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Carbohydrate-Based Synthesis of Naturally Occurring Marine Metabolites Slagenins B and C

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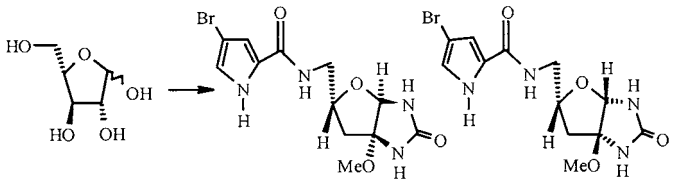
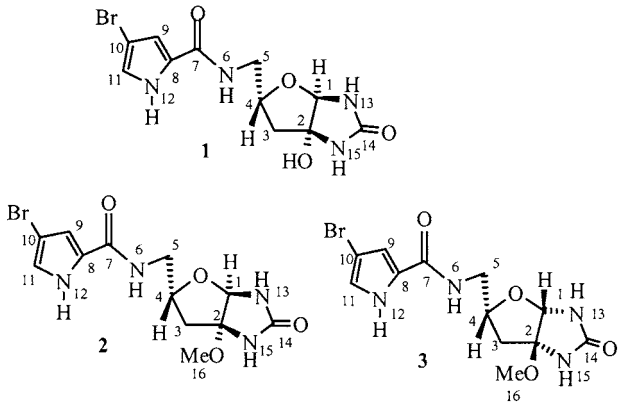
ABSTRACT



The first enantioselective syntheses of slagenins B and C, marine metabolites from *Agelas nakamurai*, starting from L-arabinose have been described.

The secondary marine metabolites slagenins A (**1**), B (**2**), and C (**3**) were isolated from the sponge *Agelas nakamurai*.[1] These natural products possess cytotoxicity against murine leukemia L1210 cells in vitro with IC_{50} values of 7.5 and 7.0 μg/mL. They are characterized by the presence of a tetrahydrofuro[2,3-d]imidazolidin-2-one moiety. Two groups have reported synthesis of these metabolites. The first synthesis described by Horne and co-workers[2] involved racemic preparations of slagenins, while a report from Jiang et al.[3] revealed synthesis of the antipodes of slagenins B and C. The latter group, on the basis of NMR studies and optical rotation values, suggested the absolute stereochemistries as (9*R*,11*R*,15*R*) for slagenin B (**2**) and (9*R*,-11*S*,15*S*) for slagenin C (**3**). We report in this letter the first enantioselective total synthesis of naturally occurring slagenins B and C starting from L-arabinose as a chiral precursor.



The known[4] 5-*O*-*tert*-butyldiphenylsilyl-1,2-*O*-isopropylidene-β-L-arabinofuranose (**4**) was subjected to Barton's deoxygenation reaction[5] in which **4** was first converted into the xanthate derivative (**5**) and then treated with tri *n*-butyltin hydride in refluxing toluene to give the 3-deoxy derivative (**6**). In the ^{1}H NMR spectrum of **6**, the characteristic signals due to H-3 and H-3′ were located at 1.97 and 2.11 ppm.

(1) Tusda, M.; Uemoto, H.; Kobayashi, J. *Tetrahedron Lett.* **1999**, *40*, 5709.
(2) Sosa, A. C. B.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2000**, *2*, 3443.
(3) Jiang, B.; Liu, J. F.; Zhao, S. Y. *Org. Lett.* **2001**, *3*, 40.
(4) Dahlman, O.; Garegg, P. J.; Meyer, H.; Schramek, S. *Acta Chem. Scand, Ser. B.* **1986**, *40*, 15.
(5) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

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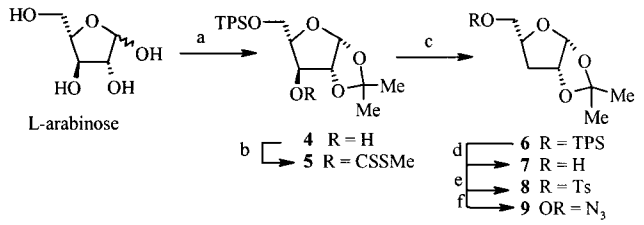
Transformation of **6** into the azido derivative **9**[6] involved removal of the silyl group, O-tosylation, and nucleophilic displacement with NaN_3 in DMF (Scheme 1).

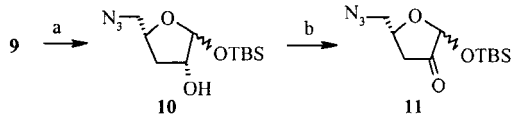
Scheme 1[a]



[a] Reagents and conditions: (a) ref 4; (b) NaH, CS_2, MeI, THF, rt, 2 h (98%); (c) Bu_3SnH, toluene AIBN, reflux, 5 h, (84%); (d) 1 M Bu_4NF, THF rt, 4 h, (81%); (e) *p*-Ts-Cl, Et_3N, CH_2Cl_2, rt, (92%); (f) NaN_3, DMF, 85 °C, 12 h, (85%).

Our next goal was to introduce an imidazolidine ring system across the C_1-C_2 segment of **9**. For this endeavor, the isopropylidene group was cleaved under acidic conditions and the resulting diol was selectively silylated with TBSCl-imidazole to give **10**. Swern oxidation[7] of **10** provided the 2-ulose derivative (**11**) whose ^1H NMR spectrum showed a downfield shift of protons located at C-1 and C-3 (Scheme 2).

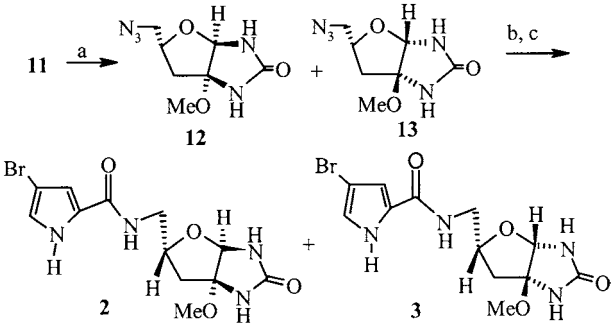
Scheme 2[a]



[a] Reagents and conditions: (a) TBSCl, imidazole, Et_3N, CH_2Cl_2, 45 min (72%); (b) $(COCl)_2$, DMSO, Et_3N, 2 h (72%).

Treatment[8] of **11** with urea in the presence of 40% aqueous HF in methanol at room temperature gave a mixture of diastereomers (**12** and **13**). Separation of this diastereomeric mixture at this juncture was difficult. Therefore, the mixture as such was subjected to catalytic reduction over Pd/C followed by reaction with 4-bromo-2-(trichloroacetyl)pyrrole in DMF at room temperature, which gave a mixture of **2** and **3** (Scheme 3).

Scheme 3[a]



[a] Reagents and conditions: (a) urea, 40% aq HF, MeOH, rt (62%); (b) 10% Pd−C, H_2, MeOH, 1 atm, 2 h (100%); 4-bromo-2-trichloroacetyl-pyrrole, DMF, rt, 16 h, (83%); (c) chromatography.

Silica gel chromatography conveniently provided slagenin B (**2**) and C (**3**) as pure products. Slagenins B and C were fully characterized by ^1H and ^{13}C NMR spectroscopic data,[9] which were found to be identical to reported values.[1] The observed optical rotation of synthetic slagenin B (**2**) was $[\alpha]_D$ + 36 (*c* 0.2, MeOH) [lit.[1] $[\alpha]_D$ + 33 (*c* 0.2, MeOH)], and that of slagenin C (**3**) was $[\alpha]_D$ −39 (*c* 0.2, MeOH) [lit.[1] $[\alpha]_D$ −35 (*c* 0.2, MeOH)]. In summary, a carbohydrate-based synthesis of naturally occurring slagenins B and C have been reported starting from L-arabinose.

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Supporting Information Available: ^1H NMR and ^{13}C NMR spectra for **10**, **11**, **2**, and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Selected spectroscopic values for **9**: ^1H NMR ($CDCl_3$, 200 MHz): δ 1.26 (s, 3 H), 1.50 (s, 3 H), 1.97 (dd, 1 H, J = 2.9, 15.1 Hz), 2.11 (ddd, 1 H, J = 5.7, 7.5, 15.1 Hz), 3.16 (dd, 1 H, J = 6.8, 12.4 Hz), 3.61 (dd, 1 H, J = 7.5, 12.4 Hz), 4.23 (m, 1 H), 4.67 (m, 1 H), 5.61 (d, 1 H, J = 4.2 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 25.8, 27.0, 34.4, 54.72, 79.6, 80.5, 106.7, 112.3. Ms: 184 ($M^+ - 15$); IR: 2100 cm^{-1} (N_3). Anal. Calcd for $C_8H_{13}N_3O_3$: C, 48.24; H, 6.53. Found: C, 47.9; H, 6.56.

(7) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

(8) (a) Grillon, E.; Gallo, R.; Pierrot, M.; Boileau, J.; Wimmer, E. *Tetrahedron Lett.* **1998**, *29*, 1015. (b) Gautam, S.; Katcham, R.; Nematullahi, J. *Synthetic Comm.* **1979**, *9*, 863.

(9) NMR data. Slagenin B (**2**): ^1H NMR ($CDCl_3$, 500 MHz) δ 1.76 (t, 1 H, J = 11.9 Hz), 2.17 (dd, 1 H, J = 3.9, 11.9 Hz), 3.15 (s, 3 H), 3.48 (m, 2 H), 4.04 (m, 2 H), 5.19 (s, 1 H), 6.86 (d, 1 H, J = 1.6 Hz), 6.96 (d, 1 H, J = 1.6 Hz), 7.50 (s, 1 H), 8.42 (t, 1 H, J = 5.7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 41.5, 41.6, 50.3, 76.1, 88.5, 94.8, 97.9, 112.0, 121.3, 126.8, 155.5, 159.8. Slagenin C (**3**): ^1H NMR ($CDCl_3$, 200 MHz) δ 1.90 (dd, 1 H, J = 6.4, 12.8 Hz), 2.29 (dd, 1 H, J = 6.7, 12.8 Hz), 3.17 (s, 3 H), 3.40 (m, 2 H), 4.19 (m, 1 H), 5.12 (s, 1 H), 6.87 (s, 1 H), 6.97 (s, 1 H) 7.65 (s, 1 H), 7.69 (s, 1 H), 8.24 (t, 1 H, J = 5.1 Hz), 11.87 (s, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) 40.8, 42.9, 49.8, 76.2, 89.5, 95, 97.3, 111.8, 121.2, 126.8, 159.4, 159.7.