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Diastereoselective formation of a quaternary center in a pyroglutamate derivative. Formal synthesis of Monatin

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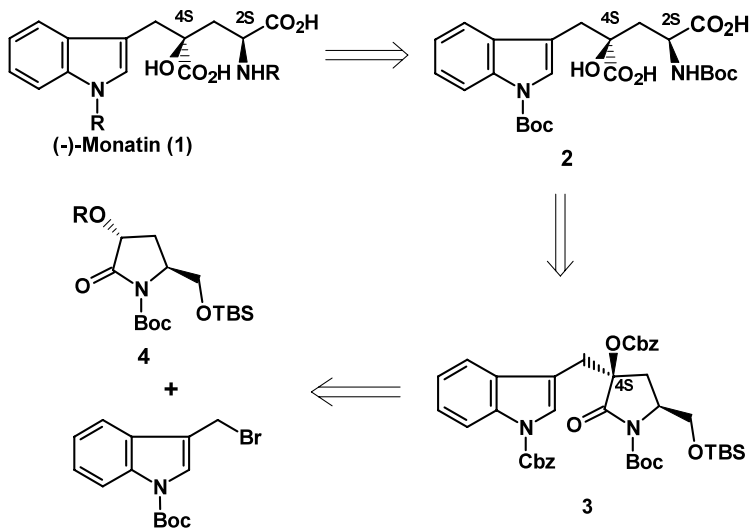
Abstract—In this communication we describe a highly diastereoselective formation of a quaternary center present in the structure of Monatin, a potent sweetening agent isolated from natural sources. The synthesis of a derivative useful for biological studies on the interactions of this type of sweetening substance on taste receptors is described. The strategy relies on the oxidation of an enolate originating from a pyroglutamate derivative followed by a highly diastereoselective alkylation with an electrophile obtained from indole.

Monatin [**1**, (2*S*,4*S*)-4-hydroxy-4-(indol-3-ylmethyl)-glutamic acid] is an unusual aminoacid isolated in South Africa from the roots of *Schlerochiton illicifolius* by Vleggaar et al.[1]

This interesting non-proteinogenic aminoacid exhibits an intense sweet taste (1200–1400 times sweeter than glucose) and is an attractive target to synthesize as a molecule having potent biological activity.

Despite the important biological properties of this molecule, very few attempts have been made to prepare it. The syntheses of racemates and an analogue of Monatin have been reported.[2]

In a current research program on the relationship between some functional groups and the sweet taste, it was necessary to have a Monatin derivative in which the two nitrogen atoms were protected (**2**, Scheme 1).



Scheme 1. Retrosynthetic analysis of **1** and **2**.

Keywords: Monatin; pyroglutamate; *N*-Boc-Monatin.

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Our interest was focused on determining the importance of the interactions of the hydrogens bonded to nitrogen with taste receptors and the perception of the sweet taste.

Recently the first asymmetric total synthesis of this substance has been described by Goodman et al.[3] This report encouraged us to disclose our results concerning a highly diastereoselective formation of a quaternary center in a pyroglutamate derivative and the synthesis of *N*-Boc-*N'*-Boc Monatin (**2**), which could be then transformed into Monatin (**1**) by the procedure of Goodman et al.[3] To achieve our objective, we utilized the strategy outlined in Scheme 1.

Monatin (**1**) and its *N*-Boc derivative (**2**) contain two stereogenic centers at C2 and C4. From our point of view, the pivotal problem in the conception of an approach to their syntheses relies upon the formation of the quaternary center at C4. If we consider **1** and **2** as direct derivatives of glutamic acid, the control of the absolute configuration at C2 can be secured if we use glutamic acid or a derivative as starting material in our strategy. In the retrosynthetic analysis shown, the quaternary center of Monatin (C4) was prepared with a high degree of diastereoselectivity by the alkylation of an enolate obtained from the derivative **4**, with the electrophile **5**, prepared from commercial indole (Scheme 1).

The lactam derivative **4** could be prepared through the oxidation of an enolate obtained from a pyroglutamate derivative. Control of the stereochemistry of the asymmetric center at C4 can be achieved in the alkylation step and is basically due to the presence of the voluminous silyl substituent at C5, which directs the electrophile preferentially to the α face of the enolate.

Our synthesis begins with the preparation of the lactam **4,** which was obtained from L-pyroglutamic acid by using a standard sequence described in the literature.[4,5] Thus, esterification of the L-pyroglutamic acid with $SOCl_2/CH_3OH$ followed by ester reduction with $NaBH_4/CH_3OH$ furnished the alcohol **7** (Scheme 2). Protection of the hydroxyl group with TBSCl, followed by nitrogen protection as a carbamate (*t*-butyloxycarbonyl, Boc) afforded the pyroglutamate derivative **9** ($[\alpha]_D^{20} = -61$ (*c* 1.1, $CHCl_3$) (lit.[6] −61 (*c* 1.1, $CHCl_3$), in four steps and with an overall yield of 65%.

Treatment of **9** with lithium bis(hexamethyldisilazide) (LHDMS) at −78°C, followed by the in situ oxidation of the enolate with dibenzyldicarbonate peroxide[7] furnished **5** in 50% yield [isolated product, purified by silica gel column chromatography (hexane:ethyl acetate 50:50); 92% yield based on recovered starting material], as the only detectable diastereoisomer. MoOPh[8] and MoOPD[9] were also tried as reagents for this oxidation step, however both failed to give lactam **5**.

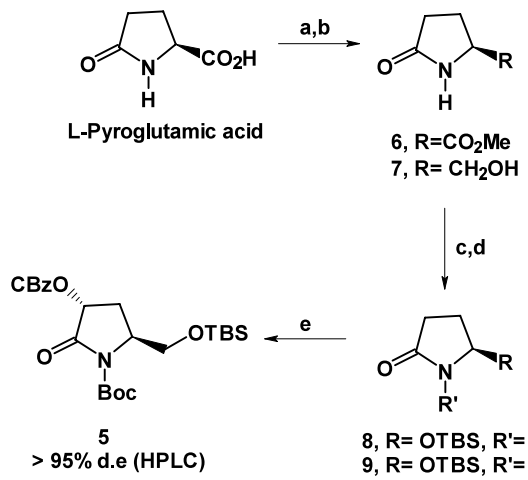
Although control of the stereochemistry in this step was unnecessary, the spatial orientation of the substituents in the new stereogenic center was determined using NOE experiments (Fig. 1).

First we irradiated the hydrogen at C5 in order to determine the spatial orientation of the hydrogens at C4. Irradiation of the hydrogen at C3 showed an increment of 2.02% in the β-oriented hydrogen at C4 and an increment of only 0.13% in the α-oriented hydrogen. These results confirm that OCBz group is α-oriented.[10]

To prepare the quaternary center of **1** and **2** we have taken advantage of a highly diastereoselective methodology for the alkylation of the pyroglutamate derivative **5**, recently described.[11] Alkylation of the enolate generated from **5** with *N*-Boc-3-bromomethylindole (**6**) at −78°C in the presence of DMPU or HMPA (10 equiv.) furnished the intermediate **3** (Scheme 3).[12] The bromoindole employed in this step as alkylating agent was prepared from indole in three steps and 76% overall yield according the procedure described by Schölkopf et al.[13]

Using chiral HPLC analysis[14] it was possible to detect only one diastereoisomer (Fig. 2).

The stereochemical assignments of **3** were established by an NOE experiment in deuterobenzene, by the irradiation of the hydrogens at C4, C5 and C6 (Fig. 3).



Scheme 2. Synthesis of the pyrogutamate derivative **5**. (a) $SOCl_2$, MeOH, 24 h, rt, 85%; (b) $NaBH_4$, *i*-PrOH, 20 h, rt, 86%; (c) imidazol, DMF, TBSCl, 0°C→rt, 24 h, 95%; (d) $(Boc)_2O$, DMAP, Et_3N, 3 h, rt, 100%; (e) (i) LHDMS, −78°C, THF, 30 min; (ii) $(BnOCO)_2O$, −78°C, 30 min; (iii) AcOH, −78→0°C, then H_2O 0°C→rt, 50%.

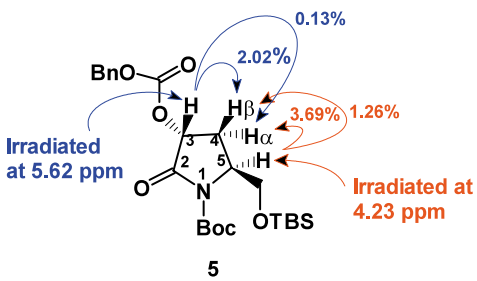


Figure 1. NOE experiments with **5**.

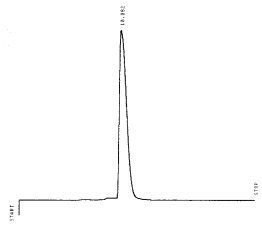
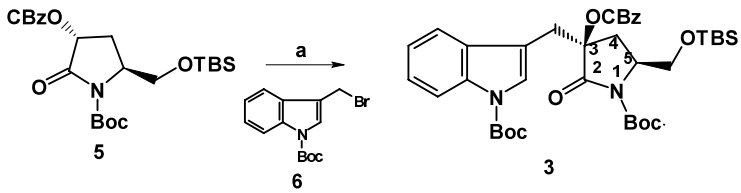


Figure 2. HPLC of **3**.[14]

This experiment was similar to the one on intermediate **5**. First we determined the orientation of the hydrogen at C4 by irradiation of the C5 hydrogen, then we separately irradiated the α- and β-oriented hydrogens.

The β-oriented hydrogen at C4 showed no increment (0%) in the absorption of the benzylic CH_2 (C6), however the α-oriented hydrogen showed an increment of 2.81%. These results indicated that the indolic moiety and the α-oriented hydrogen at C4 have a *cis* relationship. In order to evaluate the accuracy of these results we did another experiment. The methylene group at C6 (double duplet centered at δ 3.30) was irradiated and an effect was observed on the hydrogens at C4. We had no increment in the signal of the β-oriented hydrogen, however an increment of 1.19% was observed in the double doublet centered at δ 2.42, previously attributed to the α-oriented hydrogen.

At this stage of the work we have developed a highly diastereoselective methodology to generate a quaternary center in a pyroglutamate derivative. To follow our planned synthetic strategy it was necessary to remove the protective groups and cleave the lactam ring. Treatment of lactam **3** with LiOH in a mixture of THF:H_2O[15] gave **10** in 97% yield. Under these conditions the CBz protective group was also removed (Scheme 4).



Scheme 3. Formation of the quaternary center. (a) i. LHDMS, THF, −78°C, 30 min; ii. DMPU (10 equiv.), 78°C, 30 min; iii. **6**, −78°C, 3 h, 75%.

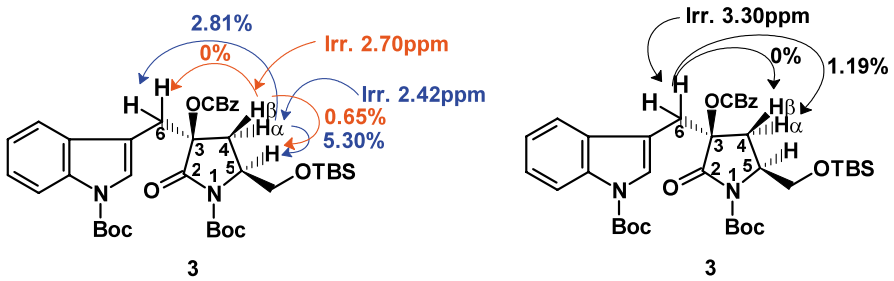
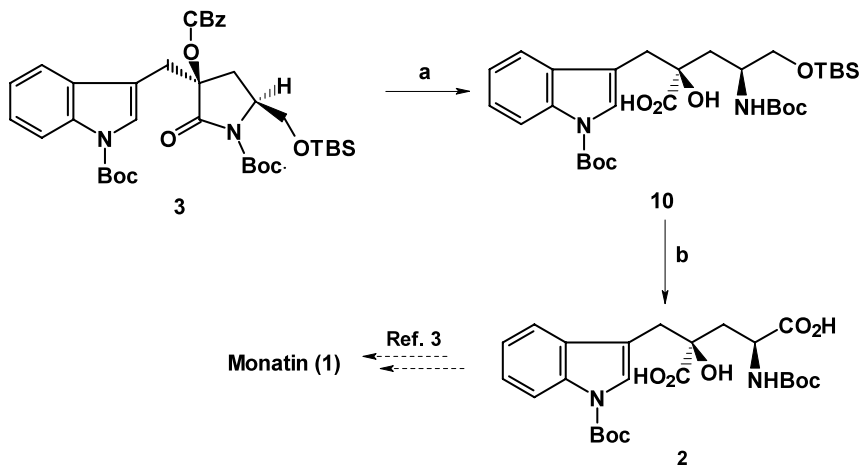


Figure 3. NOESY experiments with **3**.



Scheme 4. Synthesis of **2**. (a) LiOH, THF:H_2O (5:1), rt, 3 h, 97%; (b) Jones, 0°C, acetone, 30 min 65%.

To remove the silyl group and transform the free alcohol into the carboxylic acid, intermediate **10** was treated with Jones reagent in acetone, at 0°C, according to a known procedure,[16] to furnish the aminoacid **2**, in 65% yield (Scheme 4). From our point of view, this aminoacid (**2**)[17] should be readily transformed in Monatin, using known methodologies, such as that described by Goodman et al.[3]

In conclusion, we have developed a highly diastereoselective methodology to generate a quaternary center in a pyroglutamate derivative. This strategy has culminated with the preparation of our target compound **2**. Since the methodology to remove the *N*-Boc group is already known,[3] from our point of view, we have also made a formal synthesis of Monatin (**1**).

A simple modification in the alkylation agent used in the formation of the quaternary center permits access to other compounds of this class, this methodology seems to be versatile. Biological tests using aminoacid **2** are ongoing in our laboratory.

Supplementary material

The result of the HPLC analysis, the 500 MHz ^{1}H NMR spectra and all spectra obtained in the NOE experiments with compound **3** are available.

Acknowledgements

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17. All the spectral data are compatible for **2**. $[\alpha]_D^{20}$ −9.8 (*c*, 0.01 g/ml, CH_3OH); HRMS (M^+) calcd for $C_{24}H_{32}N_2O_9$ 492.2106; found 492.2103.