Asymmetric Synthesis of 2-(α-Aminoalkyl)oxazoles, 2-Oxazolylpyrrolidines, 2-Oxazolylpiperidines: Total Synthesis of 4,5-Dihydroxypipecolinic Acid

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Abstract: Asymmetric α-alkylation of 2-aminomethyl-4,5-diphenyloxazole was achieved by formation of azomethines **1** and *ent*-**1** with the enantiomers of 2-hydroxypinan-3-one as chiral auxiliaries, reaction with alkylating reagents and final removal of the chiral auxiliary giving rise to optically active 2-(α-aminoalkyl)oxazoles **3**, *ent*-**3**, **6** and **9**. If α,ω-dihaloalkanes were used the resulting alkylation products could be further cyclized by intramolecular alkylation of the amino group to afford optically active 2-oxazolyl-*N*-heterocycles **4**, *ent*-**4**, **7** and **10**. The latter could be used for the total synthesis of naturally occurring 4,5-dihydroxypipecolinic acid **13**.

Key words: 2-(1-aminoalkyl)-1,3-oxazoles, asymmetric synthesis, 2-oxazolylpiperidines, 2-oxazolylpyrrolidines, 4,5-dihydroxypipecolinic acid, chiral auxiliaries, heterocycles

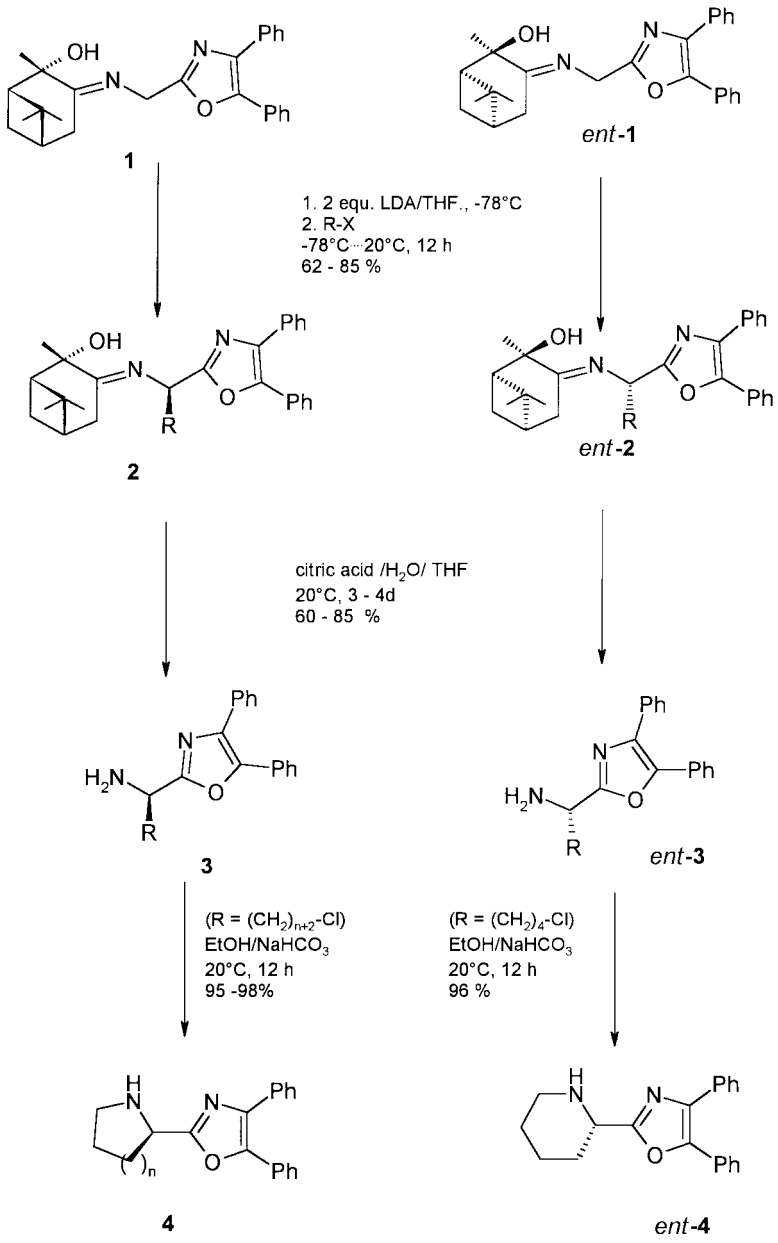
Chiral α-aminoalkyl heterocycles are found in natural products of pharmacological activity such as in dolastatin,[1,2] promothiocine A[3,4] or ibutenic acid[5] and were of interest in the synthesis of kinase inhibitors.[6] The asymmetric side chain α-alkylation of aminoalkylheterocycles provided a useful tool for the synthesis of such moieties.[1] Thus adopting a methodology originally invented by Yamada et al.[7] for the synthesis of optically active α-amino acids and further developed by Viallefont et al.,[8,9] imines of 2-aminomethylthiazole and 2-hydroxypinan-3-ones as chiral auxiliary could be α-benzylated with high stereoselectivity affording 2-(1-amino-2-phenylethyl)-thiazole as a subunit of dolaphenine after removal of the chiral auxiliary.[1] Furthermore, this method was used in asymmetric α-alkylation of other aminomethylheterocycles and benzylamine.[10] Since both enantiomers of the hydroxypinanone are commercially available each enantiomer of the corresponding alkylation product can be synthesized by this auxiliary technique, i. e. the (1*R*,2*R*,5*R*)-hydroxypinanone induces the (*S*)-configuration of the new stereogenic center while the enantiomer induces the (*R*)-configuration.[8,10] The same strategy was applied in the asymmetric alkylation of 2-aminomethylpyridine used for the synthesis of Ontazolast®, a potent LTB_4-inhibitor.[11] Optically active piperidine and pyrrolidine-2-carboxylic acids could be synthesized by alkylation of imines of hydroxypinanone and α-amino ester using α,ω-dihaloalkanes, cleaving the imine and final intramolecular alkylation of the resulting amino group.[12] In the oxazole and oxadiazole series a diastereoselective α-alkylation was achieved at prolinolylmethyl side chains.[13]

We report here the asymmetric synthesis of 2-(α-aminoalkyl)-4,5-diphenyloxazoles **3** and *ent*-**3** starting from 2-aminomethyl-4,5-diphenyl-1,3-oxazole using the enantiomers of 2-hydroxypinan-3-one as chiral auxiliaries. This concept is extended to the synthesis of oxazolylpyrrolidines, oxazolylpiperidines **4** and *ent*-**4** and dihydroxypipecolinic acid **(13)** by further cyclization and oxidative cleavage of the oxazole ring, respectively.

The starting azomethines **1** and *ent*-**1** could be easily obtained from 2-aminomethyl-4,5-diphenyl-1,3-oxadiazole and (1***S***,2***S***,5***S***)- or (1***R***,2***R***,5***R***)-2-hydroxypinanone, respectively. Treatment with two equivalents of LDA in THF and the corresponding alkyl halide afforded the envisaged alkylation products **2**, *ent*-**2**, **5** and **8** (see Schemes 1 and 2, respectively) in high yields and stereoselectivities (see Tables 1 and 2). In the case of methylation (R = Me), 5% of the corresponding *O*-methylation products were obtained as byproducts. The application of BuLi instead of LDA gave mixtures of inseparable products. The configuration of the new stereogenic center can be governed by choosing the corresponding enantiomer of hydroxypinanone, i.e. the (*S*, *S*, *S*)-hydroxypinanone generates the (*R*)-configuration and vice versa (see Tables 1 and 2, compounds **2a**/*ent*-**2a**, **2g**/*ent*-**2b** and **5**/**8** as well as the corresponding products **3**, *ent*-**3**, **6** and **9** obtained from these imines), as also found before in alkylations of α-amino esters or in the aminomethylheterocycle series.[1,8,10] It can be assumed that intermediate azaenolates formed are similar to the enolate reported by Yamada et al.[14] for imines of α-amino esters, which react with the alkylating reagent in a S_N2-like fashion.

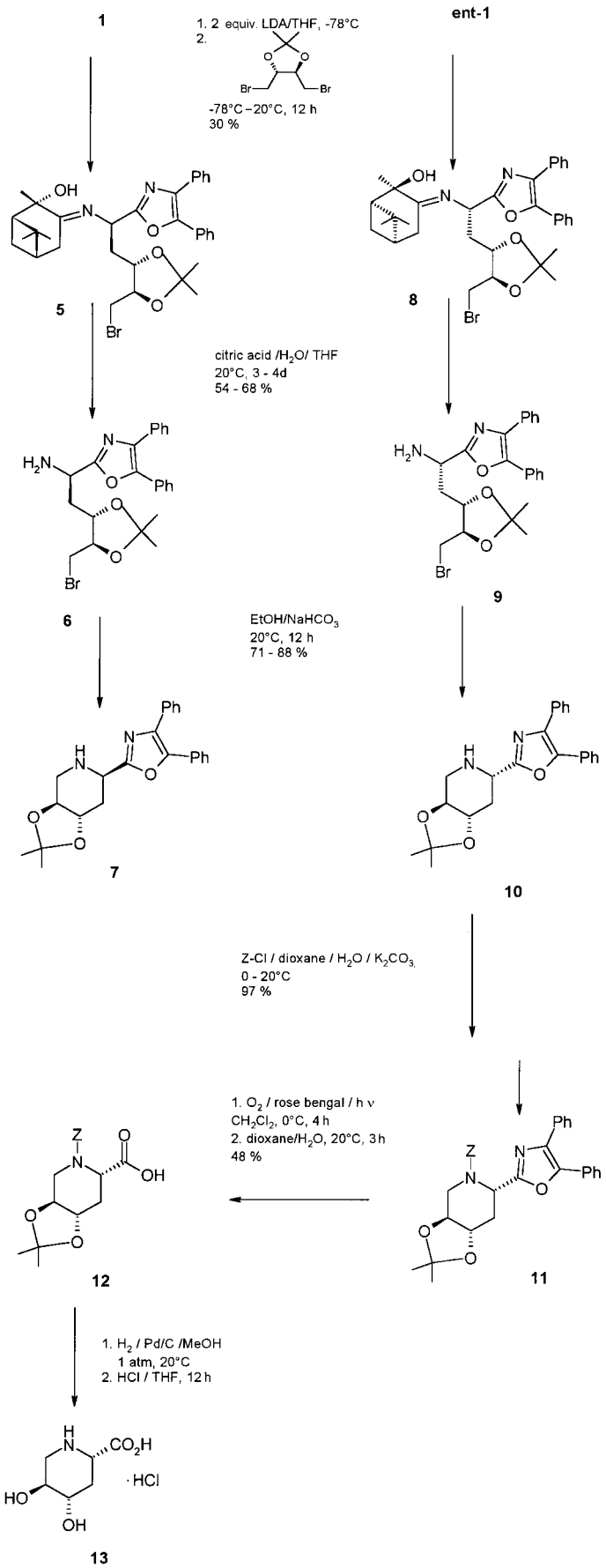
The chiral auxiliary could smoothly be split off from imines **2**, *ent*-**2**, **5** and **8** by hydrolysis in the presence of citric acid[15,16] affording the corresponding 2-(α-aminoalkyl)oxazoles **3**, *ent*-**3**, **6** and **9** (see Schemes 1, 2 and Tables 1, 2). Hydroxylamine in acetic acid, another known reagent[14] for this transformation, gave considerably lower yields.

Assignment of the configuration of the products **2**, **3**, *ent*-**2** and *ent*-**3** was based on the X-ray crystal analysis of compound **2c** [see Figure, (*R*)-configuration] and the independent synthesis of *ent*-**3a** [(*S*)-configuration] adopting literature procedures.[17] This independent synthesis, however, gave a partially racemized product thus underlining the usefulness of the asymmetric synthesis according to Scheme 1.



Scheme 1

The α-amino-ω-haloalkyloxazoles **3f, 3g**, *ent*-**3b, 6** and **9** survived the removal of the chiral auxiliary without cyclization by intramolecular nucleophilic displacement of the ω-chloro atom by the appearing amino group (see Schemes 1 and 2). Comparable cases in the α-amino ester series reported by Viallefont gave spontaneous formation of prolines and higher homologues in most cases.[12] Cyclization of the α-amino-ω-haloalkyloxazoles **3f, 3g**, *ent*-**3b**, **6** and **9** could be achieved with $NaHCO_3$ in ethanol affording optically active pyrrolidine **4f** and piperidines **4g,** *ent*-**4**, **7** and **10** (see Schemes 1 and 2). These products can be considered as nicotine analogs and are also promising candidates for chiral catalysts.[18, 19] Furthermore they can serve as precursors for cyclic α-amino acids by making use of the possibility that the 4,5-diphenyloxazole moiety can be degraded to a carboxylic acid by singlet oxygen.[20] This methodology was used to develop a new total synthesis of the (2*S*,4*S*,5*S*)-4,5-dihydroxypipecolinic acid (**13**), a natural product isolated from the seed of *Derris eliptica*, a legume species.[21] The dihydroxypiperidine **10** obtained starting from the *N*-(2-aminomethyloxazolyl)hydroxypinanoneimine *ent*-**1** with (4*R*,5*R*)-4,5-bis(bromomethyl)-2,2-dimethyl-1,3-dioxolane was *N*-protected (see Scheme 2). The resulting Z-derivative **11** was treated with oxygen under irradiation with UV-light in the presence of Rose Bengal cleaving the C-C double bond of the oxazole ring under rearrangement to afford the *N*,*N*-dibenzoylamide of the pipecolinic acid **12**, which was hydrolyzed to the free



Scheme 2

Table 1 Imines **1**, **2**, **5**, Aminoalkyloxazoles **3**, **6** and Oxazolyl-N-heterocycles **4**, **7**

	R or n	X	Yield (%)	d. r.[a]	$[\alpha]_D^{20}$ (c in g/ 100 mL) in $CHCl_3$	m. p. (°C)	Molecular Formula	^{1}H NMR ($CDCl_3$) δ (ppm), *J* (Hz)
1[b]	–	–	65	–	+5.0 (0.42)	122–125	$C_{26}H_{28}N_2O_2$ (400.5)	0.81 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.44 (s, 3 H, CH_3), 1.53 (d, *J* = 10.6 Hz, 1 H, CH), 1.99—2.01 (m, 2H, CH_2), 2.23–2.26 (m, 1 H, CH), 2.56–2.58 (m, 3 H, OH, CH_2) 4.58 (s, 2 H, CH_2), 7.23–7.30 (m, 6 H, Ph), 7.50–7.59 (m, 4 H, Ph).
2a	Me	I	75	>95:5	–	oil	$C_{27}H_{30}N_2O_2$ (414.6)	0.83 (s, 3 H, CH_3) 1.27 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 1.58 (d, *J* = 6.6 Hz, 3 H, CH_3), 1.99–2.04 (m, 2 H, CH_2), 2.25–2.28 (m, 1 H, CH), 2.53–2.55 (m, 2 H, CH_2), 2.61–2.81 (m, 1 H, CH), 4.90 (q, *J* = 6.6 Hz, 1 H, CH), 7.18–7.32 (m, 6 H, Ph), 7.49–7.58 (m, 4 H, Ph).
2b[c]	*i*Pr	I	82	>95:5	+83.2 (0.84)	oil	$C_{29}H_{34}N_2O_2$ (454.6)	0.82 (s, 3 H, CH_3), 0.91(d, *J* = 5.8 Hz, 6 H CH_3), 1.25 (s, 3 H, CH_3), 1.48 (s, 3 H, CH_3), 1.94–2.03 (m, 2 H, CH_2), 2.21–2.24 (m, 1 H, CH), 2.43–2.50 (m, 1 H, OH, CH) 2.62–2.67 (m, 3 H, OH, CH_2), 4.47 (d, *J = 7.6 Hz*, 1 H, CH), 7.16–7.30 (m, 6 H, Ph), 7.48–7.58 (m, 4 H, Ph).
2c	*c*Hex	I	62	>95:5	+52.0 (1.5)	159	$C_{32}H_{38}N_2O_2$ (482.7)	0.83 (s, 3 H, CH_3), 1.10–1.21 (m, 5 H, CH_2), 1.25 (s, 3 H, CH_3), 1.43 (d, *J* = 10.5 Hz, 1 H CH), 1.48 (s, 3 H, CH_3), 1.59–1.69 (m, 5 H, CH_2), 1.95–2.02 (s, 3 H, CH_3), 1.94–2.03 (m, 2 H, CH_2), 2.19–2.24 (m, 2 H, CH_2), 2.60–2.62 (m, 3 H, OH, CH_2) 4.50 (d, *J* = 8.1 Hz, 1 H, CH), 7.17–7.31 (m, 6 H, Ph), 7.49–7.58 (m, 4 H, Ph).
2d	Allyl	Br	72	90:10	–	oil	$C_{29}H_{32}N_2O_2$ (440.6)	0.82 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 1.49 (d, *J* = 10.6 Hz, 1 H, CH), 1.96–2.01 (m, 2 H, CH_2), 2.01–2.03 (m, 1 H, CH), 2.23–2.86 (m, 5 H, OH, CH_2), 4.58 (t, *J* = 5.1 Hz, 1 H, CH) 5.03 (dd, 2 H, CH_2), 5.68–5.74 (m, 1 H, CH), 7.16–7.30 (m, 6 H, Ph), 7.48–7.58 (m, 4 H, Ph).
2e	3-Buten-1-yl	Br	72	>95:5	–	oil	$C_{30}H_{34}N_2O_2$ (454.6)	0.83 (s, 3 H, CH_3), 1.11–1.23 (m, 2 H, CH_2), 1.25 (s, 3 H, CH_3), 1.47 (s, 3 H, CH_3), 1.94–2.03 (m, 3 H, CH_3), 1.94–2.03 (m, 3 H, CH_2, CH), 2.10–2.27 (m, 4 H, CH_2), 2.60–2.75 (m, 3 H, CH, CH_2), 4.78 (t, *J* = 5.0 Hz, 1 H, CH), 4.90–4.99 (m, 2 H, CH_2), 5.77–5.84 (m, 1 H, CH), 7.16–7.30 (m, 6 H, Ph), 7.47–7.57 (m, 4 H, Ph).
2f[d]	3-Chloro-propyl	I	85	>95:5	–	oil	$C_{29}H_{33}ClN_2O_2$ (482.7)	0.82 (s, 3 H, CH_3), 1.11–1.18 (m, 2 H, CH_2), 1.25 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 1.76–1.85 (m, 2 H, CH_2), 1.94–2.04 (m, 2 H, CH_2,), 2.23–2.25 (m, 1 H, CH), 2.26–2.28 (m, 1 H, CH,), 2.57–2.76 99 (m, 2 H, CH_2), 3.34–3.54 99 (m, 2 H, CH_2), 4.80 (t, *J* = 5.5 Hz, 1 H, CH), 7.21–7.30 (m, 6H, Ph), 7.47–7.57 (m, 4 H, Ph).
2g	4-Chloro-butyl	I	67	>95:5	–	oil	$C_{30}H_{35}ClN_2O_2$(491.1)	
3a	Me	–	63	e	+22.2 (1)	55	$C_{17}H_{13}N_2O$ (264.3)	1.60 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.86 (bs, 2 H, NH_2), 4.25 (q, *J* = 6.8 Hz, 1 H, CH), 7.30–7.41 (m, 6 H, Ph), 7.58–7.68 (m, 4 H, Ph).
3b[f]	*i*Pr	–	80		+18.8 (1.23)	oil	$C_{19}H_{20}N_2O$ (292.4)	0.95 (d, *J* = 6.7 Hz, 6 H, CH_3), 1.72 (bs, 2 H, NH_2), 2.01–2.15 (m, 1 H, CH),3.82 (d, *J* = 5.8 Hz, 1 H, CH), 7.30–7.41 (m, 6 H, Ph), 7.58–7.68 (m, 4 H, Ph).
3c	*c*Hex	–	60		+24.5 (0.89)	oil	$C_{27}H_{24}N_2O$ (332.5)	1.08–1.29 (m, 5 H, CH_2), 1.53–1.84 (m, 7 H, CH, CH_2, NH_2), 3.82 (d, *J* = 6.2 Hz, 1 H, CH), 7.17–7.31 (m, 6 H, Ph), 7.48–7.58 (m, 4 H, Ph).
3d	Allyl	–	85		+51.1 (0.7)	oil	$C_{19}H_{18}N_2O$ (290.4)	1.74 (bs, 2 H, NH_2), 2.47–2.56 (m, 1 H, CH), 4.10 (s, 1 H, CH), 5.05–5.14 (m, 2 H, CH_2), 5.70–5.84 (m, 1 H, CH), 7.16–7.29 (m, 6 H, Ph), 7.47–7.57 (m, 4 H, Ph).

Table 1 (continued)

	R or n	X	Yield (%)	d. r.[a]	$[\alpha]_D^{20}$ (c in g/ 100 mL) in $CHCl_3$	m. p. (°C)	Molecular Formula	^1H NMR ($CDCl_3$) δ (ppm), *J* (Hz)
3e	3-Buten-1-yl	–	66		+2.5 (1)	oil	$C_{20}H_{20}N_2O$ (304.4)	1.73 (bs, 2 H, NH_2), 1.76 − 1.81 (m, 1 H, CH_2), 1.84−1.89 (m, 1 H, CH_2), 1.94−2.06 (m, 2H, CH_2), 4.03 (t, *J* = 6.7 Hz, 1 H, CH), 4.90−5.02 (m, 2 H, CH_2), 5.69−5.83 (m, 1 H, CH_2), 7.16−7.30 (m, 6 H, Ph), 7.47−7.57 (m, 4 H, Ph).
3f[g]	3-Chloro-propyl	–	60		+17.7 (0.3)	oil	$C_{19}H_{19}ClN_2O$ (326.8)	1.73−1.94 (m, 2 H, CH_2), 2.02−2.19 (m, 2 H, CH_2), 2.45 (bs, 2 H, NH_2), 2.90−2.98 (m, 1 H, CH_2), 3.08−3.16 (m, 1 H, CH_2), 4.33 (t, *J* = 7.3 Hz, 1 H, CH), 7.16−7.29 (m, 6 H, Ph), 7.47−7.56 (m, 4 H, Ph).
3g	4-Chloro-butyl	–	61	e	–	oil	$C_{20}H_{21}ClN_2O$ (340.9)	
4f[h]	1	–	98		+33.4 (1.27)	oil	$C_{19}H_{18}N_2O$ (290.4)	1.87−2.00 (m, 2 H, CH_2), 2.13−2.21 (m, 2 H, CH_2), 2.39 (bs, 1 H, NH), 2.98−3.08 (m, 1 H, CH_2), 3.20−3.27 (m, 1 H, CH_2), 4.42 (t, *J* = 6.0 Hz, 1 H, CH), 7.25−7.39 (m, 6 H, C_6C_5), 7.56−7.66 (m, 4 H, C_6C_5).
4g	2	–	95	i	+22.7 (1)	114−116	$C_{20}H_{20}N_2O$ (304.4)	[j]
5	–	–	30	>95:5	–	oil	$C_{33}H_{39}BrN_2O_4$ (607.4)	0.91 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3),1.41 (s, 3 H, CH_3),1.53 (s, 3 H, CH_3), 1.55−1.69 (m, 3 H, CH, CH_2), 2.29−2.40 (m, 1 H, CH), 2.64−2.79 (m, 3 H, CH_2), 2.82−2.93 (m, 1 H, CH_2), 3.52 (dd, *J* = 1.6 Hz, *J* = 5.2 Hz, 2 H, CH_2Br), 3.99−4.12 (m, 2 H, CH), 5.10 (t, *J* = 6.7 Hz, 1 H, CH),7.32−7.41 (m, 6 H, Ph), 7.53−7.64 (m, 4 H, Ph).
6[k]	–	–	68		–	oil	$C_{33}H_{25}BrN_2O_3$ (457.4)	1.42 (s, 3 H, CH_2), 1.43 (s, 3 H, CH_3), 1.91 (bs, 2 H, NH_2), 2.05−2.20 (m, 1 H, CH_2), 2.38−2.47 (m, 1 H, CH_2), 3.49 (d, *J* = 5.8 Hz, 2 H, CH_2Br), 3.99−4.13 (m, 2 H, CH), 4.37 (t, *J* = 8.2 Hz, 1 H, CH), 7.34−7.40 (m, 6 H, Ph), 7.58−7.66 (m, 4 H, Ph).
7			71	de = 99.6%[l]	−20.6 (1)	118−120	$C_{23}H_{24}BrN_2O_3$ (376.5)	1.46 (s, 3 H, CH_2), 1.50 (s, 3 H, CH_3), 2.07−2.17 (m, 2 H, NH, CH_2), 2.89−2.92 (m, 1 H, CH_2), 3.16 (t, *J* = 13 Hz, 1 H, CH_2), 3.39 (dd, *J* = 6 Hz, *J* = 12.5 Hz, 1 H, CH_2) 3.46−3.51 (m, 1 H, CH), 3.56−3.63 (m, 1 H, CH), 4.55 (dd, *J* = 2.2 Hz, *J* = 8.3 Hz 1 H, CH), 7.33−7.38 (m, 6 H, Ph), 7.57−7.67 (m, 4 H, Ph).

[a] determined by NMR as far as not otherwise mentioned.
[b] ee > 99%, determined by HPLC Cliralcel OD; ^{13}C NMR ($CDCl_3$): δ = 23.3, 27.1, 28.5, 28.7, 34.2, 38.6, 38.9, 48.5, 50.7, 77.8, 127.0, 128.3, 128.4, 128.9, 129.0, 129.3, 132.8, 135.6, 146.3, 161.1, 180.0.
[c] ^{13}C NMR ($CDCl_3$): δ = 19.3, 19.9, 23.3, 27.7, 28.4, 28.8, 33.8, 33.8, 38.6, 38.7, 50.3, 64.3, 77.8, 126.9, 128.4, 128.8, 128.9, 129.0, 129.3, 132.8, 135.2, 145.8, 162.5, 178.6.
[d] ^{13}C NMR ($CDCl_3$): δ = 23.3, 27.6, 28.4, 28.7, 31.9, 32.1, 338, 38.7, 45.0, 50.4, 57.2, 66.2, 77.9, 126.9, 128.3, 128.5, 128.9, 129.0, 129.2, 132.7, 135.4, 146.1, 162.2, 179.3.
[e] ee > 99%, determined by HPLC Cliralcel OD.
[f] ^{13}C NMR ($CDCl_3$): δ = 18.5, 19.6, 33.9, 56.3, 126.8, 128.3, 128.4, 128.8, 128.9, 129.0, 129.4, 132.9, 135.3, 145.6, 167.1.
[g] ^{13}C NMR ($CDCl_3$): δ = 25.9, 31.3, 47.3, 55.9, 126.9, 128.3, 128.4, 128.8, 128.9, 129.0, 129.1, 129.4, 132.8, 135.3, 145.9, 165.4.
[h] ^{13}C NMR ($CDCl_3$): δ = 25.8, 31.2, 47.1, 55.9, 126.9, 128.3, 128.4, 128.9, 129.0, 129.2, 132.8, 135.3, 146.0, 165.0.
[i] ee > 99 % determined by chromatography of the (S)−Trolox-derivatives.
[j] identical with *ent*-**4**, see Table 2.
[k] ^{13}C NMR ($CDCl_3$): δ = 27.5, 27.8, 32.4, 40.1. 48.7, 78.1, 80.4, 110.0, 126.9, 128.3, 128.5, 128.9, 129.0, 129.2, 132.7, 135.4, 145.8, 165.3.
[l] determined by SFC.

Table 2 Imines **ent-1**, **ent-2**, **8** Aminoalkyloxazoles **ent-3**, **9**, and Oxazolyl-N-heterocycles **ent-4**, **10**

	R or n	X	Yield (%)	d. r.[a]	$[\alpha]_D^{20}$ (c in g/100 mL) in $CHCl_3$	m. p. (°C)	Molecular Formula	^{1}H NMR ($CDCl_3$) δ (ppm), *J* (Hz)
ent-1[b]	–	–	74		+5.2 (0.65)	115–120	$C_{26}H_{28}N_2O_2$ (400.5)	0.81 (s, 3 H, CH_3) 1.25 (s, 3 H, CH_3), 1.44 (s, 3 H, CH_3), 1.53 (d, *J* = 10.6 Hz, 1 H, CH), 1.98–2.01 (m, 2 H, CH_2), 2.26–2.29 (m, 1 H, CH), 2.58 (bs, 3 H, OH, CH_2), 7.17–7.29 (m, 6 H, Ph), 7.50–7.59 (m, 4 H, Ph).
ent-2a[c]	Me	I	74	>95:5	–83.2 (0.84)	oil	$C_{27}H_{30}N_2O_2$ (414.6)	0.83 (s, 3H, CH_3) 1.27 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 1.58 (d, *J* = 6.6 Hz, 3 H, CH_3), 1.99–2.04 (m, 2 H, CH_2), 2.25–2.28 (m, 1 H, CH), 2.53–2.55 (m, 2 H, CH_2), 2.61–2.81 (m, 1 H, CH), 4.90 (q, *J* = 6.6 Hz, 1 H, CH), 7.18–7.32 (m, 6 H, Ph), 7.49–7.58 (m, 4 H, Ph).
ent-2b[d]	4-Chloro-butyl	I	77	>95:5	–	oil	$C_{30}H_{35}ClN_2O_2$ (491.1)	0.92 (s, 3 H, CH_3) 1.34 (s, 3 H, CH_3), 1.55 (s, 3 H, CH_3), 1.581–1.60 (m, 2 H, CH_2), 1.83–1.87 (m, 2 H, CH_2), 2.04–2.06 (m, 1 H, CH), 2.08–2.10 (m, 1 H, CH), 2.11–2.18 (m, 2 H, CH_2), 2.32–2.38 (m, 2 H, CH_2), 2.65–2.85 (m, 2 H, CH_2), 3.56 (t, *J* = 6.5 Hz, 2 H, CH_2Cl), 4.85 (t, *J* = 5.2 Hz, 1 H, CH), 7.26–7.39 (m, 6 H, Ph), 7.55–7.65 (m, 4 H, Ph).
ent-3a[e]	Me	–	79	[f]	–20.5 (0.95)	58	$C_{17}H_{13}N_2O$ (264.3)	1.60 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.86 (bs, 2 H, NH_2), 4.25 (q, *J* = 6.8 Hz, 1 H, CH), 7.30–7.41 (m, 6 H, Ph), 7.58–7.68 (m, 4 H, Ph).
ent-3b	4-Chloro-butyl	–	72	[f]	–	oil	$C_{20}H_{21}ClN_2O$ (340.9)	1.57–1.76 (m, 2 H, CH_2), 1.81–1.89 (m, 4 H, CH_2), 1.96 (bs, 2 H, NH_2), 3.56 (t, *J* = 7.8 Hz, 1 H, CH_2Cl), 4.11 (t, *J* = 6.7 Hz, 1 H, CH), 7.34–7.42 (m, 6 H, Ph), 7.57–7.72 (m, 4 H, Ph).
ent−4	–	–	96	[g]	–22.1 (1)	114–116	$C_{20}H_{20}N_2O$ (303.4)	1.51–1.64 (m, 3 H, CH_2), 1.81 (bs, 1 H, NH),1.83–1.95 (m, 2 H, CH_2),2.04–2.17 (m, 1 H, CH_2), 2.75–2.83 (m, 1 H, CH_2), 3.17–3.23 (m, 1 H, CH_2), 4.03 (dd, *J* = 3.9 Hz, *J* = 8.6 Hz, 1 H, CH), 7.31–7.42 (m, 6 H, C_6H_5), 7.56–7.71 (m, 4 H, C_6H_5).
8			30	>95:5	–	oil	$C_{33}H_{39}BrN_2O_4$ (607.4)	0.93 (s, 3 H, CH_3), 1.35 (s, 6 H, CH_3), 1.42 (s, 3 H, CH_3), 1.56 (s, 3 H, CH_3), 1.59–1.64 (m, 3 H, CH, CH_2), 2.30–2.43 (m, 2 H, CH_2), 2.55–2.69 (m, 2 H, CH_2), 3.47–3.51 (m, 1 H, CH), 3.53–3.59 (m, 2 H, CH_2Br), 3.80–3.89 (m, 1 H, CH_2), 3.91–4.00 (m, 1 H, CH), 4.17–4.19 (m, 1 H, CH), 5.24 (dd, *J* = 3.0 Hz, *J* = 11.0 Hz, 1 H, CH), 7.34–7.41 (m, 6 H, Ph), 7.53–7.64 (m, 4 H, Ph).
9			54	>95:5	–	oil	$C_{23}H_{25}BrN_2O_3$ (457.4)	1.44 (s, 6 H, CH_3), 1.96 (bs, 2 H, NH_2), 2.16–2.21 (m, 1 H, CH_2), 2.25–2.30 (m, 1 H, CH_2), 3.51 (dd, *J* = 2.0 Hz, *J* = 6.2 Hz, 2 H, CH_2Br), 3.59–4.02 (m, 1 H, CH), 4.24–4.30 (m, 1 H, CH), 4.36 (dd, *J* = 4.7 Hz, *J* = 11.5 Hz, 1 H, CH), 7.32–7.40 (m, 6 H, Ph), 7.56–7.65 (m, 4 H, Ph).
10			88	>99:1[h]	+12.5 (1)	oil	$C_{23}H_{24}N_2O_3$ (376.5)	1.48 (s, 6 H, CH_3), 1.57 (bs, 1 H, NH), 2.03–2.09 (m, 1 H, CH_2), 2.64 (t, *J* = 5 Hz, 0.5 H, CH_2), 2,67 (t, *J* = 5 Hz, 0.5 H, CH_2), 2.89 (t, *J* = 13 Hz, 1 H, CH_2), 3.46–3.49 (m, 1 H, H_2), 3.51–3.55 (m, 2 H, CH), 4.07 (dd, *J* = 4.4 Hz, *J* = 16.8 Hz, 1 H, CH), 7.33–7.36 (m, 6 H, Ph), 7.56–7.65 (m, 4 H, Ph).

[a] determined by NMR as far as not otherwise mentioned.
[b] ee > 98.3%, determined by HPLC Cliralcel OD, 13C NMR (CDCl3): d = 22.8, 27.2, 28.0, 28.2, 33.8, 38.2, 38.5, 48.0, 50.2, 77.4, 126.5, 127.8, 128.0, 128.3, 128.4, 128.5, 128.8, 132.3, 135.1, 145.8, 160.6, 179.6.
[c] ^{13}C NMR ($CDCl_3$): δ = 19.6, 23.2, 27.6, 28.4, 28.8, 33.2, 38.6, 38.7, 50.5, 53.2, 77.0, 126.9, 128.4, 128.8, 128.9, 129.0, 129.3, 132.8, 135.4, 146.0, 163.8, 178.9.
[d] ^{13}C NMR ($CDCl_3$): δ = 5.1, 5.8, 17.8, 25.5, 29.9, 30.7, 31.1, 36.4, 41.1, 41.2, 52.8, 63.5, 80.1, 129.1, 130.6, 130.7, 131.1, 131.2, 131.3, 131.7, 135.2, 137.5, 148.1, 165.2, 181.1.
[e] ^{13}C NMR ($CDCl_3$): δ = 22.2, 46.1, 126.9, 128.3, 128.4, 128.8, 128.9, 129.0, 129.3, 132.8, 135.3, 145.6, 167.1.
[f] ee > 99%, determined by HPLC Cliralcel OD.
[g] ee > 99 % determined by chromatography of the (S)-Trolox-derivatives.
[h] determined by SFC.

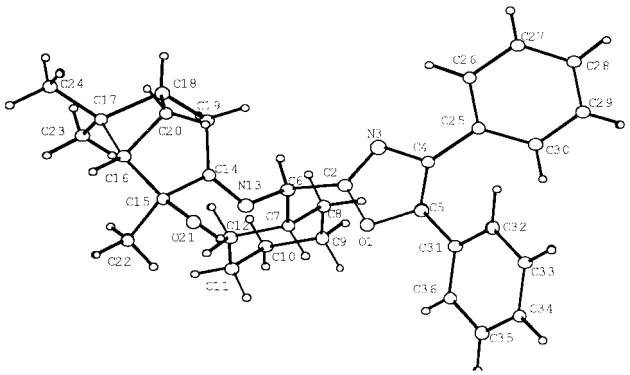


Figure X-ray crystal analysis of the Imine **2c**

acid **12** without prior isolation. Hydrogenolytic *N*-deprotection and acid hydrolysis of the acetonide moiety afforded the (2*S*,4*S*,5*S*)-4,5-dihydroxypipecolinic acid hydrochloride **(13)**. The overall transformation of 2-aminomethyl-4,5-diphenyloxazole into the (2*S*,4*S*,5*S*)-4,5-dihydroxypipecolinic acid (**13**) represents the first total synthesis of this natural product, using an auxiliary technique. The hitherto existing total syntheses of this compound were based on di-*O*-isopropylidene-α-D-glucofuranose (18 steps)[22] or on D-glucuronolactone (9 step procedure)[23] as enantiopure starting materials where the original configuration was maintained or the configuration at position 2 was inverted by elimination/addition. Since the other enantiomer of these starting materials does not exist in nature these syntheses are limited to the (2*S*,4*S*,5*S*)-isomer, while our approach should also give access to the unnatural (2*R*,4*S*,5*S*)-isomer by analogous degradation of the oxazole ring of the oxazolylpiperidine **7**.

^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively, with a Bruker AC-300 with TMS as internal standard. Optical rotations were determined with a Perkin Elmer polarimeter 241. Mass spectra (HP 5995 A) were measured at 70eV. An external tungsten 500 W halogen lamp was used to generate singlet oxygen from dioxygen. Silica gel (0.04−0.063 mm, Merck) was used for preparative column chromatography. If not otherwise mentioned, chemicals were purchased from Aldrich. (4*R*,5*R*)-4,5-Bis(bromomethyl)-2,2-dimethyl-1,3-dioxolane as reactant for the synthesis of **5** and **8** was prepared using a known procedure modified by adding an equimolar quantity of Li_2CO_3 in the last step.[24]

2-Aminomethyl-4,5-diphenyl-1,3-oxazole

A solution of 2-bromomethyl-1,3-oxazole (31.4 g, 0.1 mol) and potassium phthalimide (18.6 g, 0.1 mol) in anhyd EtOH (500 mL) was refluxed for 5 h. After cooling to r.t., the precipitate was filtered off and dissolved in $CHCl_3$ (~ 300 mL). The solution was washed with H_2O (3 × 100 mL) and dried (Na_2SO_4). After evaporation of the solvent, 4,5-diphenyl-2-phthalimidoethyl-1,3-oxazole (24.81 g, 0.066 mol, 66%) was obtained. This material was combined with EtOH (250 mL) and hydrazine hydrate (3.3 g, 0.066 mol). The mixture was refluxed until all 4,5-diphenyl-2-phthalimidoethyl-1,3-oxazole disappeared (TLC, about 2 h). The cold reaction mixture was slightly acidified with aq HCl (half-concentrated) and shortly heated to reflux. After cooling to r. t. precipitated phthalazine was filtered off and washed with H_2O (about 30 mL) The combined filtrates were basified with NaOH and extracted with Et_2O. After drying the organic phase (Na_2SO_4) and evaporating the solvent, 15.9 g (98%) of the 2-aminomethyl-4,5-diphenyl-1,3-oxazole was obtained. The compound is known, but was prepared by another procedure before.[25]

(1*S*, 2*S*, 5*S*)-3-(4,5-Diphenyl-1,3-oxazol-2-ylmethylimino)-2,6,6-trimethylbicyclo[3.1.1]heptan-2-ol (1)

BF_3.OEt_2 (0.06 mL) was added to a mixture of (1*S*,2*S*,5*S*)-hydroxypinanone (0.50 g, 30 mmol), 2-aminomethyl-4,5-diphenyl-1,3-oxazole (0.75 g, 3 mmol), anhyd toluene (10 mL) and molecular sieves 4Å under argon. After 4 h of reflux, the solution was cooled to r.t. and filtered. The solvent was evaporated from the filtrate and the residue was purified by flash chromatography (petroleum ether/hexane). The product crystallized upon concentrating; yield: 0.78 g (65%); mp 122−125 °C.

(1*R*, 2*R*, 5*R*)-3-(4,5-Diphenyl-1,3-oxazol-2-ylmethylimino)-2,6,6-trimethylbicyclo[3.1.1]heptan-2-ol (*ent*-1)

Prepared analogous to **1** by using (1*R*,2*R*,5*R*)-hydroxypinanone; yield: 0.90 g (75%); mp 115−120 °C.

Alkylation Products 2, *ent*-2, 5 and 8; General Procedure

A LDA-solution, prepared from absolute THF (3 mL), (*i*-Pr)$_2$NH (0.3 mL, 2 mmol) and 1.6 M BuLi in hexane (1.5 mL, 2.4 mmol) at −78 °C was slowly added to a solution of the azomethine **1** or *ent*-**1** (400 mg, 1 mmol) in THF (1 mL) at −78 °C. After about 10 min, the alkylating reagent R-X (3 mmol) was added. The mixture was allowed to warm up to r.t. overnight. It was quenched with satd aq NH_4Cl solution (about 10 mL) and extracted with Et_2O (4 × 15 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated. The remaining material was purified by flash chromatography. This material was used for further transformation into the aminoalkyloxazoles **3**, *ent*-**3**, **6** and **9** by hydrolytic cleavage of the imine moiety without further purification.

2-(α-Aminoalkyl)-4,5-diphenyl-1,3-oxazoles 3, *ent*-3, 6 and 9; General Procedure

A solution of 15% aq citric acid (6 mL) was added to a solution of the corresponding azomethine **2**, *ent*-**2**, **5** or **8** (1 mmol) in THF (7 mL). The mixture was stirred at r.t. for 3 to 4 days (TLC). The organic solvent was evaporated and the hydroxypinanone removed by extraction with Et_2O. The remaining aqueous solution was basified with solid Na_2CO_3 and extracted with Et_2O (3 × 15 mL). After drying ($MgSO_4$) and concentration the product was purified by flash chromatography (MeOH/CH_2Cl_2).

2-(Pyrrolidin-2-yl)-1,3-oxazole (4f) and 2-(Piperidin-2-yl)-1,3-oxazoles 4g, *ent*-4, 7 and 10; General Procedure

A mixture of the corresponding α-amino-ω-haloalkyloxazole **3**, *ent*-**3**, **6** or **9** (0.5 mmol) and $NaHCO_3$ (84 mg) in EtOH (20 mL) was stirred at r. t. overnight. After the addition of H_2O (20 mL), the mixture was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried ($MgSO_4$), the solution was concentrated and the remainder was purified by column chromatography (EtOAc or CH_2Cl_2/MeOH/NH_3, 25:1:0.1).

Benzyl (2*S*,4*S*, 5*S*)-2-(4,5-Diphenyl-1,3-oxazol-2-yl)-4,5-isopropylidenedioxypiperidine-1-carboxylate (11)

K_2CO_3 (97 mg, 0.7 mmol) and benzyl chloroformate (136.5 mg, 0.8 mmol) were added to a solution of the oxazolylpiperidine **10** (245 mg, 0.65 mmol) in dioxane/H_2O (10 mL, 1:1) at 0 °C under stirring. The mixture was allowed to warm up to r.t. and stirring was continued for 1 h. After dilution with H_2O (about 20 mL), the mixture was extracted with EtOAc (3 × 20 mL). The organic phase was dried

($MgSO_4$), concentrated and purified by flash chromatography (EtOAc/hexane); yield: 97%; colorless oil.

^{1}H NMR ($CDCl_3$): δ = 1.44 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 1.57, 2.31−2.53 (m, 1 H, CH_2), 2.80−2.89 (m, 1 H, CH_2), 3.55−3.67 (m, 1 H, CH_2), 3.57−3.86 (m, 2 H, CH, CH_2), 4.14−4.21 (m, 1 H, CH), 5.16 (s, 2 H, C*H*$_2$Ph), 5.45−5.53 (m, 1 H, CH), 7.28−7.38 (m, 11 H, C_6H_5), 7.49−7.65 (m, 4 H, C_6H_5).

MS (70eV): *m*/*z* (%) = 510 (M^+, 62), 419 (70), 375 (100), 91 (64).

(2*S*,4*S*, 5*S*)-1-Benzyloxycarbonyl-4,5-isopropylidenedioxypiperidine-2-carboxylic Acid (12)

A solution of the oxazole **11** (153 mg, 0.3 mmol) in CH_2Cl_2 (10 mL) was saturated with oxygen at 0 °C for 20 min. After the addition of Bengal Rose® (30 mg) the solution was irradiated with a 500 W tungsten halogen lamp for 4 h while the supply of oxygen was continued. The solvent was evaporated under vacuum and the remaining material was dissolved in dioxane/H_2O (20 mL, 1:1). After stirring at r.t. for 3 h, H_2O was added (about 20 mL) and the mixture was extracted with EtOAc (3 × 20 mL). The organic phases were dried ($MgSO_4$), concentrated under vacuum and purified by flash chromatography (hexane/EtOAc/AcOH); yield 48%; colorless oil.

^{1}H NMR ($CDCl_3$): δ = 1.43 (s, 6 H, CH_3), 2.67−2.71 (m, 1 H, CH_2), 3.35−3.37 (m, 1 H, CH_2), 3.57−3.59 (m, 2 H, CH), 4.15−4.19 (m, 1 H, CH_2), 4.59 (dd, *J* = 3, 10 Hz, 1 H, CH), 5.14 (m, 2 H, C*H*$_2$Ph), 7.30−7.36 (m, 5 H, C_6H_5).

MS (ESI): *m*/*z* = 334 (M^- − H), 294, 226.

(2*S*,4*S*,5*S*)-4,5-Dihydroxypiperidine-2-carboxylic Acid Hydrochloride (13)

A mixture of Pd/C (20 mg), the acetonide **12** (67 mg, 0.2 mmol) and MeOH (5 mL) was hydrogenated at r. t. and 1 atm for 5 h. The mixture was filtered through Speedex, washed with MeOH (2 × 10 mL), and concentrated. The residue was dissolved in THF/H_2O (4:1) combined with concd HCl (4 drops) and stirred at r.t. overnight. The mixture was concentrated, and the residual water was azeotropically removed by repeated dissolution in EtOAc and distilling off the solvent. The resulting product **13** was recrystallised from EtOH/Et_2O; yield: 77%; mp >219 °C (dec.); $[\alpha]_D^{20}$ +20.4 (*c* = 0.11, 2 N HCl) {Lit.[21] $[\alpha]_D^{20}$ +19.5 (*c* = 0.15, 2 N HCl), Lit.[26] $[\alpha]_D^{20}$ +24.4 (*c* = 0.64, 2 N HCl)}.

^{1}H NMR (400 MHz/D_2O): δ = 1.75−1.91 (m, 1 H, CH_2), 2.55 (dt, *J* = 3.5, 14 Hz, 1 H, CH_2), 2.93 (dt, *J* = 9, 12.5 Hz, 1 H, CH_2), 3.57 (dd, *J* = 4, 12.5 Hz, 1 H, CH_2), 3.70−3.83 (m, 2 H, CH), 3.98 (dd, *J* = 3.7, 11 Hz, 1 H, CH).

MS (ESI): *m*/*z* = 160[M^- − H]

X-Ray Crystal Structure Analysis of the Imine 2c

Crystal data: C_{32} H_{38} N_2 O_2, M_r = 482.64, monoclinic, P 21, a = 9.887(2) A, α = 90°, b = 8.2380(10) Å, ß = 95.19(2)°, c = 16.336(3) Å, γ = 90°. *T* = 180(2) K, λ(Mo Kα) = 0.71073 Å, *V* = 1325.2(3) Å^3, Z: 2, D_x (calculated): 1.210 Mg/m^3, μ = 0.075 mm^{-1}, F(000): 520.

Data collection and reduction: Crystal size: 0.92 × 0.56 × 0.40 mm, 2.32 to 26.10°, Index ranges: −12< = h< = 12, −10< = k< = 10, −19< = l< = 20, Reflections collected: 8613, Independent reflections: 5127 [R(int) = 0.0264], Absorption correction: None, Refinement method: Full-matrix least-squares on F^2, Data/restraints/parameters: 5127/1/328, Goodness-of-fit on F^2: 1.060, Final R indices [I>2σ(I)]: R1 = 0.0311, *w*R2 = 0.0769, R indices (all data): R1 = 0.0329, *w*R2 = 0.0779, Absolute structure parameter: 0.0(8), Largest diff. peak and hole: 0.180 and −0.126 e.Å^{-3}. IPDS-2.75 (Stoe, 1997), Computing cell refinement: IPDS-2.75 (Stoe, 1997), Computing data reduction: IPDS-2.75 (Stoe, 1997), Computing structure solution: SHELXS-86 (Sheldrick, 1990), Computing structure refinement: SHELXL-93 (Sheldrick, 1993), Computing molecular graphics: XSTEP-2.16 (Stoe, 1997), Computing publication material: SHELXL-93 (Sheldrick, 1993). Refinement on F^2 for all reflections except for 0 with very negative F^2 or flagged by the user for potential systematic errors. Full details have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-141584. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK

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