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[37] All reactions were run in 2 mL solutions of CH_3CN/H_2O at 22 °C. All chemicals were of reagent-grade quality and used as received. Aqueous H_2O_2 stock solution (50% w/w, Aldrich) was standardized with $KMnO_4$ and used directly or as diluted with acetonitrile.
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A Practical Asymmetric Synthesis of Enantiomerically Pure 3-Substituted Pyroglutamic Acids and Related Compounds**

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In recent years, tailor-made χ-constrained amino acids have emerged as critically important key structural units in the de novo design of peptide-based drugs with enhanced receptor selectivity and stability to metabolic degradation.[1, 2] Incorporation of these amino acids in strategic positions of a peptide chain allows rational design of the three-dimensional topographical structure of the peptide and, thus, opens a new avenue for exploration of the fundamental chemical – physical basis for peptide-mediated biological information transfer.[2] In particular, to explore the topographical requirements of the recently discovered human melanocortin receptors,[3] we need a series of hitherto unknown conformationally con-

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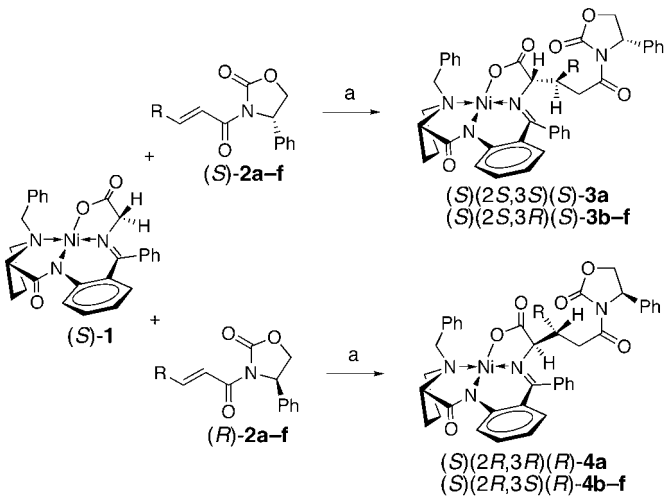
strained glutamic acid and proline derivatives. Since pyroglutamic acids (PGAs) can be readily transformed into glutamic acids, glutamines, and prolines, we reasoned that by developing a convenient asymmetric method for preparation of the corresponding PGAs, we would have access to the whole family of these extraordinarily valuable compounds.[4]

For construction of the carbon skeleton of C-substituted glutamic/pyroglutamic acids, Michael addition reactions between chiral equivalents of a nucleophilic glycine and the correspondingly substituted acrylic acid derivatives represent the most methodologically straightforward solution. These types of reactions have been extensively studied by many groups using various chiral equivalents of nucleophilic glycine.[5, 6] With the exception of a few cases which feature diastereoselectivity of over 98% *de* in the addition reactions,[7] synthetic efficiency of the reported methods is compromised by the lack of generality and poor stereochemical outcome. Accordingly, our ultimate objectives were to develop a synthetic protocol for asymmetric Michael addition reactions which fulfilled all requirements for efficacy, including complete chemical (>98% yield) and stereochemical (>98% *ee*) control, and broad substrate generality. In this communication we report a highly successful solution to the aforementioned synthetic objectives.

Recently we have discovered that addition reactions between *N*-(*E*-enoyl)oxazolidin-2-ones and nickel(II)-complexes of Schiff bases of glycine with *o*-[*N*-α-pycolylamine]-benzophenone or -acetophenone readily occurred in DMF at room temperature, in the presence of 10–15 mol% DBU (1,8-diazabicyclo[5.4.0]undec-7-ene); the corresponding products were afforded in quantitative yield and with virtually complete diastereoselectivity.[8] Our first attempt to realize the asymmetric version by employing a nickel(II) complex of the chiral Schiff base of glycine with (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone **1** for reaction with the *N*-(*E*-enoyl)oxazolidin-2-ones, though successful, did not give the desired result.[9] Specifically, the problem we met was poor *si*/*re* face stereocontrol of the complex (*S*)-**1** derived enolate, while the face selectivity of the *N*-(*E*-enoyl)oxazolidin-2-ones was perfect, giving rise only to the products of *like*[10] relative topicity.

Reasoning how to improve the stereochemical outcome, we decided to try the additions of complex (*S*)-**1** with chiral 4-substituted *N*-(*E*-enoyl)oxazolidin-2-ones (**2**, Scheme 1). Assuming that the reactions between the chiral equivalent of glycine and the Michael acceptors might have two distinct cases (matched and mismatched stereochemistry), we anticipated that the matched case would afford the target addition products with the desired stereochemical outcome. Regarding the chiral oxazolidin-2-ones (**2**), we decided to use the derivatives developed in our group, that is the 4-phenyloxazolidin-2-ones,[11] as they have been shown to be superior in controlling the stereochemistry of the conjugate addition reactions[12] compared to the more commonly used 4-benzyl and 4-isopropyl analogues.

First we investigated the addition between complex (*S*)-**1** and (4*S*)-*N*-crotonyl-4-phenyloxazolidin-2-one (**2a**, Scheme 1). To our satisfaction, the reaction, conducted in DMF at ambient temperature (22°C) in the presence of



Scheme 1. a) DMF, DBU (15 mol%). R = Me (**a**), iPr (**b**), Ph (**c**), 2-naphthyl (**d**), 4-MeO-C_6H_4 (**e**), or 4-CF_3-C_6H_4 (**f**). DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

15 mol% DBU, was complete in 5 min to afford **3a** as the only product in quantitative yield (Table 1, entry 1). The absolute stereochemistry of the glutamic acid residue in **3a** was found to be (2*S*,3*S*),[13] in agreement with the previously established diastereoselectivity in the reactions between the achiral

Table 1. Addition reactions of (*S*)-**1** with (*S*)- or (*R*)-**2a**–**f**.[a]

Entry	Compound	Time	Yield [%][b]	Product[c]
1	(*S*)-**2a**	5 min	99	(2*S*,3*S*)-**3a**
2	(*R*)-**2a**	10 min	97	(2*R*,3*R*)-**4a**
3	(*S*)-**2b**	30 min	97	(2*S*,3*R*)-**3b**
4	(*R*)-**2b**	4 hrs	67[d]	(2*R*,3*S*)-**4b**
5	(*S*)-**2c**	8 min	97	(2*S*,3*R*)-**3c**
6	(*R*)-**2c**	30 min	97	(2*R*,3*S*)-**4c**
7	(*R*)-**2d**	2 hrs	97	(2*R*,3*S*)-**4d**
8	(*S*)-**2e**	5 min	97	(2*S*,3*R*)-**3e**
9	(*S*)-**2f**	30 min	97	(2*S*,3*R*)-**3f**

[a] All reactions were performed in DMF in the presence of DBU (15 mol%) at ambient temperatures. Ratio of (*S*)-**1**:(4*S*)- or (4*R*)-**2** was 1:1.05–1.1. [b] Yield of diastereo- and enantiomerically pure products. [c] In all cases only one stereochemical product (*de* >98%) was detected by NMR analysis of the crude reaction mixtures. The absolute configuration of the products was determined on the basis of their optical properties, as well as by comparison of the optical rotations of the corresponding pyroglutamic acids later formed from the products with the literature data. [d] Incomplete (70%) conversion of the starting materials.

substrates.[8] Assuming that the reaction of (*S*)-**1** and (*S*)-**2a** represents the case of matching stereochemical requirements of the chiral auxiliaries, we expected that the addition between (*S*)-**1** and (*R*)-**2a** might be the mismatch case, and, thus, less stereoselective. To our surprise, under the same reaction conditions, the addition of complex (*S*)-**1** with (*R*)-**2a** occurred with a similar reaction rate giving rise to **4a** as the sole product in quantitative yield (entry 2). Determination of the stereochemistry of compound **4a** gave a totally unexpected result. The absolute configuration of the two newly created stereogenic centers in **4a** was found to be 2*R*,3*R*. This stereochemical outcome was not anticipated based on previous knowledge of the stereocontrolling properties of com-

plex (*S*)-**1**, which showed strong preference for the α-*S* absolute configuration in alkylation, Michael, and aldol addition products.[14, 15]

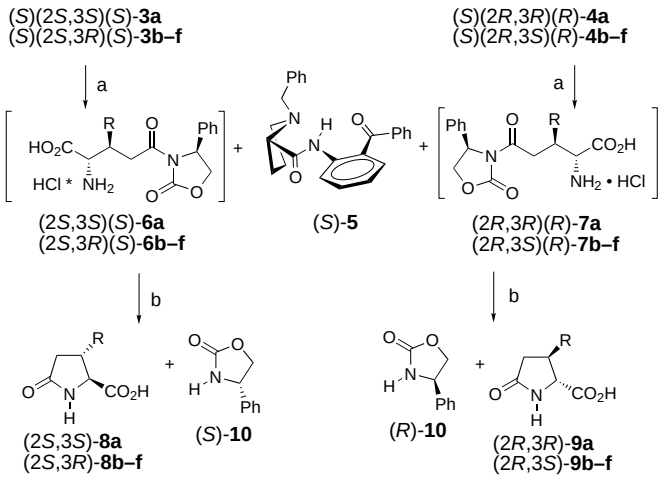
Whatever the origin of this unexpected stereochemical outcome, we next decided to study the generality of these almost diastereocomplete addition reactions. The addition of complex (*S*)-**1** with oxazolidin-2-one (*S*)-**2b**, bearing a bulky isopropyl group, occurred relatively easily (30 min) giving (2*S*,3*R*)-**3b** as the sole product, which was obtained in quantitative yield (entry 3). In contrast, the reaction of (*S*)-**1** with the 4*R*-configured enantiomer **2b**, proceeded at a substantially slower rate to give (2*R*,3*S*)-**4b** as the only diastereomeric product (entry 4). These results suggest that the reaction between complex (*S*)-**1** and (4*S*)-**2b** represents a case of matched stereochemical preferences of the chiral starting compounds, while the addition of (*S*)-**1** with (4*R*)-**2b** is a mismatched case. In contrast to our expectations, both cases featured virtually complete diastereoselectivity. The only difference was the reaction rate, a difference which was more pronounced in the additions of the sterically demanding isopropyl derivatives (4*R*)- and (4*S*)-**2b**.

Similar patterns of reactivity and stereochemical outcome were observed in the reactions between complex (*S*)-**1** with cinnamic acid derived (4*S*)- and (4*R*)-oxazolidin-2-ones **2c**. Thus, the reactions afforded as the sole products (2*S*,3*R*)-**3c** and (2*R*,3*S*)-**4c**, respectively, in quantitative chemical yields (Table 1, entries 5 and 6). The reaction rate of the former was substantially higher than that of the latter. Considering the difference in the stereochemical requirements for methyl and phenyl groups, it is interesting to note that the reactions of (*S*)-**1** with (4*S*)-**2a** and (4*S*)-**2c** occurred at virtually the same rate.

To further demonstrate the generality of our method, we investigated additions of complex (*S*)-**1** with several aromatic oxazolidin-2-ones bearing the more sterically demanding β-naphthyl group (**2d**) or derivatives of cinnamic acid with electron-withdrawing (CF_3, **2e**) or electron-donating (OMe, **2f**) substituents on the phenyl ring. All three reactions were conducted under same reaction conditions and featured virtually quantitative yields and diastereoselectivities. The sole products **4d**, **3e**, and **3f** were observed in the crude reaction mixtures by NMR analysis (entries 7–9). Regarding the reaction rates, the additions of β-naphthyl- and *p*-methoxy-containing derivatives with complex (*S*)-**1** proceeded markedly slower than the reactions of (4*R*)-**2c** and (4*S*)-**2c**, respectively (entries 6 relative to 7, and 5 relative to 9), while the reaction of trifluoromethyl derivative (4*S*)-**2e**, which possesses a more electrophilic C–C double bond, was as fast as the addition of crotonyl derivative (*S*)-**2a** (entry 1 relative to 8).

Considering the results obtained, it is reasonable to suggest that the steric and/or electronic natures of the substituents do not influence the stereochemical outcome but only affect the reaction rates; this indicates that the substituent on the C–C double bond is not directly involved in the stereoselective step of the addition reaction. On the other hand, the observed stereochemical outcome clearly suggests that the steric preferences of the chiral oxazolidin-2-ones overwhelm those of the chiral complex (*S*)-**1**. One can assume that application of achiral nickel complexes or other derivatives of glycine, instead of (*S*)-**1**, would be a feasible option to enhance the preparative value of the method, provided, of course, that the achiral derivatives feature the same high reactivity and virtually complete diastereoselective outcome of the corresponding addition reactions.[17]

With these promising results in hand, we next sought to find a simple way to prepare the target pyroglutamic acids from the addition products, along with complete recycling of both chiral auxiliaries. Following our standard procedure for preparing the pyroglutamic acids from the corresponding complexes obtained by additions of (*S*)-**1** with α,β-unsaturated carboxylic esters,[6a,b] we decomposed compounds **3a–f** and **4a–f** with 2 N hydrochloric acid in MeOH to afford $NiCl_2$, the hydrochloride of the chiral ligand (*S*)-**5**, and the corresponding glutamic acid ω-amide **6** or **7** containing the residue of the oxazolidinone (Scheme 2). We were pleased to



Scheme 2. a) MeOH/HCl; (b) 1. NH_4OH; 2. Dowex. R substituents as in Scheme 1.

find that treatment of this mixture with concentrated ammonia cleanly resulted in the intramolecular cyclization of compounds **6** and **7** to give the target pyroglutamic acids **8** and **9**, respectively, and the free (4*S*)- or (4*R*)-oxazolidinone **10**. The treatment of the reaction mixture with ammonia also converted the hydrochloride of ligand (*S*)-**5** to afford the free base (*S*)-**5**, allowing a simple and complete extraction of both chiral auxiliaries (4*S*)- and (4*R*)-**10**, and (*S*)-**5** from the aqueous ammonia solution with chloroform. Taking advantage of the basic nature of (*S*)-**5**, its further separation from (4*S*)- and (4*R*)-**10** was effectively achieved by precipitating the hydrochloric salt of (*S*)-**5** with gaseous HCl, while (4*S*)- or (4*R*)-**10** remained in the chloroform solution. By this simple procedure both chiral auxiliaries (4*S*)- or (4*R*)-**10** and (*S*)-**5** were recycled in 87–95% yield, and were used for the preparation of fresh starting Ni(II)-complex (*S*)-**1**, and (4*S*)- or (4*R*)-*N*-(*E*-enoyl)-4-phenyloxazolidin-2-ones (**2**). The enantiomerically pure pyroglutamic acids **8** and **9** were isolated effectively (93–95% yield) from the solution using a cation-exchange resin and could be recrystallized from hexane/THF for analytical purposes.

This is a highly practical asymmetric synthesis of chemically and biomedically important enantiomerically pure β-substituted pyroglutamic acids and, with the possibility of further

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transformations of the products,[4] a wide range of synthetic applications can be readily envisaged. The simplicity of the procedures, the low cost of the reagents, and the good chemical and optical yields of the products, make this a useful alternative to existing methods.[5, 6]

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A Rapid Total Synthesis of Spirotryprostatin B: Proof of Its Relative and Absolute Stereochemistry**

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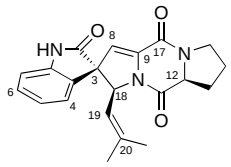
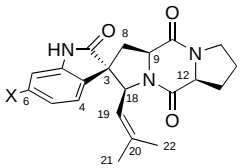
A variety of prenyl-containing alkaloids, clearly derived from the amino acids tryptophan and proline and linked by a diketopiperazine arrangement, have been isolated from natural sources.[1, 2] One such alkaloid which engaged our interest is spirotryprostatin A (**2**),[3] wherein a "prenylidene" group serves to meld N_b of the tryptophan to the β-carbon atom of the oxidized indolo sector. Recently, our laboratory



spirotryprostatin B (**1**)



X = OCH_3: spirotryprostatin A (**2**)
= H: 6-demethoxyspirotryprostatin A (**3a**)

disclosed the total synthesis of spirotryprostatin A (**2**).[4] Coproduced with the A compound in *Aspergillus fumigatus*, is spirotryprostatin B (**1**),[3] which lacks the C6-methoxyl substituent of the A congener **2**. Clearly, the additional site of unsaturation in the B system adds incremental complexity to the prospect of its total synthesis.

The relative stereochemistry of the A compound **2**, assigned on the basis of NMR "through space" connectivities between carbons 3, 18, 9, and 12 was fully corroborated by our total synthesis,[4] which also served to establish the absolute configuration. In the case of spirotryprostatin B (**1**), the "prolyl" center (C12) is spectroscopically isolated from the prenylated tryptophan domain (see Scheme 5). Thus, while the relative configurational arrangements at the C3 and C18 centers of the A and B alkaloids (**2** and **1**) are the same, the relationship between these diads and the proline-derived C12 atom could not be asserted with rigor in the latter compound. As we shall show, the surmize of the original discoverers of spirotryprostatin B (**1**) turns out to be correct.

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