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Enantioselective Synthesis for the Antipodes of Slagenins B and C: Establishment of Absolute Stereochemistry

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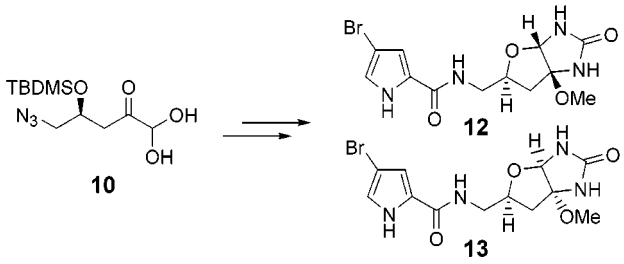
ABSTRACT



The total synthesis for the (–)-antipode of slagenin B (12) and the (+)-antipode of slagenin C (13) was achieved with the condensation of glyoxal hydrate 10 and urea as the key step. The absolute stereochemistries of naturally isolated slagenins B and C were assigned to be (9*R*,11*R*,15*R*)-1b and (9*R*,11*S*,15*S*)-1c, respectively.

Several bromopyrrole alkaloids found in marine sponges have been shown to exhibit pharmacologically useful activities and include *c-erbB*-2 kinase and cyclin-dependent kinase 4 (cdk4) inhibitors, α-adrenoceptor blockers, serotonergic receptor antagonists, and antihistamine and actomyosin ATPase activators, etc.[1] Recently, Kobayashi et al. isolated a novel class of alkaloids, slagenins A−C (**1a**−**1c**) (Figure 1), from the Okinawan sponge *Agelas nakamurai*.[2] These alkaloids possess a unique tetrahydrofuro[2,3-*d*]imidazolidin-2-one core in which the relative stereochemistry was elucidated by NOESY spectroscopy. Although slagenins exhibit biological activities similar to those of other bromopyrrole alkaloids, only preliminary tests have been carried out due to the extremely small amount of samples available from marine sources.[2] While Horne and co-workers achieved the first total synthesis of slagenins A−C,[3] their absolute stereochemistries have never been determined. We were interested in developing an enantioselective synthetic method for building the chiral tetrahydrofuro[2,3-*d*]imidazolidin-2-one core and determining the absolute configurations of naturally isolated slagenins B and C.

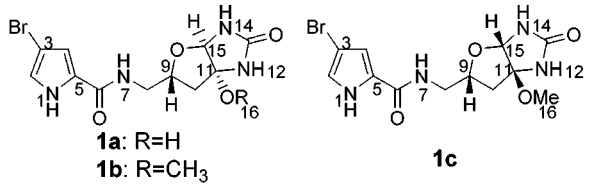


Figure 1. Structures of natural slagenins A−C.

(1) Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1 and references therein.
(2) Tsuda, M.; Uemoto, H.; Kobayashi, J. *Tetrahedron Lett.* **1999**, *40*, 5709.
(3) Sosa, A. C. B.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2000**, *2*, 3443.

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Slagenins possess a cis-fused tetrahydrofuro[2,3-*d*]imidazolidin-2-one moiety with three stereogenic centers. The key of the synthetic scheme is the generation of these three stereogenic centers in the tetrahydrofuro[2,3-*d*]imidazolidin-2-one skeleton. Retrosynthetically, we considered that the condensation reaction of glyoxal **3** and urea could be useful for accessing intermediate **2** (Figure 2) on the basis of the

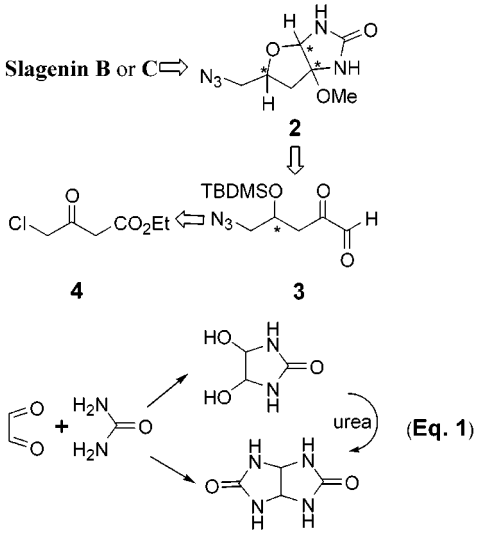


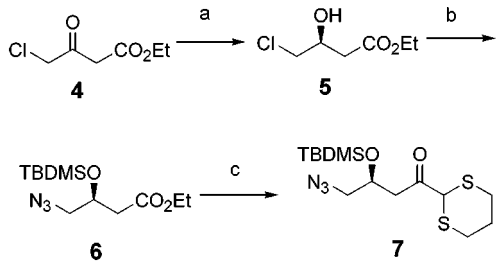
Figure 2. Retrosynthesis of slagenins B and C.

relevant synthesis of dihydroxyimidazolidin and glycoluril from glyoxal and urea (eq 1).[4] In this synthetic plan, another key issue that must be addressed is the generation of the chiral intermediate **3** so that the other two stereogenic centers can be induced.

Hydrogenation of commercially available ethyl 4-chloroacetoacetate (**4**) over Ru(OAc)$_2$(*R*-BINAP) afforded ethyl-(*S*)-4-chloro-3-hydroxybutanonate (**5**) in 95% yield (97% enantiomeric excess (ee)).[5] The 3-hydroxy group was protected as a *tert*-butyl dimethyl silyl ether, and then the 4-chloro group was displaced with azide, giving compound **6**. Next, the carbon chain was elongated with 1,3-dithiane to obtain thioketal **7**. Unfortunately, all attempts to cleave the thioketal were unsuccessful[6] (Scheme 1).

We next considered the synthesis of the glyoxal **3** from an α-diazoketone. Prato et al. reported a mild and efficient process for preparing achiral labile α-oxo-aldehydes by the oxidation of α-diazoketones with dimethyl-dioxirane.[7] Thus,

Scheme 1[a]



[a] Reagents and conditions: (a) H_2, 0.1 mol % Ru(OAc)$_2$(*R*-BINAP), EtOH, 40 atm, 100 °C, 95%; (b) (1) TBSCl, imidazole, DMF, 45 °C, and (2) NaN_3, DMF, 90 °C, 85% for two steps; (c) 1,3-dithiane, *n*-BuLi, dry THF, −30 °C ∼ room temperature, 44%.

ester **6** was saponified to give acid **8**, which was converted into α-diazoketone **9** via the mixed anhydride by treatment with ethereal diazomethane. Oxidation of diazoketone **9** using distilled dimethyl-dioxirane (DMD)[8] in acetone afforded a mixture of glyoxal **3** and glyoxal hydrate **10** in quantitative yield. The glyoxal was sensitive to air and could not be purified by distillation or chromatography. Fortunately, the crude product was pure enough to use in subsequent reactions. With the key intermediate **3** and its hydrate **10** in hand, we tried to cleave the *tert*-butyl dimethyl silyl ether. Several conditions were tested for the cleavage, and most gave complex results. Finally, we found that one-pot treatment of the glyoxal mixture containing **3** and **10** with aqueous HF and urea in methanol gave compound **2** in 50% yield. The ^{1}H NMR spectrum of **2** showed a 9:5 mixture of two diastereoisomers **2a** and **2b**, which could not be separated from each other by silica gel chromatography. We inferred that the trans-fused bicycle was not present due to the obvious strain of a trans [3.3.0]bicycle and that isomer **2a** predominated over isomer **2b** as a result of intramolecular steric hindrance. However, separation of the diastereomers required further elaboration of the core. Therefore, the azido group in intermediate **2** was reduced to an amino group by hydrogenation over 10% Pd/C in methanol, and the amine was then acylated with 4-bromo-2-(trichloroacetyl)pyrrole to give a 9:5 ratio of compounds **12** and **13** in 80% yield for two steps (Scheme 2).

Compounds **12** and **13** were separated by silica gel chromatography, allowing us to firmly establish the stereochemistries of both compounds and therefore confirm the stereochemistries inferred for diastereomers **2a** and **2b**. The NMR, IR, and mass spectral data for compound **12** were in satisfactory agreement with those reported for synthetic and naturally isolated slagenin B, while the data for compound **13** agreed well with those for synthetic and naturally isolated slagenin C.[2−3] The NOESY spectrum of **12** showed correlations for H-9 to both H-12 and H-14, H-15 to H$_3$-16, H-10β to H-7, and H-10β to H-15, indicating that the bicycle of **12** was cis-fused and that H-9, H-15, and the methoxy group at

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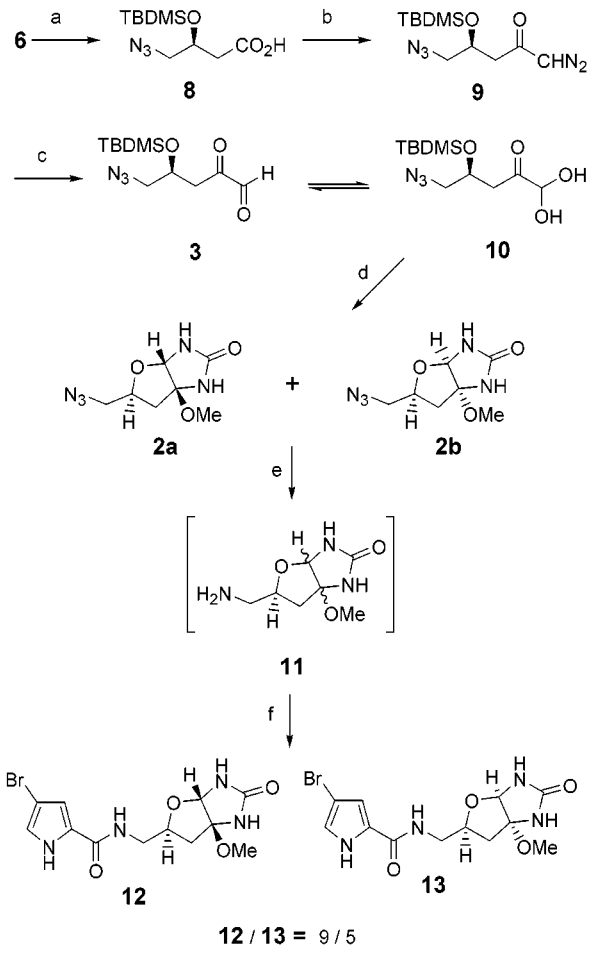
(5) (a) Ager, D. J.; Laneman, S. A. *Tetrahedron: Asymmetry* **1997**, *8*, 3327. (b) Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1996**, *7*, 1919. (c) Yuasa, Y.; Tsuruta, H. *Liebigs Ann. Chem.* **1997**, 1877.

(6) (a) Juaristi, E.; Tapia, J.; Mendez, R. *Tetrahedron* **1986**, *42*, 1253. (b) Corey, E. J.; Bock, M. G. *Tetrahedron Lett.* **1975**, 2643. (c) Cossy, J. *Synthesis* **1987**, 1113. (d) Prato, M.; Quinity, U.; Scorrano, G.; Sturaro, A. *Synthesis* **1982**, 679.

(7) Ihmels, H.; Maggini, M.; Prato, M.; Scorrano, G. *Tetrahedron Lett.* **1991**, *32*, 6215.

(8) (a) Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377. (b) Bull, J, R.; Dekoning, P. D. *Eur. J. Org. Chem.* **2001**, 1189. (c) Rainier, J. D.; Allcrein, S. P.; Cox, J. M. *J. Org. Chem.* **2001**, *66*, 1380.

Scheme 2[a]



[a] Reagents and conditions: (a) (1) 2 equiv LiOH, acetone−water, room temperature, and (2) H^+, 95%; (b) (1) isobutyl chlorocarbonate, NEt_3, dry THF, −20 °C ∼ −10 °C, and (2) 2 equiv ethereal diazomethane, 90%; (c) DMD−acetone, 100%; (d) 40% aqueous HF, 2.5 equiv urea, methanol, room temperature, 50%; (e) H_2, Pd/C, methanol; (f) 4-bromo-2-(trichloroacetyl)pyrrole, DMF, room temperature, 80% for two steps.

C-11 were α-, *β*-, and *β*-oriented, respectively. For compound **13**, the NOESY correlations for H-9 to H-15 and for H-15 to H_3-16 implied that H-9, H-15, and the methoxy group at C-11 were all *β*-oriented. Therefore, the absolute structures of **12** and **13** were respectively assigned to be (9*S*,11*S*,15*S*)-**12** and (9*S*,11*R*,15*R*)-**13** (Figure 3). Comparison of the negative specific rotation of **12** {$[\alpha]^{20}_D = -45.4°$ (*c* 0.5, MeOH)} with the positive specific rotation of naturally isolated slagenin B {$[\alpha]^{26}_D = +33°$ (*c* 0.2, MeOH)} revealed that the naturally isolated slagenin B has a (9*R*,11*R*,15*R*)-configuration, while comparison of the specific rotation of

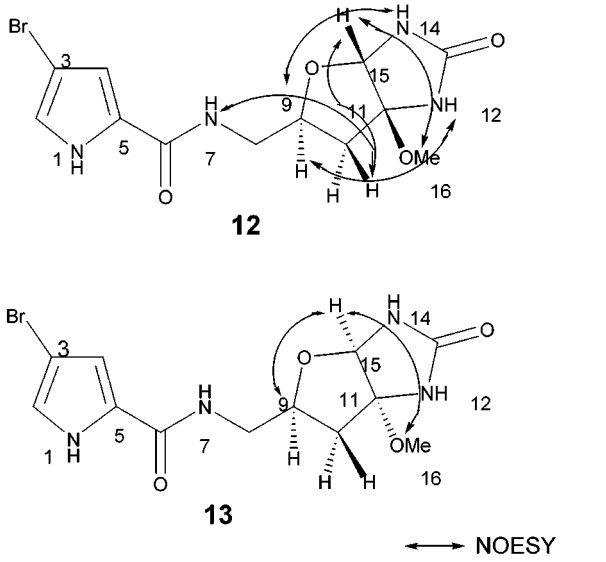


Figure 3. Structures of **12** and **13**.

13 {$[\alpha]^{20}_D = +35.0°$ (*c* 0.2, MeOH)} with that of naturally isolated slagenin C {$[\alpha]^{25}_D = -35°$ (*c* 0.2, MeOH)} suggested that the absolute structure of naturally isolated slagenin C should be (9*R*,11*S*,15*S*)-**1c** (Figure 1).

In summary, a short total synthesis for the (−)-antipode of slagenin B and the (+)-antipode of slagenin C has been accomplished. An enantioselective synthetic approach for preparing the cis-fused tetrahydrofuro[2,3-*d*]imidazolidin-2-one skeleton from glyoxal hydrate and urea has been developed. Furthermore, the absolute structures of naturally isolated slagenins B and C were established to be (9*R*,11*R*,15*R*)-**1b** and (9*R*,11*S*,15*S*)-**1c**, respectively, by comparison with the enantioselectively synthesized antipodes of slagenins B and C.

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Supporting Information Available: Spectroscopic data and experimental procedures for compounds **2**, **3** and **10**, **5**−**9**, and **12**−**13**; ^{1}H NMR spectra for compounds **2** and **3** and **10**; ^{1}H and ^{13}C NMR spectra for compounds **6**, **8**−**9**, and **12**−**13**; NOESY spectra for compounds **12**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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