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Synthesis of (+)- and (−)-Geissman-Waiss lactone from chiral sulfonium salts

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ABSTRACT

A novel series of chiral cyclic zwitterionic pyrrolidinone type intermediates was prepared *via* regioselective 5-*exo*-trig-ring-closure of the corresponding chiral sulfonium salts. This synthetic strategy allowed the rapid non-racemic synthesis of the Geissman-Waiss lactone in six steps and 35% overall yield.

Introduction

Pyrrolizidine alkaloids, specifically those that contain the 1-hydroxypyrrolizidine core, known as 'necine base' alkaloids are found in many plant families [1] and have shown a wide range of biological activities such as anticarcinogenic, antitumor, antispasmodic, hypotensive and anti-inflammatory (Fig. 1) [2].

In this sense, the Geissman-Waiss lactone (GWL: 2-oxa-6-azabicyclo[3.3.0]octan-3-one) [3] has proved to be a key intermediate for the synthesis of a variety of pyrrolidine alkaloids with a necine scaffold. Accordingly, a number of synthetic strategies to GWL have been reported starting from 4-hydroxy-L-proline [4], carbohydrates [5] *N*-protected amino acids [6] and (*R*)-(+)-malic acid [7], *via* enzymatic reduction of keto-proline [8] or by microbial Baeyer-Villiger oxidation of *N*-Cbz-2-aza-bicycloheptanone.[9] Methodologies for the diastereoselective syntheses of (+)- and (−)-GWL are based on the [2 + 2] cycloaddition reactions of ene carbamates in the presence of chiral auxiliaries [10], through selective reductive alkylation of protected (*S*)-malimide [11] and *via* intramolecular C—H insertion reactions of (*R*)-*N*-Cbz-3-hydroxypyrrolidine diazoacetates promoted by a chiral Rh(II) catalyst [12].

In a previous report we disclosed a methodology for the synthesis and synthetic applications of new chiral cyclic zwitterionic piperidine compounds starting from sulfonium salts derived from chiral primary amines (Scheme 1, top) [13]. Following on from this work and motivated by the importance of the development of novel strategies for the synthesis of necine alkaloids, we present herein a novel synthetic route to GWL highlighting the preparation of new cyclic zwitterionic pyrrolidine compounds, which were prepared *via* regiospecific ring-closure of sulfonium salts (Scheme 1, bottom).

Results and discussion

The inseparable diastereomeric mixture of chiral sulfonium salts from *trans*-fumarate and primary chiral amines (*S*)-α-methylbenzylamine **5(a + b)** and (*R*)-4-methoxy-α-methylbenzylamine **6 (a + b)** were prepared following our previously reported reaction conditions [12]. We also prepared enantiopure sulfonium salts **7** and **8** from L-aspartic acid (Scheme 2) [14].

The intramolecular ring-closure reaction was investigated with the inseparable diastereomeric mixture of sulfonium salts **5(a + b)** in the presence of KOH in CH_3CN:MeOH (9:1) at room temperature. The exclusive formation of diastereomeric cyclic zwitterionic pyrrolidine-2-one **9(a + b)** was unambiguously determined by ^1H and ^{13}C NMR and 2D HMBC spectroscopy. Typical benzylic protons at approximately δ_H 5.47 ppm [15], the S-Me singlet at δ_H 3.01 ppm and the ylide carbon resonance at δ_C 67 ppm [16] confirmed the presence of the sulfur ylide compound (Scheme 3).

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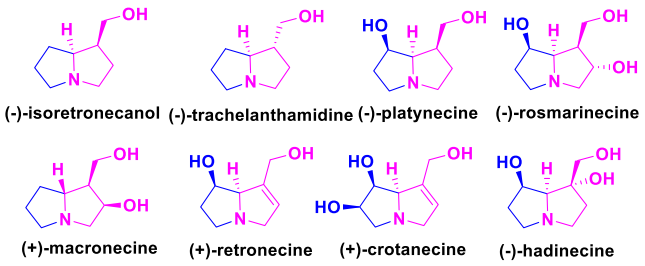
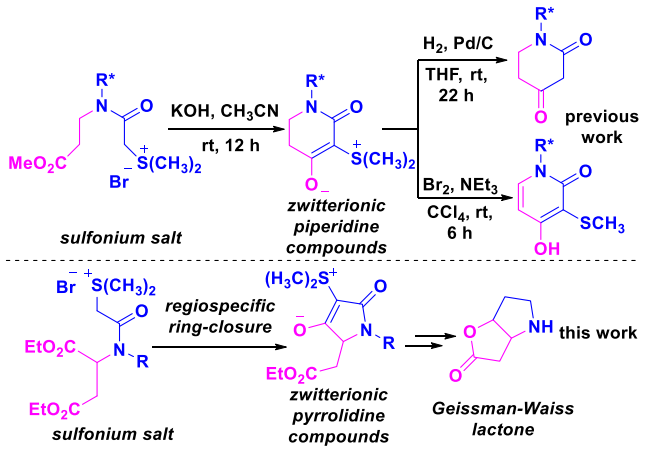
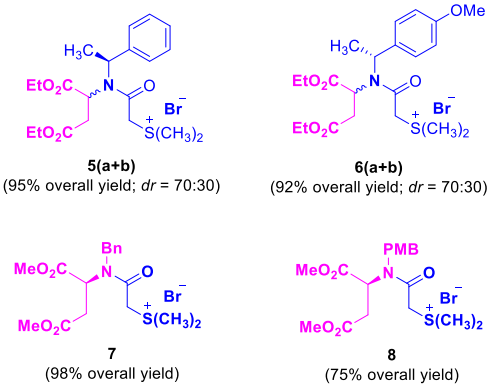


Fig. 1. Representative pyrrolidine alkaloids isolated from plants.



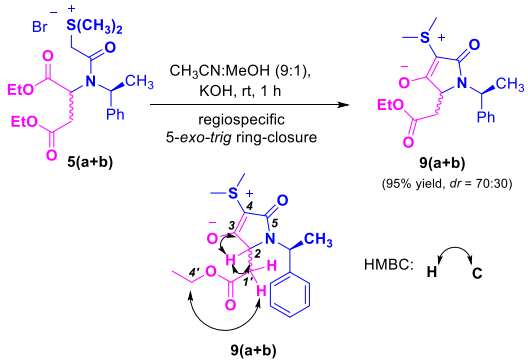
Scheme 1. Previous studies on the synthesis and reactivity of cyclic zwitterionic intermediates and the current synthetic studies of related compounds.



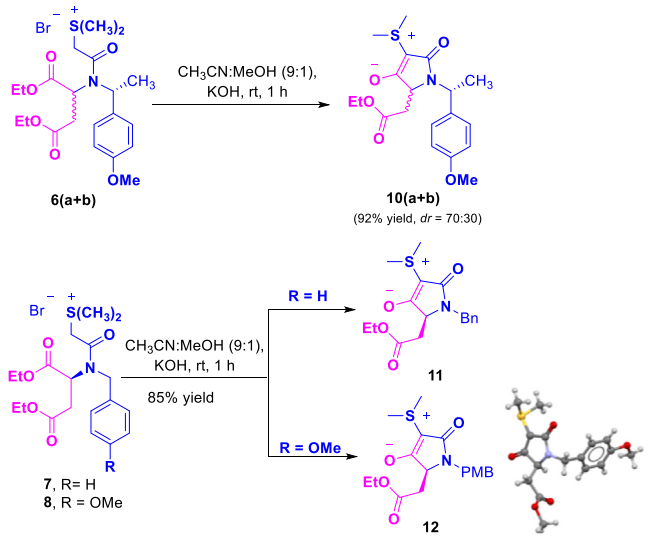
Scheme 2. Synthesis of diastereomeric mixtures of sulfonium salts **5(a + b)** and **6 (a + b)** and enantiopure sulfonium salts **7** and **8**.

Then, the diastereomeric mixture of sulfonium salts **6(a + b)** and enantiopure sulfonium salts **7** and **8** were subjected to the optimized reaction conditions affording the desired cyclic zwitterionic intermediates **10(a + b)**, **11** and **12**. Fortunately, compound **12** provided suitable crystals for X-ray crystallographic analysis to confirm the presence of a cyclic pyrrolidine-2-one structure (Scheme 4) [17].

Next, the desulfurization reaction of the diastereomeric mixture of cyclic zwitterions **9(a + b)** was studied. Initially the reaction was conducted using Pd/C as the catalyst in EtOH according to our previously reported reaction conditions (Entry 1, Table 1) [13]. Unfortunately, the starting material remained unchanged even after

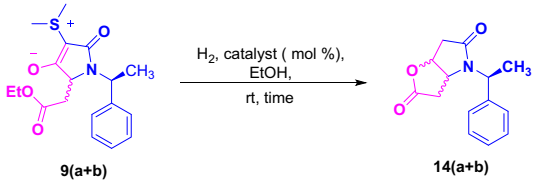


Scheme 3. Regiospecific 5-*exo*-trig ring-closure of sulfonium salts **5(a + b)** and diagnostic signals for unequivocal assignment of the sulfur ylide pyrrolidine-2-one compounds through HMBC correlations.



Scheme 4. Chiral cyclic pyrrolidine-2-one zwitterionic structures.

Table 1
Screening experiments for the desulfurization-reduction-lactonization tandem reaction.



Entry	Catalyst (mol%)	Time [h]	Yield [%]
1	Pd/C (20% mol)	48	
2	PtO_2 (20% mol)	96	
3	Raney-Ni[a]	72	35
4	Raney-Ni[a]	120	40

[a] Raney-Ni slurry 50% in water was used.

prolonged reaction time. The use of PtO_2 also proved to be unsuccessful (Entry 2, Table 1). Surprisingly, when Raney-Ni catalyst was used, not only did the desulfurization reaction occur but also the

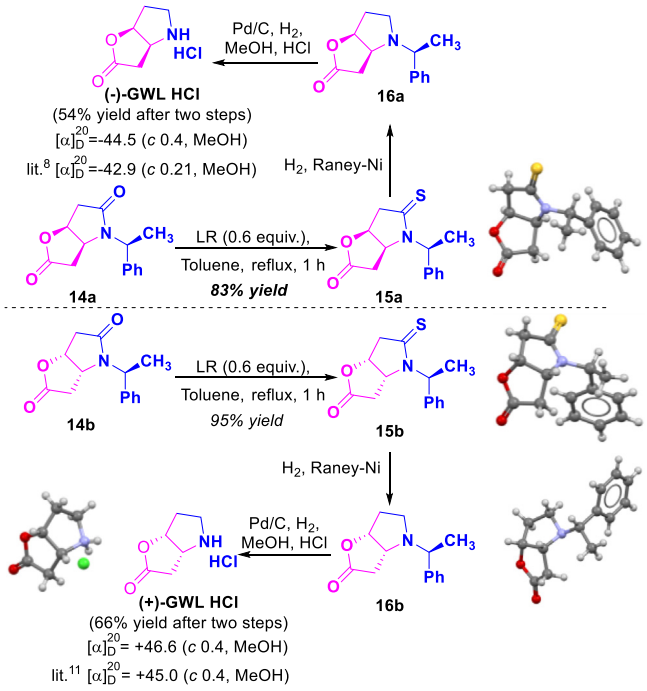
desired reduction and lactonization proceeded in low yield to give **14(a + b)**. Prolonged reaction times and increasing the amount of the catalyst did not significantly improve the yield (Entries 3 and 4, Table 1).

Due to the low yield observed in the tandem reaction, reductive desulfurization of **9(a + b)** was promoted using Zn (15 equiv.) in acetic acid [18]. Once the total consumption of starting material was confirmed by TLC, NMR analysis of the crude reaction revealed the presence of the corresponding tetramic acid **13(a + b)**. Unfortunately, this intermediate proved to be unstable under SiO_2 chromatographic conditions, and consequently the crude reaction was directly subjected to ketone reduction with $NaBH_4$ (2 equiv.) in $AcOH:CH_2Cl_2$ (1:9). The NMR spectrum of the crude reaction revealed the presence of a diastereomeric mixture of bicyclic lactones **14(a + b)** in a 30:70 diastereomeric ratio. Once the diastereomeric mixture was separated, each diastereoisomer crystalized enabling the determination of the new stereogenic centres as (*S*,*S*)- for the minor diastereoisomer **14a** and (*R*,*R*)- for the major diastereoisomer **14b** (Scheme 5) [17].

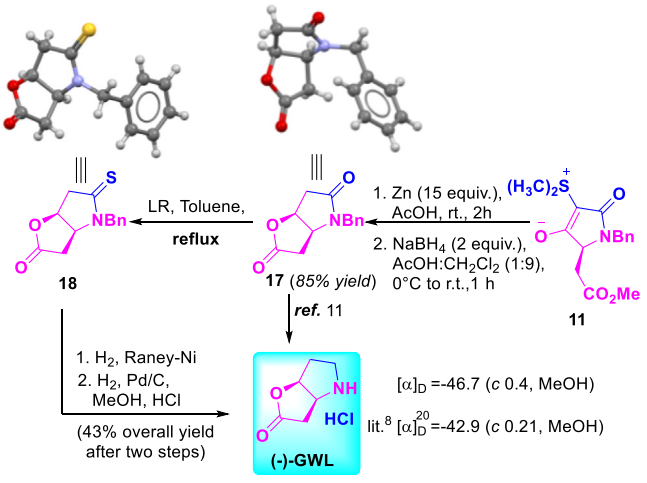
With bicyclic lactone amides **14a** and **14b** in hand, we proceeded to complete the total synthesis of (−)- and (+)-GWL. The major diastereoisomer **14b** was reacted with Lawessońs reagent (LR) to produce the desired thioamide **15b** in 95% yield. X-ray crystallographic analysis confirmed the molecular structure of **15b** [17]. Subsequent thioamide reduction with Raney-Ni catalyst afforded **16b** [17] which provided (+)-GWL HCl [17] after debenzylation. On the other hand, following the same procedure as for **14b**, (−)-GWL·HCl was obtained in 42% overall yield from thioamide **15a** [17] (Scheme 6).

Encouraged by the results described above, this approach was applied to the enantiospecific synthesis of (−)-GWL starting from cyclic zwitterion **11** derived from L-aspartic acid. Accordingly, the sequential desulfurization-reduction-lactonization reaction afforded the desired bicyclic lactone **17** [17] which was subsequently treated with LR to give thioamide **18** [17]. Then, reduction of the thioamide function with Raney-Ni and subsequent hydrogenolysis gave (−)-GWL·HCl. In addition, **17** could be reduced and debenzylated following the sequence reaction reported by Huang [11] to afford (−)-GWL·HCl (Scheme 7).

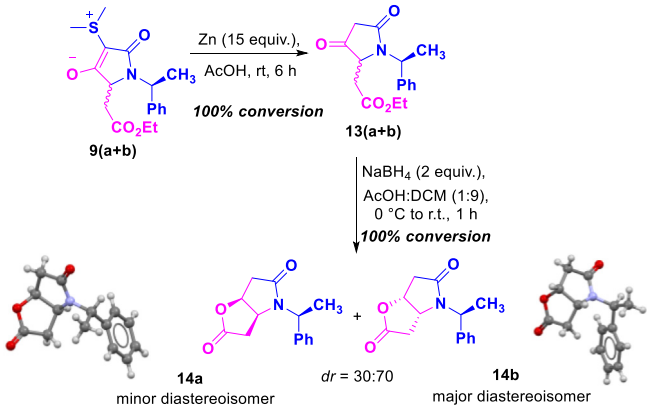
Next, cyclic zwitterion **12** derived from NPMB protected L-aspartic acid was subjected to an optimization process, affording the enantiopure bicyclic lactone **20** [17]. Then oxidative debenzylation with ammonium nitrate (CAN) furnished the valuable intermediate **21** [17], from **20** (Scheme 8).



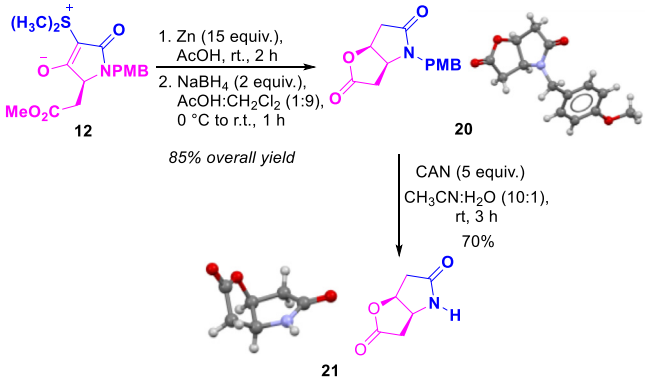
Scheme 6. Syntheses of (−)- and (+)-GWL.



Scheme 7. Enantiospecific synthesis of (−)-GWL.



Scheme 5. Sequential process to access bicyclic lactones **14a** and **14b**, and their X-ray crystal structures.



Scheme 8. Synthesis of bicyclic lactone amide derived from enantiopure zwitterion **12**.

Conclusion

In summary, we have developed a concise synthetic route to bicyclic GWL featuring a regiospecific ring-closure reaction of sulfonium salts to zwitterionic pyrrolidinone intermediates, followed by a dehydrosulfurization–reduction–lactonization sequence process. The developed methodology provides access to both enantiomers of the GWL. In addition, the efficiency of this approach was also demonstrated in a short (eight-step) enantiospecific synthesis of (−)-GWL starting from L-aspartic acid. The application of this methodology to the synthesis of structurally more complex bicyclic natural products is currently underway in our laboratory, and the results of these efforts will be reported in due course.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.151697.

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