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Enantioselective Total Syntheses of Slagenins A−C and Their Antipodes

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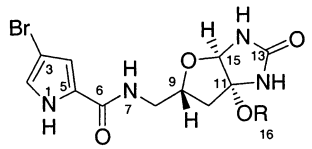
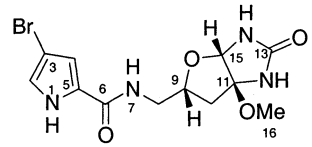
Full details of the total syntheses of slagenins A−C (**1a**−**c**) and their antipodes (**2a**−**c**), novel bromopyrrole alkaloids with a unique tetrahydrofuro[2,3-*d*]imidazolidin-2-one moiety, are described in which their absolute stereochemistry was established. The key step in the syntheses involves the efficient condensation of dihydrofuran-3-one or glyoxal with urea to construct the slagenin bicycle core.

Introduction

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, antihistamine and actomyosin ATPase activators, etc.[1] Due to their interesting physiological properties, the syntheses of these compounds have attracted considerable attention from synthetic chemists.[2−4] Slagenins A−C (**1a**−**c**) (Figure 1) comprise a group of cytotoxic secondary marine metabolites recently isolated from the Okinawan sponge *Agelas nakamurai*.[5,6] These structurally interesting bromopyrrole alkaloids possess a highly functionalized tetrahydrofuro[2,3-*d*]imidazolidin-2-one moiety in which the relative stereochemistry was elucidated by 2D NMR spectroscopy.[5] Because slagenins are available in nature in only minute amounts and may be of significant interest for more detailed pharmacological investigations, it became the goal of the current project to develop efficient total syntheses for these bromopyrrole alkaloids. While the first total synthesis of slagenins A−C was achieved in a biomimetic pathway involving the oxidative cyclization of β-hydroxyimidazolones,[7,8] their absolute stereochemistries have not been determined. Herein, we report full details of enantioselective total syntheses of slagenins A−C and their antipodes which established their absolute stereochemistry, and the efficient preparation of tetrahydrofuro[2,3-*d*]imidazolidin-2-one skeletons from the condensation of dihydrofuran-3-one or glyoxal with urea.[9,10]



1a: R=H Slagenin A
1b: R=Me Slagenin B



1c: Slagenin C

FIGURE 1. Structures of slagenins A−C

Results and Discussion

Retrosynthetic Analysis. Slagenins possess a cis-fused tetrahydrofuro[2,3-*d*]imidazolidin-2-one moiety with three stereogenic centers, one of which is the C11 quarternary carbon center. The key to the synthetic scheme is the generation of the three stereogenic centers in the moiety. In the literature, only two reports describe the preparation of tetrahydrofuro[2,3-*d*]imidazolidin-2-

* Corresponding author.

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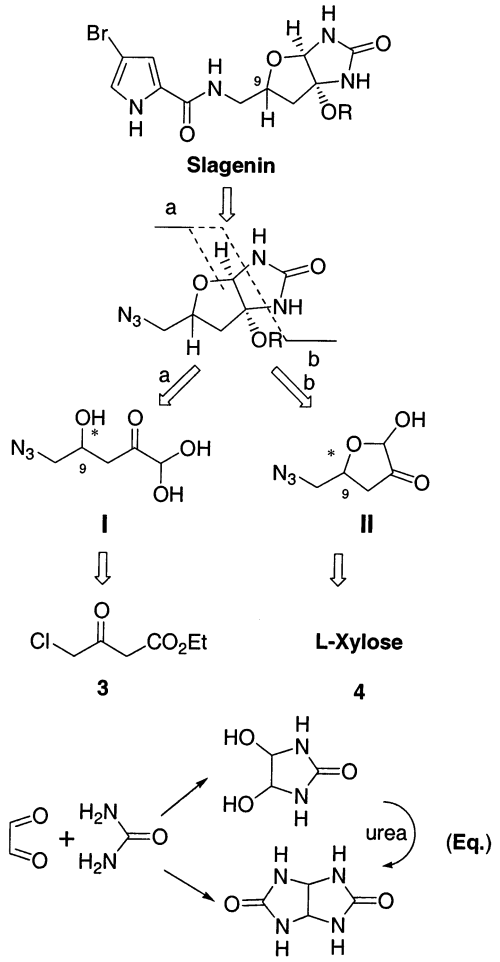
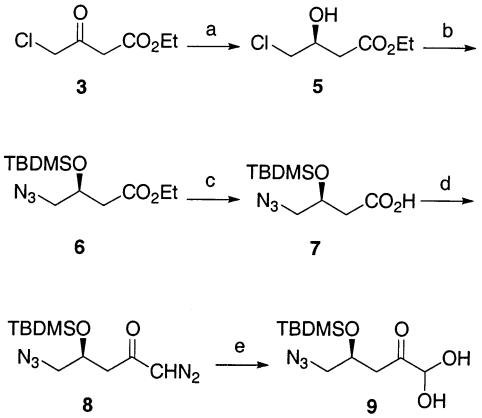


FIGURE 2. Retrosynthesis of slagenins A−C

one skeletons: one from reaction of 2-aminosugars with isocyanates;[11] another by oxidative cyclization of *β*-hydroxyimidazolones.[7] The slagenin bicycle core can be retrosynthesized, in the most direct way, to the condensation of urea with the corresponding glyoxal **I** or dihydrofuran-3-one **II** based on the relevant synthesis of dihydroxyimidazolidin and glycoluril from urea and glyoxal (**Eq.**).[12] It might be expected that, due to the obvious strain of a *trans*-[3.3.0]bicycle, the bicycle derived from the condensation must be cis-fused.[11] The other two of the three stereogenic centers would be generated in an enatioselective way induced by chiral C9 (refer to the numbering system of slagenin) as a result of intramolecular steric hindrance. So, the C9 stereogenic center was considered to be derived, in an assured way, either from Noyori hydrogenation of commercially available ethyl 4-chloroacetoacetate (**3**) or from L-xylose (**4**) (Figure 2).

SCHEME 1[a]



[a] Key: (a) H_2, 0.1 mol % of $Ru(OAc)_2$(*R*-BINAP), EtOH, 40 atm, 100 °C, 95%; (b) (1) TBDMSCl, imidazole, DMF, 45 °C; (2) NaN_3, DMF, 90 °C, 85% for two steps; (c) (1) LiOH, acetone−water, rt; (2) H^+, 95%; (d) isobutyl chlorocarbonate, NEt_3, dry THF, −20 to −10 °C; (2) 2 equiv of ethereal diazomethane, 90%; (e) DMD−acetone, 100%.

Synthesis of the Antipodes.[9] We began our research on the enantioselective synthesis of slagenins with a preparation of the key intermediate glyoxal **I** from commercially available ethyl 4-chloroacetoacetate (**3**). After some fruitless studies on the preparation of the glyoxal (vide post), we turned to the synthesis of the glyoxal **I** from an α-diazoketone.[13] Thus, Noyori hydrogenation of compound **3** afforded ethyl (*S*)-4-chloro-3-hydroxy-butanonate (**5**) in 95% yield (97% ee).[14,15] The 3-hydroxy group was protected as a *tert*-butyl dimethyl silyl ether, and then the 4-chloro group was displaced with azide to give ester **6**.[16] Ester **6** was saponified to give acid **7**, which was converted into α-diazoketone **8** via the mixed anhydride by treatment with ethereal diazomethane.[13] Oxidation of diazoketone **8** with distilled dimethyl-dioxirane (DMD)[17] in acetone quantitatively afforded glyoxal **9**,[18] which appeared to be in the corresponding α-keto aldehyde and its hydrate form. 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 (Scheme 1).[9]

With the key intermediate **9** in hand, we turned our attention to its condensation with urea. At first, 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 a treatment of the cleavage and the condensation in one pot gave out satisfactory results (Scheme 2). Reaction of the glyoxal **9** with HF and urea in acetone−water solution gave

(9) For a preliminary account of enantioselective synthesis for the antipodes of slagenin B and C, see: Jiang, B.; Liu, J.-F.; Zhao, S.-Y. *Org. Lett.* **2001**, *3*, 4011.

(10) For a preliminary account of the enantioselective synthesis of slagenins A∼C, see: (a) Jiang, B.; Liu, J.-F.; Zhao, S.-Y. *Org. Lett.* **2002**, *4*, 3951. (b) Gurjar, M. K.; Bera, S. *Org. Lett.* **2002**, *4*, 3569.

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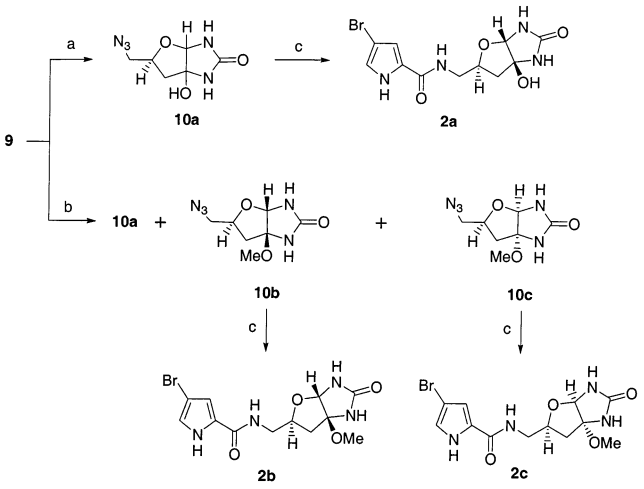
(18) Oxidation of diazoketone **8** with DMD generated in situ from oxone gave complex results.

SCHEME 2[a]

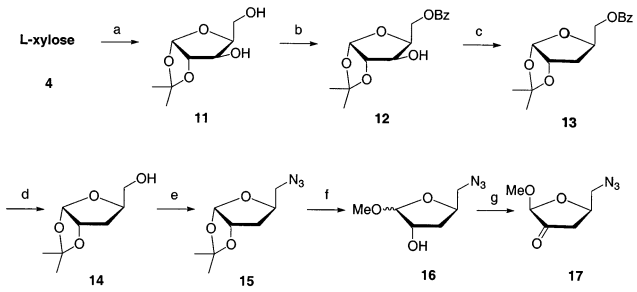


[a] Key: (a) urea, HF, acetone−water, rt, 58%; (b) urea, 40% aq HF, methanol, rt, yield **10a** (26%), **10b** and **10c** (54%, a mixture, **10b**/**10c** 9/5); (c) (1) H_2, Pd/C, methanol; (2) 4-bromo-2-(trichloroacetyl)pyrrole, DMF, rt, for two steps (77% for **10a**, 80% for **10b** and **10c**).

compound **10a** in 58% yield. Although compound **10a** was shown to be a simple compound by TLC analysis, it showed itself from the proton NMR spectral data to be a mixture of two diastereoisomers in a ratio of 5:2. However, after the reduction of intermediate **10a** by hydrogenation over 10% Pd/C in methanol and the follow-up acylation with 4-bromo-2-(trichloroacetyl)pyrrole,[19] only a simple compound **2a** was separated in 77% yield. A plausible mechanism for this strange transformation was arbitrarily brought forward (vide post). The NMR, IR, and mass spectral data for compound **2a** were in satisfactory agreement with those reported for synthetic and naturally isolated slagenin A.[5,7] And the NOESY spectrum showed correlations for H-9 to H-10α and H-8 to H-10*β*, H-15 to 11-OH, and H-10*β* to both 11-OH and H-15, indicating that the bicycle of **2a** was cis-fused and that H-9, H-15, and the hydroxy group at C-11 were α-, *β*-, and *β*-oriented, respectively. Therefore, the absolute structure of **2a** was assigned to be (9*S*,11*S*,15*S*)-**2a**. Comparison of the negative specific rotation of **2a** {$[\alpha]^{20}_D$ −7.6 (*c* 0.5, MeOH)} with the positive specific rotation of naturally isolated slagenin A {$[\alpha]^{27}_D$ +11 (*c* 1.2, MeOH)}[5] revealed that the synthetic compound **2a** was the antipode of naturally isolated slagenin A (**1a**).

A multicomponent condensation route has also been developed to construct the slagenin core with a methoxy group linked to the C11 quarternary carbon center (Scheme 2). The glyoxal **9** was treated with aqueous HF and urea in methanol at ambient temperature. After removal of the solvent, flash chromatography afforded two compounds. One was compound **10a**, which also showed itself from its proton NMR spectrum to be a mixture of two diastereoisomers in a ratio of 5:2. Another was shown by its proton NMR spectrum to be a 9:5 mixture of two diastereoisomers **10b** and **10c** which were

SCHEME 3[a]



[a] Key: (a) (1) $CuSO_4$, H_2SO_4, acetone, rt, 24 h; (2) 0.1 mol/L HCl, rt, 1 h; (b) BzCl, Py, dry CH_2Cl_2, 0 °C, 1 h, 80% yield from L-xylose; (c) (1) NaH, CS_2, rt, overnight, then MeI, 1.5 h, dry THF, rt; (2) Bu_3SnH, 5 mol % of AIBN, benzene, reflux, 4 h, 68% for two steps; (d) NaOMe/MeOH, 2 h, 93%; (e) (1) TsCl, Py, $CHCl_3$, rt, overnight, 98%; (2) NaN_3, DMF, 90 °C, overnight, 99%; (f) 1% I_2-MeOH, reflux, 18 h, 94%; (g) (from pure *β*-anomer of compound **16**) Dess−Martin oxidation, 81%.

difficult to separate by silica gel chromatography. However, we succeeded in getting some pure samples of compounds **10b** and **10c** for analysis. Fortunately, we obtained crystals of compound **10c** suitable for X-ray structure analysis.[20] Complete separation of the diastereomers required further elaboration of the core. Therefore, the azido group in the mixture of **10b** and **10c** 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[19] to give a 9:5 ratio of compounds **2b** and **2c** in 80% yield for two steps. The spectral data and specific rotations revealed that compounds **2b** and **2c** were respective antipodes of slagenins B and C.[9] Thus, with the C9 chiral center generated from asymmetric hydrogenation, an enantioselective synthesis for the antipodes of slagenins A−C, which was characterized by construction of the slagenin bicycle core from glyoxal **9** in a concerted pathway, was achieved.

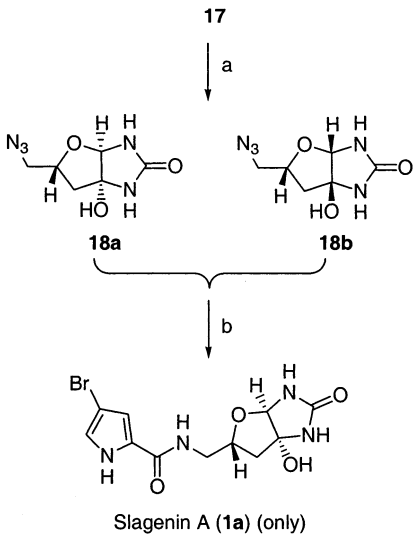
Synthesis of Slagenins A−C.[10] After the successful synthesis of antipodes of slagenins A−C, we turned our attention to a carbohydrate-based synthesis of naturally occurring slagenins A−C. The synthesis of the antipodes described above suggested the absolute stereochemistries as (9*R*,11*R*,15*R*) for slagenins A and B, and (9*R*,11*S*,15*S*) for slagenin C. The C9 chiral center to be introduced into synthetic slagenins as an *R*-configuration was considered to be derived from L-xylose. The research for the preparation of dihydrofuran-3-one **II** from L-xylose is illustrated in Scheme 3.[10a]

Starting from L-xylose, the 3-deoxy-L-ribose derivative **14** was prepared by adapting the reported procedures.[21] Ketalization of L-xylose, in acetone in the presence of anhydrous $CuSO_4$ and a catalytic amount of concentrated H_2SO_4, followed by selective hydrolysis with HCl (0.1 mol/L) afforded 1,2-*O*-isopropylidene-α-L-xylofuranose (**11**).[22] Selective protection of the 5-OH with BzCl in pyridine-CH_2Cl_2 at 0 °C gave compound **12**.[23] Following conversion of the 3-hydroxyl group to the 3-xanthate in situ, the alcohol **12** was deoxygenated by the action of tributyltin

(19) Bromo-2-(trichloroacetyl)pyrrole was prepared from pyrrole following the reported procedures: (a) Kitamura, C.; Yamashita, Y. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1443. (b) Bailey, D. M.; Johnson, R. E.; Albertson, N. F. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 618.

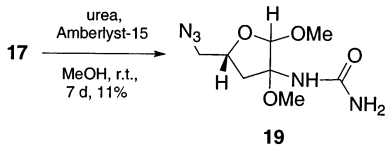
(20) ORTEP figure and tables of X-ray crystallographic data for compound **10c** can be found in the Supporting Information.

SCHEME 4[a]

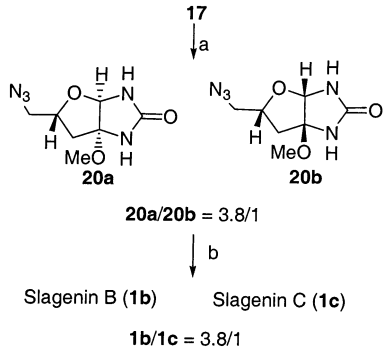


[a] Key: (a) (1) 0.1 mol/L of HCl, THF, reflux, 8 h; (2) urea, 0.01 mol/L of HCl, rt, 48 h, 75%; (b) (1) H_2, Pd/C, methanol; (2) 4-bromo-2-(trichloroacetyl)pyrrole, DMF, rt, 69% for two steps.

SCHEME 5



SCHEME 6[a]



[a] Key: (a) urea, 5% HCl−MeOH, reflux, 10 h, 77%; (b) (1) H_2, Pd/C, methanol; (2) 4-bromo-2-(trichloroacetyl)pyrrole, DMF, rt, 80% for two steps.

hydride and AIBN to give compound **13**.[24] Removal of the benzyl protecting group was smoothly accomplished, which afforded primary alcohol **14**. Treatment of **14** with TsCl and pyridine in $CHCl_3$ gave the corresponding tosylate, which was later transformed into azide **15**.[25] Methanolysis of azide **15** with refluxing 1% I_2-MeOH,[26] followed by Dess−Martin oxidation of the β-anomer of compound **16**,[27] afforded the key intermediate **17** (Scheme 3).[10a]

With the key intermediate **17** in hand, we tried to directly concentrate it with urea under acidic conditions. Thus, a treatment of compound **17** with 0.1 mol/L of aqueous HCl in THF and then condensation with urea in situ afforded **18a** and **18b** in 75% yield in a ratio of 1.1:1, which could not be separated from each other by silica gel chromatography. Undergoing the hydrogenation of this mixture over 10% Pd/C in methanol and the follow-up acylation with 4-bromo-2-(trichloroacetyl)pyrrole[19] in DMF, to our surprise, only a single compound **1a** was obtained in a yield of 69% (Scheme 4).[10a] Some further studies were done to have a better understanding of this transformation (vide post). The NMR (^{1}H, ^{13}C, and NOESY), IR, and mass spectral data for compound **1a** were in satisfactory agreement with those reported for naturally isolated slagenin A.[5,10a] Comparison of the specific rotation of synthetic **1a** {$[\alpha]^{20}_D$ +7.7 (*c* 0.8, MeOH)} with that of naturally isolated slagenins A {$[\alpha]^{27}_D$ +11 (*c* 1.2, MeOH)} further established the absolute configuration of naturally isolated slagenin A to be (9*R*,11*R*,15*R*)-**1a**.

Condensation of the compound **17** with urea and methanol in a nonaqueous system led to the syntheses of slagenins B and C. At the beginning, the treatment of **17** and urea in methanol with Amberlyst-15 resin as catalyst afforded an unstable compound **19** (Scheme 5), whose structure was proposed from its NMR data. Finally, compound **17** was heated at reflux with urea in 5% HCl−methanol solution to afford inseparable diastereoisomers **20a** and **20b** in a ratio of 3.8:1 with a yield of 77% (Scheme 6).[10a] Following the procedure described above (Scheme **2**), slagenins B (**1b**) and C (**1c**) were isolated by flash chromatography in 80% yield with a ratio of 3.8:1. The NMR (^{1}H, ^{13}C, and NOESY), IR, and mass spectral data for synthetic **1b** and **1c** were fully in agreement with those reported for naturally isolated slagenins B and C.[5,10a] Comparison of the specific rotation of synthetic **1b** {$[\alpha]^{20}_D$ +44.8 (*c* 0.5, MeOH)} with that of naturally isolated slagenin B {$[\alpha]^{26}_D$ +33 (*c* 0.2, MeOH)} and that of synthetic **1c** {$[\alpha]^{20}_D$ −36.1 (*c* 0.8, MeOH)} with that of naturally isolated slagenin C {$[\alpha]^{25}_D$ −35 (*c* 0.2, MeOH)} further confirmed the absolute configuration of naturally isolated slagenins B and C to be (9*R*,11*R*,15*R*)-**1b** and (9*R*,11*S*,15*S*)-**1c**, respectively.[10a] Thus, the enantioselective synthesis of slagenins A∼C, which was characterized by the efficient condensation of 2-methoxydihydrofuran-3-one **17** and urea to prepare the cis-fused tetrahydeofuro[2,3-*d*]imidazolidin-2-one skeleton, further established the absolute stereochemistry of slagenins. The direct condensation of dihydrofuran-3-one **17** with

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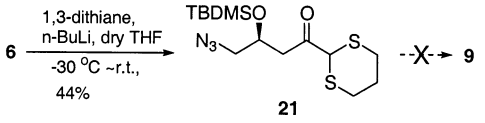
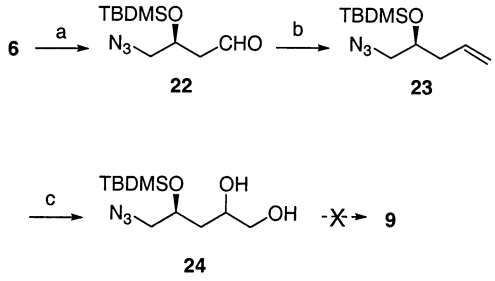
SCHEME 7



SCHEME 8[a]



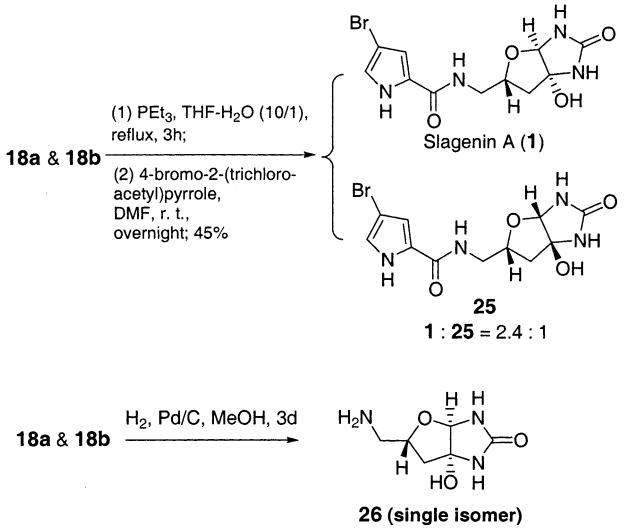
[a] Key: (a) Dibal-H, dry THF, −78 °C, 91% yield on recovery starting materials (51% recovered starting materials, 45% obtained aldehyde); (b) $Ph_3P^+CH_3Br^-$, *n*-BuLi, −30 °C, 79%; (c) $K_3[Fe(CN)_6]$, K_2CO_3, 10 mol % of OsO_4, *t*-BuOH−H_2O, 90%.

urea in a nonaqueous system, wherein the chiral furan cycle induced the formation of the imidazolidin cycle rather than the concerted pathway to the bicycle core from glyoxal **9**, led to an enhanced enantioselectivity and a higher yield for the preparation of the key intermediate to slagenins B and C.

Alternative Approaches.[28] Prior to implementing the successful preparation of the key intermediate, preliminary studies were first conducted enlisting an α-ketothioketal for glyoxal **9** (Scheme 7).[9] Thus, ester **6** was subjected to an elongation of the carbon chain with 1,3-dithiane through umpolung to afford thioketal **21**.[28] However, all attempts to cleave the thioketal failed to provide the glyoxal **9**, which we attributed to the unstable quality of glyoxals and the enhanced stability of the thioketal with an electron-withdrawing carbonyl group.[29]

We also examined an approach in which the carbon chain was elongated through a Wittig reaction (Scheme 8). Thus, ester **6** was reduced with Dibal-H at −78 °C to give aldehyde **22**,[16,28] of which the carbon chain was elongated with Wittig reagent Ph_3PCH_3Br.[30] Dihydroxylation of the obtained alkene **23**[28] in 50% aqueous *t*-BuOH in the presence of $K_3[Fe(CN)_6]$ and a catalytic amount of OsO_4 afforded 1,2-diol **24**.[28,31] However, our efforts for oxidation of compound **24** for glyoxal **9** proved fruitless.[32] Presumably, this may be attributed to the unstable quality of glyoxals and the interference of a carbonyl group that might have been generated with the neighboring hydroxy group.[33]

SCHEME 9



Plausible Mechanism. During the course of our syntheses of slagenin A and its antipode, it was observed that only the thermodynamically more stable diastereoisomer was generated from the azide intermediate comprising two isomers, that is, azide **10a**, which was composed of two isomers in a ratio of 5:2, was turned into only one diastereoisomer, the antipode of slagenin A, in a yield of 77% (Scheme 2); azides **18a** and **18b**, in a ratio of 1.1:1, were converted into only slagenin A in 69% yield (Scheme 4).[10a] In the case of a **10b**/**10c** or **20a**/**20b** mixture, each diastereoisomer was converted into the corresponding antipode of slagenin or slagenin. Accordingly, it was expected that the missing diastereoisomer of slagenin A might be obtained under different conditions. Thus, the mixture of azide **18a** and **18b** was subjected to reduction with some phosphine. Both triphenylphosphine and tri-*n*-butylphosphine were not reductive enough for the azide. Finally, reduction of the azide **18a**/**18b** mixture was achieved with triethylphosphine in a refluxing THF−H_2O (10/1) solution. Only after evaporation of the volatiles in vacuo did a one-pot treatment of the residue with 4-bromo-2-(trichloroacetyl)pyrrole[19] in DMF afford an unseparable mixture of slagenin A (**1**) and its diastereoisomer **25** in a ratio of 2.4:1 in 45% yield. At the same time, hydyogenation of the azide over 10% Pd/C for 3 days (a time long enough), followed by filtration through kieselguhr and removal of the solvent in vacuo, afforded a hygroscopic compound **26**, which was directly subjected to analysis by proton NMR and revealed to be a single isomer (Scheme 9).

According to the observations described above, we proposed that a conversion of one isomer to another occurred at the amine stage. A plausible mechanism for this conversion was arbitrarily brought forward. As is shown in Scheme 10, the potential mechanism involves a transformation of the *endo*-urea **C** into its *exo*-form **C′** via the ion pair **D** due to the obvious intramolecular hindrance. Some support for this mechanism was found in the formation of ketal **19** (Scheme 5), wherein the ketal was derived directly from urea and ketone**17**. Accordingly, there might be an equilibrium between the labile hemiketal **A** and ketone **B**, which was involved in an intramolecular nucleophilic attack leading to species **C**

(28) Experimental details and characterization may be found in the Supporting Information.

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

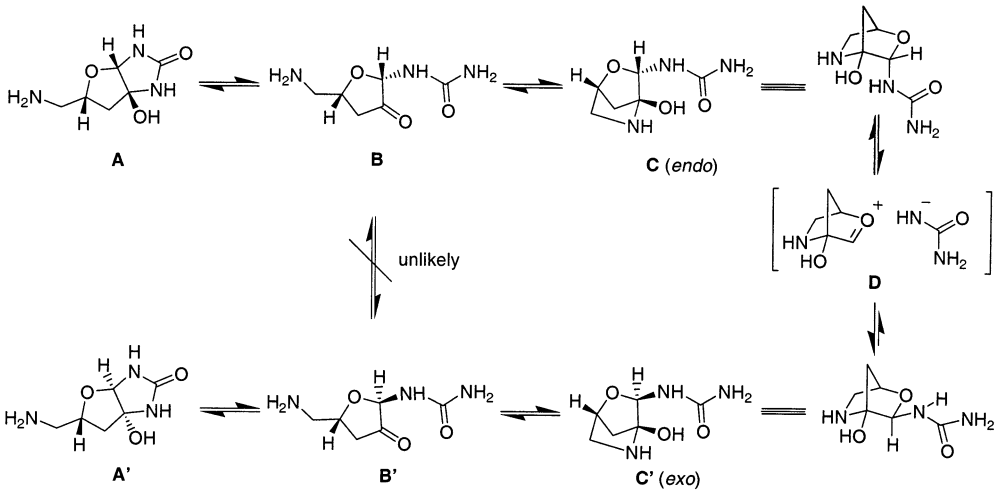
(30) Wittig, G.; Schöllkopf, U. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 751.

(31) Akashi, K.; Palermo, R. E.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2063.

(32) (a) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165. (b) Amon, C. M.; Banwell, M. G.; Gravatt, G. L. *J. Org. Chem.* **1987**, *52*, 4851. (c) Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985**, *50*, 2198. (d) Newman, M. S.; Davis, C. C. *J. Org. Chem.* **1967**, *32*, 66.

(33) Tius, M. A.; Fauq, A. H. *J. Am. Chem. Soc.* **1986**, *108*, 1035.

SCHEME 10



with a [2.2.1]bicycle. With a key transformation from **C** to **C′**, amine **A** was converted into its diastereoisomer **A′**.

Conclusion

In conclusion, the enantioselective total syntheses of salgenins A−C and their antipodes have been accomplished in which their absolute stereochemistries were established. A very direct and efficient method for preparing the cis-fused tetrahydrofuro[2,3-*d*]imidazolidin-2-one with a quarternary carbon center either from glyoxal or from dihydrofuran-3-one has been developed.

Experimental Section

General Information. Air- and water-sensitive reactions were performed in flame-dried glassware under a nitrogen atmosphere. Air- and moisture-sensitive reagents were introduced via dry syringe and cannula. THF was distilled from sodium benzophenone. Triethylamine was distilled from CaH_2. DMF was stored over molecular sieves. Flash chromatography was carried out with use of 300∼400 mesh silica gel. Melting points were recorded on WRS-1A apparatus and were uncorrected. ^{1}H NMR spectra were obtained with 300-, 400-, or 600-MHz spectrometers by using TMS (0.00) as an internal standard. ^{13}C NMR spectra were obtained with either 75 or 100 MHz spectrometers with use of chloroform (77.0) or DMSO (39.43) as the internal standards. NOESY spectra were obtained with a 400-MHz spectrometer. Optical rotations were obtained by using the sodium D line.

Ethyl (*S*)-4-Chloro-3-hydroxy-butanonate (5). An autoclave was charged with ethyl 4-chloroaceto-acetate (**3**) (20.0 g, 0.122 mol) in methanol (300 mL) and was hydrogenated over Ru(OAc)$_2$[(*R*)-(−)-BINAP] (200 mg) at a pressure of 40 atm at 100 °C for 1.5 h. The reaction mixture was concentrated on a rotatory evaporator. The residue was distilled under reduced pressure to afford **5** (19.2 g, 95%) as a colorless oil: bp 95 °C (3 mmHg). The enantiomeric excess of **5** was determined to be 97% ee by HPLC analysis of the corresponding (*R*)-MTPA ester. $[\alpha]^{20}_D$ +20.5 (*c* 5.5, $CHCl_3$) (lit.[14a] for (*S*)-**5** in 97% ee, $[\alpha]^{20}_D$ +20.9 (*c* 7.71, $CHCl_3$).

Ethyl (*S*)-4-Azido-3-(*tert*-butyl-dimethyl-siloxy)-butanonate (6). A flame-dried 250-mL round-bottom flask equipped with a reflux condenser was charged with ethyl (*S*)-4-chloro-3-hydroxy-butanonate (26.4 g, 0.158 mol), TBDMSCl (34.2 g, 0.227 mol), and 80 mL of redistilled DMF. The solution was stirred at ambient temperature under a nitrogen atmosphere and imidazole (34.8 g, 0.511 mol) was added in three portions during a period of 40 min. The resulting yellow solution was stirred for more 20 min and then heated at 45 °C overnight. After cooling to ambient temperature the reaction mixture was transferred into 500 mL of water. The resulting solution was extracted with hexane. The combined organic layers were dried ($MgSO_4$) and concentrated to give a yellow oil (44.5 g).

NaN_3 (22.9 g, 0.352 mol) was added to the yellow oil solution in 150 mL of DMF. The reaction was stirred at ambient temperature for 1 h and then heated at 90 °C overnight. After cooling to ambient temperature the reaction mixture was transferred into 500 mL of water. The solution was extracted with hexane. The combined organic layers were dried (Na_2SO_4) and concentrated to give a brown oil. The brown oil was distilled under reduced pressure to afford the title compound **6** (38.7 g, 85%) as a yellow oil: bp 114−116 °C/140 Pa; $[\alpha]^{20}_D$ +3.4 (*c* 3.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.25 (m, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.37 (dd, J = 12.5, 4.3 Hz, 1H), 3.23 (dd, J = 12.5, 5.3 Hz, 1H), 2.54 (dd, J = 6.2, 2.2 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H), 0.90 (s, 9H), 0.13 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 68.6, 60.3, 56.2, 39.9, 25.5, 17.7, 13.9, −5.0, −5.3; IR (neat) 2105, 1737 cm^{-1}; EIMS *m*/*z* (rel intensity) 272 (M − Me, 0.46), 73 (100.00). Anal. Calcd for $C_{12}H_{25}N_3O_3Si$: C, 50.14; H, 8.77; N, 14.62. Found: C, 50.29; H, 8.73; N, 14.89.

(*S*)-4-Azido-3-(*tert*-butyl-dimethyl-siloxy)-butanoic acid (7). To a solution of ethyl (*S*)-4-azido-3-(*tert*-butyl-dimethyl-siloxy)-butanonate (8.62 g, 30.0 mmol) in 50 mL of acetone was added 60 mL of aqueous LiOH (1.0 mol/L). The solution was stirred at ambient temperature for 3.5 h. The solution was concentrated on a rotatory evaporator to remove excess acetone. The residual solution was acidified with HCl (2.0 mol/L) to pH 2 and then extracted with ether. The combined organic layers were dried (Na_2SO_4). After removal of the solution the residue was purified through flash chromatography to afford the title compound **7** (7.38 g, 95%) as a colorless oil: $[\alpha]^{20}_D$ −3.5 (*c* 1.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.17 (br s, 1H), 4.16 (m, 1H), 3.28 (dd, J = 12.5, 4.4 Hz, 1H), 3.15 (dd, J = 12.5, 5.2 Hz, 1H), 2.50 (dd, J = 6.2, 4.5 Hz, 2H), 0.80 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 68.4, 56.2, 39.9, 25.5, 17.8, −4.8, −5.2; IR (neat) 2106, 1715 cm^{-1}; EIMS *m*/*z* (rel intensity) 260 (M + 1, 21.59), 73 (100.00). Anal. Calcd for $C_{10}H_{21}N_3O_3Si$: C, 46.31; H, 8.16; N, 16.20. Found: C, 46.31; H, 8.16; N, 16.27.

(*S*)-5-Azido-4-(*tert*-butyl-dimethyl-siloxy)-1-diazo-pentane-2-one (8). A flame-dried 250-mL round-bottom flask was charged with (*S*)-4-azido-3-(*tert*-butyl-dimethyl-siloxy)-butanoic acid (3.89 g, 15.0 mmol) and 100 mL of dry THF. The solution was stirred at −20 °C under a nitrogen atmosphere. To this solution was added triethylamine (2.80 mL, 20.1 mmol) followed by isobutyl chloroformate (2.60 mL, 20.0 mmol). The

solution was stirred for half an hour and then allowed to warm to −10 °C. At this temperature ethereal diazomethane (0.4 mol/L, 75 mL, 30 mmol) was added via a dry syringe in three portions over half an hour. The reaction mixture was stirred at −10 °C overnignt and allowed to warm to ambient temperature. It was then evaporated to a fifth of its original volume on a rotatory evaporator with an acetic acid trap to destroy residual diazomethane. The solution was diluted with ether (200 mL) and washed with water, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried (Na_2SO_4). After concentration, the residue was purified through flash chromatography to give the title compound **8** (3.84 g, 90%) as a yellow oil: $[\alpha]^{20}_D$ +0.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.30 (b rs, 1H), 4.33 (m, 1H), 3.40 (dd, J = 12.6, 4.0 Hz, 1H), 3.17 (dd, J = 12.6, 4.7 Hz, 1H), 2.53 (d, J = 5.6 Hz, 2H), 0.90 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.9, 68.8, 56.4, 55.7, 45.7, 25.6, 17.8, −4.9, −5.1; IR (neat) 2103, 1641 cm^{-1}; EIMS *m*/*z* (rel intensity) 283 (M, 28.27), 282 (100.00). Anal. Calcd for $C_{11}H_{21}N_5O_2Si$: C, 46.62; H, 7.47; N, 24.71. Found: C, 46.70; H, 7.55; N, 24.94.

(*S*)-5-Azido-4-(*tert*-butyl-dimethyl-siloxy)-1,1-dihydroxy-pentane-2-one (9).[18] To a solution of α-diazoketone **8** (313 mg, 1.10 mmol) in 5.0 mL of acetone was added a DMD−acetone solution (0.09−0.11 mol/L) in portions. The solution was stirred at ambient temperature and the reaction was monitored by TLC analysis. A total of 10 mL of the DMD−acetone solution was added as the first portion and evolution of nitrogen gas was observed. After 5 min of stirring, small portions (0.5 mL per portion) of the DMD−acetone solution were added before the starting material had just vanished. The reaction mixture was concentrated to give the title glyoxal **9** (319 mg, quantitatively) as a colorless oil. It showed itself from the proton NMR to be a mixture of the corresponding aldehyde and its hydrate **9**: $[\alpha]^{20}_D$ +12.9 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ [9.19 (s, 0.1H) + 5.31 (m, 0.9H), 1H], 4.33 (m, 1H), 3.35 (m, 2H), 2.96 (m, 1H), 2.18 (m, 1H), 0.90 (s, 9H), 0.09 (s, 6H); IR (neat) 3421, 2105, 1733 cm^{-1}; EIMS *m*/*z* (rel intensity) 289 (M, 0.53), 272 (0.79), 73 (100.00).

(5*S*)-5-Azidomethyl-6a-hydroxy-hexahydro-furo[2,3-*d*]-imidazol-2-one (10a). To a solution of glyoxal **9** (from 596 mg, 2.10 mmol of α-diazoketone **8**) and urea (155 mg, 2.58 mmol) in acetone−water (2:3, 20 mL) was added 1.80 mL of 40% aq HF. After being stirred at ambient temperature for 42 h, the resulting solution was quenched with solid K_2CO_3 to a pH of 7−8. The solvent was removed in vacuo and the residue was purified through flash chromatography to give azide **10a** (242 mg, 58%) as a yellow solid, which was assigned to be two isomers in a ratio of 5:2 from the proton NMR spectrum: mp 141−144 °C; ^{1}H NMR (300 MHz, DMSO-d_6, the two isomers are titled as a and b for clarification, a/b = 2/5) δ 7.59 (s, 2Ha), 7.39 (s, 2Hb), 6.35 (s, 1Hb), 6.24 (s, 1Ha), 4.97 (s, 1Hb), 4.86 (s, 1Ha), 4.22 (m, 1Ha), 4.05 (m, 1Hb), 3.55 (dd, J = 13.2, 2.9 Hz, 1Hb), 3.36−3.29 (m, 2Ha + 1Hb), 2.22 (dd, J = 12.9, 7.3 Hz, 1Ha), 2.05 (dd, J = 12.2, 4.2 Hz, 1Hb), 1.93−1.82 (m, 1Ha + 1Hb); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.4, 159.7, 93.7, 93.4, 93.1, 92.4, 77.0, 76.6, 53.5, 52.5, 42.0, 41.7; IR (KBr) 3271, 2099, 1710, 1691 cm^{-1}; HR-ESIMS calcd for $C_6H_9N_5O_3Na$ 222.0603, found 222.0603.

(3a*S*,5*S*,6a*S*)-5-Azidomethyl-6a-methoxy-hexahydro-furo[2,3-*d*]imidazol-2-one (10b)/(3a*R*,5*S*,6a*R*)-5-Azidomethyl-6a-methoxy-hexahydro-furo[2,3-*d*]imidazol-2-one (10c). To a solution of glyoxal **9** (from 1.43 g, 5.06 mmol of α-diazoketone **8**) and urea (0.344 g, 5.73 mmol) in 66 mL of methanol was added 9.0 mL of 40% aqueous HF. After being stirred at ambient temperature for 35 h, the reaction was quenched with aqueous saturated Na_2CO_3 to a pH of 6. Most of the methanol was removed under reduced pressure and diluted with 200 mL of water. The solution was extracted with ethyl acetate. The aqueous fraction was concentrated in vacuo and the residue was purified through flash chromatography to give azide **10a** (152 mg). On the other hand, the combined organic fractions were dried over Na_2SO_4. After evaporation of the solvent, flash chromatography afforded azide **10a** (112 mg, 264 mg as total, 26%), azide **10b** (23 mg), a mixture of **10b** and **10c** (515 mg), and azide **10c** (45 mg) all as yellow solids. Crystals suitable for X-ray structure analysis of compound **10c** were obtained from EtOAc.[20] From the proton NMR spectral data, the two isomers (**10b/10c**) (583 mg as total, 54%) were assigned to be in a ratio of 9:5.

Compound **10b**: mp 110−112 °C; $[\alpha]^{20}_D$ −41.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.71 (s, 1H), 6.34 (s, 1H), 5.40 (s, 1H), 4.35 (m, 1H), 3.55 (dd, J = 13.1, 3.3 Hz, 1H), 3.40−3.25 (m, 4H), 2.21 (dd, J = 12.2, 5.2 Hz, 1H), 2.11 (dd, J = 12.2, 7.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 98.7, 88.7, 76.9, 52.7, 51.5, 41.0; IR (KBr) 3233, 3084, 2092, 1724 cm^{-1}; EIMS *m*/*z* (rel intensity) 214 (M + 1, 0.31), 182 (M − OMe, 0.75), 157 (100.00).

Compound **10c**: mp 106−109 °C; $[\alpha]^{20}_D$ +93.8 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (s, 1H), 6.48 (s, 1H), 5.27 (s, 1H), 4.38 (m, 1H), 3.41 (dd, J = 13.1, 7.0 Hz, 1H), 3.32−3.26 (m, 4H), 2.48 (dd, J = 13.4, 7.3 Hz, 1H), 2.13 (dd, J = 13.4, 5.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 98.1, 89.5, 77.5, 53.9, 50.8, 41.1; IR (KBr) 3207, 3089, 2105, 1709 cm^{-1}; EIMS *m*/*z* (rel intensity) 182 (M − OMe, 0.74), 157 (100.00). Anal. Calcd for $C_7H_{11}N_5O_3$: C, 39.44; H, 5.20; N, 32.85. Found: C, 39.52; H, 5.03; N, 33.08.

5-*O*-Benzoyl-1,2-*O*-isopropylidene-α-L-xylofuranose (12). A mixture of L-xylose (15.0 g, 0.100 mol), dry $CuSO_4$ (34.4 g, 0.216 mol), and concentrated H_2SO_4 (3 mL) in acetone (150 mL) was stirred at ambient temperature for 24 h. The mixture was filtered, and the solid was washed with acetone. The filtrate was neutralized with concentrated NH_4OH, and the resulting white solid was removed by suction filtration. Removal of the solvent in vacuo from the filtrate gave a syrup that was treated with aqueous HCl (0.1 mol/L, 100 mL) for 1 h at ambient temperature. The reaction was quenched with solid $NaHCO_3$ to a pH of 7.5. The solution was washed with ether once, and the aqueous fraction was evaporated in vacuo to yield a pale yellow syrup, which was dissolved in $CHCl_3$ (100 mL) prior to drying (Na_2SO_4). Filtration and removal of the solvent in vacuo afforded a pale yellow syrup (18.6 g, 0.098 mol).

Benzoyl chloride (11.4 mL, 0.098 mol) was added dropwise over 30 min to an ice-cold solution of the syrup and pyridine (15.9 mL, 0.196 mol) in dry CH_2Cl_2 (200 mL). The resulting mixture was stirred at 0 °C for 1 h and washed with aqueous HCl (1 mol/L, 2 × 100 mL), saturated $NaHCO_3$ (2 × 100 mL), and brine (2 × 100 mL) prior to drying of the organic fraction (Na_2SO_4). After filtration and removal of the solvent in vacuo, the residue was recrystallized from ether to afford the title compound **12** as a white solid (23.5 g, 80% yield from L-xylose): $[\alpha]^{20}_D$ −10.6 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, J = 7.5 Hz, 2H), 7.63 (t, J = 7.5 Hz, 1H), 7.49 (t, J = 7.5 Hz, 2H), 5.99 (d, J = 3.7 Hz, 1H), 4.84 (dd, J = 12.9, 9.5 Hz, 1H), 4.63 (d, J = 3.7 Hz, 1H), 4.44−4.39 (m, 2H), 4.20 (br s, 1H), 3.33 (d, J = 3.7 Hz, 1H), 1.54 (s, 3H), 1.36 (s, 3H).

5-*O*-Benzoyl-3-deoxy-1,2-*O*-isopropylidene-α-L-ribofuranose (13). NaH (0.520 g, 13.0 mmol, 60% suspension in mineral oil) was washed twice with hexanes and added slowly to a well-stirred and precooled (−10 °C) solution of alcohol **12** (2.75 g, 9.34 mmol) in dry THF (30 mL). Immediately thereafter, CS_2 (0.90 mL, 15 mmol) was added, and the red solution was allowed to warm to ambient temperature, at which temperature it was stirred overnight. The reaction mixture was then re-cooled to 0 °C and treated with methyl iodide (1.50 mL, 24.1 mmol). After being stirred at ambient temperature for an additional 1.5 h, the yellow solution was quenched with ice−water (100 mL) and extracted with ethyl ether. The ethereal layers were combined, dried (Na_2SO_4), and concentrated under reduced pressure to afford the corresponding xanthate (3.5 g) as a yellow foam. This foam was dissolved in dry benzene (180 mL) and treated with Bu_3SnH (3.60 mL, 13.4 mmol). The reaction mixture was preheated at 80 °C and

treated with AIBN (78 mg, 0.48 mmol) added in six portions over a period of 3 h. After the solution was stirred for 1 h, the solvent was removed under reduced pressure and the crude residue was purified through flash chromatography to afford the title compound **13** (1.77 g, 68%) as a colrless oil: $[\alpha]^{20}_D$ −2.3 (*c* 1.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 7.5 Hz, 2H), 7.56 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 7.5 Hz, 2H), 5.88 (d, J = 3.9 Hz, 1H), 4.78 (t, J = 3.9 Hz, 1H), 4.58−4.51 (m, 2H), 4.36 (dd, J = 12.0, 5.7 Hz, 1H), 2.18 (dd, J = 13.5, 3.9 Hz, 1H), 1.76 (m, 1H), 1.54 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 132.9, 129.54, 129.51, 128.2, 111.0, 105.5, 80.0, 75.6, 65.0, 35.1, 26.5, 25.9; IR (neat) 1722, 1277 cm^{-1}; HR-ESIMS calcd for $C_{15}H_{18}O_5Na$ 301.10465, found 301.10466.

3-Deoxy-1,2-*O*-isopropylidene-α-L-ribofuranose (14). To a solution of ester **13** (790 mg, 2.84 mmol) in anhydrous methanol (10 mL) was added NaOMe (230 mg, 4.26 mmol), and the resulting solution was stirred at ambient temperature under a nitrogen atmosphere for 2 h. The solvent was evaporated and the residue was purified through flash chromatography to afford alcohol **14** (460 mg, 93%) as a colorless solid: mp 77−78 °C; $[\alpha]^{20}_D$ +15.6 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74 (d, J = 3.6 Hz, 1H), 4.67 (t, J = 4.2 Hz, 1H), 4.24 (m, 1H), 3.77 (dt, J = 11.7, 3.9 Hz, 1H), 3.47 (m, 1H), 2.80 (t, J = 5.7 Hz, 1H), 1.91 (dd, J = 13.5, 4.8 Hz, 1H), 1.74 (m, 1H), 1.42 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 111.0, 105.3, 80.5, 78.4, 62.6, 33.7, 26.5, 25.9; IR (KBr) 3482, 3381, 1267 cm^{-1}; HR-ESIMS calcd for $C_8H_{14}O_4$-Na 197.0784, found 197.0778.

5-Azido-3,5-dideoxy-1,2-*O*-isopropylidene-α-L-ribofuranose (15). *p*-Toluenesulfonyl chloride (950 mg, 4.98 mmol) was added in two portions at an interval of 30 min to a solution of alcohol **14** (570 mg, 3.27 mmol) and pyridine (0.80 mL, 9.9 mmol) in $CHCl_3$ (10 mL). After addition, the mixture was stirred at ambient temperature overnight. The reaction was quenched with ice−water (30 mL) and extracted with CH_2-Cl_2. The organic layer was washed with aqueous HCl (1 mol/L), aqueous saturated $NaHCO_3$, water, and brine in turn, and dried (Na_2SO_4). The solvent was removed in vacuo and the residue purified through flash chromatography to produce 3-deoxy-1,2-*O*-isopropylidene-5-*O*-(*p*-toluenesulfonyl)-α-L-ribofuranose (1.05 g, 98%) as a white solid: mp 62−63 °C; $[\alpha]^{20}_D$ +12.1 (*c* 1.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 5.69 (d, J = 3.9 Hz, 1H), 4.68 (t, J = 3.9 Hz, 1H), 4.32 (m, 1H), 4.15 (dd, J = 10.8, 3.3 Hz, 1H), 4.04 (dd, J = 10.8, 4.8 Hz, 1H), 2.41 (s, 3H), 2.03 (dd, J = 13.5, 7.8 Hz, 1H), 1.70 (m, 1H), 1.43 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9, 132.5, 129.7, 127.8, 111.3, 105.4, 80.1, 75.0, 69.6, 34.5, 26.6, 26.0, 21.5; IR (KBr) 1594, 1187, 1020, 959, 678 cm^{-1}; ESIMS *m*/*z* 329.1 $[M + H]^+$. Anal. Calcd for $C_{15}H_{20}SO_6$: C, 54.86; H, 6.14; S, 9.76. Found: C, 54.93; H, 5.90; S, 9.96.

NaN_3 (656 mg, 10.1 mmol) was added to a solution of 3-deoxy-1,2-*O*-isopropylidene-5-*O*-(*p*-toluenesulfonyl)-α-L-ribofuranose (827 mg, 2.52 mmol) in DMF (15 mL). The resulting mixture was heated at 90 °C overnight. After removal of the DMF in vacuo, the residue was partitioned between water and CH_2Cl_2, and the combined organic extracts were dried over Na_2SO_4. After removal of the solvent, the residue was purified through flash chromatography to afford azide **15** (498 mg, 99%) as a colorless oil: $[\alpha]^{20}_D$ −3.9 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (d, J = 3.6 Hz, 1H), 4.71 (t, J = 4.5 Hz, 1H), 4.33 (m, 1H), 3.52 (dd, J = 13.2, 3.6 Hz, 1H), 3.21 (dd, J = 13.2, 4.8 Hz, 1H), 2.01 (dd, J = 13.2, 4.5 Hz, 1H), 1.71 (m, 1H), 1.45 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 111.1, 105.3, 80.3, 76.5, 52.6, 35.3, 26.5, 25.9; IR (neat) 2102, 1217 cm^{-1}; HR-ESIMS calcd for $C_8H_{13}N_3O_3Na$ 222.0849, found 222.0853.

Methyl 5-Azido-3,5-dideoxy-α,β-L-ribofuranose (16). A solution of azide **15** (410 mg, 2.06 mmol) in 1% I_2 in MeOH (13 mL) was heated at reflux for 18 h. The solution was then concentrated to half of the volume and poured into a stirred aqueous solution of $Na_2S_2O_3$ (1%, 20 mL). The mixture was extracted with ethyl acetate, and the extract was dried (Na_2-SO_4). After evaporation, the residual brown oil (336 mg, 94%) was supposed to be a mixture of the β-anomer and the α-anomer of compound **16** (β:α ∼ 6:1) by proton NMR analysis. It was purified through flash chromatography to give the β-anomer of compound **16** (282 mg, 79%) as a brown oil. β-anomer: $[\alpha]^{20}_D$ +37.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.79 (s, 1H), 4.46 (m, 1H), 4.21 (t, J = 3.3 Hz, 1H), 3.34 (s, 3H), 3.26 (d, J = 6.0 Hz, 2H), 3.04 (d, J = 3.3 Hz, 1H), 1.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 109.4, 78.3, 75.5, 56.2, 54.7, 35.2; IR (neat) 3427, 2103, 1284 cm^{-1}; ESIMS *m*/*z* 196.1 $[M + Na]^+$. Anal. Calcd for $C_6H_{11}N_3O_3$: C, 41.62; H, 6.40; N, 24.27. Found: C, 41.62; H, 6.55; N, 24.42.

(5*R*)-5-Azidomethyl-2-methoxy-dihydro-furan-3-one (17). Alcohol **16** (pure β-anomer, 233 mg, 1.35 mmol) was added to a solution of Dess−Martin periodinane (5.50 mL, 1.95 mmol, 15 wt % in CH_2Cl_2) at 0 °C. The mixture was allowed to warm to ambient temperature and stirred for 18 h. The solvent was removed in vacuo and the residue was triturated with ethyl ether (30 mL). Following filtration through a pad of $MgSO_4$, the organic solution was stirred with an equal volume of $Na_2S_2O_3{\cdot}5H_2O$ (3.75 g) in 30 mL of aqueous saturated $NaHCO_3$ until the organic layer became clear (∼10 min). The organic layer was separated, washed with brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified through flash chromatography to give the title ketone **17** (187 mg, 81%) as a pale yellow oil: $[\alpha]^{20}_D$ −39.9 (*c* 1.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.70 (s, 1H), 4.63 (m, 1H), 3.56 (dd, J = 12.9, 6.9 Hz, 1H), 3.51 (s, 3H), 3.38 (dd, J = 12.9, 4.8 Hz, 1H), 2.67 (dd, J = 18.9, 8.1 Hz, 1H), 2.45 (dd, J = 18.9, 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.8, 99.1, 75.0, 56.3, 55.6, 36.5; IR (neat) 2106, 1776 cm^{-1}; ESIMS *m*/*z* 194.1 $[M + Na]^+$. Anal. Calcd for $C_6H_9N_3O_3$: C, 42.11; H, 5.30; N, 24.55. Found: C, 42.11; H, 5.51; N, 24.51.

5-Azidomethyl-6a-hydroxy-hexahydro-furo[2,3-*d*]imidazol-2-one [(3a*R*,5*R*,6a*R*)-18a/(3a*S*,5*R*,6a*S*)-18b]. To a solution of ketone **17** (52 mg, 0.30 mmol) in THF (6 mL) was added aqueous HCl (0.1 mol/L, 0.6 mL) and the resulting solution was heated at reflux for 8 h. The reaction mixture was then concentrated to 1 mL (a further concentration would result in a nigrescence product). The resulting yellow solution was then treated with urea (22 mg, 0.37 mmol) in 6 mL of aqueous HCl (0.01 mol/L) at ambient temperature for 48 h. The reaction mixture was neutralized with solid $NaHCO_3$, the solvent was evaporated in vacuo, and the residue was purified through flash chromatography to afford a mixture of **18a**/**18b** (45 mg, 75%) as a white solid (two diastereoisomers in a ratio of 1.1:1): mp 138−141 °C; ^{1}H NMR (300 MHz, acetone-d_6, the two isomers are arbitrarily regarded as in an equal quantity for clarification) δ 9.60 (br s, 1H), 9.54 (br s, 1H), 7.17 (br s, 1H), 6.81 (br s, 1H), 4.57 (s, 1H), 4.55 (s, 1H), 4.24−4.13 (m, 2H), 3.37−3.27 (m, 4H), 2.87 (br s, 2H), 2.02−1.96 (m, 2H), 1.87−1.67 (m, 2H).

((5*R*)-5-Azidomethyl-2,3-dimethoxy-tetrahydro-furan-3-yl)-urea (19). A mixture of ketone **17** (69 mg, 0.40 mmol), urea (32 mg, 0.53 mmol), and a little Amberlyst-15 resin in methanol (3 mL) was stirred at ambient temperature for 7 days. After removal of the solvent in vacuo, the residue was purified through flash chromatography to give recycled ketone **17** (28 mg) and a white solid that was proposed to be urea **19** (11 mg, 11% yield and a yield of 19% based on the reacted substrate): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.55 (br s, 1H), 5.27 (br s, 2H), 4.39 (m, 1H), 3.46 (s, 3H), 3.35 (s, 3H), 3.32 (d, J = 5.4 Hz, 1H), 2.57 (dd, J = 12.9, 6.3 Hz, 1H), 1.95 (dd, J = 12.9, 9.6 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.7, 102.6, 93.3, 77.6, 55.55, 55.47, 50.0, 37.5.

5-Azidomethyl-6a-methoxy-hexahydro-furo[2,3-*d*]imidazol-2-one [(3a*R*,5*R*,6a*R*)-20a/(3a*S*,5*R*,6a*S*)-20b]. Ketone **17** (24 mg, 0.14 mmol) was treated with urea (13 mg, 0.22 mmol) in 2 mL of 5% HCl−MeOH. After heating at reflux for 10 h, the volatiles were removed in vacuo and the residue was

purified through flash chromatography to produce a mixture of **20a** and **20b** (23 mg, 77%). From the ^{1}H NMR spectrum, the two isomers (**20a/20b**) were assigned to be in a ratio of 3.8:1: mp 111−114 °C; ^{1}H NMR (300 MHz, DMSO-d_6, the two isomers are titled as a and b for clarification, a/b = 3.8/1)) δ 7.80 (s, 1Ha), 7.76 (s, 1Ha), 7.60 (s, 1Hb), 7.57 (s, 1Hb), 5.23 (s, 1Hb), 5.08 (s, 1Ha), 4.23 (m, 1Ha), 4.08 (m, 1Hb), 3.57 (dd, J = 13.2, 2.9 Hz, 1Hb), 3.34−3.22 (m, 2Ha + 1Hb), 3.15 (s, 3Hb), 3.12 (s, 3Ha), 2.30 (dd, J = 13.0, 7.4 Hz, 1Ha), 2.12 (dd, J = 12.2, 4.5 Hz, 1Hb), 1.97−1.84 (m, 1Ha + 1Hb); IR (KBr) 3215, 3090, 2104, 1728, 1709 cm^{-1}.

(3a*R*,5*R*,6a*R*)-5-Aminomethyl-6*a*-hydroxy-hexahydrofuro[2,3-*d*]imidazol-2-one (26). The mixture of **18a/18b** (1.1:1)(20 mg) was hydrogenated over a little 10% Pd/C for 3 days. Filtration through kieselguhr and removal of the solvent in vacuo afforded crude amine **26** as a pale yellow syrup (18 mg, 100%). This crude product was subjected to proton NMR analysis without further purification: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.32 (s, 1H), 7.29 (s, 1H), 4.92 (s, 1H), 3.84 (m, 1H), 3.60−3.31 (m, 3H), 2.64 (br s, 2H), 2.03 (dd, J = 12.0, 6.0 Hz, 1H), 1.74 (t, J = 12.0 Hz, 1H).

(−)-Antipode of Slagenin A (2a). Azide **10a** (70 mg, 0.35 mmol) was hydrogenated over 7 mg of 10% Pd/C for 3 h. Filtration through kieselguhr and removal of the solvent in vacuo produced a yellow oil (58 mg). This oil was dissolved in DMF (7 mL). To the resulting yellow solution was added 4-bromo-2-(trichloroacetyl)pyrrole (204 mg, 0.70 mmol) and the solution turned rosy immediately. The reaction mixture was stirred at ambient temperature overnight. The solvent was evaporated in vacuo and the residue was dissolved with EtOAc. The yellow organic fraction was washed with aqueous half-saturated NaCl and dried (Na_2SO_4). After removal of the solvent in vacuo, the residue was purified through flash chromatography to afford **2a** (93 mg, 77%) as a colorless solid: mp 102−103 °C; $[\alpha]^{20}_D$ −7.6 (*c* 0.5, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.83 (s, 1H), 8.23 (t, J = 5.6 Hz, 1H), 7.34 (s, 1H), 7.32 (s, 1H), 6.97 (s, 1H), 6.87 (s, 1H), 6.26 (s, 1H), 4.95 (s, 1H), 4.00 (m, 1H), 3.34 (m, 2H), 2.04 (dd, J = 11.7, 3.3 Hz, 1H), 1.71 (t, J = 11.7 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.7, 159.1, 126.7, 121.2, 111.6, 94.9, 93.3, 91.9, 76.1, 43.0, 41.5; IR (KBr) 3288, 1706, 1632, 1566, 1525 cm^{-1}; ESIMS *m*/*z* 345.0 and 347.1 [(M + H)$^+$, 1:1], 367.0 and 369.1 [(M + Na)$^+$, 1:1]; HR-ESIMS calcd for $C_{11}H_{13}N_4O_4Na^{79}Br$ 367.0018, found 367.0015.

(−)-Antipode of Slagenin B (2b) and (+)-Antipode of Slagenin C (2c). A mixture containing **10b** and **10c** (13.0 mg, 0.061 mmol) was dissolved in 5 mL of methanol and a little 10% Pd/C was added. The mixture was hydrogenated under a hydrogen atmosphere at ambient temperature for 1.5 h and then filtered through kieselguhr. After concentration, the resulting crude amine (12 mg, colorless solid) and 4-bromo-2-(trichloroacetyl)pyrrole (40.0 mg, 0.137 mmol) were dissolved in 5 mL of DMF and the solution was stirred at ambient temperature overnight. After removal of DMF in vacuo, the residue was dissolved in ethyl acetate (50 mL) and the solution was washed with aqueous half-saturated NaCl and brine and dried (Na_2SO_4). Flash chromatography afforded the two title compounds **2b** (11.4 mg) and **2c** (6.2 mg) (17.6 mg as total, 80%) both as colorless solids. Compound **2b**: mp 98−100 °C; $[\alpha]^{20}_D$ −45.4 (*c* 0.5, MeOH); ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.78 (s, 1H), 8.21 (t, J = 6.0 Hz, 1H), 7.48 (s, 1H), 7.44 (s, 1H), 6.96 (s, 1H), 6.86 (s, 1H), 5.16 (s, 1H), 4.05 (m, 1H), 3.40 (m, 2H), 3.13 (s, 3H), 2.14 (dd, J = 12.0, 4.2 Hz, 1H), 1.75 (t, J = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.9, 159.7, 126.6, 121.3, 111.7, 97.9, 94.9, 88.4, 76.0, 50.4, 41.5, 41.3; IR (KBr) 3277, 1715, 1636, 1568 cm^{-1}; ESIMS *m*/*z* 359.1 and 361.1 [(M + H)$^+$, 1:1], 381.1 and 383.1 [(M + Na)$^+$, 1:1]; HR-ESIMS calcd for $C_{12}H_{15}N_4O_4Na^{79}Br$ 381.0174, found 381.0179.

Compound **2c**: mp 196 °C dec; $[\alpha]^{20}_D$ +39.9 (*c* 0.75, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.81 (s, 1H), 8.16 (t, J = 5.7 Hz, 1H), 7.70 (s, 1H), 7.66 (s, 1H), 6.96 (s, 1H), 6.86 (s, 1H), 4.99 (s, 1H), 4.12 (m, 1H), 3.42 (m, 2H), 3.10 (s, 3H), 2.25 (dd, J = 13.2, 6.8 Hz, 1H), 1.87 (dd, J = 13.2, 6.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.7, 159.4, 126.7, 121.2, 111.7, 97.2, 94.9, 89.3, 76.0, 49.8, 42.7, 40.9; IR (KBr) 3277, 1715, 1636, 1568 cm^{-1}; EIMS *m*/*z* (rel intensity) 328 (M − OMe, 43.30), 326 (43.65), 174 (92.13), 172 (100.00), 157 (65.47).

Slagenin A (1a). Following the procedure for the preparation of **2a** from **10a**, slagenin A (**1a**) was prepared from azide **18a/18b** in a yield of 69%. Slagenin A (**1a**): a colorless solid; mp 102−104 °C; $[\alpha]^{20}_D$ +7.7 (*c* 0.8, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.83 (s, 1H), 8.23 (t, J = 6.0 Hz, 1H), 7.32 (s, 1H), 7.30 (s, 1H), 6.97 (s, 1H), 6.87 (s, 1H), 6.26 (br s, 1H), 4.94 (s, 1H), 4.00 (m, 1H), 3.48−3.17 (m, 2H), 2.06 (dd, J = 11.7, 4.4 Hz, 1H), 1.73 (t, J = 11.7 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.7, 159.1, 126.7, 121.2, 111.6, 94.9, 93.3, 91.9, 76.1, 43.0, 41.5; IR (KBr) 3278, 1720, 1530 cm^{-1}; ESIMS *m*/*z* 367.0 and 369.0 [(M + Na)$^+$, 1:1]; HR-ESIMS calcd for $C_{11}H_{13}N_4O_4Na^{79}Br$ 367.0018, found 367.0016.

Slagenin A (1a)/Compound 25 [(9*R*,11*S*,15*S*)-isomer of Slagenin A]. A mixture of **18a/18b** (40 mg) was treated with triethylphosphine (0.22 mL, 1 mol/L in THF) in 2 mL of THF−H_2O (10/1). After the mixture was heated at reflux for 3 h, the solvent was evaporated in vacuo. The residual red-orange oil, after drying in vacuo at 40 °C for 2 h, was treated in one pot with 4-bromo-2-(trichloroacetyl)pyrrole (90 mg, 0.31 mmol) in DMF (2 mL) at ambient temperature overnight, followed by the process of separation and purification described above, to afford an unseparable mixture of slagenin A (**1a**) and its diastereoisomer **25** (31 mg, 45%) as a pale yellow solid. From the proton NMR spectral data, the two isomers (**1a**/**25**) were assigned to be in a ratio of 2.4:1: ^{1}H NMR (300 MHz, DMSO-d_6, the data for compound **1a** are omitted) δ 11.81(s, 1H), 8.17 (t, J = 5.6 Hz, 1H), 7.52 (s, 1H), 7.47 (s, 1H), 6.97 (s, 1H), 6.87 (s, 1H), 6.17 (s, 1H), 4.80 (s, 1H), 4.13 (m, 1H), 3.37−3.26 (m, 2H), 2.20 (dd, J = 13.0, 6.6 Hz, 1H), 1.86 (dd, J = 13.0, 7.0 Hz, 1H).

Slagenin B (1b) and Slagenin C (1c). Following the procedure for the preparation of **2b** and **2c** from the mixture containing **10b**/**10c**, slagenins B (**1a**) and C (**1c**) (**1b**/**1c** 3.8/1) were prepared from a mixture containing **20b**/**20c** (in a ratio of 3.8:1) in a yield of 80%. Slagenin B (**1b**): mp 98−100 °C; $[\alpha]^{20}_D$ +44.8 (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.83 (s, 1H), 8.24 (t, J = 5.9 Hz, 1H), 7.53 (s, 1H), 7.47 (s, 1H), 6.96 (s, 1H), 6.86 (s, 1H), 5.16 (s, 1H), 4.03 (m, 1H), 3.37 (m, 2H), 3.12 (s, 3H), 2.12 (dd, J = 12.1, 4.0 Hz, 1H), 1.73 (t, J = 12.1 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.9, 159.7, 126.6, 121.3, 111.7, 97.9, 94.9, 88.4, 76.0, 50.4, 41.5, 41.3; IR (KBr) 3274, 1712, 1637, 1567 cm^{-1}. Slagenin C (**1c**): mp 195 °C dec; $[\alpha]^{20}_D$ −36.1 (*c* 0.8, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.83 (s, 1H), 8.18 (t, J = 5.9 Hz, 1H), 7.71 (s, 1H), 7.68 (s, 1H), 6.97 (s, 1H), 6.87 (s, 1H), 5.01 (s, 1H), 4.13 (m, 1H), 3.34 (m, 2H), 3.09 (s, 3H), 2.27 (dd, J = 12.6, 6.9 Hz, 1H), 1.89 (dd, J = 12.6, 7.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.7, 159.4, 126.7, 121.3, 111.7, 97.2, 94.9, 89.3, 76.0, 49.8, 42.7, 40.9; IR (KBr) 3419, 3326, 3245, 3122, 1735, 1702, 1652, 1561, 1509 cm^{-1}; EIMS *m*/*z* (rel intensity) 360 (M, 15.09), 358 (M, 15.61), 172 (93.46), 43(100.00); HR-ESIMS calcd for $C_{12}H_{15}N_4O_4{}^{79}Br$ 358.02767, found 358.02883.

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Supporting Information Available: Experimental details and characterization data on compounds **21**−**24**; ORTEP figure and tables of X-ray crystallographic data for compound **10c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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