Synthesis of Chiral C_2-Symmetric Binucleating Ligands

by **Christoph J. Fahrni** and **Andreas Pfaltz**[1])*

Institut für Organische Chemie, Universität Basel, St. Johanns-Ring 19, CH-4056 Basel

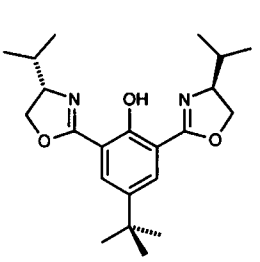
The synthesis of a series of chiral enantiomerically pure C_2-symmetric binucleating ligands is reported. Ligands of type **1**–**4**, which consist of a phenolic or heterocyclic unit bridging two chiral dihydrooxazole rings, are readily accessible from chiral amino alcohols. Ligands **5a** and **5b** are composed of a cyclic urea or thiourea unit, respectively, and two 3,4-dihydro-2*H*-pyrrole rings containing a stereogenic center next to the *N*-atom. Compounds of this type are readily assembled from ethane-1,2-diamine and an imidothioic ester derived from pyroglutamic acid. These new ligands, which can coordinate two metals in close proximity to each other, are of interest regarding possible applications in asymmetric catalysis.

1. Introduction. – Over the past two decades, the characterization of active sites of dinuclear metallo enzymes as well as the synthesis of model complexes that mimic their catalytic activity have been the subject of numerous publications [1]. Although these studies indicate a considerable potential of dinuclear metal complexes in catalysis, synthetic catalysts of this type have not found widespread application as yet. However, there are several examples demonstrating that dinuclear metal complexes can have distinct advantages over mononuclear metal catalysts. For instance, mixed-metal systems offer the possibility for selective activation of two different reactants [2]. Dinuclear metal complexes can also mediate multi-electron transfers [3] or activate a substrate by simultaneous coordination at two different metal centers [4]. Finally, complexes with weak metal–metal bonds allow the direct insertion of a substrate into the M–M bond, thus obviating the need of ligand dissociation to open up the coordination site [5].

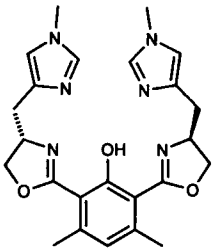
Considering the obvious potential of dinuclear metal complexes in asymmetric catalysis, we decided to prepare a series of binucleating chiral ligands. Herein, we describe the syntheses of enantiomerically pure C_2-symmetric ligands **1**–**5**, which allow the complexation of two metals in close proximity to each other. A common feature of these ligands is their rather rigid framework with two stereogenic centers in close proximity to the coordination sphere. With the exception of ligand **5**, they all consist of a phenolic or heterocyclic unit bridging two chiral dihydrooxazole rings. Ligands of type **1**–**4** are attractive, because chiral dihydrooxazoles are readily prepared from enantiomerically pure amino alcohols. Many different enantiomerically pure amino alcohols are commercially available or can be readily prepared from the corresponding α-amino acids by reduction [6], making it easy to vary the ligand structure. Over the last years, numerous ligands containing chiral dihydrooxazole rings as coordinating units have been reported, and many of them have found successful applications in asymmetric catalysis [7]. Ligand **5** is structurally related to the C_2-symmetric aza-semicorrins, which are effective

[1]) New address: Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, D-45470 Mülheim an der Ruhr.

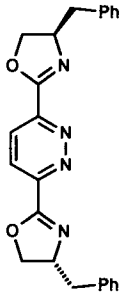
ligands for enantioselective copper-catalyzed cyclopropanation and palladium-catalyzed allylic alkylation [8]. The chiral elements of this ligand are derived from pyroglutamic acid, an inexpensive precursor commercially available in both enantiomeric forms.



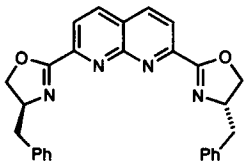
1



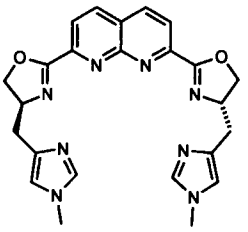
2



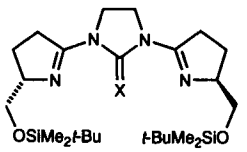
3



4a



4b



5a X = O

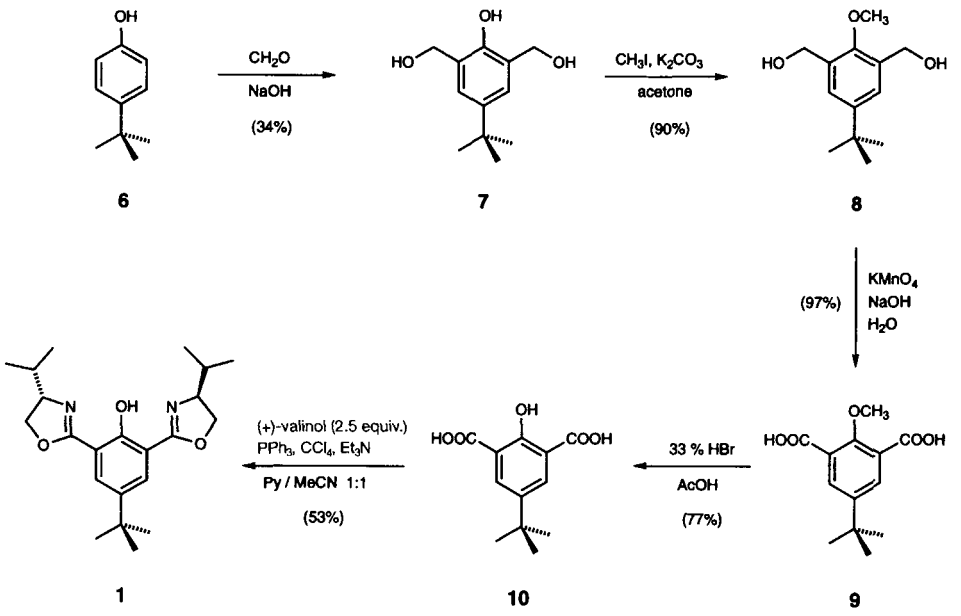
b X = S

2. Chiral 2,6-Bis(dihydrooxazolyl)-Substituted Phenol Ligands. – The syntheses of the phenol-derived ligands **1** and **2** are summarized in *Schemes 1–3*. Various efficient methods have been developed for the synthesis of dihydrooxazoles from amino alcohols [9]. The $ZnCl_2$-catalyzed condensation of nitriles with amino alcohols [9c] and the triphenylphosphine/CCl_4-mediated one-step conversion of carboxylic acids to dihydrooxazoles developed by *Vorbrüggen* and *Krolikiewicz* [9a] are among the most convenient routes. The former method was unsuccessful in our case, as treatment of 2-hydroxybenzene-1,3-dicarbonitrile [10] with 2.5 equiv. of phenylalaninol and 5 mol-% of $ZnCl_2$ in chlorobenzene did not lead to the desired product. Only the mono-condensation product was identified which, in a different experiment using 1.1 equiv. of amino alcohol, was isolated in 56% yield. Apparently, the remaining cyano group is much less reactive, and under forcing conditions, attack of the second amino alcohol occurs at the C=N double bond of the dihydrooxazole ring which is activated either by H-bonding with the neighboring OH proton or by complexation with zinc chloride.

The *Vorbrüggen* method, on the other hand, led to the desired product. However, the large excess of triphenylphosphine that had to be used made the isolation and purification of the product difficult. Therefore, a *tert*-butyl substituent in the *para*-position of the phenol ring was introduced which facilitates chromatographic separation and, at the

same time, enhances the solubility of the ligand. The required dicarboxylic acid **10** was synthesized in four steps starting from commercially available 4-(*tert*-butyl)phenol (**6**) *via* **7**–**9** (*Scheme 1*) [11]. Reaction of **10** with triphenylphosphine (6 equiv.), CCl_4, Et_3N, and valinol in pyridine/MeCN 1:1 afforded the desired product **1** in 53% yield.

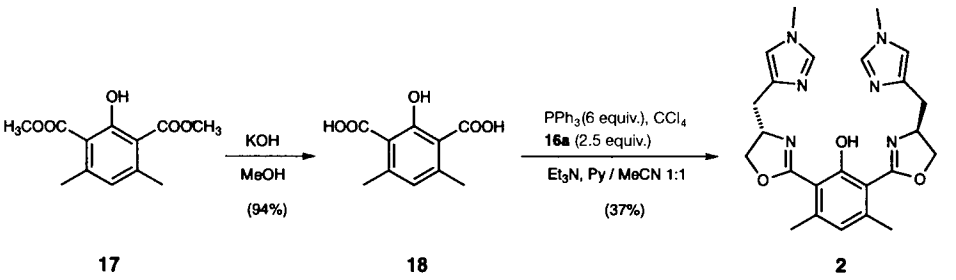
Scheme 1



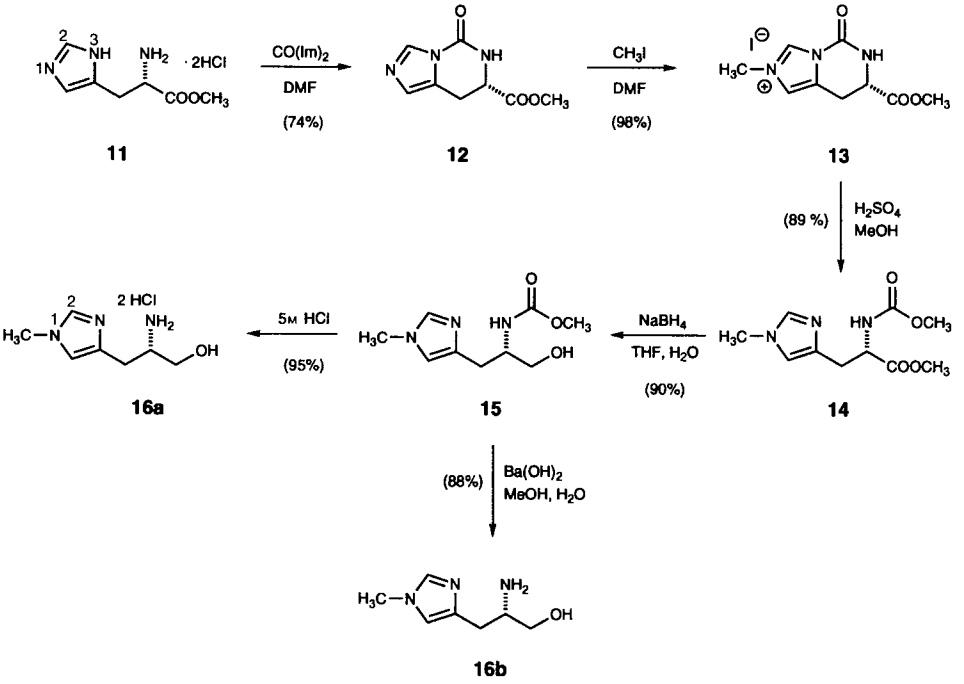
Similarly, ligand **2** having an imidazole-derived substituent at each dihydrooxazole ring was obtained by condensation of 1-methylhistidinol dihydrochloride (**16a**) with the dicarboxylic acid **18** in 37% yield (*Scheme 2*). The precursor **17** was readily prepared from acetylacetone (= pentane-2,4-dione) and dimethyl acetonedicarboxylate (= dimethyl 3-oxopentanedioate) [12]. The analogous reaction of histidinol with the *tert*-butyl-substituted dicarboxylic acid **10**, which had been used in the synthesis of ligand **1**, led to a product mixture which was much more difficult to purify by chromatography than ligand **2**. The 1-methylhistidinol (**16b**) and the corresponding hydrochloride **16a** were synthesized starting from commercially available histidine methyl ester dihydrochloride (**11**) (*Scheme 3*). Selective protection of the amino and imidazole N-atoms (N^{α} and N(3)) of **11** and subsequent methylation were accomplished following a procedure of *Noordam et al.* [13]. Conversion to the pyrimidine **12** with 1,1′-carbonylbis[1*H*-imidazole] followed by methylation yielded the pyrimidinium salt **13** in high yield [13]. After acid-catalyzed ring opening, the resulting *N*-(methoxycarbonyl)-protected amino ester **14** could be selectively reduced with $NaBH_4$ to give the corresponding alcohol **15** in 90% yield. The choice of a THF/H_2O mixture as solvent was crucial since the use of EtOH resulted in partial racemization (up to 10%). Deprotection with 5M HCl and recrystallization from $MeOH/Et_2O$ afforded enantiomerically pure amino alcohol dihydrochloride **16a** in 95% yield. Alternatively, deprotection could be achieved by hydrolysis with barium hydroxide in $MeOH/H_2O$ to give the free amino alcohol **16b** in 88%

yield. The enantiomeric excess was determined to be > 97% by ^{1}H-NMR analysis of the corresponding *Mosher* amide.

Scheme 2

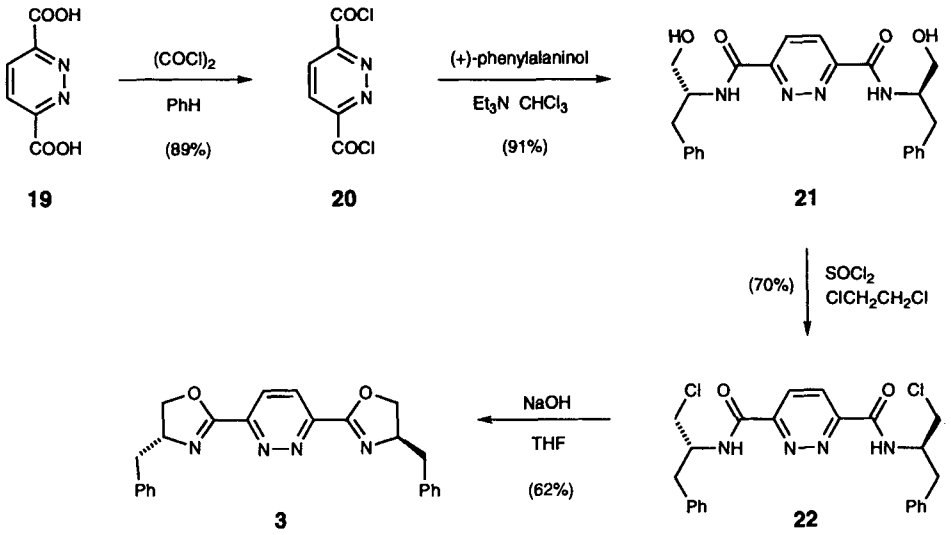


Scheme 3



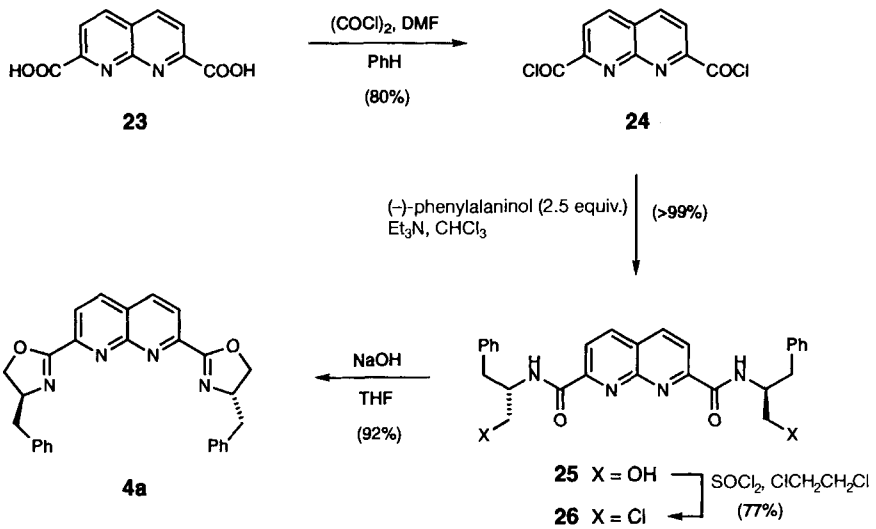
3. Chiral 3,6-Bis(dihydrooxazolyl)-Substituted Pyridazine Ligands. – Starting from pyridazine-3,6-dicarboxylic acid (**19**) [14], ligand **3** was synthesized in four steps in analogy to published procedures [9b] (*Scheme 4*). Conversion of the dicarboxylic acid **19** to the diamide **21** *via* **20** and subsequent treatment with thionyl chloride (→ **22**) followed by base-induced cyclization afforded enantiomerically pure **3** in 35% overall yield. In this case, the one-step conversion **19** → **3** with triphenylphosphine/CCl_4 resulted in a complex mixture from which the desired product **3** could not be isolated in satisfactory purity.

Scheme 4



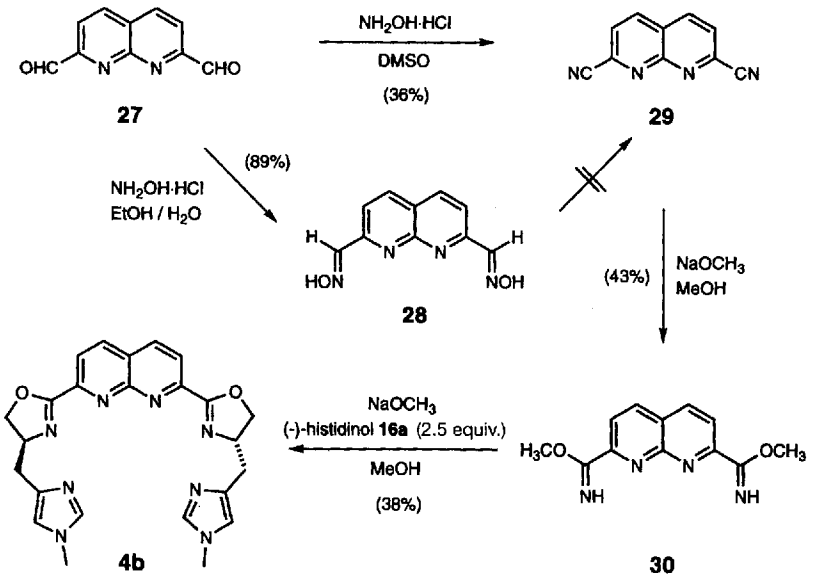
4. Chiral 2,7-Bis(dihydrooxazolyl)-Substituted Naphthyridine Ligands. – The synthesis of ligand **4a** with nonfunctionalized substituents at the dihydrooxazole rings was performed in a similar manner as described for ligand **3**, starting from 1,8-naphthyridine-2,7-dicarboxylic acid (**23**) [15] (*Scheme 5*). Formation of the acyl chloride **24**, followed by reaction with (−)-(*R*)-phenylalaninol, afforded the diamide **25** which, after treatment with thionyl chloride (→ **26**) and base-induced cyclization, gave the desired ligand **4a** in 56% overall yield.

Scheme 5



The synthesis of the corresponding bis(1-methyl-1*H*-imidazole) ligand **4b** is based on the condensation of the bis(imidate) **30** with the corresponding amino alcohol **16a** in analogy to published procedures [9d–e]. The bis(imidate) **30** was prepared from 1,8-naphthyridine-2,7-dicarbaldehyde (**27**) [9e] *via* the dinitrile **29** in 17% yield. The synthesis of the dicarbonitrile **29** proved to be more difficult than expected because the usual methods for the conversion of oximes to nitriles [16] failed for dioxime **28**[2]). However, following a procedure developed by *Audoye et al.* [17], dialdehyde **27** could be converted to the dicarbonitrile in 36% yield in one step by treatment with hydroxylamine hydrochloride in DMSO at 110°. It was essential to carefully control the temperature and reaction time, otherwise the yield and purity of the product were significantly lower. Reaction of dicarbonitrile **29** with 2 equiv. of NaOMe in MeOH led to imidate **30**, which was reacted with 2.5 equiv. of 1-methylhistidinol dihydrochloride (**16a**) and NaOMe (5 equiv.) to afford ligand **4b** in 16% overall yield.

Scheme 6

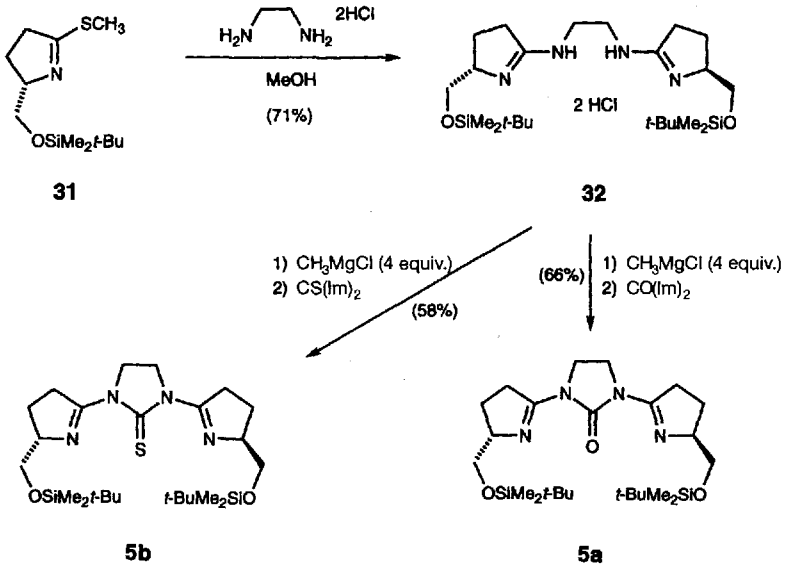


5. Chiral Bis(dihydropyrrole) Ligands 5a and 5b. – The synthesis of ligands **5a** and **5b** is summarized in *Scheme 7*. The precursor **31**, which has been previously used in the synthesis of aza-semicorrin ligands, is easily prepared in three steps from commercially available (*S*)-2-(hydroxymethyl)pyrrolidin-5-one [8]. Reaction of the imidothioate **31** with ethane-1,2-diamine dihydrochloride in refluxing MeOH afforded the bisamidine dihydrochloride **32** in 71% yield. The final ring closure was accomplished by deprotonation with methylmagnesium chloride and subsequent reaction with either 1,1′-carbonylbis[1*H*-imidazole] or 1,1′-carbonothioylbis[1*H*-imidazole] affording the corresponding

[2]) We tried to accomplish the dehydration of oxime **28** with the following reagents: Ac_2O; $SOCl_2$, or SeO_2/lutidine. For general reviews on the synthesis of nitriles, see [16].

ligands **5a** and **5b** in 66 and 58% yield, respectively. The imidazolidinethione **5b** was purified by column chromatography on basic alumina rather than on silica gel to avoid partial hydrolysis to the imidazolidinone **5a**. Both ligands were isolated as amorphous solids and could be stored in the freezer for months without considerable decomposition.

Scheme 7



The syntheses developed for ligands **1**–**5** allow the preparation of sufficient quantities for studying their complexation behavior toward different metal ions. The coordination chemistry of these ligands and the structures and properties of a series of transition-metal complexes are reported in the following communication [18].

Financial support of this work by the *Swiss National Science Foundation* is gratefully acknowledged. We thank *Andreas Salathé* for contributing experimental procedures for the synthesis of ligand **4b**.

Experimental Part

1. *General.* Quality of solvents and reagents: MeOH, EtOH, benzene, 1,2-dichloroethane, $CHCl_3$, CCl_4: *Fluka puriss.*; anh. THF: *Fluka purum*, distilled from Na/benzophenone; anh. DMSO, DMF, MeCN, pyridine: *Fluka puriss.*, absolute; anh. MeOH: refluxed over Mg and distilled before use; CH_2Cl_2, AcOEt, Et_2O, hexane: technical grade, distilled before use; 10M methanolic NH_3: MeOH saturated with NH_3(g) for 1 h; 4-(*tert*-butyl)phenol (**6**), pentane-2,4-dione, Et_3N, MeI, $SOCl_2$: *Fluka puriss.*; NaOMe: *Fluka pract.* (95%); dimethyl 3-oxopentanedioate, PPh_3, 1,1′-carbonylbis[1*H*-imidazole], 1,1′-carbonothioylbis[1*H*-imidazole], $NaBH_4$, $(COCl)_2$: *Fluka purum*; 33% HBr in AcOH: *Fluka pract.*; 80% nitric acid: *Fluka, puriss.* (99%); MeMgCl: *Aldrich*, 2.9M in THF; (−)-(*R*)-α-methoxy-α-(trifluoromethyl)benzeneacetyl chloride (−)-(*R*)-MTPA-Cl): *Fluka ChiraSelect*, > 99.5% ee; (+)-L-histidine methyl ester dihydrochloride, (+)-(*S*)-valinol, (+)-(*R*)- and (−)-(*S*)-phenylalaninol: *Fluka purum*, > 98% ee. Flash column chromatography (FC): *Chemie-Uetikon-C560* silica gel (35–70 μm) and *Fluka* aluminium oxide *5016A* (basic). TLC: 0.25 mm, *Merck* silica gel *60 F254* and *Macherey-Nagel Alox-25 UV*$_{254}$; visualizing at 254 nm or with 2% $KMnO_4$ soln. Optical rotations: *Perkin-Elmer-*

141 polarimeter; $d = 10$ cm, c in g/100 ml, $CHCl_3$, 23°; estimated error ±5%. IR ($CHCl_3$ or KBr): selected bands in cm^{-1}. NMR: δ in ppm *vs.* $SiMe_4$ (0 ppm; ^1H, 300 MHz, $CDCl_3$ (77.0 ppm; ^{13}C, 75 MHz; assignments based on DEPT, APT or $^1H/^{13}C$-HETCOR experiments), and CCl_3F (0 ppm; ^{19}F, 282 MHz). MS: selected peaks; *m/z* (%); matrix for FAB-MS: 3-nitrobenzyl alcohol (NBA).

2. *4-(*tert*-Butyl)-2,6-bis[(4S)-4,5-dihydro-4-isopropyloxazol-2-yl]phenol* (**1**). *5-(*tert*-Butyl)-2-hydroxybenzene-1,3-dimethanol* (**7**) [11]. 4-(*tert*-Butyl)phenol (**6**; 150 g, 1.0 mol) was dissolved in a mixture of 38% aq. formaldehyde (160 ml, 2.0 mol) and 10% aq. NaOH soln. (400 ml, 1.0 mol). The resulting soln. was allowed to stand at r.t. for 4 days. The colorless precipitate was filtered off, washed with H_2O and treated with 1M aq. HCl (1 l) to protonate the sodium phenolate. After stirring for 30 min at r.t., the product was filtered off, washed with H_2O, dissolved in CH_2Cl_2, and dried ($MgSO_4$). After evaporation, the residue was recrystallized from Et_2O/pentane affording 72.0 g (0.34 mol, 34%) of **7**. Colorless solid. M.p. 73–74° ([11]: 73.5–74.5°). IR ($CHCl_3$): 3312*s* (br.), 2961*s*, 2902*s*, 1611*m*, 1491*s*, 1463*s*, 1391*m*, 1362*s*, 1304*m*, 1262*m*, 1218*s*, 1120*m*, 1013*s*, 921*w*, 877*m*, 822*m*, 733*m*, 663*m*, 600*w*. ^1H-NMR ($CDCl_3$): 1.25 (*s*, *t*-Bu); 4.70 (*s*, CH_2OH); 7.03 (*s*, arom. CH). ^{13}C-NMR ($CDCl_3$): 31.4 (Me_3C); 34.0 (Me_3C); 63.6 (CH_2OH); 124.8 (C(4), C(6)); 125.4 (C(1), C(3)); 142.5 (C(5)); 15.2 (C(2)). EI-MS: 211 (2.2), 210 (19.3, M^+), 192 (8), 178 (12), 177 (100, $[M - 2\,OH]^+$), 163 (17), 159 (6), 131 (7), 108 (20), 107 (7), 105 (7), 91 (17), 77 (13), 65 (6), 57 (31), 41 (15), 39 (9).

*5-(*tert*-Butyl)-2-methoxybenzene-1,3-dimethanol* (**8**). To a soln. of **7** (40.0 g, 190 mmol) in acetone (760 ml), anh. K_2CO_3 (131 g, 950 mmol) and MeI (24 ml, 380 mmol) were added. The resulting suspension was stirred vigorously (mechanical stirring) at reflux temp. for 18 h, cooled to r.t., and filtered. After evaporation, the residue was taken up in CH_2Cl_2 (500 ml) and extracted with sat. aq. $NaHCO_3$ soln. (300 ml). After reextraction of the aq. phase with CH_2Cl_2, the combined org. phase was washed with sat. aq. NaCl soln., dried ($MgSO_4$), and evaporated. The resulting colorless oil was dried for 6 h at 0.05 Torr yielding 38.3 g (90%) of **8** which was used without further purification. An anal. sample was obtained by FC (silica gel, hexane/AcOEt 1:1; R_f (prod.) 0.23) affording a colorless oil which solidified upon standing. M.p. 52–55°. IR ($CHCl_3$): 3342*s* (br.), 2960*s*, 2870*s*, 2828*m*, 2706*w*, 1781*w*, 1685*w* (br.) 1482*s*, 1434*s*, 1393*m*, 1361*s*, 1305*m*, 1206*s*, 1176*m*, 1112*m*, 1057*s*, 1013*s*, 992*m*, 976*m*, 923*m*, 886*s*, 810*m*, 776*m*, 658*m*, 528*w*. ^1H-NMR ($CDCl_3$): 1.31 (*s*, *t*-Bu); 2.17 (*t*, $J = 5.8$, OH); 3.83 (*s*, MeO); 4.72 (*d*, $J = 5.8$, CH_2OH); 7.34 (*s*, arom. H). ^{13}C-NMR ($CDCl_3$): 31.4 (Me_3C); 34.4 (Me_3C); 61.0 (CH_2OH); 62.0 (MeO); 125.9 (C(1) C(3)); 133.1 (C(4), C(6)); 147.5 (C(2)); 153.7 (C(5)). EI-MS: 225 (3.5), 224 (27.4, M^+), 223 (2.8), 210 (13), 209 (100, $[M - Me]^+$), 207 (5), 131 (7), 91 (11), 77 (6), 43 (6), 41 (10).

*5-(*tert*-Butyl)-2-methoxyisophthalic Acid* (**9**). To a soln. of NaOH (18.4 g, 460 mmol) and *Adogen 464* (trialkyl(methyl)ammonium chloride, *Aldrich*; 1.0 g in H_2O (780 ml), **8** (22.4 g, 100 mmol) was added. The mixture was heated to 50° and with vigorous stirring, $KMnO_4$ (63.2 g, 400 mmol) was added in portions. After stirring at 50° for 1 h, the mixture was refluxed for 5 min and cooled down to 60–70°. Excess of $KMnO_4$ was cautiously destroyed by slow addition of EtOH. The warm mixture was filtered through a pad of *Celite* and washed with hot 5% aq. NaOH soln. After chilling in an ice bath, the colorless filtrate was acidified with conc. aq. HCl soln. to pH 1. The precipitated product was filtered off, washed with H_2O, and dried *in vacuo* affording 24.6 g (97%) of **9** as colorless powder. An anal. sample was obtained by recrystallization from H_2O. M.p. 178–180°. IR (KBr): 2964*s*, 2586*m*, 1716*s*, 1699*s*, 1677*s*, 1599*w*, 1575*m*, 1478*m*, 1442*m*, 1395*w*, 1364*m*, 1297*m*, 1270*s*, 1201*w*, 1160*w*, 1120*m*, 1007*m*, 920*m*, 918*m*, 821*m*, 731*w*, 695*m*, 664*w*, 619*w*, 520*w*. ^1H-NMR ((D_6)DMSO): 1.29 (*s*, *t*-Bu); 3.2–3.5 (br. *s*, COOH); 3.78 (*s*, MeO); 7.79 (*s*, arom. CH). ^{13}C-NMR ((D_6)DMSO): 30.9 (Me_3C); 34.2 (Me_3C); 62.9 (MeO); 127.3 (C(1), C(3)); 130.1 (C(4), C(6)); 145.8 (C(5)); 155.5 (C(2)); 167.3 (COOH). EI-MS: 253 (1.3), 252 (11.9, M^+), 239 (1), 238 (13), 237 (100, $[M - Me]^+$), 103 (7), 91 (9), 77 (11), 41 (11), 39 (8). Anal. calc. for $C_{13}H_{16}O_5$: C 61.89, H 6.39; found: C 62.27, H 6.34.

*5-(*tert*-Butyl)-2-hydroxyisophthalic Acid* (**10**). A suspension of **9** (12.9 g, 51.5 mmol) in 33% HBr/AcOH (60 ml) was heated to 120° with vigorous stirring until the gas evolution subsided (10 min). The homogeneous orange mixture was cooled to r.t. and diluted with H_2O until the product started to precipitate (300 ml). The product was filtered off, washed with H_2O, and dried *in vacuo* yielding 9.47 g (77%) of **10** as colorless powder. An anal. sample was obtained by recrystallization from H_2O. M.p. 255–258°. IR (KBr): 2965*s* (br.), 2635*m*, 2557*m*, 1856*w*, 1711*s*, 1603*s*, 1445*s*, 1396*m*, 1365*m*, 1329*m*, 1246*s*, 1215*s*, 1191*s*, 1164*m*, 1117*m*, 909*m*, 828*m*, 808*m*, 697*m*, 608*w*, 526*w*, 504*w*. ^1H-NMR ((D_6)DMSO): 1.28 (*s*, Me_3C); 7.97 (*s*, arom. H–C(4), H–C(6)). ^{13}C-NMR ((D_6)DMSO): 31.0 (CMe_3); 33.8 (Me_3C); 116.8 (C(1), C(3)); 132.1 (C(4), C(6)); 140.2 (C(5)); 159.2 (C(2)); 169.4 (COOH). EI-MS: 241 (1.3), 239 (2.5), 238 (19.6), 224 (7), 223 (57, $[M - Me]^+$), 206 (11), 205 (100, $[M - Me - H_2O]^+$), 176 (19), 161 (9), 133 (11), 103 (8), 77 (10). Anal. calc. for $C_{12}H_{14}O_5$: C 60.50, H 5.92; found: C 60.41, H 5.88.

*4-(*tert*-Butyl)-2,6-bis[(4S)-4,5-dihydro-4-isopropyloxazol-2-yl]phenol* (**1**). To a soln. of **10** (3.60 g, 15.1 mmol) and (+)-L-valinol (3.26 g, 31.7 mmol) in anh. pyridine/MeCN 1:1, 48 ml) under Ar, Et_3N (14.8 ml) and CCl_4

(10.2 ml, 105.6 mmol were added). To the resulting homogeneous mixture, a soln. of PPh_3 (23.6 g, 90.6 mmol) in anh. pyridine/MeCN 1:1 (48 ml) was gradually added within 2 h, maintaining the temp. below 25° (water bath). After stirring overnight at r.t., the precipitated salt was filtered off and washed with MeCN. The filtrate was diluted with H_2O (200 ml) and extracted with cyclohexane (3 × 150 ml). The combined org. phase was dried ($MgSO_4$) and evaporated and the residue chromatographed (silica gel (6 × 18 cm), hexane/AcOEt 3:1) affording 3.0 g (8.1 mmol, 53%) of **1** as yellow oil. Lyophilization from cyclohexane (0.1 mbar) yielded an amorphous powder. $[\alpha]_D = -32.1$ ($c = 0.50$, $CHCl_3$). UV (MeOH): 322 (7000), 221 (28200). R_f 0.68 (silica gel, AcOEt/hexane 1:3). IR (KBr): 2959*s*, 2905*m*, 2871*m*, 1645*s*, 1596*m*, 1465*s*, 1383*m*, 1365*m*, 1346*w*, 1267*s*, 1210*w*, 1173*s*, 1127*w*, 1094*w*, 1076*w*, 1038*m*, 981*m*, 927*w*, 900*w*, 826*m*, 724*w*. ^{1}H-NMR ($CDCl_3$): 0.94 (*d*, $J = 6.8$, Me_2CH); 1.03 (*d*, $J = 6.7$, Me_2CH); 1.32 (*s*, *t*-Bu); 1.84–2.04 (*m*, Me_2CH); 4.10–4.21 (*m*, 2 H, $CHCH_2O$); 4.37–4.44 (*m*, 1 H, $CHCH_2O$); 7.85 (*s*, arom. H); 13.30 (*s*, OH). ^{13}C-NMR ($CDCl_3$): 18.1, 18.8 (Me_2CH); 31.1 (Me_3C); 32.7 (Me_2CH); 34.0 (Me_3C); 69.5 (CH_2O); 72.1 ($CHCH_2O$); 113.2 (C(2), C(6)); 129.7 (C(3), C(5)); 140.5 (C(4)); 157.0 (C(1)); 163.4 (C=N). EI-MS: 373 (7), 372 (18, M^+), 358 (2), 357 (9, $[M - Me]^+$), 330 (21), 329 (100, $[M - Me_2CH]^+$), 203 (19), 185 (8), 57 (11), 41 (13).

3. *2,6-Bis{(4S)-4,5-dihydro-4-[(1-methyl-1*H*-imidazol-4-yl)methyl]oxazol-2-yl}-3,5-dimethylphenol* (**2**). *Dimethyl 2-Hydroxy-4,6-dimethylisophthalate* (**17**) [12]. To a soln. of NaOMe (11.32 g, 210 mmol) in MeOH (120 ml), pentane-2,4-dione (20.6 ml, 200 mmol) and dimethyl 3-oxopentanedioate (29.0 ml, 200 mmol) were added, and the resulting homogeneous mixture was stirred vigorously at r.t. for 24 h. After dilution with H_2O (100 ml), the mixture was acidified with 6M HCl (60 ml) and extracted with CH_2Cl_2 (3 × 100 ml). The combined org. phase was dried ($MgSO_4$) and evaporated and the residue recrystallized from CH_2Cl_2/pentane: 37.9 g (79%) of **17**. Colorless prisms. M.p. 103–104°. IR ($CHCl_3$): 2954*m*, 2848*m*, 1720*s*, 1659*s*, 1615*s*, 1558*m*, 1455*s*, 1385*m*, 1366*s*, 1321*m*, 1302*m*, 1263*s*, 1203*s*, 1180*s*, 1132*m*, 1077*m*, 1051*m*, 1026*m*, 964*m*, 949*m*, 852*m*, 809*m*, 785*w*, 771*m*, 668*w*, 615*w*, 598*w*, 578*w*, 564*w*, 457*w*. ^{1}H-NMR ($CDCl_3$): 2.38 (*s*, Me–C); 3.92 (*s*, COOMe); 6.57 (*s*, arom. H); 11.78 (*s*, OH). ^{13}C-NMR ($CDCl_3$): 21.8 (*Me*–C); 52.2 (COO*Me*); 115.6 (C(1), C(3)); 124.7 (C(5)); 142.5 (C(4), C(6)); 160.1 (C(2)); 169.8 (*C*OOMe). EI-MS: 239 (2.9), 238 (26.3, M^+), 207 (24), 206 (72, $[M - MeOH]^+$), 178 (13), 176 (11), 175 (100), 174 (48), 148 (58), 147 (12), 119 (8), 91 (17), 65 (14).

2-Hydroxy-4,6-dimethylisophthalic Acid (**18**). A soln. of **17** (34.0 g, 143 mmol) in 20% KOH/MeOH (500 ml) was refluxed for 20 h. After cooling to r.t., the potassium salt was filtered off, dissolved in H_2O and treated with 1M HCl to precipitate the free acid. The colorless product was filtered off, washed several times with H_2O, and dried *in vacuo*: 28.0 g (94%) of **18**. Colorless prisms. M.p. > 300° (dec.). IR (KBr): 3024*s*, 2692*m*, 1686*s*, 1646*s*, 1614*s*, 1554*m*, 1502*m*, 1444*s*, 1382*m*, 1333*m*, 1291*s*, 1260*s*, 1213*s*, 1145*m*, 1077*m*, 1031*w*, 981*w*, 856*m*, 810*m*, 783*w*, 735*w*, 618*w*, 579*w*, 488*w*, 461*w*. ^{1}H-NMR ($CDCl_3$): 2.36 (*s*, Me–C); 6.66 (*s*, arom. H); 11.0–12.0 (br. *s*, COOH). ^{13}C-NMR ($CDCl_3$): 21.3 (Me); 116.7 (C(1), C(3)); 124.0 (C(5)); 141.1 (C(4), C(6)); 159.2 (C(2)); 170.7 (COOH). EI-MS: 211 (2.4), 210 (15.3, M^+), 193 (11), 192 (22, $[M - H_2O]^+$), 175 (15), 174 (45, $[M - 2\,H_2O]^+$), 149 (12), 148 (100, $[M - H_2O - CO_2]^+$), 120 (21), 119 (16), 92 (12), 91 (37), 77 (11), 67 (11), 65 (20), 63 (10), 53 (9), 51 (16), 45 (9), 39 (21).

*2,6-Bis{(4S)-4,5-dihydro-4-[(1-methyl-1*H*-imidazol-4-yl)methyl]oxazol-2-yl}-3,5-dimethylphenol* (**2**). Under Ar, **18** (1.05 g, 5.0 mmol) and 1-methyl-L-histidinol dihydrochloride (**16a**; 2.39 g, 10.5 mmol) were dissolved in anh. pyridine/MeCN 1:1 (20 ml). Subsequently, Et_3N (7.1 ml, 50.9 mmol) and CCl_4 (4.61 g, 30.0 mmol) were added. Finally, a soln. of PPh_3 (7.86 g, 30.0 mmol) in anh. pyridine/MeCN 1:1 (10 ml) was added gradually within 1 h maintaining the temp. below 25° (water bath). After stirring for 3 h at r.t., the mixture was diluted with CH_2Cl_2 (80 ml) and extracted with *ice-cold* 1M HCl (80 ml). The aq. phase was neutralized by adding solid $NaHCO_3$ and the product extracted with CH_2Cl_2 (2 × 60 ml). The combined org. phase was dried ($MgSO_4$) and evaporated and the residue chromatographed (silica gel, 4 × 18 cm, 10M methanolic NH_3/CH_2Cl_2 1:15): 840 mg (37%) of **2**. Pale yellow glassy solid. $[\alpha]_D = +10.0$ ($c = 0.42$, $CHCl_3$). UV (MeOH): 312 (2800), 258 (5100), 218 (16800). IR (KBr): 3404*m* (br.), 2922*m*, 1644*m*, 1614*s*, 1560*m*, 1508*m*, 1474*w*, 1447*m*, 1419*m*, 1381*w*, 1353*m*, 1270*m*, 1190*s*, 1076*m*, 1043*m*, 1008*m*, 987*w*, 957*m*, 905*w*, 847*w*, 737*w*, 669*w*, 636*w*, 620*m*. ^{1}H-NMR ($CDCl_3$): 2.37 (*s*, 2 Me–C); 2.80 (*dd*, $J = 14.6, 7.4$, CH_2–Im); 3.05 (*dd*, $J = 14.6, 5.7$, CH_2–Im); 3.63 (*s*, 2 MeN); 4.26 (*dd*, $J = 8.4, 7.7$, CH_2O); 4.46 (*dd*, $J = 9.4, 8.5$, CH_2O); 4.60–4.68 (*m*, CH); 6.52 (*s*, arom. H); 6.74 (*s*, H–C(5), Im); 7.33 (*d*, $J = 1.0$, H–C(2), Im); 14.0–14.2 (br. *s*, OH). ^{13}C-NMR ($CDCl_3$): 21.2 (Me); 33.1 (MeN); 34.3 (CH_2–Im); 65.0 (CH); 71.5 (CH_2O); 111.6 (C(2), C(6)); 117.6 (C(5), Im); 123.4 (C(4)); 137.1 (C(2), Im); 138.7 (C(4), Im); 141.3 (C(3), C(5)); 160.0 (C(1)); 164.8 (C=N). EI-MS: 449 (3.4), 448 (13.7, M^+), 354 (5), 353 (25, $[M - CH_2ImMe]^+$), 285 (10), 148 (11), 139 (14), 138 (17), 122 (19), 121 (21), 109 (13), 107 (15), 96 (100, $[C_5H_7N_2 + H]^+$), 95 (40), 91 (10), 81 (16), 44 (26), 42 (21). FAB-MS (NBA): 451 (4.7), 450 (28.9), 449 (100, $[M + H]^+$), 448 (27), 353 (23), 312 (19), 139 (15), 121 (22), 109 (23), 107 (12), 96 (19), 95 (45, $C_5H_7N_2^+$), 89 (24), 77 (19), 69 (10), 63 (18), 62 (12), 57 (11), 55 (18), 51 (24), 50 (20), 39 (30).

4. *1-Methyl-L-histidinol* (**16**). *Methyl (7S)-5,6,7,8-Tetrahydro-5-oxoimidazo[1,5-c]pyrimidine-7-carboxylate* (**12**) [13]. (+)-L-Histidine methyl ester dihydrochloride (**11**; 50.0 g, 206 mmol) and 1,1'-carbonylbis[1*H*-imidazole] (34.4 g, 212 mmol) were dissolved in anh. DMF (1 l) and stirred under Ar for 3 h at 60°. After cooling to r.t. and evaporation (1 Torr), the dark yellow residue was taken up in 1M aq. $NaHCO_3$ (1 l) and extracted with $CHCl_3$ (9 × 180 ml). The combined org. phase was dried ($MgSO_4$) and evaporated and the residue recrystallized from AcOEt/pentane: 29.6 g (74%) of **12**. Colorless crystals. M.p. 163–164° ([13]: 156–157°). $[\alpha]_D = +59.5$ ($c = 1.2$, MeOH). IR (KBr): 3116*m*, 2957*w*, 1757*s*, 1715*s*, 1588*w*, 1442*m*, 1408*m*, 1352*m*, 1256*w*, 1218*m*, 1202*m*, 1185*m*, 1079*m*, 1010*w*, 949*w*, 931*m*, 906*w*, 859*w*, 841*w*, 760*m*, 704*w*, 583*m*. ^{1}H-NMR ($CDCl_3$): 3.16 (*ddd*, $J = 15.7$, 8.7, 1.1 CH_2–Im); 3.39 (*dd*, $J = 15.7$, 5.3, CH_2–Im); 3.82 (*s*, COOMe); 4.35–4.40 (*m*, CHCOOMe); 6.45 (br. *s*, NH); 6.89 (*s*, CCHN); 8.16 (*s*, NCHN). ^{13}C-NMR ($CDCl_3$): 23.1 (CH_2); 52.7 (COO*Me*); 53.3 (CH_2CH); 123.8 (CH_2CC); 126.3 (*C*CHN); 135.2 (*N*CHN); 147.9 (*N*CON); 169.6 (*C*OOMe). EI-MS: 196 (1.8), 195 (17.7, M^+), 152 (26), 136 (38, $[M - COOMe]^+$), 135 (13), 81 (100, $[CH_2Im]^+$), 80 (7), 53 (8).

(7S)-5,6,7,8-Tetrahydro-7-(methoxycarbonyl)-2-methyl-5-oxoimidazo[1,5-c]pyrimidinium Iodide (**13**) [13]. To a soln. of **12** (28.0 g, 143 mmol) in anh. DMF (280 ml), MeI (140 ml) was added, and the mixture was refluxed at 60° for 2.5 h. After cooling to r.t., the product was crystallized by adding Et_2O (500 ml) with vigorous stirring. The product was filtered off, washed with Et_2O, and dried at r.t. *in vacuo* yielding 47.5 g (98%) of **13** as colorless needles (used without further purification). An anal. sample was obtained by recrystallization from MeOH. M.p. 180–185° (dec.). $[\alpha]_D = +46.4$ ($c = 0.7$, H_2O). IR (KBr): 3147*m*, 3088*s*, 3012*m*, 2954*m*, 2893*m*, 1760*s*, 1634*w*, 1602*w*, 1552*m*, 1460*m*, 1428*m*, 1414*m*, 1389*m*, 1348*m*, 1329*m*, 1312*m*, 1246*m*, 1227*s*, 1214*s*, 1184*m*, 1179*m*, 1136*s*, 1066*m*, 1026*w*, 1005*m*, 959*w*, 942*m*, 909*w*, 836*m*, 780*w*, 755*m*, 709*w*, 675*w*, 608*m*, 582*m*. ^{1}H-NMR ((D$_6$)DMSO): 3.31–3.39 (*m*, CH_2); 3.68 (*s*, COOMe); 3.89 (*s*, MeN); 4.64–4.69 (*m*, CHCOOMe); 7.62 (*s*, CCHN); 9.50 (*d*, $J = 4.0$, NH); 9.75 (*s*, NCHN). ^{13}C-NMR ((D$_6$)DMSO): 21.5 (CH_2); 36.6 (MeN); 51.2 (CH_2CH); 53.1 (COO*Me*); 120.4 (*C*CHN); 127.8 (CH_2CC); 135.3 (NCHN); 144.4 (NCON); 170.3 (*C*OOMe). FAB-MS (NBA): 212 (0.9), 211 (11), 210 (100, M^+), 151 (2), 150 (7, $[M - COOMe]^+$).

N^a-*(Methoxycarbonyl)-1-methyl-L-histidine Methyl Ester* (**14**). To a soln. of **13** (44.0 g, 130 mmol) in MeOH (1 l), conc. H_2SO_4 soln. (2.8 ml) was dropwise added and the mixture refluxed for 4 h. After addition of NaOMe (3.2 g), the soln. was concentrated to 200 ml, subsequently diluted with CH_2Cl_2 (400 ml), and extracted with $NaHCO_3$ soln. (300 ml; sat. soln./H_2O 1:1). The org. layer was dried ($MgSO_4$), and evaporated to give a colorless oil which crystallized upon standing at r.t. The solid was ground in a mortar and dried for 5 h at 0.05 Torr: 28.0 g (89%) of **14**. Colorless powder. M.p. 115–117°. $[\alpha]_D = +12.5$ ($c = 0.99$, $CHCl_3$). IR (KBr): 3204*m*, 3113*m*, 2981*m*, 2810*w*, 1736*s*, 1712*s*, 1557*m*, 1514*m*, 1436*m*, 1417*w*, 1371*w*, 1284*s*, 1258*s*, 1216*s*, 1189*m*, 1171*m*, 1153*m*, 1075*w*, 1038*m*, 1002*w*, 959*w*, 860*w*, 750*w*, 619*w*. ^{1}H-NMR ($CDCl_3$): 2.89–3.03 (*AB* of *ABX*, $J_{AB} = 14.7$, $J_{AX} = 5.5$, $J_{BX} = 4.7$, CH_2); 3.55, 3.60, 3.63 (3*s*, Me); 4.46–4.53 (*m*, *X* of *ABX*, CHCOOMe); 6.24 (*d*, $J = 7.8$, NH); 6.58 (*s*, H–C(5), Im); 7.24 (*d*, $J = 1.1$, H–C(2), Im). ^{13}C-NMR ($CDCl_3$): 29.9 (CH_2); 33.2 (MeN); 52.09 (*C*HCOOMe); 52.14, 53.9 (COO*Me*); 117.5 (C(5), Im); 137.3 (C(4), Im); 137.4 (C(2), Im); 156.5 (NHCOOMe); 172.0 (*C*OOMe). EI-MS: 242 (0.5), 241 (5.0, M^+), 210 (3, $[M - OMe]^+$), 182 (30, $[M - COOMe]^+$), 166 (35), 150 (23), 96 (35), 95 (100, $[Im - Me]^+$), 81 (8), 43 (33), 42 (20). Anal. calc. for $C_{10}H_{15}N_3O_4$: C 49.79, H 6.27, N 17.42; found: C 49.81, H 6.24, N 17.41.

N^a-*(Methoxycarbonyl)-1-methyl-L-histidinol* (**15**). A soln. of **14** (26.0 g, 108 mmol) in THF (650 ml) and H_2O (160 ml) was chilled in an ice bath, and $NaBH_4$ (20.4 g, 540 mmol) was gradually added. The mixture was stirred for 40 min at r.t. (evolution of H_2!) and conc. aq. HCl soln. (90 ml) was added cautiously (ice bath). The aq. phase was saturated with anh. K_2CO_3, separated from the org. layer and extracted with CH_2Cl_2 (3 × 150 ml). The combined org. phase was dried ($MgSO_4$) and evaporated and the resulting residue chromatographed (silica gel (4 × 10 cm), CH_2Cl_2/10M NH_3/MeOH 10:1, R_f (prod.) 0.30: 20.8 g (90%) of **15**. Colorless oil which crystallized upon standing at r.t. M.p. 84–86°. $[\alpha]_D = +40.5$ ($c = 2.26$, $CHCl_3$). IR (KBr): 3216*m*, 3058*m*, 2957*m*, 2855*m*, 1708*s*, 1559*m*, 1512*m*, 1444*w*, 1423*w*, 1373*w*, 1356*w*, 1270*s*, 1245*m*, 1177*m*, 1069*m*, 1040*m*, 995*m*, 907*w*, 820*w*, 771*w*, 621*w*, 579*w*. ^{1}H-NMR ($CDCl_3$): 2.74–2.85 (*m*, CH_2–Im); 3.66, 3.51 (*AB* of *ABX*, $J_{AB} = 11.5$, $J_{AX} = 3.5$, $J_{BX} = 4.9$, CH_2OH); 3.57 (*s*, *Me*–Im, COO*Me*); 3.80–3.86 (*m*, CH); 4.73 (br. *s*, OH); 5.61 (*d*, $J = 6.3$, NH); 6.63 (*s*, H–C(5), Im); 7.28 (*s*, H–C(2), Im). ^{13}C-NMR ($CDCl_3$): 30.1 (CH_2–Im); 33.3 (MeN); 51.8 (CH); 52.0 (COO*Me*); 64.0 (CH_2OH); 118.2 (C(5), Im); 137.1 (C(2), Im); 138.2 (C(4), Im); 156.8 (NHCOOMe). EI-MS: 213 (0.20, M^+), 183 (6), 182 (16, $[M - MeO]^+$), 150 (12), 138 (11), 109 (16), 97 (7), 96 (100, $[M - MeIm]^+$), 81 (17), 42 (13). Anal. calc. for $C_9H_{15}N_3O_3$: C 50.69, H 7.09, N 19.71; found: C 50.72, H 7.08, N 19.67.

1-Methyl-L-histidinol Dihydrochloride (**16a**). A mixture of **15** (19.0 g, 89 mmol) and 6M aq. HCl (360 ml) was refluxed for 8 h. After removal of the solvent, the colorless oily residue was crystallized from MeOH/Et_2O yielding 19.4 g (95%) of **16a**. M.p. 158–159°. $[\alpha]_D = -3.8$ ($c = 1.06$, MeOH). Enantiomeric purity > 97% ee (^{1}H-NMR; *Mosher* amide). IR (KBr): 3385*s* (br.), 3026*s* (br.), 2038*m* (br.), 1623*s*, 1556*m*, 1505*m*, 1402*w*, 1328*w*, 1168*m*,

1055*m*, 1000*w*, 836*m*, 622*m*. ^{1}H-NMR ((D$_6$)DMSO): 3.02 (*d*, *J* = 6.5, C*H*$_2$–Im); 3.47–3.52 (*m*, C*H*$_2$OH); 3.58–3.62 (*m*, C*H*$_2$OH); 3.82 (*s*, Me); 7.55 (*s*, H–C(5), Im); 8.36 (br. *s*, NH$_3$); 9.06 (*s*, H–C(2), Im). ^{13}C-NMR ((D$_6$)DMSO): 24.2 (*C*H$_2$–Im); 35.5 (MeN); 51.6 (*C*HCH$_2$OH); 60.0 (CH$_2$OH); 121.6 (C(5), Im); 128.3 (C(4), Im); 135.4 (C(2), Im). EI-MS: 156 (0.46), 125 (3), 124 (31, [*M* – CH$_2$OH]$^+$), 97 (10), 96 (100, [MeImCH$_2$ + H]$^+$), 95 (14), 81 (50, Im$^+$), 68 (9), FAB-MS: 156 (100, [*M* + H]$^+$). Anal. calc. for C$_7$H$_{13}$N$_3$O · 2 HCl: C 36.85, H 6.63, N 18.42; found: C 36.58, H 6.81, N 18.23.

*1-Methyl-*L*-histidinol* (**16b**). To a soln. of **15** (3.15 g, 14.8 mmol) in H$_2$O (160 ml) and MeOH (80 ml), Ba(OH)$_2$ · 8 H$_2$O (6.32 g, 33.4 mmol) was added, and the mixture was stirred at 90° for 48 h, having added more Ba(OH)$_2$ · 8 H$_2$O (3.0 g) after 24 h. The mixture was cooled to r.t., and solid CO$_2$ was added. After stirring for 2 h at r.t., the precipitated BaCO$_3$ was filtered off through a pad of *Celite*. The filtrate was evaporated and the resulting residue recrystallized from AcOEt yielding 2.0 g (88%) of **16b**. Colorless needles. M.p. 80–81°. $[\alpha]_D$ = – 7.2 (*c* = 1.04, MeOH). Enantiomeric purity > 98% ee (^{1}H-NMR, *Mosher* amide). IR (CHCl$_3$): 3342*s*, 3127*s*, 2912*s*, 1839*s*, 1603*m*, 1569*w*, 1510*s*, 1463*m*, 1427*m*, 1401*w*, 1364*w*, 1336*w*, 1304*w*, 1288*m*, 1235*w*, 1204*m*, 1181*m*, 1164*w*, 1104*m*, 1052*s*, 1021*m*, 996*m*, 954*s*, 894*s*, 833*s*, 793*m*, 771*m*, 699*w*, 623*s*, 532*m*. ^{1}H-NMR ((D$_6$)DMSO): 2.27 (*dd*, *J* = 14.2, 7.6, C*H*$_2$–Im); 2.51 (*dd*, *J* = 14.2, 5.3, C*H*$_2$–Im); 2.82–2.90 (*m*, CH); 3.0–3.5 (br. *s*, NH$_2$); 3.17 (*dd*, *J* = 10.3, 6.5, C*H*$_2$OH); 3.30 (*dd*, *J* = 10.3, 5.0, C*H*$_2$OH); 3.58 (*s*, MeN); 6.83 (*s*, H–C(2), Im); 7.43 (*s*, H–C(5), Im). ^{13}C-NMR ((D$_6$)DMSO): 32.6 (Me); 32.7 (*C*H$_2$–Im); 53.0 (*C*HCH$_2$OH); 66.2 (CH$_2$OH); 117.3 (C(5), Im); 137.1 (C(2), Im); 139.5 (C(4), Im). EI-MS: 125 (4), 124 (29, [*M* – CH$_2$OH + H]$^+$), 97 (8), 96 (100, $C_5H_8N_2^+$), 81 (29), 60 (8), 42 (18), 41 (5). CI-MS: 157 (8.4), 156 (100, [*M* + H]$^+$), 138 (7), 123 (5).

Mosher *Derivative for the Determination of the Enantiomeric Purity of* **16a** *and* **16b**. *General Procedure*. To a soln. of the free amino alcohol **16b** (0.1 mmol) in abs. MeOH (250 µl), Et$_3$N (14 µl, 10.1 mg, 0.1 mmol) and (–)-(*R*)-MTPA-Cl (18.6 µl, 0.1 mmol) were added (for the derivatization of the dihydrochloride **16a**, 0.32 mmol of Et$_3$N were used). The resulting mixture was stirred at r.t. for 24 h. The soln. was diluted with CH$_2$Cl$_2$ (5 ml), extracted with sat. aq. NaHCO$_3$ soln., dried (MgSO$_4$), and evaporated. The enantiomeric purity was determined by ^{1}H-NMR without further purification. Selected chemical shifts for diastereoisomeric derivatives: ^{1}H-NMR (CD$_3$OD): 6.60, 6.84 (H–C(5), Im); ^{13}C-NMR (CD$_3$OD): 64.34, 64.00 (CH$_2$OH); ^{19}F-NMR (CD$_3$OD): 2.36, 2.38 (CF$_3$, no baseline separation).

A prep. sample was synthesized from (–)-L-histidinol (**16b**; 0.2 mmol) and (–)-(*R*)-MTPA-Cl and purified by FC (1 × 20 cm, CH$_2$Cl$_2$/10M methanolic NH$_3$ 20:1): 50 mg (67%) of (αR)-N-*{(1S)-2-hydroxy-1-[(1-methyl-1*H*-imidazol-4-yl)methyl]ethyl}-α-methoxy-α-(trifluoromethyl)benzeneacetamide*. Colorless crystals. M.p. 164–165°. $[\alpha]_D$ = – 20.3 (*c* = 0.3, MeOH). IR (KBr): 3294*m*, 3148*m*, 3108*m*, 2997*w*, 2954*m*, 2919*w*, 2866*m*, 2735*w*, 2445*m*, 2334*m*, 1674*s*, 1556*w*, 1504*m*, 1469*m*, 1447*m*, 1436*m*, 1407*w*, 1382*w*, 1284*m*, 1227*m*, 178*s*, 1166*s*, 1153*s*, 1128*m*, 1101*s*, 1070*w*, 1034*w*, 1019*w*, 996*m*, 986*m*, 974*m*, 951*m*, 834*m*, 805*m*, 796*m*, 742*w*, 699*m*, 638*m*, 590*m*, 482*w*. ^{1}H-NMR (CD$_3$OD): 2.69 (*dd*, *J* = 14.9, 9.3, CH$_2$); 2.83 (*dd*, *J* = 14.9, 5.2, CH$_2$); 3.42 (*d*, *J* = 1.6, MeO); 3.56 (*s*, MeN); 3.60 (*dd*, *J* = 5.4, 2.1, CH$_2$OH); 4.22–4.30 (*m*, CH); 6.60 (*s*, H–C(5), Im); 7.33–7.42 (*m*, arom. H); 7.44 (*s*, H–C(2), Im). ^{19}F-NMR (CD$_3$OD): 2.36 (*s*, CF$_3$). ^{13}C-NMR (CD$_3$OD): 30.1 (*C*H$_2$–Im); 33.6 (MeN); 52.7 (CH); 55.5 (MeO); 64.3 (CH$_2$OH); 85.2 (*q*, *J*(C,F) = 26, CF$_3$*C*(Ph)(OMe)); 119.2 (H–C(5), Im); 125.2 (*q*, *J*(C,F) = 288, CF$_3$); 128.5, 129.1, 130.3 (arom. C); 134.3 (C(4), Im); 138.3 (C(2), Im); 139.1 (C(1), Ph); 167.9 (CONH). EI-MS: 374 (1.3), 373 (4.1), 372 (3.8, [*M* + H]$^+$), 341 (11), 189 (32), 184 (20), 183 (22), 182 (7), 164 (10), 139 (21), 138 (19) 111 (8), 110 (34), 109 (32), 105 (18), 98 (13), 97 (64), 96 (100, [*M* – Me–Im–CH$_2$ + H]$^+$), 95 (67), 82, (9), 81 (9), 77 (12), 69, (8), 68 (8), 42 (22).

5. *3,6-Bis[(4*R*)-4-benzyl-4,5-dihydrooxazol-2-yl]pyridazine* (**3**). *Pyridazine-3,6-dicarbonyl Dichloride* (**20**). To a suspension of **19** (5.0 g, 29.7 mmol) [14] in benzene (300 ml), one drop of DMF was added. After addition of oxalyl chloride (7.6 ml, 89.2 mmol), the mixture was refluxed until the gas evolution subsided (30 min). The solvent and excess oxalyl chloride was removed by distillation and the residue dried *in vacuo* 5.4 g (89%) of **20**. Light yellow needles. M.p. 208–210° (dec.). IR (KBr): 3458*w*, 3060*m*, 1735*s*, 1708*m* (sh), 1562*w*, 1356*m*, 1232*s*, 1204*m*, 1105*m*, 882*s*, 732*s*, 678*m*. ^{1}H-NMR (CDCl$_3$): 8.38 (*s*, CH). ^{13}C-NMR (CDCl$_3$): 128.3 (H–C(4), H–C(5)); 154.1 (C(3), C(6)); 168.3 (COCl). EI-MS: 206 (6.9), 204 (10.8, *M*$^+$), 172 (2), 171 (32), 170 (7), 169 (100, [*M* – Cl]$^+$), 85 (13), 78 (11, $C_4H_2N_2^+$), 77 (10), 65 (11), 63 (36, COCl), 53 (40), 51 (16), 50 (15), 49 (8). Anal. calc. for C$_6$H$_2$Cl$_2$N$_2$O$_2$: C 35.15, H 0.98, N 13.67; found: C 35.17, H 1.20, N 13.66.

N,N′-*Bis[(1*R*)-1-(hydroxymethyl)-2-phenylethyl]pyridazine-3,6-dicarboxamide* (**21**). (+)-(*R*)-Phenylalaninol (3.09 g, 20.5 mmol) and Et$_3$N (2.85 ml, 20.5 mmol) were dissolved in CHCl$_3$ (50 ml) under Ar. The soln. was chilled to 0°, and a soln. of **20** (1.67 g, 8.18 mmol) in CHCl$_3$ (50 ml) was added dropwise within 30 min. The mixture was stirred overnight at r.t., diluted with CH$_2$Cl$_2$ (150 ml), and extracted with sat. aq. NaHCO$_3$ soln. (150 ml). After further extraction of the aq. phase with CH$_2$Cl$_2$ (100 ml), the combined org. phase was dried (MgSO$_4$) and evaporated. The residue was recrystallized from CH$_2$Cl$_2$/pentane yielding 3.25 g (91%) of **21**.

Colorless plates. M.p. 173–175°. $[\alpha]_D = +170.7$ ($c = 0.48$, MeOH). IR ($CHCl_3$): 3630*w*, 3387*m*, 3066*w*, 3006*m*, 2940*w*, 1678*s*, 1602*w*, 1561*w*, 1516*s*, 1455*w*, 1415*w*, 1368*m*, 1368*w*, 1296*w*, 1165*w*, 1089*w*, 1037*w*, 914*w*, 880*w*. ^{1}H-NMR ((D_6)DMSO): 2.90, 2.99 (*AB* of *ABX*, $J_{AX} = 5.4$, $J_{BX} = 8.8$, $J_{AB} = 13.6$, PhCH_2); 3.50–3.55 (*m*, CH_2OH); 4.22–4.30 (*m*, *X* of *ABX*, CH); 4.98 (*s*, OH); 7.12–7.27 (*m*, arom. H); 8.26 (*s*, CH pyridazine); 8.88 (*d*, $J = 8.8$, NH). ^{13}C-NMR ((D_6)DMSO): 36.4 (PhCH_2); 53.2 (CH); 62.4 (CH_2OH); 126.0, 127.0, 128.2 (arom. C, Ph); 129.1 (C(4), C(5), pyridazine); 138.9 (C(1), Ph); 153.8 (C(3), C(6), pyridazine); 161.5 (CONH). EI-MS: 435 (2.4), 434 (8.0, M^+), 403 (19, $[M - CH_2OH]^+$), 344 (22), 343 (100, $[M - PhCH_2]^+$), 325 (15), 134 (9), 120 (8), 117 (9), 105 (12), 92 (18), 91 (98, $PhCH_2^+$), 79 (11), 65 (7). Anal. calc. for $C_{24}H_{26}N_4O_4$: C 66.34, H 6.03; found: C 66.48, H 6.00.

N,N′-*Bis[(1*R*)-1-(chloromethyl)-2-phenylethyl]pyridazine-3,6-dicarboxamide* (**22**). To a soln. of **21** (3.0 g, 6.9 mmol) in 1,2-dichloroethane (35 ml), $SOCl_2$ (3.5 ml) was added, and the resulting mixture was refluxed until the gas evolution subsided. After dilution with CH_2Cl_2 (150 ml), the mixture was extracted cautiously with sat. aq. Na_2CO_3 soln. (100 ml) and the aq. phase reextracted with additional CH_2Cl_2 (70 ml). The combined org. phase was dried ($MgSO_4$) and evaporated and the resulting light brown solid chromatographed (silica gel, 5 × 18 cm, AcOEt/hexane 1:3): 2.28 g (70%) of **22**. Colorless, crystalline solid. M.p. 180–182° (dec.). $[\alpha]_D = +84.3$ ($c = 0.6$, $CHCl_3$). IR ($CHCl_3$): 3384*m*, 3066*w*, 3006*m*, 2963*w*, 1727*m*, 1683*s*, 1602*w*, 1563*w*, 1514*s*, 1455*w*, 1436*w*, 1416*w*, 1375*w*, 1342*w*, 1292*m*, 1168*w*, 1135*w*, 1074*w*, 1046*w*, 898*w*, 879*w*, 842*w*. ^{1}H-NMR ($CDCl_3$): 3.10 (*d*, $J = 7.4$, PhCH_2); 3.65 (*dd*, $J = 11.4$, 3.6, CH_2Cl); 3.79 (*dd*, $J = 11.4$, 4.0, CH_2Cl); 4.69–4.77 (*m*, CH); 7.23–7.36 (*m*, CH, Ph); 8.40 (*d*, $J = 8.0$, NH); 8.45 (*s*, CH, pyridazine). ^{13}C-NMR ($CDCl_3$): 37.6 (PhCH_2); 46.3 (CH_2Cl); 51.3 (CH); 127.1, 127.2, 128.8 (arom. C); 129.2 (C(4), C(5), pyridazine); 136.5 (C(1), Ph); 153.3 (C(3), C(6), pyridazine); 161.2 (NC=O). EI-MS: 399 (11), 398 (39), 309 (9), 308 (17), 307 (88), 294 (7), 292 (21), 188 (11), 175 (10), 119 (11), 118 (9), 117 (20), 115 (12), 103 (12), 92 (12), 91 (100), 77 (10), 66 (15), 65 (17). FAB-MS (NBA): 474 (15), 473 (51), 472 (25), 471 (77, $[M + H]^+$), 379 (11, $[M - PhCH_2]^+$), 136 (9), 117 (21), 115 (9), 92 (8), 91 (100, $PhCH_2^+$), 89 (11), 77 (12), 39 (10). Anal. calc. for $C_{24}H_{24}Cl_2N_4O_2$: C 61.15, H 5.13, N 11.89; found: C 61.10, H 5.12, N 11.81.

*3,6-Bis[(4*R*)-4-benzyl-4,5-dihydrooxazol-2-yl]pyridazine* (**3**). To a soln. of **22** (2.0 g, 4.3 mmol) in anh. THF (100 ml), 0.5M NaOH/MeOH (17.2 ml, 8.6 mmol) was added. The resulting mixture was refluxed for 3 h and then most of the solvent removed by distillation. The residue was taken up in CH_2Cl_2 (200 ml) and extracted with aq. NaCl soln. (200 ml; sat. soln./H_2O 1:1). After reextraction of the aq. phase with CH_2Cl_2 (100 ml), the combined org. phase was dried ($MgSO_4$) and evaporated to give 1.26 g of crude product which was chromatographed (silica gel (4 × 15 cm), Et_2O/acetone 3:1): 1.06 g (62%) of **3** as colorless needles (in reactions on a larger scale (30 mmol), the yields decreased to 20–30% due to partial decomposition of the product on the column). M.p. 166–167°. $[\alpha]_D = +8.8$ ($c = 0.50$, $CHCl_3$). UV ($CHCl_3$): 277 (13700). IR ($CHCl_3$): 3066*w*, 3005*s*, 1644*s*, 1604*w*, 1584*w*, 1550*w*, 1496*m*, 1475*w*, 1454*m*, 1438*w*, 1406*m*, 1383*w*, 1357*s*, 1281*w*, 1260*m*, 1112*s*, 1042*w*, 1030*w*, 961*m*, 921*m*, 867*w*, 693*w*. ^{1}H-NMR ($CDCl_3$): 2.82 (*dd*, $J = 13.8$, 8.4, PhCH_2); 3.26 (*dd*, $J = 13.8$, 5.4, PhCH_2); 4.33 (*t*, $J = 8.0$, CH_2O); 4.56 (*t*, $J = 9.1$, CH_2O); 4.66–4.76 (*m*, CH); 7.22–7.34 (*m*, CH, Ph); 8.28 (*s*, CH, pyridazine). ^{13}C-NMR ($CDCl_3$): 41.5 (PhCH_2); 68.1 (CH); 73.0 (CH_2O); 126.7 (Ph); 127.1 (C(4), C(5), pyridazine); 128.6, 129.2 (Ph); 137.3 (C(1), Ph); 151.0 (C(3), C(6), pyridazine); 161.4 (C=N). EI-MS: 399 (14), 398 (47, M^+), 308 (19), 307 (100, $[M - PhCH_2]^+$), 279 (7), 216 (10), 188 (15), 133 (8), 132 (9), 119 (15), 117 (10), 103 (6), 94 (8), 92 (9), 91 (77, $PhCH_2^+$), 77 (8), 69 (10), 66 (21), 65 (13). Anal. calc. for $C_{24}H_{22}N_4O_2$: C 72.34, H 5.57, N 14.06; found: C 72.20, H 5.55, N 14.04.

6. *2,7-Bis[(4*S*)-4-benzyl-4,5-dihydrooxazol-2-yl]-1,8-naphthyridine* (**4a**). *1,8-Naphthyridine-2,7-dicarboxylic Acid* (**23**). A mixture of 1,8-naphthyridine-2,7-dicarboxaldehyde (4.11 g, 22.1 mmol) [15] and 80% nitric acid (100 ml) was refluxed for 3 h (caution!, evolution of NO and NO_2). After cooling to r.t., the mixture was poured on ice-water (200 ml) and the resulting homogeneous orange soln. treated with 30% aq. NaOH soln. until the product began to precipitate. After cooling in an ice-bath, the product was filtered off, washed with H_2O, and dried *in vacuo* yielding 3.53 g (73%) of **23** as pale yellow powder which was used without further purification. M.p. > 300°. IR ($CHCl_3$): 3054*m*, 3003*m*, 2849*m* (br.), 2552*m*, 1690*s*, 1601*m*, 1540*m*, 1505*w*, 1455*m*, 1435*s*, 1328*m*, 1289*s*, 1198*w*, 1167*m*, 1150*m*, 1135*m*, 1005*w*, 934*m*, 878*m*, 800*m*, 777*m*, 762*w*, 633*w*, 615*w*, 571*w*, 527*w*. ^{1}H-NMR ((D_6)DMSO): 3.0–3.8 (br. *s*, COOH); 8.30 (*d*, $J = 8.4$, H–C(3), H–C(6)); 8.77 (*d*, $J = 8.4$, H–C(4), H–C(5)). ^{13}C-NMR ((D_6)DMSO): 122.8 (C(3), C(6)); 124.9 (C(4a)); 139.3 (C(4), C(5)); 152.4 (C(2), C(7)); 153.5 (C(8a)); 165.8 (COOH). EI-MS: 174 (25, $[M - CO_2]^+$), 131 (9), 130 (100, $[M - 2\,CO_2]^+$), 129 (34), 128 (24), 104 (17), 103 (20), 102 (26), 79 (10), 77 (7), 76 (21), 75 (17), 51 (16), 50 (16), 44 (62, CO_2^+).

1,8-Naphthyridine-2,7-dicarbonyl Dichloride (**24**). As described for **20**, with (2.18 g, 10 mmol), benzene (100 ml), oxalyl chloride (2.6 ml, 30 mmol), and one drop of DMF: 2.04 g (80%) of **24**. Pale yellow needles. M.p. 245–248° (dec.). IR ($CHCl_3$): 3690*w*, 3005*m*, 1762*s*, 1721*s*, 1600*m*, 1545*m*, 1498*w*, 1425*w*, 1371*w*, 1323*m*, 1283*w*,

1140*m*, 1119*m*, 1009*m*, 867*s*, 853*s*. ^{1}H-NMR ($CDCl_3$): 8.37 (*d*, *J* = 8.5, H–C(3), H–C(6)); 8.58 (*d*, *J* = 8.5, H–C(4), H–C(5)). ^{13}C-NMR ($CDCl_3$): 123.2 (C(3), C(6)); 127.2 (C(4a)); 139.3 (C(4), C(5)); 152.9 (C(2), C(7)); 154.0 (C(8a)); 170.5 (COCl). EI-MS: 256 (2), 254 (3.3, M^+), 221 (24), 220 (8), 219 (76, $[M - Cl]^+$), 193 (32), 192 (10), 191 (100, $[M - COCl]^+$), 165 (8), 163 (27), 156 (5), 128 (29, $[M - 2\,COCl]^+$), 127 (10), 101 (22), 100 (12), 76 (10), 75 (12), 64 (18), 63 (12), 50 (15).

N,N′-*Bis[(1S)-1-(hydroxymethyl)-2-phenylethyl]-1,8-naphthyridine-2,7-dicarboxamide* (**25**). As described for **21**, with (–)-(*S*)-phenylalaninol (1.66 g, 11.0 mmol), Et_3N (1.74 ml, 12.5 mmol), $CHCl_3$ (30 ml), **24** (1.28 g, 5.0 mmol), and $CHCl_3$ (30 ml). Workup with CH_2Cl_2 (100 ml), sat. aq. $NaHCO_3$ soln. (100 ml), and CH_2Cl_2 (70 ml). The residue (2.46 g, > 99%) was anal. pure and used without further purification. M.p. 176–178°. $[\alpha]_D$ = – 194.0 (*c* = 1.89, $CHCl_3$). IR ($CHCl_3$): 3604*w*, 3382*m*, 3064*w*, 3005*m*, 2949*w*, 1670*s*, 1600*m*, 1528*s*, 1495*m*, 1455*w*, 1425*m*, 1373*w*, 1296*w*, 1162*w*, 1039*w*, 1872*m*. ^{1}H-NMR ($CDCl_3$): 3.13 (*d*, *J* = 7.7, PhCH_2); 3.10–3.40 (br. *s*, CH_2OH); 3.88 (*dd*, *J* = 11.6, 5.6, CH_2OH); 3.95 (*dd*, *J* = 11.6, 3.5, CH_2OH); 4.42–4.50 (*m*, CH); 7.17–7.36 (*m*, *Ph*CH_2); 8.02 (*d*, *J* = 8.4, H–C(3), H–C(6)); 8.14 (*d*, *J* = 8.4, H–C(4), H–C(5)); 8.58 (*d*, *J* = 8.5, NH). ^{13}C-NMR ($CDCl_3$): 37.1 (PhCH_2); 53.9 (CH); 63.5 (CH_2OH); 121.1 (C(3), C(6)); 124.6 (C(4a)); 126.6, 128.6, 129.3 (CH, Ph); 137.8 (C(4), C(5)); 138.2 (C(1), Ph); 151.9 (C(8a)); 153.7 (C(2), C(7)); 163.7 (CONH). EI-MS: 484 (4.3, M^+), 454 (6), 453 (20, $[M - CH_2OH]^+$), 394 (24), 393 (100, $[M - PhCH_2]^+$), 375 (16), 219 (8), 216 (15), 212 (7), 172 (7), 130 (12), 129 (26), 128 (21), 91 (38, $PhCH_2^+$). FAB-MS: 487 (7), 486 (37), 485 (100, $[M + H]^+$), 393 (15), 173 (8), 172 (13).

N,N′-*Bis[(1S)-1-(chloromethyl)-2-phenylethyl]-1,8-naphthyridine-2,7-dicarboxamide* (**26**). As described for **22**, with **25** (2.18 g, 4.5 mmol), 1,2-dichloroethane (25 ml), and $SOCl_2$ (2.3 ml). Workup with CH_2Cl_2 (100 ml), sat. aq. Na_2CO_3 soln. (100 ml), and CH_2Cl_2 (70 ml). The combined org. phase was dried ($MgSO_4$) and evaporated. Chromatography (silica gel (5 × 18 cm), AcOEt/hexane 1:1) gave 1.80 g (77%) of **25**. Colorless, crystalline solid. M.p. 173–174° (dec.). $[\alpha]_D$ = – 48.8 (*c* = 1.67, $CHCl_3$). IR ($CHCl_3$): 3379*m*, 3006*m*, 1677*s*, 1600*m*, 1522*s*, 1492*m*, 1425*m*, 1166*w*. ^{1}H-NMR ($CDCl_3$): 3.18 (*d*, *J* = 7.8, PhCH_2); 3.68 (*dd*, *J* = 11.3, 3.8, CH_2Cl); 3.82 (*dd*, *J* = 11.3, 4.3, CH_2Cl); 4.71–4.78 (*m*, CH); 7.24–7.38 (*m*, Ph); 8.44 (*d*, *J* = 8.4, H–C(3), H–C(6)); 8.49 (*d*, *J* = 8.4, H–C(4), H–C(5)); 8.58 (*d*, *J* = 8.8, NH). ^{13}C-NMR ($CDCl_3$): 37.7 (PhCH_2); 46.2 (CH_2Cl); 51.5 (CH); 121.2 (C(3), C(6)); 125.5 (C(4a)); 127.0, 128.8, 129.3 (CH, Ph); 136.7 (C(1), Ph); 138.9 (C(4), C(5)); 152.7 (C(8a)); 153.4 (C(2), C(7)); 163.1 (CONH). EI-MS: 452 (12), 450 (15, $[M - 2\,Cl]^+$), 362 (8), 361 (32), 359 (11), 357 (9), 117 (13), 92 (38), 91 (100, $PhCH_2^+$). FAB-MS: 525 (13), 524 (23), 523 (70), 522 (37), 521 (100, $[M + H]^+$), 431 (9), 429 (13, $[M - PhCH_2]^+$), 325 (11), 219 (9), 129 (12), 128 (14), 117 (16), 115 (8), 91 (73, $PhCH_2^+$), 77 (10). Anal. calc. for $C_{28}H_{26}Cl_2N_4O_2$: C 64.50, H 5.03, N 10.74; found: C 64.20, H 5.07, N 10.73.

2,7-Bis[(4S)-4-benzyl-4,5-dihydrooxazol-2-yl]-1,8-naphthyridine (**4a**). As described for **3**, with **26** (1.52 g, 2.91 mmol), THF (70 ml), and 0.5M methanolic NaOH (11.6 ml, 5.8 mmol; 1 h). Workup with CH_2Cl_2 (150 ml), and aq. NaCl soln. (150 ml), and CH_2Cl_2 (100 ml). Chromatography (silica gel (4 × 10 cm), CH_2Cl_2/10M methanolic NH_3 20:1) gave 1.20 g (92%) of **4a**. Colorless powder. M.p. 274–276° (dec.). $[\alpha]_D$ = – 102.8 (*c* = 0.62, $CHCl_3$). UV ($CHCl_3$): 344 (18500), 329 (16700). IR (KBr): 3084*w*, 3056*m*, 3023*m*, 2918*m*, 1948*w*, 1879*w*, 1809*w*, 1628*s*, 1600*s*, 1535*m*, 1512*m*, 1496*m*, 1451*m*, 1444*m*, 1372*s*, 1298*m*, 1246*m*, 1124*s*, 1094*s*, 1023*m*, 985*m*, 960*m*, 873*m*, 817*m*, 777*m*, 733*s*, 698*s*, 620*w*, 571*w*, 538*w*, 504*w*. ^{1}H-NMR ($CDCl_3$): 2.82 (*dd*, *J* = 13.8, 8.5, PhCH_2); 3.28 (*dd*, *J* = 13.8, 5.5, PhCH_2); 2.30 (*t*, *J* = 8.1, CH_2O); 4.53 (*t*, *J* = 9.1, CH_2O); 4.67–4.77 (*m*, CH); 7.21–7.35 (*m*, CH, Ph); 8.30 (*d*, *J* = 8.5, H–C(3), H–C(6)); 8.36 (*d*, *J* = 8.5, H–C(4), H–C(5)). ^{13}C-NMR ($CDCl_3$): 41.6 (PhCH_2); 68.2 (CH); 72.7 (CH_2O); 122.8 (C(3), C(6)); 124.1 (C(4a)); 126.6, 128.5, 129.2 (CH, Ph); 137.3 (C(4), C(5)); 137.6 (C(1), Ph); 150.7 (C(2), C(7)); 154.6 (C(8a)); 163.3 (OC=N). EI-MS: 450 (9), 449 (15), 448 (34, M^+), 359 (23), 358 (25), 357 (100, $[M - PhCH_2]^+$), 355 (18), 329 (12), 327 (10), 289 (8), 183 (11), 169 (32), 91 (37, $PhCH_2^+$). Anal. calc. for $C_{28}H_{24}N_4O_2$: C 74.98, H 5.39, N 12.49; found: C 74.70, H 5.47, N 12.56.

7. *2,7-Bis{(4S)-4,5-dihydro-4-[(1-methyl-1H-imidazol-4-yl)methyl]oxazol-2-yl}-1,8-naphthyridine* (**4b**). N,N′-*Dihydroxy-1,8-naphthyridine-2,7-dicarbaldehyde Dioxime* (**28**). To a suspension of **27** (372 mg, 2.0 mmol) [15] in EtOH/H_2O 1:1 (2 ml), a soln. of $NH_2OH \cdot HCl$ (278.0 mg, 4 mmol) and anh. $NaHCO_3$ (336 mg, 4 mmol) in H_2O (2.0 ml) were added with vigorous stirring. The dark brown mixture was stirred at 90° for 1 h and, after cooling to r.t., neutralized with 5% aq. NaOH soln. The precipitated product was filtered off, washed with H_2O, and dried *in vacuo*: 383 mg (89%) of **28**. Brown powder. M.p. 237–239° (dec.). IR (KBr): 3161*s*, 3075*s*, 2999*s*, 2867*s*, 2763*s* (all br.), 1607*s*, 1596*s*, 1538*m*, 1511*s*, 1398*m*, 1288*m*, 1206*w*, 1136*m*, 1122*m*, 994*s*, 944*m*, 852*s*, 812*m*, 781*m*, 688*w*, 648*m*, 629*w*, 614*w*, 596*m*, 517*w*, 468*w*. ^{1}H-NMR ((D_6)DMSO): 8.03 (*d*, *J* = 8.4, H–C(3), H–C(6)); 8.25 (*s*, HC=N); 8.47 (*d*, *J* = 8.4, H–C(4), H–C(5)); 12.12 (*s*, C=NOH). ^{13}C-NMR ((D_6)DMSO): 118.6 (C(3), C(6)); 122.5 (C(4a)); 137.9 (C(4), C(5)); 149.1 (C(2), C(7)); 155.1 (C(8a)); 155.8 (HC=NOH). EI-MS: 217 (13), 216 (100, M^+), 199 (8), 198 (54, $[M - H_2O]^+$), 180 (36), 173 (42, $[M - HC{=}NO]^+$), 172 (32), 168 (17), 156 (16),

155 (68, $[M - H_2O - HC{=}NO]^+$), 154 (21), 143 (16), 142 (27), 141 (42), 129 (16), 128 (30), 127 (24), 116 (11), 115 (11), 114 (16), 102 (14), 101 (20), 100 (21), 76 (25), 75 (21), 64 (15), 63 (14), 52 (11), 51 (15), 50 (23).

1,8-Naphthyridine-2,7-dicarbonitrile (**29**). A soln. of **27** (4.73 g, 25.4 mmol) [15] and $NH_2OH \cdot HCl$ (3.83 g, 55.1 mmol) in DMSO (160 ml) was stirred for 35 min at 110°. The mixture was subsequently diluted with ice-water (250 ml) and the precipitate filtered off. The crude product was dissolved in acetone, refluxed with charcoal for 15 min, and filtered hot through a pad of *Celite*. After cooling to r.t., the product was precipitated by addition of Et_2O. The purification procedure was repeated affording 1.83 g (40%; purity by NMR, 90%) of **29** as pale-brown solid which is poorly soluble in all common solvents. An anal. sample was obtained by chromatography (silica gel (2 × 15 cm), 180 mg of dinitrile, AcOEt/hexane 1:1 → AcOEt): 98 mg (55%) of **29**. R_f (hexane/AcOEt 1:1) 0.13. M.p. 240–242° (dec.). ^{1}H-NMR ((D$_6$)DMSO): 8.33 (*d*, *J* = 8.4, H–C(3), H–C(6)); 8.93 (*d*, *J* = 8.4, H–C(4), H–C(5)). ^{1}H-NMR ($CDCl_3$): 7.96 (*d*, *J* = 8.4, H–C(3), H–C(6)); 8.51 (*d*, *J* = 8.4, H–C(4), H–C(5)). ^{13}C-NMR ((D$_6$)DMSO): 116.7 (C≡N); 125.1 (C(4a)); 126.9 (C(3), C(6)); 140.8 (C(4), C(5)); 148.7 (C(2), C(7)); 153.5 (C(8a)). EI-MS: 181 (12), 180 (100, M^+), 155 (40, $[M + H - CN]^+$), 154 (17), 153 (8), 129 (7), 128 (17, $[M - 2\,CN]^+$), 127 (9), 101 (15), 100 (9), 76 (9), 75 (10), 50 (11).

Dimethyl 1,8-Naphthyridine-2,7-dicarboximidate (**30**). A mixture of **29** (1.34 g, 7.43 mmol) and NaOMe (800 mg, 14.86 mmol) in MeOH (110 ml) was refluxed for 2 h. After concentration *in vacuo* to half of the volume, the soln. was diluted with CH_2Cl_2 (280 ml), extracted with Na_2CO_3 soln. (50 ml; sat. soln./H_2O 1:1) and washed with sat. aq. NaCl soln. (60 ml). The combined org. phase was dried ($MgSO_4$), and after evaporation, the residue was recrystallized from CH_2Cl_2/pentane: 788 mg (43%) of **30**. Pale yellow plates. M.p. 232–237° (dec.). IR ($CHCl_3$): 3294*m*, 3004*w*, 1650*s*, 1598*m*, 1534*m*, 1448*s*, 1422*m*, 1350*s*, 1293*w*, 1198*m*, 1167*m*, 1125*w*, 1068*s*, 1014*m*, 967*w*, 909*m*, 856*m*, 810*m*, 782*m*, 742*m*. ^{1}H-NMR ($CDCl_3$): 1.57 (*s*, MeO); 8.15 (*d*, *J* = 8.4, H–C(3), H–C(6)); 8.40 (*d*, *J* = 8.4, H–C(4), H–C(5)); 9.64 (*s*, NH). ^{13}C-NMR ($CDCl_3$): 54.3 (MeO); 120.3 (C(3), C(6)); 124.0 (C(4a)); 138.8 (C(4), C(5)); 151.5 (C(2), C(7)); 154.0 (C(8a)); 165.5 (C=NH). EI-MS: 244 (17, M^+), 214 (38, $[M + H - OMe]^+$), 213 (21), 188 (7), 187 (68, $[M + H - C(=NH)OMe]^+$), 186 (7), 182 (16), 181 (56), 180 (25), 156 (16), 155 (100, $[C_8H_4N_2 - (C=NH)]^+$), 154 (30), 129 (15), 128 (17, $C_8H_4N_2^+$), 127 (13), 102 (9), 101 (12), 100 (9), 76 (11), 75 (9), 58 (22), 50 (8).

*2,7-Bis{(4S)-4,5-dihydro-4-[(1-methyl-1*H*-imidazol-4-yl)methyl]oxazol-2-yl}-1,8-naphthyridine* (**4b**). A soln. of **30** (611 mg, 2.50 mmol), dihydrochloride **16a** (1.43 g, 6.25 mmol), and NaOMe (674 mg, 12.5 mmol) in MeOH (15 ml) was refluxed for 2 h under Ar. After cooling to r.t., the mixture was diluted with CH_2Cl_2 (15 ml) and extracted with sat. aq. Na_2CO_3 soln. (20 ml). The aq. phase was reextracted with CH_2Cl_2 (3 × 20 ml), the combined org. phase dried ($MgSO_4$) and evaporated, and the crude product chromatographed (silica gel (3 × 18 cm), CH_2Cl_2/10M methanolic NH_3 12:1): 435 mg (38%) of **4b** as colorless powder. An anal. sample was prepared by recrystallization from EtOH/Et_2O. M.p. 258–260° (dec.). $[\alpha]_D = -112.4$ (*c* = 0.53, MeOH). $[\alpha]_D = -150.8$ (*c* = 0.12, $CHCl_3$). UV ($CHCl_3$): 344 (21500), 329 (20000). IR ($CHCl_3$): 3412*m* (br.), 3108*m*, 3021*m*, 2921*m*, 1629*s*, 1600*s*, 1535*m*, 1508*s*, 1468*m*, 1444*m*, 1419*m*, 1370*s*, 1349*m*, 1300*m*, 1255*m*, 1233*m*, 1192*w*, 1173*m*, 1157*w*, 1123*s*, 1101*m*, 1028*m*, 983*m*, 948*m*, 918*w*, 973*m*, 818*m*, 773*m*, 737*m*, 621*m*, 576*w*, 535*m*. ^{1}H-NMR ($CDCl_3$): 2.83 (*dd*, *J* = 14.5, 8.0, CH_2–Im); 3.17 (*dd*, *J* = 14.5, 5.4, CH_2–Im); 3.63 (*s*, Me); 4.38 (*t*, *J* = 8.2, CH_2O); 4.61 (*t*, *J* = 9.0, CH_2O); 4.73–4.82 (*m*, CH); 6.74 (*s*, H–C(4), Im); 7.36 (*s*, H–C(2), Im); 8.28 (*d*, *J* = 8.5, H–C(3), H–C(6), naphthyridine); 8.36 (*d*, *J* = 8.5, H–C(4), H–C(5), naphthyridine). ^{13}C-NMR ($CDCl_3$): 33.3, (Me); 34.3 (CH_2–Im); 67.1 (CH); 73.1 (CH_2O); 117.7 (C(4), Im); 122.9 (C(3), C(6), naphthyridine); 124.1 (C(4a)); 137.3, 137.4 (C(4), C(5), naphthyridine; C(2), Im); 138.9 (C(5), Im); 150.9 (C(2), C(7)); 154.6 (C(8a)); 163.4 (C=N). FAB-MS (NBA): 459 (7), 458 (36), 457 (100, $[M + H]^+$), 456 (13), 361 (7, $[M - (CH_2$–Im) – Me$]^+$), 164 (17), 149 (17), 121 (13), 109 (9), 107 (8), 96 (26), 95 (37), 77 (13), 51 (10).

8. *1,3-Bis{(2S)-2-{{[(*tert*-butyl)dimethylsilyl]oxy}methyl}-3,4-dihydro-2*H*-pyrrol-5-yl}imidazolidin-2-one* (**5a**). N,N′-*Bis[(2S)-2-{{[(*tert*-butyl)dimethylsilyl]oxy}methyl}-3,4-dihydro-2*H*-pyrrol-5-yl]ethane-1,2-diamine Dihydrochloride* (**32**). A mixture of (2*S*)-2-{{[(*tert*-butyl)dimethylsilyl]oxy}methyl}-2-(methylthio)-2*H*-pyrrole (**31**; 6.46 g, 24.9 mmol) [8] and ethane-1,2-diamine dihydrochloride (1.66 g, 1.2 mmol) in anh. MeOH (100 ml) was refluxed for 2 h to give a homogeneous soln. After evaporation, the residue was recrystallized from CH_2Cl_2/Et_2O: 4.92 g (71 %) of **32**. Colorless solid. M.p. 284–286° (dec.). $[\alpha]_D = -67.4$ (*c* = 1.18, MeOH). IR (KBr): 3010*s*, 2953*s*, 2928*s*, 2858*s*, 1672*s*, 1577*w*, 1271*m*, 1462*m*, 1413*w*, 1386*w*, 1360*w*, 1342*w*, 1308*m*, 1251*m*, 1175*w*, 1126*m*, 1080*m*, 1034*m*, 1005*w*, 966*w*, 879*m*, 882*m*, 837*m*, 777*m*. ^{1}H-NMR ($CDCl_3$): 0.017 (*s*, 2 MeSi); 0.022 (*s*, 2 MeSi); 0.82 (*s*, *t*-Bu); 2.04–2.19 (*m*, CH_2(4), CH_2(4′)); 2.91–2.99 (*m*, CH_2(3), CH_2(3′)); 3.66–3.78, 3.81–3.86 (2*m*, NCH_2CH_2N, CH_2OSi); 4.10–4.13 (*m*, CH); 10.30 (br. *s*, NH_2Cl); 10.89 (br. *s*, NH_2Cl). ^{13}C-NMR ($CDCl_3$): −5.6 (2 MeSi); −5.4 (2 MeSi); 17.9 (2 *t*-BuSi); 23.0 (CH_2(4), CH_2(4′)); 25.6 (2 Me_3C); 31.0 (CH_2(3), CH_2(3′)); 42.3 (NCH_2CH_2N); 61.7 (2 CH); 64.2 (2 CH_2OSi); 168.4 (C=N, C(2), C(2′)). EI-MS: 483 (0.5, $[M + H]^+$), 425 (15, $[M - C_4H_9]^+$), 338 (25), 337 (100, $[M - CH_2OSiMe_2(t\text{-Bu})]^+$), 242 (8), 241 (11), 230 (8), 229 (48), 184 (7),

109 (15), 75 (8), 73 (15). FAB-MS (NBA): 485 (14), 484 (38), 483 (100, $[M + H]^+$), 255 (9), 229 (12), 109 (8), 83 (9), 72 (22). Anal. calc. for $C_{24}H_{50}N_4O_2Si_2 \cdot 2$ HCl: C 51.87, H 9.43, N 10.08; found: C 51.52, H 9.13, N 9.99.

*1,3-Bis{(2S)-2-{{[(*tert*-butyl)dimethylsilyl]oxy}methyl}-3,4-dihydro-2*H*-pyrrol-5-yl}imidazolidin-2-one* (**5a**). To a suspension of **32** (535 mg, 0.96 mmol) in anh. THF (10 ml), MeMgCl (1.41 ml, 4.1 mmol; 2.9 M in THF) was gradually added under Ar. To the resulting colorless homogeneous mixture, a soln. of 1,1′-carbonylbis[1*H*-imidazole] (243.2 mg, 1.5 mmol) in anh. THF (6 ml) was added at r.t. After stirring overnight, the slurry was diluted with CH_2Cl_2 (50 ml), extracted with sat. aq. $NaHCO_3$ soln. (50 ml), and the aq. phase reextracted wtih CH_2Cl_2 (30 ml). The combined org. phase was dried ($MgSO_4$) and evaporated. The residue was chromatographed (silica gel (3 × 18 cm), acetone/(*tert*-butyl) methyl ether 1:20): 326 mg (66%) of **5a**. Colorless solid. M.p. 82–84°. $[\alpha]_D = +43.0$ ($c = 0.8$, $CHCl_3$). IR (KBr): 2952*m*, 2928*m*, 2900*m*, 2856*m*, 1720*s*, 1685*w*, 1620*s*, 1485*m*, 1471*w*, 1414*s*, 1361*m*, 1309*w*, 1257*m*, 1199*w*, 1129*m*, 1093*m*, 1079*m*, 1006*m*, 938*w*, 878*m*, 837*m*, 779*m*, 747*m*, 718*w*, 668*w*. ^{1}H-NMR ($CDCl_3$): 0.0 (*s*, 2 MeSi); 0.02 (*s*, 2 MeSi); 0.84 (*s*, 2 *t*-BuSi); 1.88–1.93 (*m*, 2 H, CH_2(4), CH_2(4′)); 2.02–2.08 (*m*, 2 H, CH_2(4), CH_2(4′)); 2.99–3.06 (*m*, CH_2(3), CH_2(3′)); 3.51 (*dd*, $J = 10.0$, 3.9, CH_2OSi); 3.76 (*dd*, $J = 10.0$, 5.7, CH_2OSi); 3.87 (*s*, CH_2, imidaz.); 3.95–3.99 (*m*, CH). ^{13}C-NMR ($CDCl_3$): −5.34 (2 MeSi); −5.31 (2 MeSi); 18.3 (2 Me_3CSi); 25.84 (CH_2(4), H_2C(4′)); 25.87 (2 Me_3CSi); 33.0 (CH_2(3), CH_2(3′)); 41.2 (2 CH_2, imidaz.); 66.6 (2 CH_2OSi); 68.8 (2 CH); 153.3 (C=O); 163.3 (C=N). EI-MS: 493 (6, $[M - Me]^+$), 453 (12), 452 (32), 451 (100, $[M - t\text{-Bu}]^+$), 364 (19), 363 (80, $[M - CH_2OSiMe_2(t\text{-Bu})]^+$), 197 (26), 73 (11). CI-MS: 511 (14), 510 (38), 509 (100, $[M + H]^+$), 451 (9), 363 (7), 214 (10). Anal. calc. for $C_{25}H_{48}N_4O_3Si_2$: C 59.01, H 9.51, N 11.01; found: C 59.05, H 9.29, N 10.88.

9. *1,3-Bis{(2S)-2-{{[(*tert*-butyl)dimethylsilyl]oxy}methyl}-3,4-dihydro-2*H*-pyrrol-5-yl}imidazolidine-2-thione* (**5b**). To a suspension of **32** (500 mg, 0.89 mmol) in anh. THF (10 ml), MeMgCl (1.32 ml, 4.1 mmol; 2.9M in THF) was added dropwise under Ar. To the resulting colorless homogeneous mixture, a soln. of 1,1′-carbonothioylbis[1*H*-imidazole] (249.5 mg, 1.39 mmol) in THF (6 ml) was added. After stirring overnight at r.t., the slurry was diluted with CH_2Cl_2 (50 ml) and extracted with sat. aq. $NaHCO_3$ soln. (50 ml), the aq. phase reextracted with CH_2Cl_2 (30 ml), the combined org. phase dried ($MgSO_4$) and evaporated, and the residue chromatographed (bas. alumina (3 × 18 cm), acetone/*t*-BuOMe 1:20): 273 mg (58%) of **5b**. Pale yellow wax. M.p. 84–85°. $[\alpha]_D = +90.6$ ($c = 0.37$, $CHCl_3$). IR (KBr): 2953*m*, 2928*m*, 2894*m*, 2855*m*, 1734*w*, 1596*s*, 1472*m*, 1431*m*, 1399*s*, 1350*m*, 1312*m*, 1256*s*, 1192*m*, 1164*w*, 1126*m*, 1089*s*, 1042*m*, 1030*m*, 1006*m*, 988*w*, 938*w*, 837*s*, 777*m*, 670*w*, 630*w*, 567*w*, 539*w*. ^{1}H-NMR ($CDCl_3$): −0.01 (*s*, 2 MeSi); 0.01 (*s*, 2 MeSi); 0.83 (*s*, 2 *t*-BuSi); 1.85–1.93 (*m*, 2 H, CH_2(4), CH_2(4′)); 2.00–2.09 (*m*, 2 H, CH_2(4), CH_2(4′)); 3.39 (*t*, $J = 8.0$, CH_2(3), CH_2(3′)); 3.52 (*dd*, $J = 10.0$, 5.7, CH_2OSi); 3.74 (*dd*, $J = 10.0$, 3.9, CH_2OSi); 3.86–3.96 (*m*, CH); 4.04 (*s*, CH_2, imidaz.). ^{13}C-NMR ($CDCl_3$): −5.3 (4 MeSi); 18.3 (2 Me_3CSi); 25.9 (2 Me_3CSi); 26.6 (2 CH_2(4), CH_2(4′)); 35.6 (2 CH_2(3), CH_2(3′)); 46.5 (2 CH_2, imidaz.); 66.4 (2 CH_2OSi); 68.3 (2 CH); 165.6 (C=S); 178.4 (C=N). EI-MS: 525 (9), 524 (22, M^+), 509 (6, $[M - Me]^+$), 468 (13), 467 (36, $[M - t\text{-Bu}]^+$), 451 (10), 381 (11), 380 (27), 379 (100, $[M - CH_2OSiMe_2(t\text{-Bu})]^+$), 363 (8), 75 (7), 73 (30), 59 (8). Anal. calc. for $C_{25}H_{48}N_4O_2SSi_2$: C 57.20, H 9.22, N 10.67; found: C 57.41, H 9.11, N 10.61.

REFERENCES

[1] For general reviews, see N. Sträter, W. N. Lipscomb, T. Klabunde, B. Krebs, *Angew. Chem.* **1996**, *108*, 2159; *ibid., Int. Ed. Engl.* **1996**, *35*, 2024; 'Mechanistic Bioinorganic Chemistry', Eds. H. H. Thorp and V. L. Pecoraro, ACS, Washington, DC, 1995, Vol. 246; for reviews on specific metalloenzymes, see *e.g.* 'Bioinorganic Chemistry of Copper', Eds. K. D. Karlin and Z. Tyeklár, Chapman & Hall, New York-London, 1993; A. C. Rosenzweig, X. Feng, S. J. Lippard, in 'Applications of Enzyme Biotechnology', Eds. J. W. Kelly and T. O. Baldwin, Plenum, New York, 1991, pp. 69.

[2] M. Sawamura, H. Nagata, H. Sakamoto, Y. Ito, *J. Am. Chem. Soc.* **1992**, *114*, 2586.

[3] R. Guilard, S. Brandès, C. Tardieux, A. Tabard, M. L'Her, C. Miry, P. Gouerec, Y. Knop, J. P. Collman, *J. Am. Chem. Soc.* **1995**, *117*, 11721.

[4] M. Reilly, T. Oh, *Tetrahedron Lett.* **1995**, *36*, 217; K. Nozaki, M. Yoshida, H. Takaya, *Angew. Chem.* **1994**, *106*, 2574; *ibid., Int. Ed. Engl.* **1994**, *33*, 2452.

[5] M. E. Broussard, B. Juma, S. G. Train, W.-J. Peng, S. A. Laneman, G. G. Stanley, *Science* **1993**, *260*, 1784; S. A. Laneman, G. G. Stanley, in 'Homogeneous Transition Metal Catalyzed Reactions', Ed. W. R. Moser and D. W. Slocum, American Chemical Society, 1992, pp. 349.

[6] A. Abiko, S. Masamune, *Tetrahedron Lett*, **1992**, *33*, 5517; M. J. McKennon, A. I. Meyers, *J. Org. Chem.* **1993**, *58*, 3568.

[7] Reviews: A. Pfaltz, *Acta Chem. Scand.* **1996**, *50*, 189; A. Pfaltz, *Acc. Chem. Res.* **1993**, *26*, 339.

[8] U. Leutenegger, G. Umbricht, C. Fahrni, P. von Matt, A. Pfaltz, *Tetrahedron* **1992**, *48*, 2143.
[9] Synthesis of dihydrooxazoles starting from carboxylic acids: a) H. Vorbrüggen, K. Krolikiewicz, *Tetrahedron* **1993**, *49*, 9353; H. Vorbrüggen, K. Krolikiewicz, *Tetrahedron Lett.* **1981**, *22*, 4471; b) H. Nishiyama, M. Kondo, T. Nakamura, K. Itoh, *Organometallics* **1991**, *10*, 500; D. A. Evans, K. A. Woerpel, M. M. Hinman, M. M. Faul, *J. Am. Chem. Soc.* **1991**, *113*, 726; from nitriles: c) H. Witte, W. Seeliger, *Liebigs Ann. Chem.* **1974**, 996; C. Bolm, K. Weickhardt, M. Zehnder, T. Ranff, *Chem. Ber.* **1991**, *124*, 1173; from imidic esters: d) K. Mori, Y. Funaki, *Tetrahedron* **1985**, *41*, 2379; A. I. Meyers, R. J. Himmelsbach, *J. Am. Chem. Soc.* **1985**, *107*, 682; e) S. Gladiali, L. Pinna, G. Delogu, E. Graf, H. Brunner, *Tetrahedron: Asymmetry* **1990**, *1*, 937; from carboxylic acid esters: f) R. E. Lowenthal, A. Abiko, S. Masamune, *Tetrahedron Lett.* **1990**, *31*, 6005; from aziridines: g) G. S. Bates, M. A. Varelas, *Can. J. Chem.* **1980**, *58*, 2562.
[10] R. B. Chapas, R. D. Knudsen, R. F. Nystrom, H. R. Snyder, *J. Org. Chem.* **1975**, *40*, 3746.
[11] K. Brychcy, K. Dräger, K.-J. Jens, M. Tilset, U. Behrens, *Chem. Ber.* **1994**, *127*, 465.
[12] S. H. Bertz, *Synthesis* **1980**, 708; V. Prelog, O. Metzler, O. Jeger, *Helv. Chim. Acta* **1947**, *30*, 675.
[13] A. Noordam, L. Maat, H. C. Beyerman, *Recl. Trav. Chim. Pay-Bas* **1978**, *97*, 293.
[14] S. Sueur, M. Lagrenee, F. Abraham, C. Bremard, *J. Heterocycl. Chem.* **1987**, *24*, 1285.
[15] C. J. Chandler, L. W. Deady, J. A. Reiss, V. Tzimos, *J. Heterocycl. Chem.* **1982**, *19*, 1017.
[16] K. Friedrich, K. Wallenfels, 'The Chemistry of the Cyano Group', Ed. Z. Rappoport, Intersience, New York, 1970; D. T. Mowry, *Chem. Rev.* **1948**, *42*, 189.
[17] P. Audoye, A. Gaset, J.-P. Gorrichon, *Chimia* **1982**, *36*, 4.
[18] C. J. Fahrni, A. Pfaltz, M. Neuburger, M. Zehnder, *Helv. Chim. Acta* **1998**, *81*, 507.

Received September 15, 1997