126. A Reinvestigation of the α-Alkylation of 4-Monosubstituted 2-Phenyloxazol-5(4*H*)-ones ('Azlactones'): A General Entry into Highly Functionalized α,α-Disubstituted α-Amino Acids

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Dedicated to Prof. *R. E. Ireland* on the occasion of his 65th birthday

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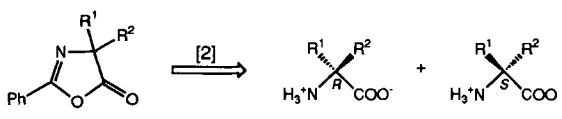
Novel, more reliable and general reaction conditions for the α-alkylation of 4-monosubstituted 2-phenyloxazol-5(4*H*)-ones (= 4-monosubstituted 2-phenyl-azlactones) *rac*-**2** to 4,4-disubstituted 2-phenyloxazol-5(4*H*)-ones *rac*-**1** were found (*Scheme 2*). Thus, a whole range of highly functionalized *rac*-**1** were prepared in medium-to-good overall yields (40–90%, see *Table*). Azlactones *rac*-**1** are ideal precursors for the synthesis of optically pure α,α-disubstituted (*R*)- and (*S*)-α-amino acids.

1. Introduction. – Among the growing family of non-coded amino acids, the α,α-disubstituted glycines play an important role, due to their ability to induce and stabilize different types of conformations when incorporated into small peptides [1].

Recently, we presented a general approach for the synthesis of enantiomerically pure open-chain and cyclic α,α-disubstituted amino acids [2] which is based on the observation that racemic 4,4-disubstituted 2-phenyl(or methyl)oxazol-5(4*H*)-ones *rac*-**1** (*Scheme 1*) can be efficiently resolved by reaction with optically pure amines derived from L-phenylalanine [2–5].

Scheme 1

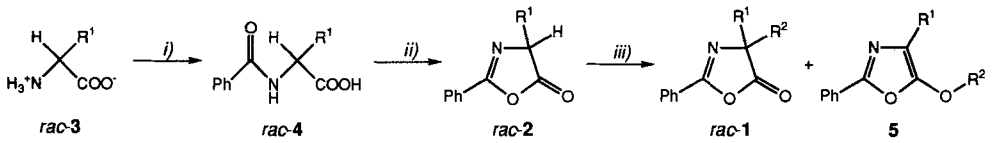


rac-**1**

α,α-disubstituted glycines of (*R*)- and (*S*)-configuration

There are several known approaches for the synthesis of the crucial racemic 4,4-disubstituted 2-phenyloxazol-5(4*H*)-ones *rac*-**1** [2]. Among those, the α-alkylation of 4-monosubstituted 2-phenyloxazol-5(4*H*)-ones *rac*-**2** [6–9], originally described by *Steglich* and coworkers [6], constitutes the most straightforward and versatile approach. This α-alkylation of *rac*-**2**, however, gives only good yields of *rac*-**1** in the case of highly reactive electrophiles such as benzyl bromide, allyl bromide, and propargyl bromide. For less reactive electrophiles, major side reactions like *O*-alkylation to oxazoles to type **5**

Scheme 2



i) Aq. NaOH soln., PhCOCl. *ii*) DCC, CH_2Cl_2, 0°→r.t. *iii*) R^2–X, NaH, solvent (see *Table*).

(*Scheme 2*) and dimerization to *Ruegheimer* compounds [10] reduce significantly the yields of the desired products of type **1** [7] [8].

The 4-monosubstituted azlactones *rac*-**2** can be obtained in high yields by *Schotten-Baumann* benzoylation [11] of the corresponding racemic amino acids *rac*-**3** and subsequent dehydration of the *N*-benzoylated amino acids *rac*-**4** (*Scheme 2*).

Since the azlactones *rac*-**1** are the key percursors in our synthetic approach to optically pure α,α-disubstituted (*R*)- and (*S*)-α-amino acids and for reasons associated with the side reactions of the α-alkylation of 4-monosubstituted azlactones *rac*-**2** mentioned above, we aimed at improving the conversion *rac*-**2** → *rac*-**1**. We found that inverse addition of NaH dispersion to a mixture of *rac*-**2** and excess of the corresponding electrophile in *N*,*N*-dimethylformamide (DMF) at 10–15° followed by stirring at room temperature gave medium to good yields of *rac*-**1**. This procedure is general and easy to perform and gives reliable and reproducible yields also when working on larger scales.

2. α-Alkylation of 4-Monosubstituted 2-Phenyloxazol-5(4*H*)-ones (*rac*-**2**). – During earlier work [2] [6] [7] we found that *N*-benzoylated amino acids of type **4** (*Scheme 2*) were superior to the *N*-acetylated analogues, both in terms of higher yields in their preparation as well as in terms of the efficacy of the separation of the corresponding diastereoisomeric peptides and their cleavage [2]. It was also established that the 2-phenyl group in the azlactones *rac*-**2** was favourable for the α-alkylations [6] [7]. Thus, we primarily focussed on the α-alkylations of 4-monosubstituted 2-phenyl-azlactones *rac*-**2**.

The starting *N*-benzoylated amino acids *rac*-**4** were synthesized in high yields under standard *Schotten-Baumann* conditions [11] from the corresponding commercially available amino acids *rac*-**3** (*Scheme 2*). Due to their relative instability, the azlactones *rac*-**2** were prepared from *rac*-**4** *in situ* by treatment with *N*,*N*′-dicyclohexylcarbodiimide (DCC) in CH_2Cl_2, filtration of the corresponding urea, and evaporation. The dried crude *rac*-**2** were then subjected immediately to the α-alkylations with a variety of electrophiles $R^2 - X$ (results in the *Table*): Addition of solid NaH dispersion (55% in oil, *ca.* 1.1 equiv.) under Ar to *rac*-**2** and $R^2 - X$ (1.2–5.0 equiv.) in DMF (*Method B*) or DMF/THF 1:1 (*Method C*) at 10–15° and subsequent stirring at room temperature yielded the desired azlactones *rac*-**1** in good overall yields. Due to the formation of precipitates during the reactions and because of inverse addition, we anticipated that only small amounts of the enolates of *rac*-**2** would be in solution, thus minimizing the undesired self-condensation. Usually these precipitates formed during the addition of the NaH dispersion, indicating the low solubility of the sodium enolates of *rac*-**2** in DMF (*Method B*). In certain cases, addition of THF (*Method C*) was beneficial for the α-alkylation. Concerning the choice of the substituents R^1 and R^2, we primarily focussed on the synthesis of *rac*-**1** bearing two

substituents corresponding to side chains of proteinogenic amino acids (so-called 'α-chimeras').

From the selected examples described in this work, the following conclusions can be drawn (see *Table*): *1*) Reactive electrophiles R^2-X[1]) like 4-$MeOC_6H_4CH_2Cl$ and X-CH_2COOR^3 (R^3 = *t*-Bu, Et, Bn; X = Cl, Br) gave high yields of **1b** (from **2a**), **1e** (from **2b**), **1f** (from **2b**), **1g** (from **2b**), **1l** (from **2c**), **1m** (from **2d**), **1o** (from **2e**), and **1s** (from **2g**) using *Methods B* and *C*. These *rac*-**1** can be regarded as precursors for the synthesis of α-substituted tyrosines and aspartates. *2*) α-Methylation using MeI as electrophile gave respectable yields of **1a** (from **2a**), **1d** (from **2b**), **1k** (from **2c**), **1q** (from **2f**), and **1r** (from **2g**) using primarily *Method B*. *3*) Iodomethylation using CH_2I_2 produced in moderate to good yields 4-iodomethylated azlactones **1c** (from **2a**), **1h** (from **2b**), **1n** (from **2d**), and **1p**

Table. *α-Alkylation of the 4-Monosubstituted 2-Phenyloxazol-5(4H)-ones* rac-**2** *to the 4,4-Disubstituted 2-Phenyloxazol-5(4H)-ones* rac-**1**

Entry	*rac*-**2**	R^1	R^2-X	Products (yield [%][a]))		*Method*
				rac-**1**	**5**	
1	**2a**	i-Pr	Me	**1a** (81.5)	[b])	*B*
2			4-$MeOC_6H_4CH_2Cl$	**1b** (81.0)	[b])	*B*
3			CH_2I_2	**1c** (65.2)	[b])	*B*
4	**2b**	$PhCH_2$	Me	**1d** (67.0)	[b])	*B*
5			4-$MeOC_6H_4CH_2Cl$	**1e** (88.1)	[b])	*B*
6			$EtOOCCH_2Cl$	**1f** (75.0)	[b])	*B*
7			*t*-$BuOOCCH_2Cl$	**1g** (68.5)	**5g** (6.0)	*B*
8			*t*-$BuOOCCH_2Cl$	**1g** (69.0)	**5g** (8.0)	*C*
9			*t*-$BuOOCCH_2Cl$	**1g** (42.0)	**5g** (< 1.0)	*E*
10			CH_2I_2	**1h** (76.4)	[b])	*B*
11			$BrCH_2CH_2Br$	**1i** (59.0[c]))	**5i** (11.8[c]))	*B*
12	**2c**	Ph	Me	**1k** (70.0)	[b])	*B*
13			4-$MeOC_6H_4CH_2Cl$	**1l** (73.0)	[b])	*B*
14	**2d**	Me	4-$MeOC_6H_4CH_2Cl$	**1m** (65.0)	[b])	*B*
15			CH_2I_2	**1n** (30–40[d]))	[b])	*C*
16	**2e**	Me_2CHCH_2	*t*-$BuOOCCH_2Cl$	**1o** (58.0)	**5o** (5.0)	*B*
17			*t*-$BuOOCCH_2Cl$	**1o** (56.0)	**5o** (7.0)	*C*
18			*t*-$BuOOCCH_2Cl$	**1o** (41.0)	**5o** (8.0)	*D*
19			*t*-$BuOOCCH_2Br$	**1o** (67.0)	**5o** (3.0)	*D*
20			*t*-$BuOOCCH_2Br$	**1o** (68.0)	**5o** (2.0)	*E*
21			CH_2I_2	**1p** (82.3)	[b])	*B*
22	**2f**	*t*-$BuOOCCH_2$	Me	**1q** (68.0)	[b])	*B*
23			Me	**1q** (46.0)	[b])	*C*
24	**2g**	*t*-$BuOOC(CH_2)_2$	Me	**1r** (48.5)	[b])	*B*
25			Me	**1r** (50.0)	[b])	*C*
26			$BnOOCCH_2Br$	**1s** (57.0)	[b])	*B*
27			$BnOOCCH_2Br$	**1s** (55.0)	[b])	*C*

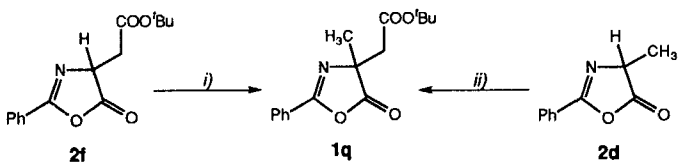
[a]) Yields of pure isolated products after FC [13].
[b]) Not isolated; less than 1%.
[c]) Inseparable mixture, yields determined from ^{1}H-NMR spectrum.
[d]) Significant amounts of dimeric *Ruegheimer* compounds [10] were observed.

[1]) Other reactive electrophiles like allyl bromide, propargyl bromide, and other benzyl bromides (chlorides), originally described by *Steglich* and coworkers [6], gave high yields of *rac*-**1** using *Methods B* and *C*.

(from **2e**) following *Methods B* and *C*. These compounds were excellent precursors for the synthesis of α-alkylated serines [12]. *4*) DMF turned out to be the solvent of choice since the α-alkylations took place at *ca.* 10–15° under very mild conditions, in contrast to the original procedure [6], and the amount of *O*-alkylation products **5** was minimal. Yield improvements on addition of THF (*Method C*) was not general. THF alone gave unsatisfactory results since the reaction temperatures had to be raised to 60° and the amount of *O*-alkylation products **5** increased. In some cases, to reduce *O*-alkylation 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one (DMPU; 10%) was added to DMF (*Method D*, *Entries 18* and *19*) or the reaction carried out in pure DMPU (*Method E*, *Entries 9* and *20*).

3. Conclusions. – The present work describes a new generally applicable procedure for the efficient α-alkylation of 4-monosubstituted 2-phenyloxazol-5(4*H*)-ones *rac*-**2** with a variety of electrophiles $R^2 - X$ to give 4,4-disubstituted azlactones *rac*-**1**. A valuable feature of this approch is that depending on the ease of availability and preparation of the starting α-amino acid *rac*-**3** and the reactivity of the electrophiles $R^2 - X$, two different ways of access to *rac*-**1** can be anticipated, as schematically outlined in *Scheme 3* in the case of *rac*-**1q**.

Scheme 3



i) NaH, MeI, DMF, 0°→r.t. *ii*) NaH, $ClCH_2COO(^tBu)$.

We presume that the inverse addition of solid NaH dispersion to *rac*-**2** and $R^2 - X$ in DMF, the low solubility of the formed sodium enolates of *rac*-**2** in DMF or DMF/THF 1:1, and the efficient alkylation in these solvents are responsible for the improvements of this access to *rac*-**1**. It opens interesting perspectives for the synthesis of novel optically pure (*R*)- and (*S*)-α-amino acids combining two side chains of proteinogenic or non-proteinogenic amino acids at the same C(α), so-called 'α-chimeras', from *rac*-**1** according to [2]. Work in this direction is in progress and will be published in due course.

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Experimental Part

General. All reactions with air- or moisture-sensitive reactants were carried out in oven- or flame-dried glassware under a positive pressure of dry Ar. Reaction solvents and liquid reagents were purified by distillation shortly before use. THF was distilled under Ar from Na with benzophenone ketyl as indicator, CH_2Cl_2 from powdered CaH_2, and DMF from ninhydrin and kept over 4 Å molecular sieves. All other reactants were 'reagent grade' unless described otherwise. Anal. TLC: 2.5 × 10 cm precoated TLC plates, SiO_2 *60F*-254, layer thickness 0.25 mm (*E. Merck & Co.*, Darmstadt, Germany). Flash chromatography (FC): *E. Merck* SiO_2 *60* (230–400 mesh ASTM); according to [13]. M.p.: *Mel-Temp-II* apparatus *Laboratory Devices*, USA; uncorrected. IR Spectra:

Nicolet-7199-FT spectrophotometer; solids in KBr pellets, liquids as thin films; characteristic bands in cm^{-1} ^{1}H-NMR Spectra: *Bruker-AC-250* apparatus, at 250 MHz; $SiMe_4$ as internal standard; chemical shifts of signal centres and ranges in ppm (δ), J in Hz. MS: *Finnigan MS-9-AEI* or *Mat90; m/z* (rel.-%).

General Methods. – *Method A.* To a stirred mixture of *rac*-**3** (10.0 mmol) in CH_2Cl_2 (40) was added under Ar and ice-bath cooling DCC (2.17 g, 10.5 mmol) in small portions. The mixture was stirred for 30 min at 0° and for 1 h at r.t. and then filtered, the filtrate washed (H_2O) and evaporated, and the residue dried under reduced pressure for 2 h; crude azlactones *rac*-**2** which were directly used without further purification.

Method B. To a stirred soln. of crude *rac*-**2** (10.0 mmol) and electrophile $R^2 - X$ (12.0–50.0 mmol) in DMF (30 ml) was added under Ar and ice-bath cooling *ca.* 55% NaH dispersion in oil (480 mg) in small portions (temp. < 10–15°). The mixture was stirred for 30 min at 10–15° and for 2–4 h at r.t. was indicated and then poured onto ice (50 g), 0.1N aq. HCl (30 ml), and AcOEt (100 ml), the org. phase washed with H_2O (2 × 30 ml) and brine (50 ml), dried ($MgSO_4$), and evaporated, and the residue chromatographed (SiO_2 (250 g) AcOEt/hexane).

Method C. As described in *Method B*, except that DMF/THF 1:1 (30 ml) was used as solvent.

Method D. As described in *Method B*, except that DMF/DMPU 9:1 was used as solvent.

Method E. As described in *Method B*, except that DMPU was used as solvent.

Compounds 1a–s. rac-*4-Isopropyl-4-methyl-2-phenyloxazol-5(4*H*)-one* (**1a**). From *rac*-**4a** (10.0 g, 45.2 mmol) according to *Method A*. The crude *rac*-**2a** was treated according to *Method B* with MeI (7.7 ml, 0.123 mmol) for 3 h at r.t. Chromatography (SiO_2 (300 g) AcOEt/hexane 1:7) gave 8.0 g (81.4%) of *rac*-**1a**. M.p. 72–73°. IR (KBr): 3060*w*, 2971*m*, 2934*w*, 2875*w*, 1813*s*, 1656*s*, 1579*w*, 1492*w*, 1446*m*, 1318*m*, 1290*m*, 1201*m*, 1001*s*, 879*m*, 701*s*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.0–7.9 (*m*, 2 arom. H); 7.75–7.55 (*m*, 3 arom. H); 2.07 (*sept.*, J = 6.8, Me_2CH); 1.44 (*s*, Me); 0.99, 0.86 (2*d*, J = 6.8, Me_2CH). FAB-MS: 218 ($[M + H]^+$).

rac-*4-Isopropyl-4-(4-methylbenzyl)-2-phenyloxazol-5(4*H*)-one* (**1b**). From *rac*-**4a** (2.18 g, 9.84 mmol) according to *Method A*. The crude *rac*-**2a** was treated according to *Method B* with 4-methoxybenzyl chloride (2.0 ml, 14.8 mmol) for 2 h at r.t. Chromatography (SiO_2 (160 g) AcOEt/hexane 1:9) and crystallization from Et_2O/hexane gave 2.57 g (80.8%) of *rac*-**1b**. M.p. 61.5–63.5°. IR (KBr): 3040*w*, 3028*w*, 2967*w*, 2836*w*, 1813*s*, 1656*s*, 1612*m*, 1581*w*, 1512*s*, 1452*m*, 1321*m*, 1295*m*, 1252*s*, 1179*m*, 1038*m*, 970*m*, 694*s*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.9–7.8 (*m*, 2 arom. H); 7.55–7.35 (*m*, 3 arom. H); 7.1–7.05 (*m*, 2 arom. H); 6.75–6.65 (*m*, arom. H); 3.69 (*s*, MeO); 3.26, 3.09 (2*d*, *AB*, J_{AB} = 13.7, CH_2); 2.30 (*sept.*, $J \approx$ 6.8, Me_2CH); 1.15, 1.00 (2*d*, J = 6.8, Me_2CH). FAB-MS: 3.24 (100, $[M + H]^+$). Anal. calc. for $C_{20}H_{21}NO_3$ (323.40): C 74.28, H 6.55, N 4.33; found: C 73.97, H 6.67, N 4.24.

rac-*4-(Iodomethyl)-4-isopropyl-2-phenyloxazol-5(4*H*)-one* (**1c**). From *rac*-**4a** (1.09 g, 4.92 mmol) according to *Method A*. The crude *rac*-**2a** was treated with CH_2I_2 (2.0 ml, 24.6 mmol) according to *Method B* for 1.5 h at r.t. Chromatography (SiO_2 (100 g), AcOEt/hexane 1:20) and crystallization from hexane gave 1.10 g (65.2%) of *rac*-**1c**. White solid. M.p. 45–47°. IR (KBr): 3065*w*, 3038*w*, 2969*m*, 2877*wm*, 1813*s*, 1654*s*, 1589*w*, 1454*w*, 1448*m*, 1321*m*, 1292*m*, 1042*s*, 1022*m*, 881*m*, 693*s*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.1–8.0 (*m*, 2 arom. H); 7.65–7.45 (*m*, 3 arom. H); 3.7–3.55 (*m*, *AB*, CH_2I); 2.31 (*sept.*, J = 6.8, Me_2CH); 1.10, 1.02 (2*d*, J = 6.8, Me_2CH). MS: 343 (2, M^+), 301 (5), 216 (10), 174 (99), 105 (100), 77 (62), 51 (20), 41 (20).

rac-*Benzyl-4-methyl-2-phenyloxazol-5(4*H*)-one* (**1d**). From *rac*-**4b** (1.07 g, 3.98 mmol) according to *Method A*. The crude *rac*-**2b** was treated with MeI (0.75 ml, 11.9 mmol) according to *Method B* for 2 h at r.t. Chromatography (SiO_2 (50 g), AcOEt/hexane 1:3) and drying gave 710 mg (67.2%) of *rac*-**1d**. Colourless oil. IR (film): 3063*w*, 3031*w*, 2980*w*, 2930*w*, 1816*s*, 1655*s*, 1580*w*, 1451*m*, 1321*m*, 1290*m*, 1116*w*, 1005*s*, 892*m*, 697*s*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.9–7.8 (*m*, 2 arom. H); 7.5–7.4 (*m*, 3 arom. H); 7.2–7.1 (*m*, 5 arom. H); 3.23, 3.15 (*ca.* 2*d*, *AB*, J_{AB} = 12.0, CH_2); 1.62 (*s*, Me). MS: 265 (16, M^+), 105 (88), 91 (100), 77 (34).

rac-*4-Benzyl-4-(4-methoxybenzyl)-2-phenyloxazol-5(4*H*)-one* (**1e**). From *rac*-**4b** (1.07 g, 3.98 mmol) according to *Method A*. The crude *rac*-**2b** was treated according to *Method B* for 2.5 h at r.t. Chromatogrpahy (SiO_2 (100 g), AcOEt/hexane 1:3) and crystallization from AcOEt/hexane gave 1.33 g (88%) of *rac*-**1e**. White solid. M.p. 91–92°. IR (KBr): 3062*w*, 3030*w*, 2929*w*, 1806*s*, 1660*w*, 1612*w*, 1513*s*, 1452*w*, 1292*m*, 1251*m*, 1034*w*, 982*s*, 684*s*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.75–7.65 (*m*, 2 arom. H); 7.55–7.4 (*m*, 1 arom. H); 7.4–7.3 (*m*, 2 arom. H); 7.25–7.05 (*m*, 7 arom. H); 6.75–6.65 (*m*, 2 arom. H); 3.69 (*s*, MeO); 3.28, 3.24 (2*s*, 2 CH_2). MS: 371 (1, M^+), 122 (18), 121 (100), 105 (22), 77 (18).

rac-*Ethyl 4-Benzyl-4,5-dihydro-5-oxo-2-phenyloxazole-4-acetate* (**1f**). From *rac*-**4b** (644 mg, 2.39 mmol) according to *Method A*. The crude *rac*-**2b** was treated with ethyl 2-chloroacetate (1.27 ml, 11.95 mmol) for 3 h at r.t. Chromatography (SiO_2 (70 g), AcOEt/hexane 1:6) and drying gave 605 mg (75.0%) of *rac*-**1f**. Colourless oil. IR (film): 3069*w*, 3033*w*, 2982*w*, 2926*w*, 1820*s*, 1735*s*, 1654*m*, 1496*m*, 1452*m*, 1374*m*, 1323*m*, 1217*m*, 1101*m*, 1027*m*, 989*s*, 896*m*, 698*s*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.9–7.85 (*m*, 2 arom. H); 7.6–7.5 (*m*, 1 arom. H); 7.5–7.4 (*m*, 2 arom. H); 7.25–7.15 (*m*, 5 arom. H); 4.15–3.95 (*m*, $MeCH_2O$); 3.2–3.0 (*m*, CH_2COOEt, $PhCH_2$); 1.26 (*t*, J = 7.1, Me_2CH_2O). MS: 337 (8, M^+), 309 (8), 105 (100), 91 (90), 77 (30).

rac-*(* tert-*Butyl) 4-Benzyl-4,5-dihydro-5-oxo-2-phenyloxazole-4-acetate* (**1g**). From *rac*-**4b** (5.0 g, 18.64 mmol) according to *Method A*. The crude residue was treated with *tert*-butyl 2-chloroacetate (6.12 ml, 55.9 mmol) according to *Method C* for 18 h at r.t. Chromatography (SiO_2 (600 g), AcOEt/hexane 1:6) gave first 0.42 g (8.0%) of tert-*butyl 4-benzyl-(2-phenyloxazol-5-yloxy)acetate* (**5g**). Colourless oil. IR (film): 2979*w*, 1754*s*, 1740*m*, 1659*m*, 1491*w*, 1227*m*, 1154*s*, 730*w*, 695*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.9–7.85 (*m*, 2 arom. H); 7.4–7.2 (*m*, 8 arom. H); 4.55 (*s*, OCH_2CO); 3.9 (*s*, $PhCH_2$); 1.48 (*s*, *t*-Bu). MS: 365 (M^+).

Further elution yielded, after crystallization with hexane and drying, 3.59 g (68.6%) of *rac*-**1g**. White solid. IR (KBr): 2977*m*, 1817*s*, 1733*s*, 1658*m*, 1495*w*, 1156*s*, 745*w*, 700*s*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.9–7.85 (*m*, 2 arom. H); 7.5–7.4 (*m*, 3 arom. H); 7.18 (*s*, 5 arom. H); 3.11, 3.08 (2*d*, *AB*, J_{AB} = 12, CH_2); 2.96 (*d*, *J* = 20, CH_2); 1.29 (*s*, *t*-Bu). MS: 365 (M^+).

rac-*4-Benzyl-4-(iodomethyl)-2-phenyloxazol-5(4*H*)-one* (**1h**). From *rac*-**4b** (5.36 g, 19.9 mmol) according to *Method A*. The crude *rac*-**2b** was treated with CH_2I_2 (8.03 ml, 99.5 mmol) according to *Method B* for 2 h at r.t. Chromatography (SiO_2 (250 g) AcOEt/hexane 1:15→1:9) and crystallization from hexane gave 5.95 g (76.4%) of *rac*-**1h**. White solid. M.p. 107–109°. IR (KBr): 3065*w*, 3020*w*, 2959*w*, 1816*s*, 1659*s*, 1493*w*, 1451*w*, 1321*w*, 1291*m*, 1052*m*, 972*m*, 782*w*, 698*s*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.95–7.85 (*m*, 2 arom. H); 7.6–7.5 (*m*, 1 arom. H); 7.5–7.4 (*m*, 2 arom. H); 7.25–7.1 (*m*, 5 arom. H); 3.66, 3.58 (2*d*, *AB*, J_{AB} = 10.3, CH_2I); 3.27 ('*s*', $PhCH_2$). MS: 264 (13, M^+), 105 (60), 91 (100), 77 (34), 51 (14).

rac-*4-Benzyl-4-(bromoethyl)-2-phenyloxazol-5(4*H*)-one* (**1i**). From *rac*-**4b** (5.0 g, 18.57 mmol) according to *Method A*. The crude *rac*-**2b** was treated with 1,2-dibromoethane (8.0 ml, 92.15 mmol) according to *Method C* for 18 h at r.t. Chromatography (SiO_2 (400 g), AcOEt/hexane 1:9), crystallization from hexane, and drying gave 3.85 g (58.8%) of *rac*-**1i**. White solid. M.p. 108–110°. IR (KBr): 3070*w*, 3033*w*, 1814*s*, 1648*s*, 1493*w*, 1450*m*, 1318*m*, 1231*w*, 1201*m*, 1091*m*, 1061*w*, 986*s*, 895*w*, 699*s*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.9–7.8 (*m*, 2 arom. H); 7.6–7.5 (*m*, 1 arom. H); 7.5–7.4 (*m*, 2 arom. H); 7.25–7.1 (*m*, 5 arom. H); 3.45–3.25 (*m*, CH_2CH_2Br); 3.18 (*d*, *AB*, J_{AB} = 6.7, $PhCH_2$); 2.62 ('*t*', *J* = 7.9, CH_2CH_2Br). MS: 359, 357 (2, M^+), 105 (56), 91 (100), 77 (32), 51 (16).

rac-*4-Methyl-2,4-diphenyloxazol-5(4*H*)-one* (**1k**). From *rac*-**4c** (2.0 g, 7.83 mmol) according to *Method A*. The crude *rac*-**2c** was treated with MeI (2.44 ml, 39.15 mmol) according to *Method B* for 2 h at r.t. Chromatography (SiO_2 (150 g), AcOEt/hexane 1:7) and crystallization from Et_2O/hexane gave 1.38 g (70.1%) of *rac*-**1k**. White solid. M.p. 54–56°. IR (KBr): 3066*w*, 2976*w*, 1819*s*, 1651*s*, 1579*w*, 1493*w*, 1450*w*, 1321*m*, 1292*w*, 1192*w*, 1007*s*, 893*m*, 773*w*, 698*s*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.15–8.05 (*m*, 2 arom. H); 7.7–7.45 (*m*, 5 arom. H); 7.45–7.25 (*m*, 3 arom. H); 1.89 (*s*, Me). MS: 251 (1, M^+), 223 (10), 207 (39), 105 (100), 77 (53), 51 (20). Anal. calc. for $C_{16}H_{13}NO_2$ (251.285): C 76.48, H 5.21, N 5.57; found: C 76.24, H 5.31, N 5.60.

rac-*4-(4-Methoxybenzyl)-2,4-diphenyloxazol-5(4*H*)-one* (**1l**). From *rac*-**4c** (1.61 g, 6.32 mmol) according to *Method A*. The crude *rac*-**2c** was treated with 4-methoxybenzyl chloride (1.10 ml, 8.10 mmol) according to *Method B* for 3 h at r.t. Chromatography (SiO_2 (120 g), AcOEt/hexane 1:10) and crystallization from AcOEt/hexane gave 1.65 g (73%) of *rac*-**1l**. White solid. M.p. 106–108°. IR (KBr): 3059*w*, 3020*w*, 2940*w*, 2841*w*, 1810*s*, 1660*s*, 1612*w*, 1510*s*, 1448*m*, 1301*w*, 1250*s*, 1176*m*, 1061*m*, 987*m*, 957*m*, 699*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.0–7.9 (*m*, 2 arom. H); 7.85–7.75 (*m*, 2 arom. H); 7.6–7.3 (*m*, 6 arom. H); 7.2–7.1 (*m*, 2 arom. H); 6.8–6.65 (*m*, 2 arom. H); 3.71 (*s*, MeO); 3.48, 3.40 ('2*d*', *AB*, J_{AB} = 13,7, CH_2). IS-MS: 380.3 (30, $[M + Na]^+$), 358.3 (80, $[M + H]^+$), 330.2 (100). Anal. calc. for $C_{23}H_{19}NO_3$ (357.409): C 77.29, H 5.36, N 3.92; found: C 77.24, H 5.48, N 3.90.

rac-*4-(4-Methoxybenzyl)-4-methyl-2-phenyloxazol-5(4*H*)-one* (**1m**). From *rac*-**4d** (5.0 g, 25.9 mmol) according to *Method A*. The crude *rac*-**2d** was treated with 4-methoxybenzyl chloride (7.72 ml, 28.5 mmol) according to *Method B* for 1 h at r.t. Chromatography (SiO_2 (500 g), AcOEt/hexane 1:10) and crystallization from hexane gave 4.97 g (65%) of *rac*-**1m**. White solid. M.p. 91–92°. IR (KBr): 3064*w*, 2934*w*, 2905*w*, 1809*s*, 1655*s*, 1612*w*, 1513*m*, 1448*w*, 1323*w*, 1289*m*, 1246*m*, 1005*s*, 687*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.9–7.85 (*m*, 2 arom. H); 7.6–7.4 (*m*, 3 arom. H); 7.15–7.05 (*m*, 2 arom. H); 3.71 (*s*, MeO); 3.16, 3.10 (2*d*, J_{AB} = 14.1, CH_2–C(4)); 1.61 (*s*, Me–C(4)). MS: 295 (< 1, M^+), 121 (100), 105 (6), 77 (12).

rac-*4-(Iodomethyl)-4-methyl-2-phenyloxazol-5(4*H*)-one* (**1n**). From *rac*-**4d** (10.0 g, 51.74 mmol) according to *Method A*. The crude *rac*-**2d** was treated with CH_2I_2 (20.9 ml, 0.259 mol) according to *Method C* for 30 min at r.t. Chromatography (SiO_2 (500 g), AcOEt/hexane 1:10→1:7) and crystallization from hexane gave 5.50 g (33.7%) of *rac*-**1n**. White solid. 98–100°. IR (KBr): 3064*w*, 3028*w*, 2969*w*, 2926*w*, 1814*s*, 1649*s*, 1577*w*, 1450*m*, 1317*m*, 1293*m*, 1229*m*, 1006*s*, 929*m*, 884*m*, 694*s*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.1–8.0 (*m*, 2 arom. H); 7.65–7.45 (*m*, 3 arom. H); 3.6–3.45 (*m*, *AB*, CH_2I); 1.70 (*s*, Me). MS: 315 (3, M^+), 188 (35), 174 (12), 105 (100), 77 (44), 51 (16).

rac-*(* tert-*Butyl) 4,5-Dihydro-4-(2-methylpropyl)-5-oxo-2-phenyloxazole-4-acetate* (**1o**). From *rac*-**4e** (2.16 g, 9.21 mmol) according to *Method A*. The crude *rac*-**2e** was treated with *tert*-butyl 3-chloroacetate (3.96 ml, 27.63 mmol) according to *Method C* for 18 at r.t. Chromatography (SiO_2 (400 g), Et_2O/hexane 1:9) gave first 0.15 g (4.9%) of tert-*butyl [4-(2-methylpropyl)-2-phenyloxazol-5-yloxy]acetate* (**5o**). Colourless oil. IR (film): 2930*w*,

1758*s*, 1729*m*, 1657*m*, 1605*w*, 1154*s*, 692*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.9–7.85 (*m*, 2 arom. H); 4.59 (*s*, OCH_2); 2.57 (*d*, *J* = 8, Me_2CHCH_2); 2.1–2.0 (*m*, Me_2CHCH_2); 1.51 (*s*, *t*-Bu); 0.96 (*d*, *J* = 8, 6 H, Me_2CHCH_2). MS: 331 (M^+).

Further elution yielded, after crystallization from hexane, 1.76 g (57.7%) of *rac*-**1o**. M.p. 82–83°. IR (KBr): 2930*m*, 1822*s*, 1729*s*, 1651*s*, 1579*w*, 1161*s*, 760*w*, 700*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.1–8.0 (*m*, 2 arom. H); 7.6–7.5 (*m*, 3 arom. H); 2.97, 2.88 (2*d*, *AB*, J_{AB} = 16, CH_2); 1.89–1.63 (*m*, Me_2CHCH_2); 1.29 (*s*, *t*-Bu); 0.95 (*d*, *J* = 8, Me_2CHCH_2). MS: 331 (M^+). Anal. calc. for $C_{19}H_{25}NO_4$ (331.41): C 68.86, H 7.60, N 4.23; found: C 68.80, H 7.59, N 4.07.

rac-*4-(Iodomethyl)-4-(2-methylpropyl)-2-phenyloxazol-5(4*H*)-one* (**1p**). From *rac*-**4e** (10.0 g, 42.5 mmol) according to *Method A*. The crude *rac*-**2e** was treated with CH_2I_2 (17.1 ml, 0.213 mol) according to *Method B* for 2 h at r.t. Chromatography (SiO_2 (500 g), AcOEt/hexane 1:10→1:7) and crystallization from hexane gave 12.5 g (82.3%) of *rac*-**1p**. White solid. M.p. 91.0–92.0°. IR (KBr): 3065*w*, 3022*w*, 2957*w*, 1814*s*, 1655*s*, 1449*w*, 1318*m*, 1292*w*, 1042*s*, 968*m*, 896*m*, 698*s*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.1–8.0 (*m*, 2 arom. H); 7.7–7.45 (*m*, 3 arom. H); 3.6–3.45 (*m*, *AB*, CH_2I); 2.1–1.85 (*m*, Me_2CHCH_2); 1.75–1.6 (*m*, Me_2CHCH_2); 0.92, 0.87 (2*d*, *J* = 6.6, Me_2CHCH_2). MS: 357 (< 1, M^+), 230 (16), 174 (13), 105 (100), 77 (36). Anal. calc. for $C_{14}H_{16}INO_2$ (357.191): C 47.08, H 4.52, I 35.53, N 3.92; found: C 47.14, H 4.72, I 35.33, N 3.91.

rac-*(* tert*-Butyl) 4,5-Dihydro-4-methyl-5-oxo-2-phenyloxazole-4-acetate* (**1q**). From (*S*)-**4f** (3.0 g, 10.23 mmol) according to *Method A*. The crude *rac*-**2f** was treated with MeI (3.19 ml, 51.2 mmol) according to *Method B* for 2 h at r.t. Chromatography (SiO_2 (180 g), AcOEt/hexane 1:4) and crystallization from hexane gave 2.0 g (67.6%) of *rac*-**1q**. White solid. M.p. 54–56°. IR (KBr): 3066*w*, 2977*w*, 2935*w*, 1827*s*, 1728*s*, 1652*s*, 1579*w*, 1494*w*, 1448*w*, 1354*m*, 1324*m*, 1297*m*, 1243*w*, 1165*m*, 1131*s*, 1009*s*, 898*w*, 698*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.05–7.95 (*m*, 2 arom. H); 7.65–7.45 (*m*, 3 arom. H); 3.01, 2.88 (2*d*, *AB*, J_{AB} = 16.4, CH_2); 1.51 (*s*, Me); 1.30 (*s*, *t*-Bu). MS: 289 (< 1, M^+), 234 (7), 216 (15), 188 (20), 161 (13), 105 (100), 77 (38), 57 (60). Anal. calc. for $C_{16}H_{19}NO_4$ (289.331): C 66.42, H 6.62, N 4.84; found: C 66.27, H 6.70, N 4.78.

rac-*(* tert*-Butyl) 4,5-Dihydro-4-methyl-5-oxo-2-phenyloxazole-4-propanoate* (**1r**). From (*S*)-**4g** (5.0 g, 16.27 mmol) according to *Method A*. The crude *rac*-**2g** was treated with Me (2.16 ml, 81.4 mmol) according to *Method C* for 18 h at r.t. Chromatography (SiO_2 (200 g), AcOEt/hexane 1:10) and crystallization from hexane gave 1.01 g (48.3%) of *rac*-**1**. White solid. M.p. 75–76°. IR (KBr): 2936*m*, 2872*w*, 1819*s*, 1727*s*, 1654*s*, 1291*s*, 1095*m*, 1005*s*, 696*s*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.0–7.95 (*m*, 2 arom. H); 7.6–7.5 (*m*, 3 arom. H); 2.2–2.1 (*m*, 4 aliph. H); 1.54 (*s*, Me); 1.39 (*s*, *t*-Bu). MS: 303 (M^+). Anal. calc. for $C_{17}H_{21}NO_4$ (303.36): C 67.31, H 6.98, N 4.62; found: C 67.31, H 6.97, N 4.39.

rac-*(* tert*-Butyl) 4-[(Benzyloxycarbonyl)methyl]-4,5-dihydro-5-oxo-2-phenyloxazole-4-propanoate* (**1s**). From (*S*)-**4g** (2.12 g, 6.91 mmol) according to *Method A*. The crude *rac*-**2g** was treated with benzyl 2-bromoacetate (2.37 g, 10.37 mmol) according to *Method B* for 12 h at r.t. Chromatography (SiO_2 (200 g), AcOEt/hexane 9:1) gave 1.50 g (51.2%) of *rac*-**1r**. Pale yellow oil. IR (film): 2992*w*, 1822*s*, 1735*s*, 1652*m*, 1496*m*, 1154*m*, 1008*m*, 697*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.95–7.9 (*m*, 2 arom. H); 7.6–7.55 (*m*, 1 arom. H); 7.50–7.49 (*m*, 2 arom. H); 7.26–7.23 (*m*, 5 arom. H); 5.05, 4.97 (2*d*, *J* = 8, CH_2); 3.08 (*s*, CH_2); 2.20–2.18 (*m*, 2 CH_2); 1.38 (*s*, *t*-Bu). MS: 437 (< 1, M^+), 381, 105. Anal. calc. for $C_{25}H_{27}NO_6$ (437.47): C 68.64, H 6.22, N 3.20; found: C 68.67, H 6.62, N 2.83.

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