**3b**	1.5	100	89	233 (dec)	$C_{13}H_{13}NO_5$ (263.2)	1.99 (d, 3H, J = 1.0), 2.28 (d, 3H, J = 1.2), 7.18, 7.64 (2d, 4H, J = 8.0), 7.22 (s, 1H), 9.51 (s, 1H)	263 (M$^+$, 10), 179 (100)
2c	**3c**	1.5	100	88	157–158	$C_{13}H_{13}NO_5$ (263.2)	1.98 (s, 3H), 2.28 (s, 3H), 7.20 (s, 1H), 7.14 (d, 1H, J = 7.7), 7.37–7.52 (m, 3H), 9.53 (s, 1H)	263 (M$^+$, 9), 179 (91)
2d	**3d**	1	100	91	186–187	187–188[14]	2.00 (s, 3H), 2.29 (2s, 6H), 7.20 (s, 1H), 7.29, 7.54 (2d, 2H, J = 8.3), 7.50 (s, 1H), 9.53 (s, 1H)	321 (M$^+$, 3), 195 (57)
2e	**3e**	1.5	80	92	198.5–199	$C_{14}H_{15}NO_6$ (293.3)	2.00 (s, 3H), 2.27 (s, 3H), 3.80 (s, 3H), 7.09–7.22 (m, 3H), 7.41 (s, 1H), 9.56 (s, 1H)	293 (M$^+$, 8), 209 (100)
2a	**4a**	0.5	80	87	192–193	191–192[11]	1.99 (s, 3H), 7.22 (s, 1H), 7.36–7.49 (m, 3H), 7.62 (d, 2H, J = 6.6), 9.50 (s, 1H)	205 (M$^+$, 10), 117 (100)
2b	**4b**	0.5	100	90	210–211	$C_{11}H_{11}NO_4$ (221.2)	1.98 (s, 3H), 7.19 (s, 1H), 6.79, 7.50 (2d, 4H, J = 8.6), 9.30 (s, 1H), 9.93 (s, 1H)	221 (M$^+$, 28), 179 (100)
2c	**4c**	1	100	89	176–177	$C_{11}H_{11}NO_4$ (221.2)	1.99 (s, 3H), 6.77 (dd, 1H, J = 8.1, 1.3), 7.00–7.07 (m, 2H), 7.11 (s, 1H), 7.20 (t, 1H, J = 7.8, 7.8), 9.46 (s, 1H), 9.58 (s, 1H)	221 (M$^+$, 3), 133 (53)
2d	**4d**	1	100	86	211 (dec)	$C_{11}H_{11}NO_5$ (237.2)	2.00 (s, 3H), 6.75 (d, 1H, J = 8.2), 6.92 (dd, 1H, J = 8.2, 1.8), 7.11 (s, 1H), 7.15 (d, 1H, J = 1.7), 9.17 (s, 1H), 9.27 (s, 1H), 9.45 (s, 1H)	237 (M$^+$, 32), 195 (86)
2e	**4e**	1	100	90	217 (dec)	$C_{16}H_{13}NO_5$ (299.3)	6.71 (d, 1H, J = 8.3), 6.97 (dd, 1H, J = 8.3, 1.5), 7.18 (d, 1H, J = 1.5), 7.29 (s, 1H), 7.48–7.62 (m, 3H), 8.01 (dd, 2H, J = 8.0, 1.3), 9.09 (s, 1H), 9.47 (s, 1H), 9.75 (s, 1H), 12.46 (s, 1H)	299 (M$^+$, 2), 105 (100)
2f	**4f**	1	80	95	204 (dec)	206–207[19]	2.00 (s, 3H), 3.78 (s, 3H), 6.80 (d, 1H, J = 8.2), 7.10 (dd, 1H, J = 8.2, 1.3), 7.21 (s, 1H), 7.30 (d, 1H, J = 1.3), 9.38 (s, 1H), 9.56 (s, 1H)	251 (M$^+$, 22) 209 (44)
2g	**4g**	1	100	92	205 (dec)	$C_{17}H_{15}NO_5$ (313.3)	3.59 (s, 3H), 6.77 (d, 1H, J = 8.2), 7.12 (dd, 1H, J = 8.2, 1.7), 7.33 (d, 1H, J = 1.7), 7.42 (s, 1H), 7.49–7.62 (m, 3H), 8.01 (d, 2H, J = 6.7), 9.55 (s, 1H), 9.84 (s, 1H), 12.53 (brs, 1H)	313 (M$^+$, 11) 105 (100)

Table. (continued)

Starting Material	Product	Conditions Time (h)	Temp. (°C)	Yield (%)	mp (°C)	Molecular Formula or Lit. mp (°C)[a]	^{1}H NMR (DMSO-d_6/TMS)[b] δ, J (Hz)	MS (m/z)
2h	**4h**	0.5	90	89	204–205	212–214[10]	2.01 (s, 3H), 3.77 (s, 3H), 3.80 (s, 3H), 6.98 (d, 1H, J = 1.7), 7.20 (dd, 1H, J = 8.4, 1.6), 7.24 (s, 1H), 7.31 (d, 1H, J = 1.6), 9.42 (s, 1H)	265 (M$^+$, 57), 223 (100)
2i	**4i**	8	100	91	205–206	196–198[20]	3.60 (s, 3H), 3.78 (s, 3H), 6.95 (d, 1H, J = 8.4), 7.25 (dd, 1H, J = 8.4, 1.6), 7.35 (d, 1H, J = 1.6), 7.47 (s, 1H), 7.50–7.58 (m, 3H), 8.03 (d, 2H, J = 7.1), 9.86 (s, 1H)	327 (M$^+$, 35), 105 (100)
2j	**4j**	0.5	90	94	216–216.5	219[17]	1.99 (s, 3H), 6.06 (s, 2H), 6.93 (d, 1H, J = 8.1), 7.12 (dd, 1H, J = 8.1, 1.4), 7.20 (s, 1H), 7.23 (d, 1H, J = 1.3), 9.36 (s, 1H)	249 (M$^+$, 43), 207 (100)
2k	**4k**	6	100	92	220–221	$C_{17}H_{13}NO_5$ (311.3)	6.02 (s, 2H), 6.92 (d, 1H, J = 8.1), 7.18 (dd, 1H, J = 8.0, 1.6), 7.26 (d, 1H, J = 1.6), 7.42 (s, 1H), 7.49–7.59 (m, 3H), 7.99 (d, 2H, J = 6.9), 9.83 (s, 1H)	311 (M$^+$, 2), 105 (100)
2l	**4l**	1	90	95	199–199.5	$C_{14}H_{17}NO_6$ (295.3)	2.00 (s, 3H), 3.69 (s, 3H), 3.78 (s, 6H), 7.00 (s, 2H), 7.20 (s, 1H), 9.48 (s, 1H)	295 (M$^+$, 100), 253 (82)
2m	**4m**	1	80[c]	88	179.5–180	$C_{19}H_{19}NO_6$ (357.4)	3.65, 3.66 (2s, 9H), 7.06 (s, 2H), 7.46 (s, 1H), 7.52–7.60 (m, 3H), 8.00 (s, 1H), 8.03 (s, 1H), 9.94 (s, 1H)	357 (M$^+$, 48), 105 (100)
2n	**4n**	0.5	100	93	158–158.5	$C_{11}H_{10}N_2O_5$ (250.2)	2.13 (s, 3H), 7.40 (s, 1H), 7.56 (t, 1H, J = 8.0, 8.0), 7.81 (d, 1H, J = 7.7), 8.13 (dd, 1H, J = 8.1, 1.2), 9.11 (s, 1H)	250 (M$^+$, 2), 208 (41)
2o	**4o**	0.5	100	89	177–178	$C_{11}H_{10}N_2O_5$ (250.2)	2.01 (s, 3H), 7.25 (s, 1H), 7.83, 8.24 (2d, 4H, J = 7.7), 9.74 (s, 1H)	250 (M$^+$, 4), 208 (76)
4a	**5a**	6	100	75	203 (dec)	159–161 (dec)[16]	6.40 (s, 1H), 7.21–7.38 (m, 3H), 7.76 (d, 2H, J = 7.2)	164 (M$^+$, 4), 91 (100)
4b	**5b**	8	80	79	207 (dec)	$C_9H_8O_4$ (180.2)	6.37 (s, 1H), 6.63, 6.77 (2d, 4H, J = 8.6), 8.84 (s, 1H), 9.63 (s, 1H)	180 (M$^+$, 20), 107 (100)
4c	**5c**	10	100	80	172 (dec)	$C_9H_8O_4$ (180.2)	6.31 (s, 1H), 6.65 (d, 1H, J = 7.2), 7.06–7.16 (m, 2H), 7.31 (s, 1H), 9.13 (brs, 1H), 9.29 (brs, 1H)	180 (M$^+$, 24), 107 (100)
4d	**5d**	6	100	73	181 (dec)	$C_9H_8O_5$ (196.2)	6.27 (s, 1H), 6.67 (d, 1H, J = 8.2), 6.94 (dd, 1H, J = 8.3, 2.0), 7.37 (d, 1H, J = 2.0), 8.80 (s, 1H), 8.98 (s, 1H), 9.09 (s, 1H)	196 (M$^+$, 35), 123 (100)
4f	**5f**	6	100	83	176 (dec)	$C_{10}H_{10}O_5$ (210.2)	3.85 (s, 3H), 6.51 (s, 1H), 6.83 (d, 1H, J = 8.2), 7.31 (dd, 1H, J = 8.3, 1.9), 7.53 (d, 1H, J = 1.9), 7.84 (brs, 2H)	210 (M$^+$, 25), 137 (100)
4h	**5h**	4	100	71	201–202	$C_{11}H_{12}O_5$ (224.2)	3.75 (s, 3H), 3.76 (s, 3H), 6.38 (s, 1H), 6.94 (d, 1H, J = 8.5), 7.32 (dd, 1H, J = 8.5, 1.8), 7.43 (d, 1H, J = 1.8), 9.00 (brs, 1H)	224 (M$^+$, 72), 151 (100)
4j	**5j**	4	90	84	206 (dec)	$C_{10}H_8O_5$ (208.2)	6.02 (s, 2H), 6.37 (s, 1H), 6.88 (d, 1H, J = 8.2), 7.19 (dd, 1H, J = 8.2, 1.5), 7.46 (d, 1H, J = 1.5), 9.15 (s, 1H)	208 (M$^+$, 60), 135 (100)
4l	**5l**	4	100	78	170–170.5	$C_{12}H_{14}O_6$ (254.2)	3.67 (s, 3H), 3.77 (s, 6H), 6.39 (s, 1H), 7.14 (s, 2H)	254 (M$^+$, 34), 181 (100)
4n	**5n**	6	100	76	144 (dec)	$C_9H_7NO_5$ (209.2)	6.51 (s, 1H), 7.53 (t, 1H, J = 8.0, 8.0), 8.00–8.06 (m, 2H), 8.71 (t, 1H, J = 1.9, 1.9)	209 (M$^+$, 5), 136 (100)
4o	**5o**	6	100	80	188 (dec)	$C_9H_7NO_5$ (209.2)	6.50 (s, 1H), 7.94, 8.15 (2d, 4H, J = 8.0), 9.25 (brs, 1H)	165 (M$^+$-CO_2 5), 91 (25)
5a	**6a**	6	100	83	95–96	95.5–96.5[14]	2.79 (dd, 1H, J = 13.7, 8.3), 2.98 (dd, 1H, J = 13.7, 4.5), 4.17 (dd, 1H, J = 8.3, 4.5), 7.17–7.37 (m, 5H)	166 (M$^+$, 2), 91 (100)
5b	**6b**	8	100	78	138–139	139–140[14]	2.67 (dd, 1H, J = 13.8, 8.0), 2.84 (dd, 1H, J = 13.8, 4.7), 3.46 (brs, 2H), 4.07 (dd, 1H, J = 8.0, 4.7), 5.23 (brs, 1H), 6.65, 7.02 (2d, 4H, J = 8.4)	182 (M$^+$, 6), 107 (100)
5c	**6c**	8	100	84		$C_9H_{10}O_4$ (182.2)	2.71 (dd, 1H, J = 13.7, 8.2), 2.90 (dd, 1H, J = 13.7, 4.5), 4.14 (dd, 1H, J = 8.1, 4.6), 6.59–6.75 (m, 3H), 7.06 (t, 11H, J = 8.1, 8.1), 9.25 (brs, 1H)	182 (M$^+$, 18), 107 (100)
5d	**6d**	4	120	63		$C_9H_{10}O_5$ (198.2)	2.77 (dd, 1H, J = 14.0, 7.8), 2.97 (dd, 1H, J = 14.0, 4.3), 4.35 (dd, 1H, J = 7.7, 4.3), 6.59 (dd, 1H, J = 8.0, 2.0), 6.70 (d, 1H, J = 8.1), 6.77 (d, 1H, J = 1.9), 7.70 (brs, 3H)	198 (M$^+$, 11), 123 (100)
5f	**6f**	4	120	73		$C_{10}H_{12}O_5$ (212.2)	2.66 (dd, 1H, J = 13.7, 8.1), 2.85 (dd, 1H, J = 13.7, 4.4), 3.73 (s, 3H), 4.07 (dd, 1H, J = 8.1, 4.4), 6.60 (dd, 1H, J = 8.1, 1.4), 6.65 (d, 1H, J = 8.0), 6.79 (d, 1H, J = 1.3), 8.71 (s, 1H)	213 (M$^+$ + 1, 3), 138 (54)
5h	**6h**	6	90	79	123–124	$C_{11}H_{14}O_5$ (226.2)	($CDCl_3$): 2.94 (dd, 1H, J = 14.1, 7.0), 3.14 (dd, 1H, J = 14.1, 4.1), 3.85 (s, 6H), 4.48 (dd, 1H, J = 7.0, 4.1), 6.83 (s, 3H)	226 (M$^+$, 28), 151 (100)

Table. (continued)

Starting Material	Product	Conditions Time (h)	Conditions Temp. (°C)	Yield (%)	mp (°C)	Molecular Formula or Lit. mp (°C)[a]	^{1}H NMR (DMSO-d_6/TMS)[b] δ, J (Hz)	MS (m/z)
5j	**6j**	6	90	81	97–98	95–97[9]	2.81 (dd, 1H, J = 13.9, 7.6), 2.99 (dd, 1H, J = 13.9, 4.2), 4.22 (dd, 1H, J = 7.6, 4.2), 5.92 (s, 2H), 6.70 (s, 1H), 6.71 (s, 1H), 6.78 (s, 1H)	210 (M$^+$, 40), 135 (100)
5l	**6l**	3	110	78		$C_{12}H_{16}O_6$ (256.3)	(CDCl$_3$): 2.90 (dd, 1H, J = 14.0, 7.4), 3.21 (dd, 1H, J = 14.0, 3.9), 3.80, 3.81 (2s, 9H), 4.48 (dd, 1H, J = 7.4, 3.9), 6.48 (s, 2H)	256 (M$^+$, 66), 181 (100)
2b	**6b**	6 + 3[d]	100	53[e]				
2c	**6c**	6 + 3[d]	100	56[e]				
2d	**6d**	8 + 3[d]	90	50[e]				
2f	**6f**	8 + 3[d]	90	55[e]				
2h	**6h**	8 + 4[d]	95	60[e]				
2j	**6j**	4 + 3[d]	100	67[e]				
2l	**6l**	4 + 3[d]	100	62[e]				
4e	**7e**	4	120	76	175–176	$C_{16}H_{15}NO_5$ (301.3)	2.91 (dd, 1H, J = 13.5, 10.5), 3.02 (dd, 1H, J = 13.6, 4.5), 4.52 (dd, 1H, J = 10.5, 4.5), 6.57 (dd, 1H, J = 8.0, 1.7), 6.63 (d, 1H, J = 7.9), 6.72 (d, 1H, J = 1.7), 7.43–7.57 (m, 3H), 7.82–7.85 (d, 2H, J = 8.2), 8.62 (d, 1H, J = 8.0), 8.69 (brs, 1H), 8.76 (brs, 1H)	301 (M$^+$, 5), 135 (53)
4g	**7g**	4	120	78	160.5–161	$C_{17}H_{17}NO_5$ (315.3)	2.96 (dd, 1H, J = 13.9, 10.5), 3.04 (dd, 1H, J = 13.9, 4.6), 3.70 (s, 3H), 4.56 (dd, 1H, J = 10.4, 4.6), 6.65 (d, 1H, J = 8.0), 6.71 (dd, 1H, J = 8.0, 1.6), 6.90 (d, 1H, J = 1.5), 7.42–7.53 (m, 3H), 7.82 (dd, 2H, J = 7.9, 1.7), 8.64 (d, 1H, J = 8.1), 8.74 (s, 1H)	315 (M$^+$, 0.2), 137 (100)
4i	**7i**	4	80	91	181–182	$C_{18}H_{19}NO_5$ (329.4)	3.03 (dd, 1H, J = 14.0, 10.0), 3.15 (dd, 1H, J = 14.0, 4.5), 3.72 (s, 6H), 4.63 (dd, 1H, J = 10.0, 4.5), 6.82 (s, 2H), 6.93 (s, 1H), 7.43–7.51 (m, 3H), 7.83 (d, 2H, J = 7.0), 8.56 (brs, 1H)	329 (M$^+$, 5), 151 (100)
4k	**7k**	5	80	85	175–176	$C_{17}H_{15}NO_5$ (313.3)	3.00 (dd, 1H, J = 13.7, 10.0), 3.08 (dd, 1H, J = 13.7, 4.5), 4.56 (dd, 1H, J = 10.0, 4.5), 5.94 (s, 2H), 6.79 (s, 2H), 6.90 (s, 1H), 7.43–7.53 (m, 3H), 7.79 (d, 2H, J = 8.0), 8.65 (d, 1H, J = 8.0)	313 (M$^+$, 5), 192 (100)
4m	**7m**	3	100	81	149–150	$C_{19}H_{21}NO_6$ (359.4)	3.00 (dd, 1H, J = 14.0, 10.6), 3.13 (dd, 1H, J = 14.0, 4.4), 3.59 (s, 3H), 3.70 (s, 6H), 4.59 (dd, 1H, J = 10.6, 4.4), 6.64 (s, 2H), 7.43–7.54 (m, 3H), 7.82 (d, 2H, J = 6.7), 8.66 (d, 1H, J = 10.6)	359 (M$^+$, 29), 181 (100)

[a] Satisfactory microanalyses: C ± 0.5, H ± 0.2, N ± 0.3; Accurate mass measurements were carried out for unstable samples **6c, d, f, h** and **l**.

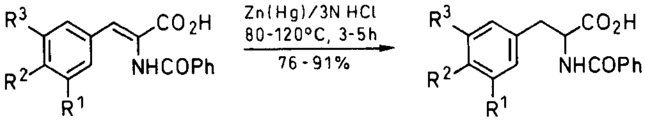
[b] Unless otherwise stated.

[c] Acetone was added as co-solvent.

[d] Time of refluxing only in 3N HCl + time of refluxing after addition of Zn(Hg).

[e] The physical and spectroscopic data of these compounds are identical to authentic samples prepared.

chromatography. Subsequent addition of zinc amalgam as anticipated led to the reduction of the olefinic bond in **5**, producing our target compounds **6**. The yields of this "one-pot" reaction ranged from 50 to 67% (see Table).



4 e, g, i, k, m **7e, g, i, k, m**

4, 7	R^1	R^2	R^3	**4, 7**	R^1	R^2	R^3
e	OH	OH	H	**k**	OCH$_2$O		H
g	OMe	OH	H	**m**	OMe	OMe	OMe
i	OMe	OMe	H				

Furthermore, reduction of **4** (R^4 = Ph) with zinc amalgam in 3N hydrochloric acid afforded (±)-3-aryl-2-benzoylaminopropanoic acids **7**.

Melting points were determined on a hot-stage microscope and are uncorrected. Mass spectra were recorded with a VG Micromass 7070F spectrometer. ^{1}H NMR spectra were recorded with a Bruker Cryospec WM 250 (250 MHz) spectrometer.

Preparation of 4-Benzylideneoxazol-5-ones 2; General Procedure:[11,12]

Aromatic aldehyde **1** (100 mmol), N-acylglycine (120 mmol), anhydr. NaOAc (10.7 g, 130 mmol) and Ac$_2$O (51 g, 500 mmol) were mixed and stirred at the temperature and for the time given in Table. After completion of the reaction, the mixture was allowed to cool to r.t. Then ice water (50 mL) was added. The resulting yellow precipitate was filtered, washed with 50% aq EtOH (4 × 20 mL), dried under vacuum and was recrystallized from acetone to give slightly yellow crystals of **2**.

Conversion of 4-Benzylideneoxazol-5-ones 2 to α-(Aroylamino)cinnamic Acids 3; General Procedure:

A solution of the 4-benzylideneoxazol-5-one **2** (10 mmol), NaOAc (0.04 g, 0.5 mmol) in H_2O/acetone (100 mL, 4:1 v/v) was refluxed at the temperature and for the time given in Table. The mixture was then filtered while it was still hot and the filtrate was allowed to stand overnight. The resulting precipitate was collected by filtration, dried under vacuum and was recrystallized from EtOAc to give **3**.

Conversion of 4-Benzylideneoxazol-5-ones 2 to α-(Aroylamino)cinnamic Acids 4 (with Concomitant Deprotection); General Procedure:

A mixture of the 4-benzylideneoxazol-5-one **2** (10 mmol) in 0.2 N HCl (100 mL) was refluxed at the temperature and for the time given in Table. The mixture was then filtered while it was still hot and the filtrate was allowed to cool to r.t. The resulting precipitate was filtered, washed consecutively with H_2O and EtOH and was dried under vacuum. The α-(aroylamino)cinnamic acid **4** was obtained after recrystallization of the product from acetone.

Conversion of α-(Aroylamino)cinnamic Acids 4 to α-Hydroxycinnamic Acids 5; General Procedure:

A mixture of the α-(aroylamino)cinnamic acid **4** (10 mmol) in 3 N HCl *(60 mL)* was refluxed at the temperature and for the time given in Table. After that the resulting mixture was allowed to cool to r.t. and the resulting precipitate was collected by filtration. The filtrate was extracted with EtOAc (4 × 20 mL). The organic extract was evaporated to give a residue which was combined with the filtered precipitate. The total product was dried under vacuum and was recrystallized from $EtOH/H_2O$ to afford the α-hydroxycinnamic acid **5** as slightly yellow crystals.

Preparation of (±)-β-Aryllactic Acids 6 from α-Hydroxycinnamic Acids 5; General Procedure:

To a solution of the α-hydroxycinnamic acid **5** (10 mmol) in toluene (10 mL) was added Zn(Hg)[21] (8 g) and 3 N HCl (60 mL). The mixture was refluxed at the temperature and for the time given in Table. After that the mixture was filtered while it was still hot. The filtrate was allowed to cool to r.t. and was extracted with EtOAc (5 × 20 mL). The combined organic extract was again extracted with 5% aq Na_2CO_3 (3 × 20 mL). All the aqueous layers were combined and are acidified to pH 5 with 6 N HCl. The resulting mixture was extracted with Et_2O (5 × 20 mL). The combined ethereal extract was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica gel (100 g, 230–400 mesh; EtOAc/acetone, 9:1) and some of the chromatographed products could be recrystallized from $CHCl_3$ to give crystalline (±)-β-aryllactic acids **6**. Due to their instabilities, analytically pure samples cannot be obtained.

"One-Pot" Conversion of 4-Benzylideneoxazol-5-ones 2 to (±)-β-Aryllactic Acids 6; General Procedure:

A mixture of the 4-benzylideneoxazol-5-one **2** (10 mmol) in 3 N HCl (60 mL) was refluxed at the temperature and for the time given in Table. After that Zn(Hg) (9 g) and toluene (10 mL) were added and the mixture was again refluxed at the temperature and for the time given in Table. The resulting mixture was filtered while it was still hot. The filtrate was allowed to cool to r.t., and was extracted with EtOAc (5 × 20 mL). The combined filtrate was then dried (Na_2SO_4), and was evaporated to give **6**, which could be purified by chromatography and recrystallizaton as described in the previous experiment.

Preparation of (±)-3-Aryl-2-benzoylaminopropanoic Acids 7; General Procedure:

To a mixture of the α-benzoylaminocinnamic acid **4** (10 mmol) in 3 N HCl heated at the temperature given in Table was added Zn(Hg) (10 g). The resulting mixture was refluxed at the temperature and for the time given in Table. After that the mixture was filtered while it was still hot and the filtrate was allowed to cool to r.t. The filtrate was extracted with EtOAc (5 × 20 mL). The combined EtOAc extract was dried (Na_2SO_4) and was evaporated to give **7**, which was recrystallized either from EtOH or from EtOAc to give colorless crystals.

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