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Enantioselective Synthesis of Slagenins A–C

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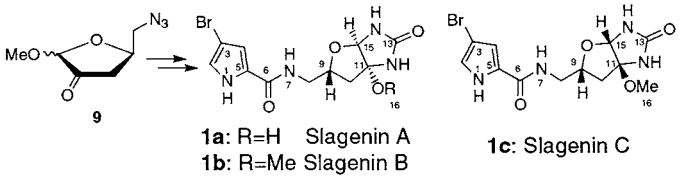
ABSTRACT



An enantioselective synthesis of slagenins A–C (1a–c) is described in which their absolute stereochemistries were established. The key step in the synthesis involved the efficient condensation of 2-methoxy-dihydro-furan-3-one 9 and urea to construct the slagenin bicycle core.

Slagenins A−C (**1a**−**c**) (Figure 1) comprise a group of cytotoxic secondary marine metabolites recently isolated from the Okinawan sponge *Agelas nakamurai*.[1,2] 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. Because slagenins are available in nature in only minute amounts and may be of significant interest for more detailed pharmacological investigations, it was the goal of the current project to develop efficient total synthesis for these bromopyrrole alkaloids. While the first total synthesis of racemic slagenins A−C was reported by Horne from ornithine,[3,4] we achieved the enantioselective synthesis for the antipodes of slagenins B and C and established the absolute stereochemistry of naturally isolated slagenin B and C, which was assigned as (9*R*,11*R*,15*R*)-**1b** and (9*R*,11*S*,15*S*)-**1c**, respectively.[5] Herein, we report an enantioselective synthesis of slagenins A−C from L-xylose and further confirmation of their absolute stereochemistry.

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 these three stereogenic centers in the moiety. In the literature, only two reports describe the preparation of tetrahydrofuro[2,3-*d*]imidazolidin-2-one skeletons: one starting from urea and 2-aminosugars;[6] another by oxidative cyclization of β-hydroxyimidazolone.[3] We have developed a route using the condensation reaction of urea and glyoxal to prepare the slagenin bicycle skeleton, by which we synthesized the antipodes of slagenins B and C.[5] Since the condensation reaction proved to be a very direct

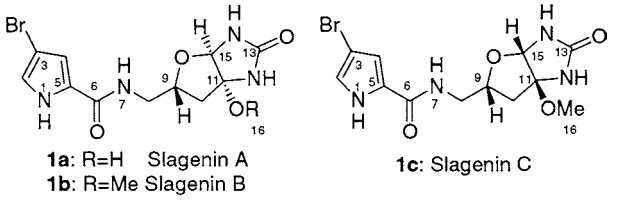


Figure 1. Structures of natural slagenins A−C.

(1) Tsuda, M.; Uemoto, H.; Kobayashi, J. *Tetrahedron Lett.* **1999**, *40*, 5709.

(2) Several bromopyrrole alkaloids have been isolated from marine sponge *Agelas nakamurai*: Uemoto, H.; Tsuda, M.; Kobayashi, J. *J. Nat. Prod.* **1999**, *62*, 1581.

(3) Sosa, A. C. B.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2000**, *2*, 3443.

(4) For a latter account of hypothetical biogenetic mechanism studies, see: Al Mourabit, A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237.

(5) Jiang, B.; Liu, J.-F.; Zhao, S.-Y. *Org. Lett.* **2001**, *3*, 4011.

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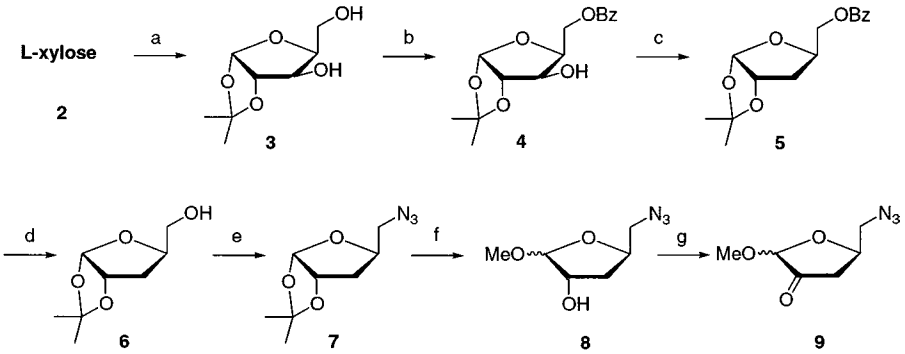
Scheme 1[a]



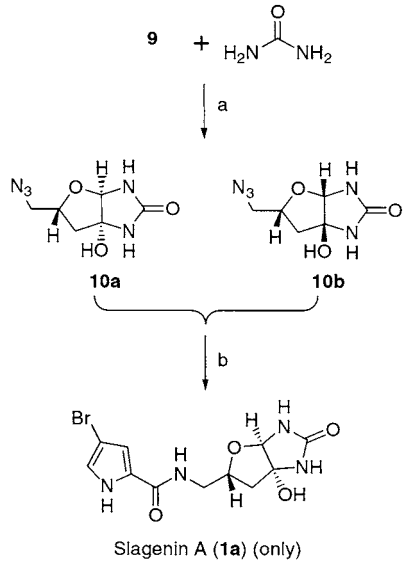
[a] Reagents and conditions: (a) (1) 2.0 equiv of $CuSO_4$, H_2SO_4, acetone, rt, 24 h; (2) 0.1 mol/L HCl, rt, 1 h; (b) 1.0 equiv of BzCl, 2.0 equiv of Py, dry CH_2Cl_2, 0 °C, 1 h, 80% yield from L-xylose; (c) (1) 1.4 equiv of NaH, 1.6 equiv of CS_2, overnight, then 2.6 equiv of MeI, 1.5 h, dry THF, rt, (2) 1.5 equiv of Bu_3SnH, 0.05 equiv of AIBN, benzene, reflux, 4 h, 68% two steps; (d) 1.3 equiv of NaOMe/MeOH, 2 h, 93%; (e) (1) 1.5 equiv of TsCl, 3.0 equiv of Py, $CHCl_3$, rt, overnight, 98%, (2) 4 equiv of NaN_3, DMF, 90 °C, overnight, 99%; (f) 1% I_2-MeOH, reflux, 18 h, 94%; (g) Dess−Martin oxidation, 81%.

and efficient way for the slagenin core, we envisioned that urea might be condensed with 2-methoxy-dihydro-furan-3-one, which was easily prepared from simple sugar, to construct the tetrahydrofuro[2,3-*d*]imidazolidin-2-one skeleton of slagenins. The (9*R*)-chiral center in slagenins (refer to the numbering system of slagenin) could be derived from the C4-chiral carbon in L-xylose.

Starting from L-xylose, the 3-deoxy-L-ribose derivative **6** was prepared by adapting reported procedures.[7] 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 0.1 N HCl afforded 1,2-*O*-isopropylidene-α-L-xylofuranose (**3**).[8] Selective protection of the 5-OH using BzCl in pyridine-CH_2Cl_2 at 0 °C gave ester **4** in 80% yield from L-xylose.[9] Following conversion of the 3-hydroxyl group to the 3-xanthate in situ, the alcohol **4** was deoxygenated by the action of tributyltin hydride and AIBN to give **5** in a yield of 68%.[10] Removal of the benzyl protecting group in **5** afforded primary alcohol **6** in 93% yield. Treatment of **6** with TsCl and pyridine in $CHCl_3$ gave the corresponding tosylate, which was transformed to the azide **7** in 97% yield for two steps.[11] The key intermediate, 2-methoxy-dihydro-furan-3-one **9**, was obtained by methanolysis of compound **7** with refluxing 1% I_2-MeOH (in 94% yield)[12] and following Dess−Martin oxidation (in 81% yield)[13] (Scheme 1).

With the key intermediate **9** in hand, we tried to directly condense it with urea under acidic conditions. Thus, a treatment of compound **9** with aqueous HCl and then condensation with urea in situ afforded **10a** and **10b** in 75% yield in a ratio of 1.1:1, which could not be separated from each other by silica gel chromatography. Hydrogenation of this mixture over 10% Pd/C in methanol and the following acylation with 4-bromo-2-(trichloroacetyl)pyrrole in DMF, to our surprise, produced only a single compound **1a** in a yield of 69% (Scheme 2). The NMR (^1H, ^{13}C, and NOESY),

Scheme 2[a]



[a] Reagents and conditions: (a) (1) 0.1 mol/L HCl, THF, reflux, 8 h; (2) 1.2 equiv of urea, 0.01 mol/L HCl, rt, 48 h, 75% yield from **9**; (b) (1) H_2, Pd/C, methanol, (2) 4-bromo-2-(trichloroacetyl)pyrrole, DMF, rt, 69% for two steps.

(6) Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C.; Valencia, C. *Tetrahedron* **1993**, *49*, 2676.

(7) (a) Nicolaou, K. C.; Daines, R. A.; Uenishi, J.; Li, W. S.; Papahatjis, D. P.; Chakraborty, T. K. *J. Am. Chem. Soc.* **1987**, *109*, 2208. Nicolaou, K. C.; Daines, R. A.; Uenishi, J.; Li, W. S.; Papahatjis, D. P.; Chakraborty, T. K. *J. Am. Chem. Soc.* **1988**, *110*, 4673. (b) For another report of the preparation of compound **6** from diacetone-L-glucose, see: Jones, M. F.; Noble, S. A.; Robertson, C. A.; Storer, R.; Highcock, R. M.; Lamont, R. B. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1427.

(8) Baker, B. R.; Schaub, R. E. *J. Am. Chem. Soc.* **1955**, *77*, 5900.

(9) Gumina, G.; Schinazi, R. F.; Chu, C. K. *Org. Lett.* **2001**, *3*, 4177.

(10) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574. (b) Jacobson, K. A.; Siddiqi, S. M.; Olah, M. E.; Ji, X.-d.; Melman, N.; Bellamkonda, K.; Meshulam, Y.; Stiles, G. L.; Kim, H. O. *J. Med. Chem.* **1995**, *38*, 1720.

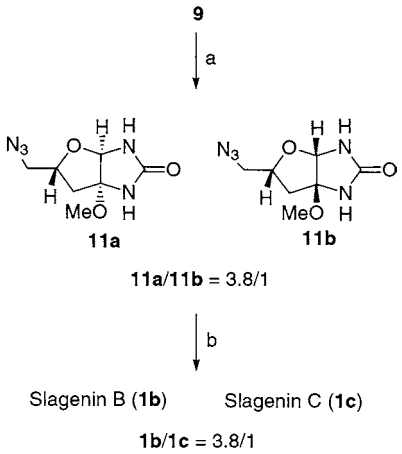
(11) A preparation of the antipode of compound **7** from glucose was reported: Bentley, N.; Dowdeswell, C. S.; Singh, G. *Heterocycles* **1995**, *41*, 2499.

IR, and mass spectral data for compound **1a** were in satisfactory agreement with those reported for naturally isolated slagenin A.[1] Comparison of the specific rotation of synthetic **1a** {$[\alpha]_D^{20}$ +7.7° (*c* 0.8, MeOH)} with naturally isolated slagenins A {$[\alpha]_D^{27}$ +11° (*c* 1.2, MeOH)} established the absolute configuration of naturally isolated slagenin A to be (9*R*,11*R*,15*R*)-**1a**.

For the synthesis of slagenins B and C, compound **9** was heated with urea in 5% HCl−methanol solution to afford inseparable diastereoisomers **11a** and **11b** in a ratio of 3.8:1 with a yield of 77%. Following our previous reported procedure,[5] 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.[1] Comparison of the specific rotation of synthetic **1b** {$[\alpha]_D^{20}$ +44.8° (*c* 0.5, MeOH)} with naturally isolated slagenin B {$[\alpha]_D^{26}$ +33° (*c* 0.2, MeOH)] and synthetic **1c** {$[\alpha]_D^{20}$ −36.1° (*c* 0.8, MeOH)} with naturally isolated slagenin C {$[\alpha]_D^{25}$ −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. In summary, a total synthesis of slagenins A−C (**1a**−**c**) has been accomplished in which their absolute stereochemistries were further established. The key to the synthesis involved the efficient condensation of 2-methoxy-dihydro-furan-3-one **9** and urea to prepare the *cis*-fused tetrahydrofuro[2,3-*d*]imidazolidin-2-one skeleton.

(12) (a) Huang, B.-G.; Bobek, M. *Carbohydr. Res.* **1998**, *308*, 319. (b) Lu, D.-M.; Min, J.-M.; Zhang, L.-H. *Carbohydr. Res.* **1998**, *317*, 193.
(13) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

Scheme 3[a]



[a] Reagents and conditions: (a) 1.5 equiv of urea, 5% HCl−methanol, reflux, 10 h, 77%; (b) (1) H_2, Pd/C, methanol, (2) 4-bromo-2-(trichloroacetyl)pyrrole, DMF, rt, 80% for two steps.

Acknowledgment. We are grateful for financial support from the Shanghai Municipal Committee of Science and Technology. We also thank Prof. David A. Horne (Oregon State University) for providing NMR data for synthetic slagenin.

Supporting Information Available: NMR (^{1}H, ^{13}C, NOESY) spectra for synthetic slagenins A (**1a**), B (**1b**), and C (**1c**). This material is available free of charge via the Internet at http://pubs.acs.org.

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