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ORIGINAL ARTICLE

Asymmetric synthesis of enantiomerically and diastereoisomerically enriched 4-[F or Br]-substituted glutamic acids

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Abstract A novel simple synthetic protocol for the preparation of both (2*S*,4*R*)- and (2*S*,4*S*)-FGlu, applying Michael addition of methyl α-fluoroacrylate to a Ni^{II} complex of glycine Schiff base with *BPB*, was elaborated. In addition, same reaction of mentioned complex with ethyl α-bromoacrylate leads to the Ni^{II} complex of the Schiff base of *BPB* with (2*S*,4*R*)-4-bromo-glutamic acid monoester, that can be transformed into the corresponding complexes of 1-aminocyclopropane-1,2-dicarboxylic acid. The decomposition of the diastereoisomerically pure complexes leads to corresponding enantiomerically enriched (*ee* > 98%) amino acids.

Keywords Asymmetric synthesis · Chiral Ni^{II} Schiff base complexes · (2*S*)-4-[^{19}F or ^{18}F]fluoroglutamic acid · (1*S*,2*R*)-1-aminocyclopropane-1,2-dicarboxylic acid · (1*S*,2*S*)-1-aminocyclopropane-1,2-dicarboxylic acid · (2*S*,4*R*)-4-bromoglutamic acid

Abbreviations

Glu	Glutamic acid
FGlu	4-Fluoroglutamic acids
FDG	2-Fluorodeoxyglucose
PET	Positron emission tomography
BPB	(*S*)-2-*N*-(*N*′-benzylprolyl)aminobenzophenone
Ni-*BPB*-Gly (**1**)	Ni^{II} complex of a Schiff's base of *BPB* and glycine
AA	Amino acid
d.r.	Diastereomers ratio
de	Diastereomeric excess
ee	enantiomeric excess

Introduction

The search for new methods for the stereoselective synthesis of nonproteinogenic amino acids is a topical task because these compounds are widely used in biochemistry, pharmacology, and synthetic chemistry (Barrett 1985; Kuchar' and Soloshonok 1994; Goodman and Ro 1995; Haufe and Kroger 1996; Kroger and Haufe 1997; Williams 1989; Cativiela and Díaz de Villegas 1998, 2000; Wirth 1997; North 1996; Duthaler 1994; Ager and Laneman 2004; Nájera et al. 2000; Nájera and Sansano 2007; O'Donnell 2004; Hughes et al. 2004; Lygo and Andrews 2004; Maruoka and Ooi 2003; Ma 2003; Kotha 2003).

In particular, the fluorinated analogs of proteinogenic amino acids find wide application in biochemistry, pharmacology, and microbiology (Goodman and Ro 1995). Stereoselective fluorination may drastically modify the characteristics of those amino acids, significantly influencing their biological and chemical activities. The comparable

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sizes of fluorine and hydrogen atoms diminish steric inhibition of binding of such a fluorinated analog at the active site of the receptor or enzyme. On the other hand, the fluorinated amino acids often cannot be metabolized in the same way as the usual amino acids. As a result, the fluorinated amino acids can be used as potent agonists and antagonists of natural amino acids, sometimes functioning as antiproliferation agents, inhibiting the synthesis of proteins (Goodman and Ro 1995). In addition, β-fluorinated amino acids sometimes serve as irreversible inhibitors of pyridoxal enzymes (Barrett 1985).

Naturally, the properties of the amino acids crucially depend on their absolute configuration. Thus, the elaboration of the novel synthesis of fluorinated amino acids should involve enantioselective stages in the protocol (Barrett 1985; Kuchar' and Soloshonok 1994; Goodman and Ro 1995; Williams 1989; Cativiela and Díaz de Villegas 1998, 2000; Wirth 1997; North 1996; Duthaler 1994; Ager and Laneman 2004; Nájera et al. 2000; Nájera and Sansano 2007; O'Donnell 2004; Hughes et al. 2004; Lygo and Andrews 2004; Maruoka and Ooi 2003; Ma 2003; Kotha 2003).

Glu is a mammal central nervous system neurotransmitter and activate several types of synaptic sites subdivided on subspecies (Dodd et al. 2000; Girault et al. 1997). Additionally, Glu is a human vital function important agent and glutamine-precursor (Newsholme et al. 2003). Elaboration of new medicines for Parkinsonism and Alzheimer's dementia, myocardial and cerebral ischemia and several types of epilepsy are based, at present, on Glu derivatives (Dodd et al. 2000).

The impact of fluorine atom introduction at the C-4 position of Glu has been tested in the screening of modulators for folate poly-γ-glutamate biosynthesis and to study the role of analogous derivatives of antifolates such as methotrexate in the cytotoxic action of these drugs. In one of the crucial steps, the γ-carboxyl group of the C-terminal glutamate is activated by the enzyme prior to peptide coupling. Therefore, introducing one or more fluorine atoms in the γ-position of the side chain could interfere with the biological processes (Hart et al. 1996; Tsukamoto and Coward 1996). As a second illustration, enantiomerically pure FGlu were employed for investigating the mechanism of the vitamin K-dependent carboxylation of Glu residues present in several proteins (Dubois et al. 1983).

Another highly important off-shoot of enantiomerically pure FGlu might be its [^{18}F]-substituted derivative. [^{18}F]-Labeled compounds and [^{18}F]-labeled amino acids, in particular, are perspective tools believed to become perspective diagnostic molecular imaging agents in PET (Anderson and Shokeen 2009; Krasikova et al. 2004, 2008 and references cited therein). Because Glu plays a crucial role in ammonia exchange in organism, its [^{18}F]-derivative might be expected to concentrate in fast-growing tissues such as tumors and, thus, become a novel radiopharmaceutical for PET cancer imagining, supplementing [^{18}F]-labeled FDG, the only PET radiotracer practically used, at present, for routine clinical evaluation.

The existing procedures for the synthesis of enantiomerically pure forms of FGlu utilize tedious resolution of racemic mixtures (Dubois et al. 1983; Tolman 1993 and Tolman and Simek 2000) or involve use of enantiomerically pure precursors in a multistage procedure (Hudlický and Merola 1990, 1991, Hudlický 1993; Konas and Coward 2001). For this purpose both (*S*)- or (*R*)-hydroxyproline (Hudlický and Merola 1990, 1991 and (*S*)-Glu (Konas and Coward 2001) were employed, furnishing the target compound in a low total yield (15–18%).

Earlier, we developed a simple synthetic protocol for the synthesis of enantiomerically and diasteroisomerically pure nonproteinogenic amino acids, including alkyl substituted Glu via Michael addition to a Ni-*BPB*-Gly to substituted acrylic acid (Belokon et al. 1985, 1986, 1998; Belokon 1992). The method was later further elaborated by Soloshonok et al. for the synthesis of Glu derivatives and its alkylated analogs (Soloshonok et al. 1997, 1999).

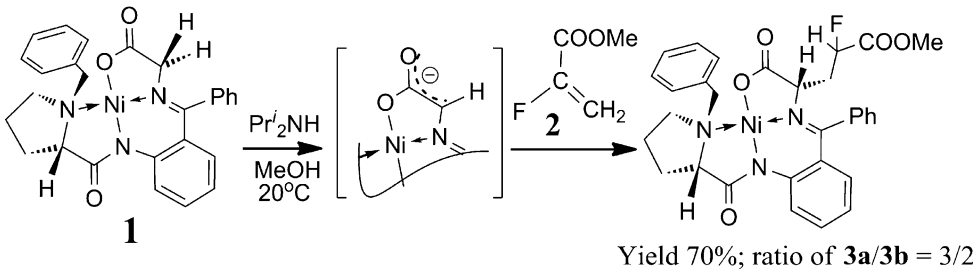
In this work, we put ourselves a task of developing a simple procedure for the synthesis of enantiomerically pure FGlu. In addition, we planned to develop a protocol for the asymmetric synthesis of 4-Br substituted Glu which could become a useful precursor for many 4-substituted Glu (Krasnov et al. 2003) (including ^{18}F-substituted enantiomerically pure Glu) or aminocyclopropanecarboxylic acids.

Herein, we report a novel simple synthetic protocol for the preparation of both (2*S*,4*R*)- and (2*S*,4*S*)-FGlu, applying Michael addition of methyl α-fluoroacrylate (**2**) to Ni-*BPB*-Gly (**1**) (Schemes 1, 2). In addition, the diastereoselective addition of **1** to ethyl α-bromoacrylate was shown to lead to the Ni^{II} complex of the Schiff base of *BPB* with (2*S*,4*R*)-4-bromo-glutamic acid monoester. Further transformations of the complex into the corresponding complexes of 1-aminocyclopropane-1,2-dicarboxylic acid was elaborated.

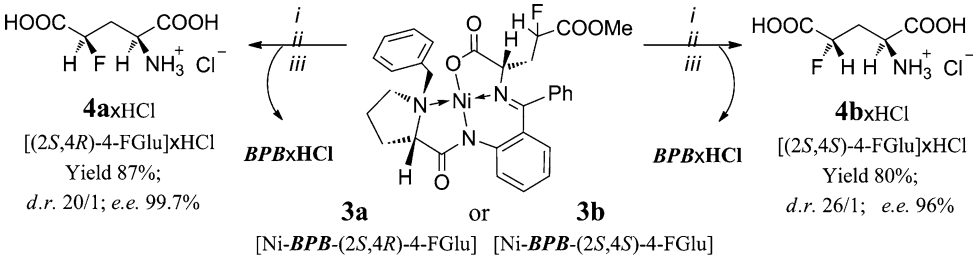
Results and discussion

As expected, methyl α-fluoroacrylate (**2**) added to **1** in MeOH in the presence of Pr^i_2NH at 20°C within a 10-day-period (see Scheme 1) to give a mixture of two diastereoisomeric complexes, differing at their γ-carbon atom configuration of the side chain and having the same (*S*)-configuration of the α-carbon atom. This type of stereoselectivity in Ni-*BPB*-AA complexes is well documented (Belokon and Soloshonok).

Scheme 1 Key step in the asymmetric synthesis of FGlu



Scheme 2 *Reagents and conditions*: *i*) HCl, MeOH, H_2O, reflux 20 min; *ii*) Dowex 50 W × 8 in H^+ form, eluent – 5%-NH_3; *iii*) 6N HCl, reflux 1 h



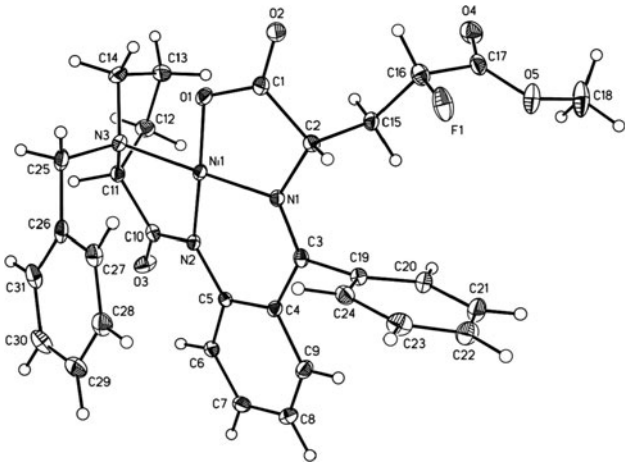


Fig. 1 Structure of Ni^{II} complex of (2*S*,4*R*)-FGlu Schiff base with *BPB* as revealed by X-ray analysis data

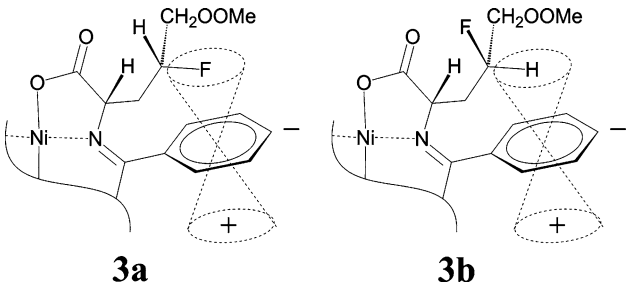


Fig. 2 Magnetic anisotropy effects influencing relative 19F chemical shifts in **3a** and **3b**

The resulting mixture of the diastereomeric complexes, incorporating (2*S*,4*R*)- and (2*S*,4*S*)-moieties of FGlu (**3a** and **3b** correspondingly), was isolated in a 70% isolated yield after flash chromatography on silica. The ratio of **3a**/**3b** was 3/2, according to ^{1}H NMR data. The separation of the diastereomeric (2*S*,4*R*)- and (2*S*,4*S*)-complexes (**3a** and **3b** correspondingly) was carried out on a Toyopearl HW-55F column.

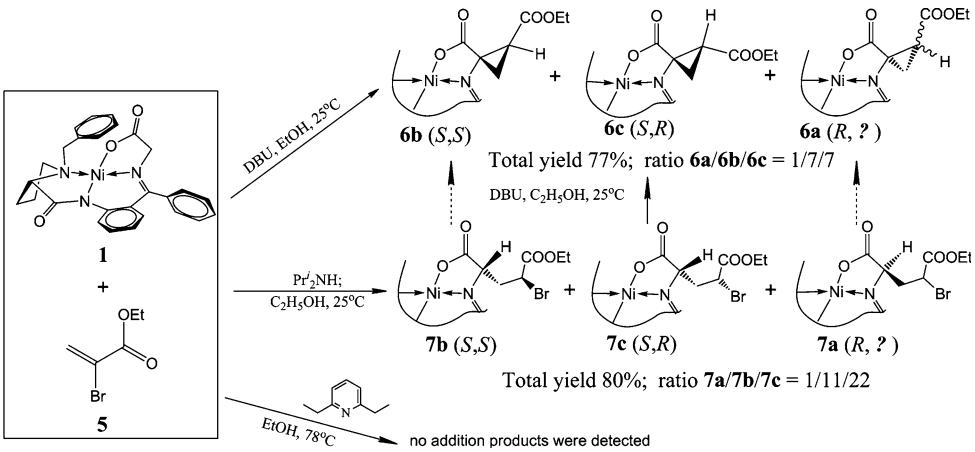
The individual diastereomeric complexes **3a** and **3b** were characterized with ^{1}H, ^{19}F and ^{13}C NMR spectroscopy, elemental analysis, and specific rotations. The configurations of the FGlu moiety of **3a** (with greater mobility on Toyopearl HW-55F (benzene/THF, 7:2) were assigned as (2*S*,4*R*)- according to the X-ray structure analysis data (see Fig. 1).

The configuration of the AA moiety of another diastereoisomeric complex **3b** was assigned as (2*S*,4*S*)- accordingly. Additionally, ^{1}H and ^{19}F NMR spectroscopy data corroborate this assignment. For example, the resonance of ^{19}F in the **3a** spectrum was shifted 5 ppm upfield relative to that of **3b** as a result of the aromatic ring anisotropy effect, as presented on Fig. 2. The 0.12 ppm upfield shift of γ-hydrogen resonances of **3b** relative to that of **3a** can also rationalized in the same way.

Enantiomerically enriched (2*S*,4*R*)- and (2*S*,4*S*)-FGlu (**4a** and **4b** correspondingly) were isolated (see Scheme 2) after the decomposition of complexes **3a** and **3b** with aqueous 6N HCl, accompanied by simultaneous ester group hydrolysis.

After recovery of the initial *BPB* (*BPB* × HCl in 90–95% yield) the amino acids were purified by the ion-exchange technique. The resulting amino acid solutions consisted of both open and closed forms of the FGlu, according to their ^{1}H NMR spectra. The additional acidic hydrolysis of the mixture with 6N HCl furnished the hydrochlorides of target amino acids (2*S*,4*R*)- or (2*S*,4*S*)-FGlu (**4a** and **4b**) correspondingly. *D.r.* of amino acids, as determined with chiral GLC, exceeded 20/1 for **4a** × HCl and 26/1 for **4b** × HCl, and for each stereoisomer *e.e.* >96%. Once crystallization of samples **4a** × HCl and

Scheme 3 Reaction product manifold formed in addition of 5 to 1



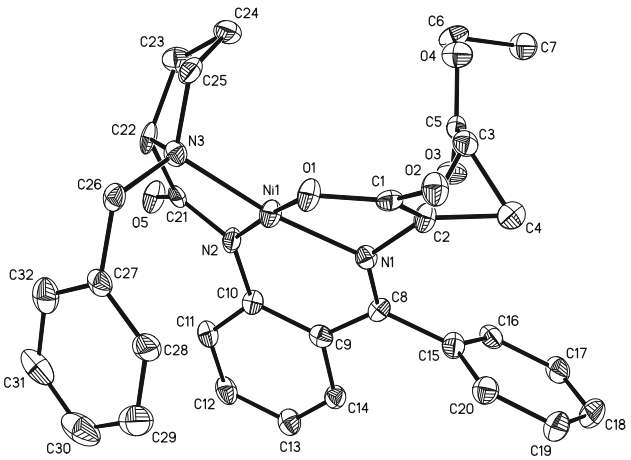


Fig. 3 Molecular structure of the Ni^{II} complex of the Schiff base of *BPB* with (1*S*,2*R*)-1-aminocyclopropane-1,2-dicarboxylic acid monoethyl ester, **6c**, with displacement ellipsoids drawn at the 50% probability level

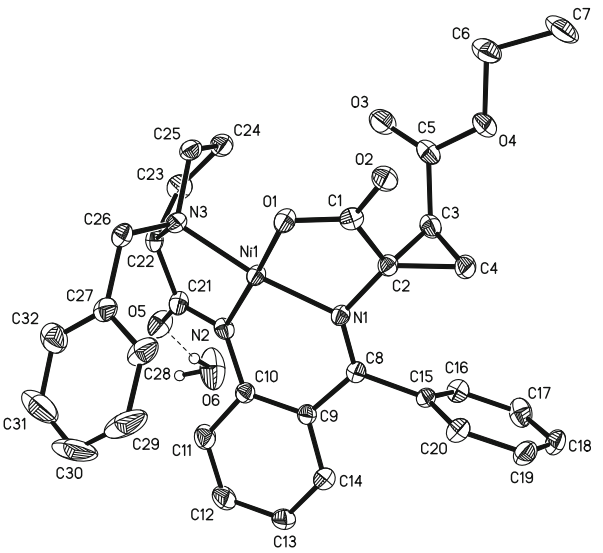


Fig. 4 Molecular structure of the Ni^{II} complex of the Schiff base of *BPB* with (1*S*,2*S*)-1-aminocyclopropane-1,2-dicarboxylic acid monoethyl ester, **6b**, with displacement ellipsoids drawn at the 50% probability level

4b × HCl allowed raising *e.e.* and *d.e.* of the products up to 100%.

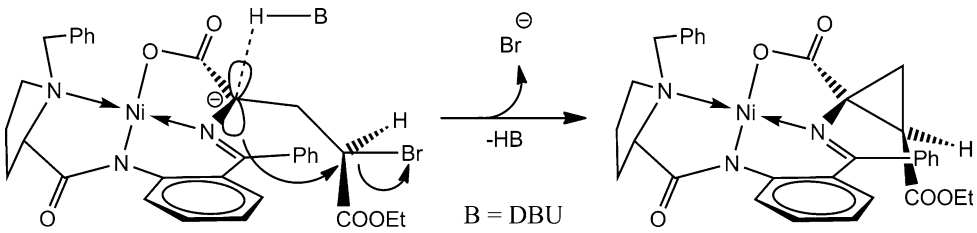
It seemed likely that a straightforward Michael condensation of **1** with unsaturated ester **5** in EtOH would furnish the desired product. The use of 2,6-diethylpyridine as a promoter did not lead to the addition of compound **1** to **2** (see Scheme 3) even on heating in EtOH. However, DBU-promoted reaction of complex **1** with unsaturated ester **5** in EtOH afforded individual diastereomers of Ni^{II} complexes of Schiff bases of *BPB* with stereoisomers of 1-aminocyclo-propane-1,2-dicarboxylic acid monoesters **6a**, **6b**, and **6c** (Scheme 3) easily separated by chromatography (SiO_2).

The configuration of the proline residue is omitted for simplicity, because the configuration of this residue in the starting complex **1** (R_N,*S*) is retained in the reaction. The absolute configuration of the minor isomer **6a** was not determined. X-ray diffraction study demonstrated that compounds **6b** and **6c** (Fig. 3) represented Ni^{II} complexes of the Schiff bases of (1*S*,2*S*)- and (1*S*,2*R*)-1-aminocyclopropane-1,2-dicarboxylic acid monoesters, respectively (Fig. 4). The ratio of isomers **6b** and **6c** determined by ^1H NMR spectroscopy was 1:1, and their total yield was 70%.

Most likely, the formation of cyclic complexes **6a–c** instead of the expected linear Michael adduct, viz., the Schiff base of 4-bromo-Glu monoester, results from the secondary reaction of this derivative. Presumably, the Ni^{II} complex of the Schiff base of *BPB* with 4-bromo-Glu that formed in the first step undergoes cyclization under the reaction conditions (Scheme 4).

An attempt to recover the corresponding 1-aminocyclopropane-1,2-dicarboxylic acids from the parent complexes by simple hydrolysis, followed by ion exchange technique, failed. The result was not a surprise as the decomposition of the racemic amino acids in basic media

Scheme 4 A possible mechanism of aminocyclopropanedicarboxylic acid formation, according to Scheme 3



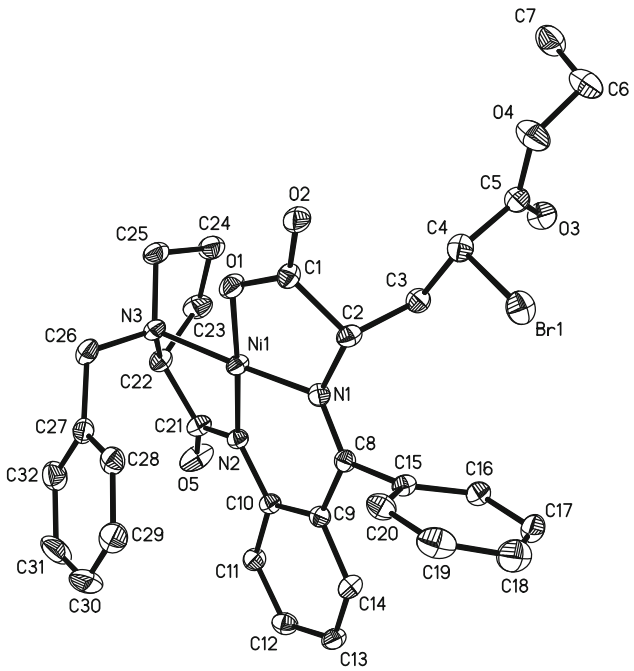


Fig. 5 Molecular structure of the Ni^{II} complex of the Schiff base of *BPB* with (2*S*,4*R*)-4-bromoglutamic acid monoethyl ester, **7c**, with displacement ellipsoids drawn at the 50% probability level

was earlier described (Krasnov et al. 2003). A special procedure should be developed to avoid the decomposition and it is now under elaboration.

Synthesis of the Michael adduct requires that cyclization was retarded, which could be achieved if sterically hindered amine $Pr^{i}_{2}NH$ was used instead of DBU. The reaction in the presence of this base did produce diastereomeric complexes **7a–c** containing a fragment of 4-bromo-Glu monoester (see Scheme 3) with a total yield of 80%. Complexes **6b** and **6c** were also obtained as by-products (<5%). The diastereomer ratio **7a**:**7b**:**7c** = 1:11:22 was determined by ^{1}H NMR spectroscopy. Complex **7c** was obtained as the major product, which was isolated in 52% yield. Studies by elemental analysis, ^{1}H and ^{13}C NMR spectroscopy, and X-ray diffraction analysis (Fig. 5) showed that this compound is the Ni^{II} complex of the Schiff base of *BPB* with (2*S*,4*R*)-4-bromo-Glu monoester.

The recovery of pure 4-bromo-Glu from the parent complex by the routine simple hydrolysis of the parent complex, followed by ion exchange technique, led to an unidentified mixture of amino acids.

Treatment of complex **7c** with DBU in EtOH resulted in its selective transformation into **6c** in full accord with Schemes 3 and 4. The formation of compounds **6a** and **6b** was not observed. Presumably, the cyclization proceeds by either the E2 mechanism, which involves simultaneous α-proton abstraction from the amino acid fragment under the action of DBU accompanied by intramolecular replacement of the bromide ion and the three-membered ring closure, or the E1*cB* mechanism involving the successive α-proton abstraction and generation of the carbanion followed by cyclization and elimination of the Br^{-} ion (see Scheme 4).

The stereochemistry of the transformation can be adequately described by both the E2 and E1*cB* mechanisms. Apparently, the DBU-catalyzed synthesis of **6b** involves intramolecular cyclization of the initially formed **7b**. Hence, the (*S*,*S*)-configuration can be tentatively assigned to the amino acid fragment of **7b**.

To summarize, the Ni^{II} complex of the Schiff base of *BPB* with (2*S*,4*R*)-4-bromoglutamic acid monoester (**7c**) was synthesized and characterized. This complex is a convenient precursor of various derivatives that can be prepared by nucleophilic substitution reactions in analogy with literature data (Krasnov et al. 1989, 2004). Preliminary experiments indicated that substitution of Br by CN or RO-groups could be easily brought about.

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