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Synthesis of dihydrooxazole analogues derived from linezolid

Jürgen Einsiedel,[a] Christoph Schoerner[b] and Peter Gmeiner[a,*]

[a]*Department of Medicinal Chemistry, Emil Fischer Center, Friedrich Alexander University, Schuhstraße 19, D-91052 Erlangen, Germany*
[b]*Institute of Clinical Microbiology, Immunology and Hygiene, Friedrich Alexander University, Wasserturmstraße 3, D-91054 Erlangen, Germany*

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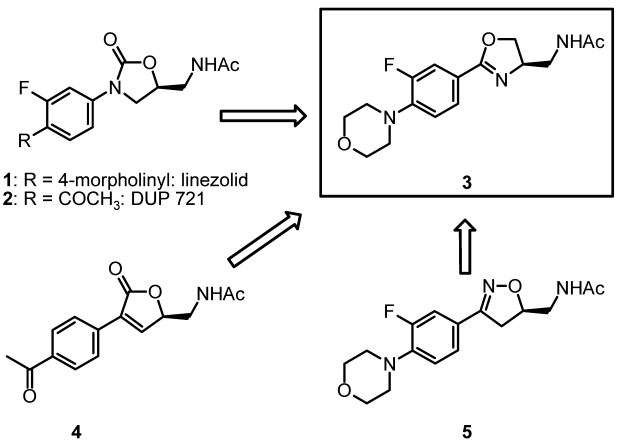
Dedicated to Professor H.-D. Stachel on the occasion of his 75th birthday

Abstract—Starting from (*S*)-serine, the linezolid analogue **3** with dihydrooxazole partial structure was synthesized and pharmacologically investigated. With the help of MEP comparisons structural requirements for antibacterial activity were evaluated.

1. Introduction

The bioisosteric replacement of functional groups in receptor ligands, enzyme inhibitors or antimetabolites has become a promising strategy for the design of new drug candidates.[1] Thus, a modification of target affinity, activity, selectivity and lipophilicity can be beneficial for the reduction of side effects and an increase of bioavailability. The value of this principle was also demonstrated by our recent investigations in the field of dopamine receptor ligands, when bioisosteric exchanges led to highly selective dopamine D4 antagonists,[2] D3 agonists[3] and partial agonists.[4]

To exploit our ex-chiral pool approach to aminomethyl substituted dihydrooxazoles[5] for structure activity relationship studies in the field of antibiotics, we chose linezolid (**1**),[6] a recently introduced antibiotic incorporating an oxazolidinone substructure, as a pharmacological lead. SAR studies on linezolid, being employed as the more active (*S*)-enantiomer, were chiefly carried out by modification of the 5-acetamidomethyl side chain[7] and exchange of the morpholine moiety.[8] With respect to structural variations of the heterocyclic core unit, the bioactive butenolid derivative **4** is described,[9] demonstrating, that the carbamate nitrogen can be replaced by the bioisosteric sp^2-carbon without losing the antibacterial activity compared to the oxazolidinone analogue DUP 721 (**2**).[10] Furthermore, the dihydroisoxazole derivative **5** exhibited a strong activity against Gram-positive bacteria.[11] In all probability, the H-accepting function of the oxazolidinone carbonyl group was adopted by the dihydroisoxazole nitrogen.



We were intrigued by the question of whether a dihydrooxazole substructure, which looks quite similar to the dihydroisoxazole moiety, could serve as a suitable bioisostere for the oxazolidinone moiety. In this paper, we describe an ex-chiral pool synthesis and pharmacological investigation of the target compound **3** in both stereoisomeric forms. Furthermore, computational studies of the heterocyclic core structures are presented.

Our strategy for a stereocontrolled synthesis of the target compound **3** was to build up the dihydrooxazole scaffold by condensation of a suitable benzoic acid derivative and (*S*)-serine methyl ester and subsequent reductive functionalization of the side chain.

Keywords: serine; dihydrooxazoles; antibiotics.

* Corresponding author. Tel.: +49-9131-8529383; fax: +49-9131-8522585; e-mail: gmeiner@pharmazie.uni-erlangen.de

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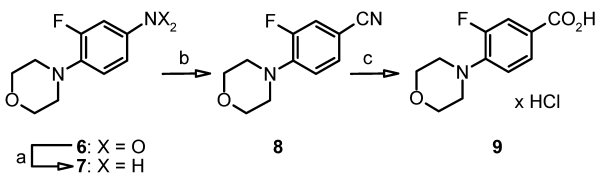
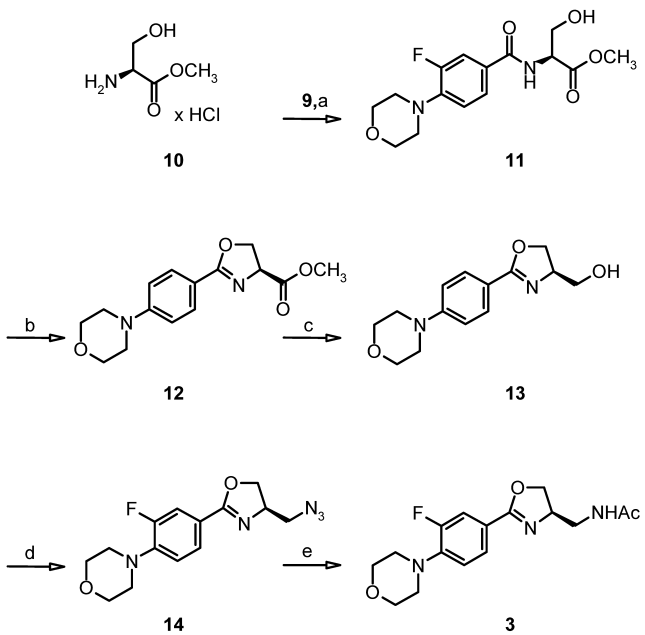
2. Results and discussion

The readily available nitrobenzene derivative **6**[12] should give rise to the synthetic intermediate **9** (Scheme 1). Since the reduction of the nitro group using ammonium formate in presence of Pd/C[12] did not proceed quantitatively and therefore required an awkward workup procedure, we performed a low pressure hydrogenation to furnish the aniline derivative **7** in 100% yield. Thus, the aromatic amine **7**, being also the central intermediate for the technical synthesis of linezolid (**1**),[12] is now available by a convenient, simplified methodology. Sandmeyer reaction[13] allowed the introduction of the cyano group to give the nitrile derivative **8**, that was subsequently hydrolyzed to furnish the carboxylic acid derivative **9**.



Scheme 1. (a) H_2, $Pd(OH)_2/C$, MeOH, room temperature, 1 h (100% crude); (b) (1) $NaNO_2$, H_2SO_4, 0°C, 30 min, (2) Na_2CO_3, 0°C to room temperature, (3) CuCN, KCN, room temperature to 50°C, 2 h (51%); (c) HCl conc., refl., 1 h (99% crude).

Starting from **9**, peptide coupling with (*S*)-serine methyl ester hydrochloride (**10**) afforded the carboxamide **11**, that underwent a smooth cyclization by the reaction with Burgess-reagent[14] to give the dihydrooxazole derivative **12** (Scheme 2).



Scheme 2. (a) DCC, HOBt; NMM, DMF/CH_2Cl_2 9:1, 0°C, 1 h, 0°C to room temperature, 18 h (98%); (b) $MeO_2CNSO_2NEt_3$ (Burgess reagent), THF, 70°C, 1 h (88%); (c) $LiAlH_4$, Et_2O, −30°C, 1 h (26%) or $NaBH_4$, MeOH, room temperature, 3.5 h (57%); (d) (1) MesCl, NEt_3, THF, −23°C, 30 min; (2) NaN_3, DMSO, 65°C, 12 h (82%); (e) H_2, $Pd(OH)_2/C$, Ac_2O/EtOAc=1:1, room temperature, 1 h (79%).

Low temperature $LiAlH_4$-reduction afforded the primary alcohol **13** in only 26% yield. However, the reaction could be improved by the application of $NaBH_4$ in methanol (yield: 57%). In order to investigate the optical purity of the primary alcohols **13** (synthesized using $LiAlH_4$) and *ent***13** (analogously prepared from (*R*)-serine via $NaBH_4$ reduction), HPLC separation on a chiral stationary phase was performed indicating 92.8% ee for **13** and 92.4% ee for the optical antipode *ent***13** (see Section 3).

The transformation of the primary alcohol **13** into the azide **14** was performed by sulfonylation and subsequent S_N2-reaction with NaN_3. Finally, the target compound **3** was synthesized by catalytic hydrogenation in presence of Ac_2O. The enantiomer *ent***3** was prepared analogously starting from (*R*)-serine methyl ester.

The test compounds **3** and *ent***3** were microbiologically screened for their antibacterial properties using the disk diffusion technique according to National Committee for Clinical Laboratory Standards (NCCLS).[15] Antibiotic free test disks (Sensidisc™) were loaded with 1, 10, 30 and 100 μg of the compounds dissolved in EtOH and dried under aseptic conditions. Suspensions of three clinically significant Gram-positive bacteria (*Staphylococcus aureus* ATCC 29212, hemolytic Streptococci Gr. A (*Streptococcus pyogenes* VA 27659), *Enterococcus faecalis* ATCC 29212) were adjusted photometrically to Mc Farland turbidity standard 0.5 and streaked out on Mueller–Hinton–Agar plates (Oxoid™) supplemented with 5% sheep blood. The disks were put on the agar plates, when the plates were incubated for 18 h at 36°C and then examined for inhibiting zones around the disks. Disks containing vancomycin and linezolid were used as the control. The screened test substances indicated no antibacterial activity.

In order to understand the structural requirements for target recognition, we decided to take a closer look at the molecular electrostatic potentials (MEPs) of the heterocyclic pharmacophore. To allow a direct comparability of the different compounds, linezolid (**1**), dihydrooxazole **3**, the butenolid **4** and the dihydroisoxazole **5** were formally defunctionalized to give the respective core scaffolds **A**–**D**. The structures were preminimized at the MM-level with MAXIMIN2 applying the Tripos force field implemented in Sybyl 6.81. Subsequently, we performed ab initio calculations (Gaussian98) using a 6-31G(d) basis set. The charges used to contour the MEPs were calculated on the resulting structures applying Breneman's CHelpG charge distribution scheme. After reimporting the results into Sybyl 6.81, the positive and negative isopotential surfaces were contoured with MOLCAD Plus at 5.0 or −5.0 kcal/mol, respectively. Qualitatively, the negative isopotential surfaces (light gray marked MEPs) of the oxazolidinone **A** and the cardenolide **C**, which mainly consist of two extended bulbs surrounding both the heterocyclic and the acetamido carbonyl oxygens, are very similar. Analogously, but to a lesser extend, these potentials can be found in the dihydroisoxazole **D**, obviously due to the sterically less demanding oxime ether substructure. However, the dihydrooxazole substructure **B** shows quite different properties: the negative isopotential surface is mainly localized on the bottom of the molecule. Obviously, this significant change is due to the shifted heteroatoms in the ring and might lead to unfavourable interactions at the bacterial ribosome (Fig. 1).

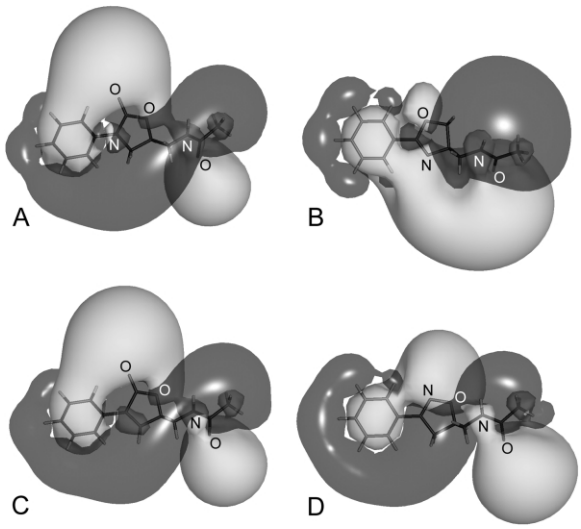


Figure 1. Isopotential surfaces of the core scaffolds of the antiinfective linezolid analogues: **A**: phenyloxazolidinone; **C**: phenylbutenolid; **D**: phenyldihydroisoxazole and the non-active phenyldihydrooxazole **B** contouring positive (dark gray, +5 kcal/mol) and negative (light gray, −5 kcal/mol) electrostatic potentials.

In conclusion, we were able to develop an EPC-synthesis leading to a new class of linezolid analogues incorporating a dihydrooxazole substructure.

The test compounds did not show antibacterial activity. However, with the help of **3**, MEP based structure activity relationship studies indicated structural requirements of the heterocyclic moiety to serve as a pharmacophoric unit, which might be of interest for future drug development.

3. Experimental

3.1. General

Solvents and reagents were purified and dried by standard procedures or purchased in pure, dry quality from Fluka or Aldrich. All reactions were performed under dry N_2. Evaporations of final product solutions were done in vacuo using a rotary evaporator. Flash chromatography was carried out with 230–400 mesh silica gel. Melting points were determined on a Büchi apparatus and are uncorrected. If not otherwise stated, MS were run by EI ionization (70 eV) with solid inlet. ^{1}H NMR spectra were recorded on BrukerAC 250 (250 MHz) and AM 360 (360 MHz) spectrometers, if not otherwise stated, in $CDCl_3$ relative to TMS (*J* values are given in Hertz). Optical rotation was measured on a Perkin–Elmer polarimeter 241 at 20°C. IR spectra were recorded on a Jasco FT/IR 410 spectrometer. Micro analyses were performed by the Institute of Organic Chemistry of the Friedrich-Alexander University Erlangen-Nürnberg.

3.1.1. 3-Fluoro-4-morpholinylaniline (7).[8] To a solution of 3-fluoro-4-morpholinylnitrobenzene (**6**)[8] (4000.0 mg, 17.69 mmol) in MeOH (250 ml) was added $Pd(OH)_2$/C (850.0 mg) and the mixture was stirred under a balloon with H_2 at room temperature. After 1 h, the mixture was filtered through Celite and evaporated to give **7** (3570.0 mg, 100%) as a gray–white solid, that was used without further purification in the next step. All spectra data were in accordance to those reported in the literature.[8]

3.1.2. 3-Fluoro-4-morpholinylbenzonitrile (8). To a stirred solution of 3-fluoro-4-morpholinylaniline (**7**) (1500.0 mg, 7.65 mmol) in H_2SO_4 30% (10 ml) was added dropwise a solution of 528.1 mg (7.65 mmol) sodium nitrite in 2 ml of water at 0°C. When an excess of nitrous acid could be detected with KI–starch paper, the mixture was adjusted to pH 7 with a saturated solution of Na_2CO_3 in H_2O, then poured into a solution of 2741.0 mg Cu(I)CN (30.61 mmol) and 2491 mg (28.27 mmol) KCN in 15 ml H_2O and heated to 50°C for 2 h. After being cooled, the solution was extracted with CH_2Cl_2 (3×15 ml) and dried over $MgSO_4$. After evaporation, the residue was purified by flash chromatography (petroleum ether–EtOAc, 9:1) to give **8** (819.0 mg, 51%) as a yellow–orange solid (mp 94°C). TLC R_f 0.19 (petroleum ether–EtOAc, 1:1); IR (NaCl) 3072–2831, 2225, 1612, 1240, 1119, 1068 cm^{-1}; ^{1}H NMR ($CHCl_3$, 360 MHz): δ (ppm)=3.19–3.22 (m, 4H, CH_2N), 3.85–3.98 (m, 4H CH_2O), 6.92 (dd, 1H, *J*=8.5, 8.5 Hz, 5-Ph), 7.29 (dd, *J*=12.8, 1.7 Hz, 1H, 2-Ph), 7.38 (ddd, *J*=8.5, 1.7, 0.6 Hz, 1H, 6-Ph). Analysis calcd for $C_{11}H_{11}FN_2O$: C, 64.07 H, 5.38 N, 13.58. Found: C, 63.93 H, 5.29 N, 13.86. EIMS (*m*/*z*): 206 (M^+).

3.1.3. 3-Fluoro-4-morpholinylbenzoic acid HCl (9). A solution of 3-fluoro-4-morpholinylbenzonitrile (**8**) (592.6 mg, 2.88 mmol) in HCl 38% (7 ml) was refluxed for 1 h. After being cooled, the solution was evaporated to give **9** (746.0 mg, 99% crude) as an orange solid, that was taken 'as is' for the next reaction step. For the analytical data, a small sample was purified by adjusting to pH 3 with $NaHCO_3$ to give the free base, extracting with EtOAc, drying with $MgSO_4$, evaporating and performing a flash chromatography (CH_2Cl_2–MeOH, 97:3) to afford an orange solid (mp. 226–227°C). TLC R_f 0.3 (CH_2Cl_2–MeOH, 9:1); IR (NaCl) 3120–2576, 1690, 1666, 1616, 1450, 1404, 1304, 1250, 1122 cm^{-1}; ^{1}H NMR ($CHCl_3$, 360 MHz): δ (ppm)=3.11–3.13 (m, 4H, CH_2N), 3.73–3.76 (m, 4H CH_2O), 7.08 (dd, 1H, *J*=8.8, 8.7 Hz, 5-Ph), 7.58 (dd, *J*=14.0, 2.0 Hz, 1H, 2-Ph), 7.69 (dd, *J*=8.7, 2.0 Hz, 1H, 6-Ph). Analysis calcd for $C_{11}H_{12}FNO_3$×0.3H_2O: C, 57.29 H, 5.51 N, 6.07. Found: C, 57.33 H, 5.46 N, 5.92. EIMS (*m*/*z*): 225 (M^+).

3.1.4. (*S*)-*N*-(3-Fluoro-4-morpholinylbenzoyl)-serine methyl ester (11). To a solution of crude 3-fluoro-4-morpholinylbenzoic acid HCl (**9**) (1000.0 mg, 3.82 mmol) and (*S*)-serine methyl ester hydrochloride (**10**, 595.0 mg, 3.82 mmol) in CH_2Cl_2/DMF 8:1 (45 ml) was added NMM (1.28 ml, 11.5 mmol) at 0°C and then a solution of HOBt (722.5 mg, 5.35 mmol) and DCC (947.5 mg, 4.59 mmol) in CH_2Cl_2 (15 ml). The mixture was stirred for 1 h at 0°C and then for 18 h at room temperature. The solution was evaporated and the resulting solid was extracted with CH_2Cl_2 (10 ml) and filtered. The filtrate was evaporated and purified by flash chromatography (gradient: petroleum ether–EtOAc 4:1–3:1) to give **11** (1116.0 mg, 98%) as a yellowish solid (mp 158–159°C). *ent***11** was prepared under the same reaction conditions, starting from (*R*)-serine methyl ester hydrochloride. TLC R_f 0.25 (petroleum

ether–acetone 1:1); **11**: $[\alpha]_D^{20}=+40.5°$ (c=0.7, $CHCl_3$); *ent***11**: $[\alpha]_D^{20}=-40.2°$ (c=1.0, $CHCl_3$); IR (NaCl) 3375, 2958, 2854, 1743, 1643, 1620, 1543, 1504, 1450, 1246, 1211, 1119 cm^{-1}; ^1H NMR ($CHCl_3$, 360 MHz): δ (ppm)=3.15–3.17 (m, 4H, CH_2N), 3.27 (brs, 1H, CH_2OH), 3.82 (s, 3H, $COOCH_3$), 3.86–3.88 (m, 4H CH_2O), 4.03 (dd, J=11.3, 3.5 Hz, 1H, CH_2OH), 4.08 (dd, J=11.3, 3.8 Hz, 1H, CH_2OH), 4.84 (ddd, J=7.3, 3.8, 3.5 Hz, 1H, $CH_2(NHCH)CH_2$), 6.90 (dd, 1H, J=8.6, 8.4 Hz, 5-Ph), 7.07 (d, J=7.3 Hz, 1H, CONH), 7.52 (dd, J=13.2, 2.2 Hz, 1H, 2-Ph), 7.54 (ddd, J=8.6, 2.2, 0.7 Hz, 1H, 6-Ph). Analysis calcd for $C_{15}H_{19}FN_2O_5$: C, 55.21 H, 5.87 N, 8.58. Found: C, 54.87 H, 5.81 N, 8.22. EIMS (m/z): 326 (M^+).

3.1.5. (*S*)-2-(3-Fluoro-4-morpholinylphenyl)-4,5-dihydrooxazole-4-carboxylic acid methyl ester (12). To a solution of (*S*)-*N*-(3-fluoro-4-morpholinyl-benzoyl)-serine methyl ester (**11**) (582.4 mg, 1.79 mmol) in THF (16 ml) was added (methoxycar-bonylsulfamoyl)-triethylammonium-*N*-betaine (492.5 mg, 2.07 mmol) at room temperature. The solution was transferred to a sealed tube and heated to 70°C. After 1 h, the solution was evaporated and the residue was purified by flash chromatography (gradient: petroleum ether–EtOAc 4:1–3:1–2:1) to give **12** (487.2 mg, 88%) as a yellowish solid (mp 86°C). *ent***12** was prepared under the same reaction conditions, starting from *ent***11**. TLC R_f 0.5 (petroleum ether–acetone 1:1); **12**: $[\alpha]_D^{20}=+55.8°$ (c=1.0, $CHCl_3$); *ent***12**: $[\alpha]_D^{20}=-54.4°$ (c=0.23, $CHCl_3$); IR (NaCl) 2954–2854, 1743, 1639, 1620, 1516, 1442, 1362, 1269, 1250, 1207, 1119 cm^{-1}; ^1H NMR ($CHCl_3$, 360 MHz): δ (ppm)=3.16–3.18 (m, 4H, CH_2N), 3.82 (s, 3H, $COOCH_3$), 3.85–3.88 (m, 4H CH_2O), 4.57 (dd, J=10.5, 8.6 Hz, 1H, H-5a), 4.67 (dd, J=8.6, 8.0 Hz, 1H, H-5b), 4.93 (dd, J=10.5, 8.0 Hz, 1H, H-4), 6.90 (dd, 1H, J=8.5, 8.4 Hz, 5-Ph), 7.65 (dd, J=13.7, 2.0 Hz, 1H, 2-Ph), 7.69 (dd, J=8.4, 2.0 Hz, 1H, 6-Ph). Analysis calcd for $C_{15}H_{17}FN_2O_4$: C, 58.44 H, 5.56 N, 9.09. Found: C, 58.28 H, 5.63 N, 8.93. EIMS (m/z): 308 (M^+).

3.1.6. (*R*)-[2-(3-Fluoro-4-morpholinylphenyl)-4,5-dihydrooxazol-4-yl]-methanol (13). *Method 1*. To a solution of (*S*)-2-(3-fluoro-4-morpholinylphenyl)-4,5-dihydro-oxazole-4-carboxylic acid methyl ester (**12**) (487.2 mg, 1.58 mmol) in Et_2O (30 ml) was added a 1 M solution of $LiAlH_4$ in Et_2O (3.36 ml, 3.36 mmol) at −30°C. After 1 h, the solution was quenched with H_2O (1 ml) and warmed to room temperature. The solution was filtered through Celite, the filtrate was evaporated and the residue was purified by flash chromatography (petroleum ether–acetone 4:1) to give **13** (116.9 mg, 26%) as a gray–white solid (mp 148–149°C). *ent***13** was prepared under the same reaction conditions, starting from *ent***12**.

Method 2. To a solution of (*S*)-2-(3-fluoro-4-morpholinyl-phenyl)-4,5-dihydrooxazole-4-carboxylic acid methyl ester (**12**) (10.0 mg, 0.032 mmol) in MeOH (3 ml) was added $NaBH_4$ (6.5 mg, 0.17 mmol) at room temperature. After 4 h, the solution was quenched with a saturated aqueous NH_4Cl solution (0.3 ml) and subsequently evaporated. The residue was purified by flash chromatography (petroleum ether–acetone 2:1) to give **13** (5.1 mg, 57%). *ent***13** was prepared under the same reaction conditions, starting from *ent***12**. TLC R_f 0.15 (petroleum ether–acetone 1:1); **13**: $[\alpha]_D^{20}=+15.9°$ (c=0.68, $CHCl_3$); *ent***13**: $[\alpha]_D^{20}=-16.0°$ (c=0.025, $CHCl_3$); IR (NaCl) 3178, 2962–2858, 1647, 1616, 1516, 1439, 1373, 1265, 1250, 1192, 1119 cm^{-1}; ^1H NMR ($CHCl_3$, 360 MHz): δ (ppm)=2.52 (brs, 1H, −OH), 3.16–3.18 (m, 4H, CH_2N), 3.66 (dd, J=11.4, 3.9 Hz, 1H, $-CH_2OH$), 3.86–3.89 (m, 4H CH_2O), 3.96 (dd, J=11.4, 3.4 Hz, 1H, $-CH_2OH$), 4.35 (dd, J=7.2, 7.1 Hz, 1H, H-5a), 4.43 (dd, J=9.4, 7.2, 3.9, 3.4 Hz, 1H, H-4), 4.50 (dd, J=9.4, 7.1 Hz, 1H, H-5b), 6.87 (dd, 1H, J=8.5, 8.4 Hz, 5-Ph), 7.55 (dd, J=13.7, 2.1 Hz, 1H, 2-Ph), 7.64 (ddd, J=8.4, 2.1, 0.4 Hz, 1H, 6-Ph). Analysis calcd for $C_{14}H_{17}FN_2O_3$: C, 59.99 H, 6.11 N, 9.99. Found: C, 59.93 H, 6.13 N, 9.84. EIMS (m/z): 280 (M^+).

13 (synthesized by method 2) and *ent***13** (synthesized by method 1) were investigated by performing chiral HPLC (Chiralcel OD; petroleum ether/*i*PrOH 9:1; 1 ml/min; 215 nm): **13**: *R* (rt=19.57 min): *S* (rt=21.40 min)=96.4:3.6; *ent***13**: *S*/*R*=96.2:3.8.

3.1.7. (*R*)-4-[4-(4-Azidomethyl-4,5-dihydrooxazol-2-yl)-2-fluorophenyl]-morpholine (14). To a solution of (*R*)-[2-(3-fluoro-4-morpho-linylphenyl)-4,5-dihydrooxazol-4-yl]-methanol (**13**) (200.0 mg, 0.71 mmol) and NEt_3 (323 μl, 2.5 mmol) in THF (7 ml) was added methansulfonyl chloride (195 μl, 2.5 mmol) at −23°C. After 30 min, the mixture was filtered and the filtrate was evaporated. The residue was dissolved in Et_2O (30 ml) and the solution was washed with sat. aqueous $NaHCO_3$. After drying with $MgSO_4$, the solution was evaporated and NaN_3 (232.2 mg, 3.57 mmol) and DMSO (7 ml) were added. The mixture was stirred for 12 h at 65°C and then diluted with sat. aqueous $NaHCO_3$ and Et_2O. The organic layer was washed with brine, dried with $MgSO_4$ and evaporated. The residue was purified by flash chromatography (petroleum ether–acetone 4:1) to give **14** (178.2 mg, 82%) as a colorless solid (mp 79°C). *ent***14** was prepared under the same reaction conditions, starting from *ent***13**. TLC R_f 0.4 (petroleum ether–acetone 1:1); **14**: $[\alpha]_D^{20}=+110.3°$ (c=0.53, $CHCl_3$); IR (NaCl) 2962–2854, 2102, 1643, 1616, 1516, 1446, 1361, 1254, 1188, 1119 cm^{-1}; ^1H NMR ($CHCl_3$, 360 MHz): δ (ppm)=3.15–3.18 (m, 4H, CH_2N), 3.42–3.47 (m, 1H, $-CH_2N_3$), 3.51–3.56 (m, 1H, $-CH_2N_3$), 3.85–3.88 (m, 4H CH_2O), 4.20–4.28 (m, 1H, H-5a or H-4), 4.43–4.52 (m, 1H, H-5b and H-4 or H-5a), 6.91 (dd, 1H, J=8.5, 8.4 Hz, 6-Ph), 7.61 (dd, J=13.7, 2.0 Hz, 1H, 3-Ph), 7.66 (ddd, J=8.4, 2.0, 0.5 Hz, 1H, 5-Ph). Analysis calcd for $C_{14}H_{16}FN_5O_2$: C, 55.08 H, 5.28 N, 22.49. Found: C, 55.12 H, 5.32 N, 22.53. EIMS (m/z): 305 (M^+).

3.1.8. (*R*)-*N*-[2-(3-Fluoro-4-morpholin-4-yl-phenyl)-4,5-dihydro-oxazol-4-ylmethyl]-acetamide (3). To a solution of (*R*)-4-[4-(4-azidomethyl-4,5-dihydro-oxazol-2-yl)-2-fluorophenyl]-morpholine (**14**) (100.0 mg, 0.33 mmol) in EtOAc/Ac_2O (1:1; 10 ml) was added $Pd(OH)_2/C$ (80 mg) and the mixture was stirred under a balloon with H_2 at room temperature. After 1 h, the mixture was filtered through Celite and evaporated. The residue was purified by flash chromatography (gradient: petroleum ether–acetone 3:1–2:1–1:1) to give **3** (83.3 mg, 79%) as a yellowish solid (mp 169–170°C). *ent***3** was prepared under the same reaction conditions, starting from *ent***14**. TLC R_f 0.05 (petroleum ether–acetone 2:1); **3**: $[\alpha]_D^{20}=+19.3°$ (c=0.57, $CHCl_3$);

*ent***3**: $[\alpha]_D^{20}=-19.3°$ (c=0.72, $CHCl_3$); IR (NaCl) 3317, 3078, 2966–2854, 2102, 1647, 1543, 1516, 1439, 1373, 1265, 1119 cm^{-1}; ^1H NMR ($CHCl_3$, 360 MHz): δ (ppm)=3.16–3.19 (m, 4H, CH_2N), 3.37 (ddd, J=13.7, 6.2, 6.2 Hz, 1H, $-CH_2NHAc$), 3.66 (ddd, J=13.7, 6.2, 3.6 Hz, 1H, $-CH_2NHAc$), 3.86–3.89 (m, 4H CH_2O), 4.09 (dd, J=7.8, 7.8 Hz, 1H, H-5a), 4.39 (dd, J=9.9, 7.9, 6.2, 3.6 Hz, 1H, H-4), 4.47 (dd, J=9.9, 7.8 Hz, 1H, H-5b), 6.91 (dd, 1H, J=8.5, 8.5 Hz, 5-Ph), 7.61 (dd, J=13.7, 2.0 Hz, 1H, 2-Ph), 7.64 (dd, J=8.5, 2.0 Hz, 1H, 6-Ph). Analysis calcd for $C_{16}H_{20}FN_3O_3$: C, 59.80 H, 6.27 N, 13.08. Found: C, 59.35 H, 6.33 N, 12.87. EIMS (m/z): 321 (M^+).

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