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High 1,3-*trans* Stereoselectivity in Nucleophilic Substitution at the Anomeric Position and β-Fragmentation of the Primary Alkoxyl Radical in 3-Amino-3-deoxy-ribofuranose Derivatives: Application to the Synthesis of 2-*epi*-(−)-Jaspine B

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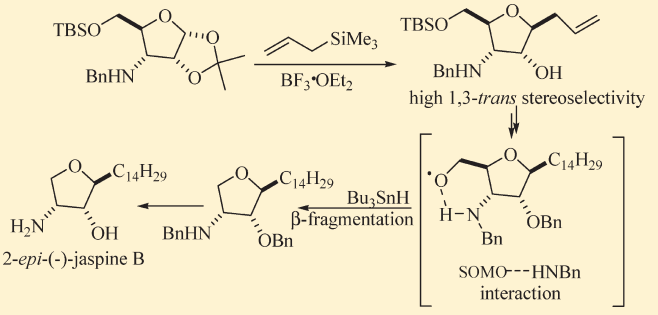
Supporting Information

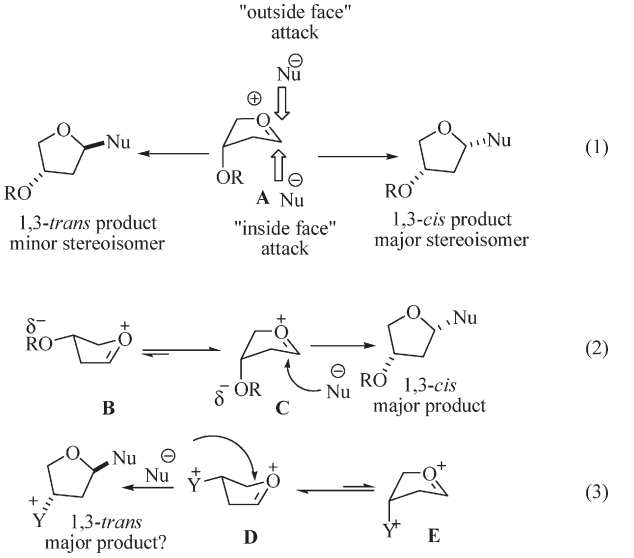
ABSTRACT: The high inverse stereoselectivity in the nucleophilic substitution at the anomeric position of 3-amino-3-deoxy-ribofuranose derivatives is reported. This unprecedented stereoselectivity is explained in terms of preferential nucleophilic attack on the "inside face" of the respective five-membered ring oxocarbenium ion that orients pseudoequatorially to the benzylamine group placed at the C-3 position. In addition, an unusual β-fragmentation of a primary alkoxyl radical generated from its corresponding *N*-phthalimide derivative was achieved, and thus taking advantages of both reactions, the total synthesis of 2-*epi*-(−)-jaspine B was completed.



The application of stereoselective nucleophilic substitution at the anomeric position to a suitable carbohydrate derivative represents an important reaction for the preparation of optically pure tetrahydrofurans.[1] Given that the tetrahydrofuran moiety is found in many biologically active compounds,[2] this transformation has become a very important transformation in the synthetic organic chemistry scenario.[1a,e]

Until recently, the stereoselectivity of this reaction was explained in terms of the steric hindrance imposed by substituents within the tetrahydrofuran ring;[3] however, since the seminal publication of Woerpel and co-workers,[4] an elegant stereoelectronic model named "the inside attack model" has emerged as a powerful stereochemical tool for predicting stereoselectivity in most nucleophilic substitutions.[5] In summary, this stereoelectronic model proposes that a cyclic five-membered oxocarbenium ion preferentially adopts an enveloped conformation where the C=O$^+$ segment resides in the flattened portion. Thus, there are two well-defined diasterotopic faces (**A**) that can be attacked by a nucleophile, termed "the inside face" or the "outside face". Interestingly, the preferred pathway is that in which the nucleophile attacks on the inside face of the oxocarbenium ion that orients axially to the *O*-alkoxyl group at the C-3 position (see eq 1 in Scheme 1).[4,5] Woerpel postulated that *the lowest energy conformer is one where the positive charge is brought closest to a C-3 substituent bearing a partial negative charge* (**C**) *favoring thus the 1,3-cis stereoselectivity* (eq 2).[6] In light of this rational scenario, we postulate that if the charge of the functional group at the C-3 position is changed (e.g., **D** and **E**), then the lowest energy conformer should be the one where both positive charges are repelled from each other (**D**), and therefore the 1,3-*trans* stereoisomer should be the major product (eq 3).

Scheme 1. Woerpel's Model That Predicts 1,3-*cis* Stereoselectivities in 3-Alkoxyl-furanose Derivatives (eqs 1 and 2) and a Postulated Process That May Afford 1,3-*trans* Stereoselectivities (eq 3)



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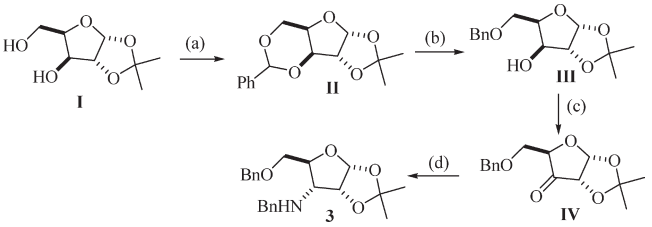
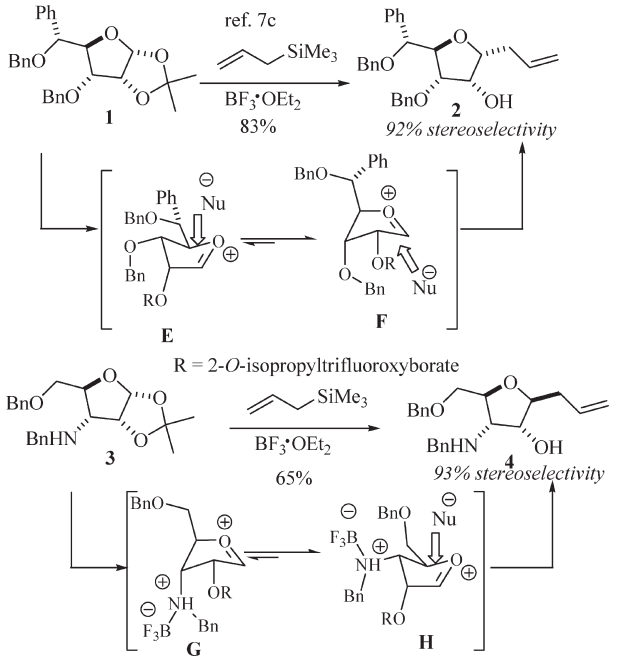
Scheme 2. Preparation of Amine Precursor 3[a]



[a] Reagents and conditions: (a) PhCHO/CSA/CH_2Cl_2, 95%; (b) Et_3SiH/TFA, 60%; (c) oxalyl chloride/DMSO/NEt_3/CH_2Cl_2, 95%; (d) benzylamine/$TiCl_4$/$NaBH_4$, 60%.

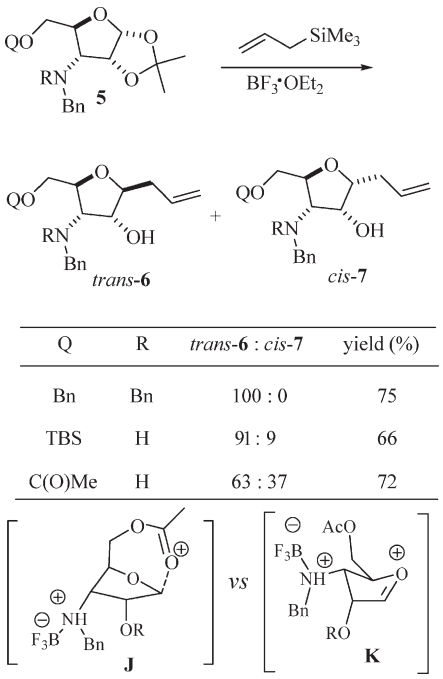
Scheme 3. Electrostatic and Stereoelectronic Effects on Nucleophilic Substitution



In this sense, we thought that if the oxocarbenium ion is generated by adding a Lewis acid (e. g., $BF_3 \cdot OEt_2$) to a proper carbohydrate derivative, then a NHBn group placed at C-3 position would provide the formal positive charge by its coordination with the Lewis acid. Therefore, taking the xylofuranose derivative **1** as a comparative model (because **1** contains an OBn group at the C-3 position and showed high 1,3-*cis* selectivity, **2**),[7c] we proceeded to prepare the 3-amino-3-deoxy-ribofuranose derivative **3** in order to prove the above-mentioned electrostatic model (eq 3). Thus, amine **3** was prepared from 1,2-*O*-isopropyliden-α-D-xylofuranose derivative **I** according to Scheme 2. Xylofuranose derivative **I** was protected to acetal **II** with benzaldehyde and catalytic amounts of camphorsulfonic acid (CSA) to give 95% yield. Selective cleavage of acetal **II** with triethylsilane in the presence of trifluoroacetic acid (TFA) afforded alcohol **III** in 60% yield. Then, oxidation of **III** under Swern conditions to ketone **IV** followed by reaction with benzylamine and $NaBH_4$ gave amine **3** in 57% yield from **III**.

As expected, treatment of **3** under the same reactions conditions as for **2** gave 1,3-*trans* stereoisomer **4** in 65% yield

Scheme 4. Nucleophilic Substitution at the Anomeric Position in 3-Amino-3-deoxy-ribofuranoses



Q	R	*trans*-**6** : *cis*-**7**	yield (%)
Bn	Bn	100 : 0	75
TBS	H	91 : 9	66
C(O)Me	H	63 : 37	72

and 93% stereoselectivity. Unlike the 1,3-*cis* stereoselectivity observed in compound **1**, wherein the nucleophile approach occurs on the inside face of the most stable conformer (**F**), the *trans*-stereoselectivity observed for compound **3** should arise now from the inside face attack of the most stable oxocarbenium ion **H** (Scheme 3). Furthermore, it is important to note that a small preference for the nucleophilic approach on the outside of **G** contributes also to the overall *trans*-stereoselectivity.[5a]

Pleased with this unprecedented result, we prepared other amines and submitted them to nucleophilic substitution reaction. Dibenzylamine **5** (Q = Bn, R = Bn) showed absolute *trans*-stereoselectivity. This is also attributed to steric hindrance provided by the additional benzyl group attached at the nitrogen atom, leading thus to an even more preferential *trans* approaching to the amine group. Although secondary amine **5** (Q = TBS, R = H) showed very similar stereoselectivity as for amine **3** (93:7), an important erosion in the stereoselectivity (*trans*/*cis*: 63:37) was observed for the acetyl substrate **5** (Q = acetyl, R = H). The latter could be explained in terms of a moderated anchimeric participation of the acetyl group attached at the C-5 position (Scheme 4).[7c] Indeed, this is an interesting result, in context that the inverse conformational preference exerted by the positive charge (**K**) overcomes the also favored anchimeric assistance by the acetyl group at C-5, **J** (Scheme 4).

As an application of this highly stereoselective reaction, we planned to convert compound **6** (Q = TBS, R = H) into 2-*epi*-(−)-jaspine B (**7**),[8] which is an unnatural biologically important compound with significant cytotoxicity.[8e] Thus, observing the molecular structure of **7**, we realized that a contrasting transformation is needed, i.e., for one side, chain elongation, and on the other side, a chain shortening. Although the first transformation is quite easy to accomplish, the latter is not (eq 4).

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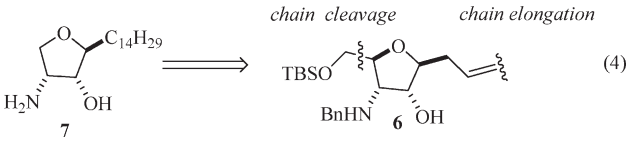
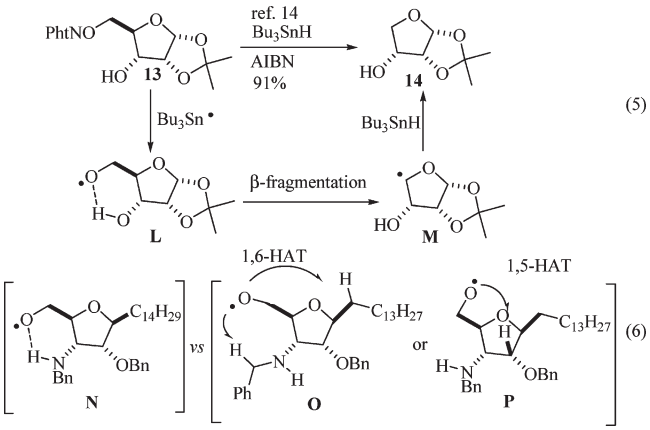


The use of olefin cross-coupling metathesis[9] for chain elongation, and β-fragmentation of the primary alkoxyl radical[10] for chain shortening was envisioned. To this end, 1,2-aminoalcohol **6** was benzylated to afford **8** in 92% yield, and then **8** was submitted to cross-coupling metathesis with 1-tridecene and second generation Hoveyda−Grubbs catalyst **9**.[11] It is important to mention that protection of the hydroxyl group of **6** was needed for obtaining a good 70% yield of **10** (Scheme 4). Removal of the silicon protecting group with TBAF (tetra-*n*-butylammonium floride) afforded the 1,3-aminoalcohol **11**, which was reacted with *N*-hydroxy-phtalimide (NHPht) under Mitsunobu condition[12] to give the *N*-phthalimide derivative **12** in good yield (Scheme 5).

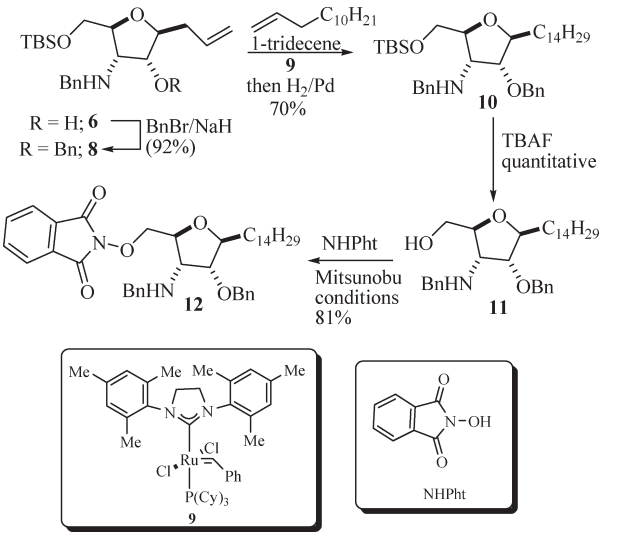
Although in the previous report[13] the chain shortening of *N*-phthalimido derivative **13** to D-erythrose derivative **14** was successfully achieved via β-fragmentation of primary alkoxyl radical (**L** → **M**), presumably favored by the presence of an internal hydrogen bonding between the semifilled p-orbital (SOMO) of the alkoxyl radical and the hydroxyl group (SOMO···HO, see **L** in eq 5), in the current model, there is an additional handicap that needed to be overcome in order to get β-fragmentation: the highly favorable 1,6-hydrogen atom transfer (HAT) from a benzylic hydrogen atom (**O**). In other words, to accomplish now the β-fragmentation, the internal hydrogen bonding interaction SOMO···HNBn (**N**), which would provide suitable conformation for hyperconjugative stabilization of SOMO,[13] should be more significant than the 1,5- and 1,6-hydrogen atom transfer reactions (**O** and **P**, respectively; see eq 6).



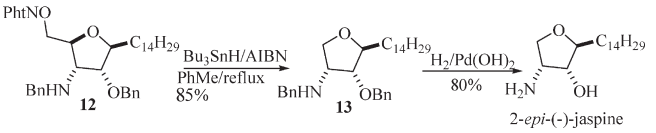
As expected, treatment of radical alkoxyl precursor **12** under the same reaction condition as for **13** gave β-fragmentation product **14** in very similar yield (85% yield). With this gratifying result, experimental evidence for the previouisly postulated beneficial effect of an internal hydrogen bonding (SOMO···HO) on the β-fragmentation of primary alkoxyl radical is provided. Having achieved the chain shortening of **12**, the completion of the synthesis of 2-*epi*-(−)-jaspine B was completed by simple double debenzylation of compound **13** (Scheme 6).

In summary, we have described an inverse stereoselectivity in nucleophilic substitution at the anomeric position of 3-amino-3-deoxy-ribofuranose derivatives, which is controlled by an amine group placed at the C-3 position. This unusual stereoselectivity is the result of changing the electrostatic nature of the five-membered-ring oxocarbenium ion. Additionally, the β-fragmentation of a primary alkoxyl radical presumably favored by an intramolecular hydrogen bonding between SOMO···HO (previously postulated) was extended to a novel interaction (SOMO···HN). Thus, taking advantages from both reactions, the synthesis of 2-*epi*-(−)-jaspine B was achieved.

Scheme 5. Preparation of the Primary Alkoxyl Radical Precursor 12



Scheme 6. Completion of the Synthesis of 2-*epi*-(−)-Jaspine B



EXPERIMENTAL SECTION

Preparation of 3-Amino-3-deoxy-ribofuranose (3). To a solution of 1,2-*O*-isopropylidene-α-D-xylofuranose **I** (3 g, 15.7 mmol) dissolved in 100 mL of CH_2Cl_2 at 0 °C were added benzaldehyde (5.0 g, 47.3 mmol) and catalytic amount of camphorsulfonic acid (15 mg). The reaction mixture was warmed to room temperature and allowed to react for 3 h. The reaction mixture was treated with a saturated aqueous solution of $NaHCO_3$ (5 mL), extracted with EtOAc (3 × 80 mL), and processed as usual. Flash chromatography on silica gel (eluent: hexane/ethyl acetate 5/1) gave 4.2 g of **II**[14] in 95% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.34 (s, 3H), 1.52 (s, 3H), 4.16 (m, 2H), 4.46 (m, 2H), 4.65 (d, J = 3.6 Hz, 1H), 5.47 (s, 1H), 6.08 (d, J = 3.2 Hz, 1H), 7.35−7.49 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.1, 26.7, 66.7, 72.2, 79.0, 84.0, 99.3, 105.6, 112.0, 126.0, 128.3, 129.1, 137.3. To a solution of benzyl acetal **II** (2 g, 7.19 mmol) dissolved in Cl_2CH_2 (150 mL) was added TFA (4.91 g, 43.14 mmol) and Et_3SiH (4.18 g, 35.9 mmol). The reaction mixture was stirred for 12 h before addition of a saturated aqueous solution of $NaHCO_3$ (5 mL), and extracted with EtOAc (3 × 80 mL and processed as usual. Flash chromatography on silica gel (eluent: hexane/ethyl acetate 4/1) gave 1.32 g of 1,2-*O*-isopropyliden-5-*O*-benzyl-α-D-xylofuranose **III**[15] in 60% yield. To a solution of oxalyl chloride (1.35 g 10.7 mmol) in dry CH_2Cl_2 (200 mL) at −78 °C was added dry DMSO (1.6 g, 21.4 mmol), and the reaction mixture was

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allowed to stirred for 30 min. Then, compound **III** (1 g, 3.56 mmol) dissolved in CH_2Cl_2 (30 mL) was slowly added, and the mixture was stirred for 2 h at −78 °C before the very slow addition of triethylamine (2.70 g, 26.7 mmol). The reaction mixture was kept at the same low temperature for 3 h. The formed solids were filtered off, and the liquid mother solution was evaporated under reduced pressure. The residue was purified by column chromatography (eluent: hexane/ethyl acetate 3/1) to give 0.95 g of 1,2-*O*-isopropyliden-5-*O*-benzyl-3-ulose-α-D-xylofuranose **IV**[15] in 95% yield. $[\alpha]^{25}_D$ = +98.7 (*c* 1.0 $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.43 (s, 3H), 1.46 (s, 3H), 3.73 (d, *J* = 2.4 Hz, 2H), 4.34 (d, *J* = 4.4 Hz, 1H), 4.45 (broad-s, 1H), 4. 50 (d, *J* = 12.0 Hz, 1H), 4.53 (d, *J* = 12.0 Hz, 1H), 6.13 (d, *J* = 4.4 Hz, 1H), 7.24−7.34 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.1, 27.6, 70.0, 73.6, 76.7, 79.8, 103.5, 114.1, 127.5, 127.8, 128.5, 137.3, 210.0. Ulose **IV** (0.5 g, 1.78 mmol) was dissolved in THF (30 mL) at 0 °C and treated with $TiCl_4$ (0.68 g, 3.56 mmol) and $BnNH_2$ (0.38 g, 3.59 mmol). The mixture reaction was stirred for 2 h, and solids were filtered off. The liquid mother solution was evaporated under reduced pressure, and the residue was dissolved in 100 mL of methanol at −30 °C. The reaction mixture was stirred for 30 min before addition of $NaBH_4$ (0.135 g, 3.59 mmol) and allowed to react for 2 h. The reaction was quenched with 30 mL of water, and the aqueous layer was extracted three times with ethyl acetate (100 mL) and processed as usual. Flash chromatography on silica gel (eluent: hexane/ethyl acetate 5/1) gave 0.4 g of 1,2-*O*-isopropyliden-5-*O*-benzyl-3-deoxy-3-benzylamine-α-D-ribofuranose **3** in 60%. $[\alpha]^{25}_D$ = +94.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35 (s, 3H), 1.51 (s, 3H), 3.07 (dd, *J* = 10.0, 4.8 Hz, 1H) 3.60 (dd, *J* = 11.2, 4.8 Hz, 1H), 3.76 (d, *J* = 13.2 Hz, 1H), 3.80 (m, 2H), 3.93 (d, *J* = 13.2 Hz, 1H), 4.51−4.60 (m, 3H), 5.80 (d, *J* = 4 Hz, 1H), 7.26−7.33 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.5, 26.7, 52.0, 60.5, 68.7, 73.4, 77.1, 79.6, 104.6, 111.8, 127.0, 127.5, 127.7, 128.1, 128.3, 128.4, 138.2, 140.1. FAB-HRMS *m*/*z* 370.2011 $[M + H]^+$ calcd for $C_{22}H_{28}N_1O_4$: 370.2018.

General Procedure for the Stereoselective Substitution Reaction of Ribofuranose Derivatives 5[7]. A solution of the corresponding ribofuranose derivative **5** (1.0 mmol) in 50 mL of dry CH_2Cl_2 at 0 °C was treated with allyltrimethylsilane (6.0 mmol) and $BF_3 \cdot OEt_2$ (5.0 mmol). The reaction mixture was warmed to room temperature and allowed to react for 15 h (3 days is needed for compound **5**: R = acetyl, Q = H). The reaction mixture was treated with saturated aqueous solutions of $NaHCO_3$ (50 mL), extracted with EtOAc (3 × 50 mL), and processed as usual. Flash chromatography on silica gel and using hexane and ethyl acetate as eluent.

(2*S*,3*R*,4*R*,5*S*)-2-Allyl-4-benzylamino-5-*O*-methylbenzyloxy-tetrahydrofuran-3-ol (4). Purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 2/1) in 65% yield. $[\alpha]^{25}_D$ = +1.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.3 (apparent-t, *J* = 6.8 Hz, 2H), 3.03 (dd, *J* = 8.4, 6.4 Hz, 1H), 3.48 (dd, *J* = 9.6, 6.4 Hz, 1H), 3.67 (dd, *J* = 9.6, 4.8 Hz, 1H), 3.72 (d, *J* = 12.8 Hz, 1H), 3.76−3.82 (m, 3H), 3.94 (apparent-td, *J* = 9.6, 6.4, Hz, 1H), 4.53 (s, 2H), 5.05−5.12 (m, 2H), 5.76−5.86 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 38.3, 52.6, 63.3, 71.7, 72.3, 73.6, 79.8, 85.4, 117.4, 127.4, 127.6 127.7, 128.1, 128.4, 128.5 134.1, 137.8, 139.2. FAB-HRMS *m*/*z* 352.1883 $[M + H]^+$ calcd for $C_{22}H_{26}N_1O_3$: 352.1913.

(2*S*,3*R*,4*R*,5*S*)-2-Allyl-5-(methylbenzyloxy)-4-(dibenzylamino)-tetrahydrofuran-3-ol (*trans*-6, Q = R = Bn). Purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 2/1) in 75% yield. $[\alpha]^{25}_D$ = −6.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.34 (m, 2H), 3.38 (dd, *J* = 8.4, 5.2 Hz, 1H), 3.43 (dd, *J* = 10.0, 5.2 Hz, 1H), 3.49 (dd, *J* = 10.0, 4.8 Hz, 1H), 3.58 (d, *J* = 13.6 Hz, 2H), 3.66 (t, *J* = 6.8 Hz, 1H), 3.81 (q, *J* = 6.4 Hz, 1H), 3.86 (d, *J* = 13.6 Hz, 2H), 4.40 (q, *J* = 8.0 Hz, 1H), 4.55 (s, 2H), 5.07 (m, 2H), 5.80 (m, 1H), 7.24−7.31 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 39.1, 55.8, 63.5, 72.0, 73.3. 73.4, 76.6, 84.9, 117.3, 127.4, 127.7, 128.4, 128.5, 128.7, 134.2, 138.0, 138.3. FAB-HRMS *m*/*z* 444.2428 $[M + H]^+$ calcd for $C_{29}H_{34}N_1O_3$: 444.2439.

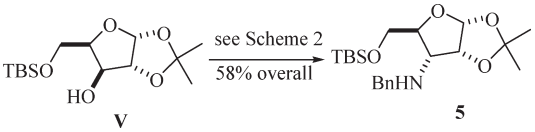
(2*S*,3*R*,4*R*,5*S*)-2-Allyl-5-methylacetate-4-benzylamino-tetrahydrofuran-3-ol (*trans*-6, Q = acetyl, R = H). Purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 2/1) in 72% yield. $[\alpha]_D$ = +12.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.0 (s, 3H), 2.30 (t, *J* = 6.4 Hz, 2H), 2.96 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.73−3.84 (m, 4H), 3.94 (td, *J* = 6.4, 2.8 Hz 1H), 4.05 (dd, *J* = 12.0 5.6 Hz, 1H) 4.22 (dd, *J* = 12.0, 4 Hz, 1H), 5.1−5.21 (m, 2H), 5.78 (m, 1H), 7.26−7.37 (m, 5H). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 20.8, 38.1, 52.6, 61.3, 65.0, 72.0, 79.5, 85.3, 117.6, 127.6, 128.1, 128.6, 133.7, 139.0, 170.8. FAB-HRMS *m*/*z* 306.1705 $[M + H]^+$ calcd for $C_{17}H_{24}N_1O_4$: 306.1754.

(2*S*,3*R*,4*R*,5*S*)-2-Allyl-5-(methyl-*tert*-butyldimethylsilyloxy)-4-benzylamino-tetrahydrofuran-3-ol (*trans*-6, Q = TBS, R = H). Purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 2/1) in 66% yield. $[\alpha]^{25}_D$ = −1.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.05 (s, 3H), 0.06 (s, 3H), 0.86 (s, 9H), 2.28 (m, 2H), 3.07 (dd, *J* = 7.6, 6.0 Hz, 1H), 3.57 (dd, *J* = 10.0, 7.2 Hz, 1H), 3.69 (td, *J* = 7.6, 4.0 Hz, 1H), 3.76 (m, 1H), 3.78 (s, 2H), 3.84 (dd, *J* = 9.6, 4.0, 1H), 3.94 (td, *J* = 6.0, 2.4 Hz, 1H), 5.06−5.15 (m, 2H), 5.79 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: −5.5, −5.4, 18.2, 25.8, 38.4, 52.7, 63.7, 65.0, 72.6, 81.0, 85.2, 117.3, 127.4, 128.1, 128.5, 134.2, 139.2. FAB-HRMS *m*/*z* 378.2490 $[M + H]^+$ calcd for $C_{21}H_{36}N_1O_3Si_1$: 378.2464.

Preparation of Amine Derivatives (5).

1,2-*O*-Isopropylidene-5-*O*-benzyl-3-deoxy-3-dibenzylamino-α-D-ribofuranose (5, Q = R = Bn). To a suspension of amine **3** (0.20 g, 0.54 mmol) and $NaHCO_3$ (0.18 g, 2.17 mmol) in CH_3CN (30 mL) was added benzylbromide (0.18 g, 1.1 mmol). The reaction mixture was allowed to react for 24 h at room temperature before addition of 30 mL of water. The aqueous layer was extracted three times with CH_2Cl_2 (30 mL) and processed as usual. Flash chromatography on silica gel (eluent: hexane/ethyl acetate 10/1) gave 0.2 g of **5** (Q = R = Bn) in 80% yield. $[\alpha]^{25}_D$ = +100.1 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.36 (s, 3H), 1.57 (s, 3H), 3.05 (dd, *J* = 10.8, 4.4 Hz, 1H), 3.49 (dd, *J* = 11.2, 4.8 Hz, 1H), 3.78 (d, *J* = 14.0 Hz, 2H), 3.83 (dd, *J* = 10.8, 2.0 Hz, 1H), 4.00 (d, *J* = 14.0 Hz, 2H), 4.43 (ddd, *J* = 10.8, 4.8, 2.0 Hz, 1H), 4.52 (d, *J* = 12.8 Hz, 1H), 4.54 (d, *J* = 12.8 Hz, 1H), 4.68 (t, *J* = 4.4 Hz, 1H), 6.15 (d, *J* = 3.6 Hz, 1H), 7.20−7.34 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.4, 27.0, 56.0, 61.6, 69.5, 73.5, 75.4, 78.6, 104.2, 112.3, 127.0, 127.5, 127.8, 128.3, 128.5, 138.1, 140.0. FAB-HRMS *m*/*z* 460.2536 $[M + H]^+$ calcd for $C_{29}H_{34}N_1O_4$: 460.2488.

1,2-*O*-Isopropylidene-5-*O*-(*tert*-butyldimethylsilyloxy)-3-deoxy-3-benzylamino-α-D-ribofuranose (5, Q = TBS, R = H). Ribofuranose derivative **5** (Q = TBS, R = H) was prepared form xylofuranose derivative **V**[16] by following the same procedure that for xylofuranose derivative **III** → **3** (see above) in 58% overall. $[\alpha]^{25}_D$ = +96.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.05 (s, 3H), 0.06 (s, 3H), 0.87 (s, 9H), 1.34 (s, 3H), 1.51 (s, 3H), 3.1 (dd, *J* = 9.6, 4.4 Hz, 1H), 3.70−3.78 (m, 3H), 3.90 (d, *J* = 1.6 Hz, 1H), 3.95 (d, *J* = 13.6 Hz, 1H), 4.55 (t, *J* = 4.4 Hz, 1H), 5.76 (d, *J* = 3.6 Hz, 1H), 7.22−7.38 (m, 5H). ^{13}C NMR (400 MHz, $CDCl_3$) δ: −5.3, −5.2, 25.9, 26.5, 26.7, 52.1, 59.8, 61.7, 77.3, 81.1, 104.5, 111.7, 127.0, 128.0, 128.3, 140.3. FAB-HRMS *m*/*z* 394.2380 $[M + H]^+$ calcd for $C_{21}H_{36}N_1O_4Si_1$, 394.2414.



V 5

1,2-*O*-Isopropylidene-5-*O*-acetyl-3-deoxy-3-benzylamino-α-D-ribofuranose (5, Q = acetyl, R = H). A solution of amine **5**

(Q = TBS, R = H) (2.0 g, 5.1 mmol) and TBAF (2.0 g, 7.62 mmol) in 20 mL of THF was allowed to react for 1 h, quenched with 10 mL of water, extracted tree times with ethyl acetate (50 mL), and processed as usual. The crude reaction was used as is in the following reaction. Respective 1,3- aminoalcohol (1 g, 3.58 mmol) was dissolved in 10 mL of CH_2Cl_2 at 0 °C, and acetic acid (0.10 g, 1.78 mmol) and acetic anhydride (0.73 g, 7.15 mmol) were slowly added. The reaction mixture was allowed to react for 3 h. The reaction mixture was treated with a saturated aqueous solution of $NaHCO_3$ (5 mL), extracted three times with ethyl acetate (100 mL), and processed as usual. Flash chromatography on silica gel (eluent: hexane/ethyl acetate 2/1) gave 0.7 g of **5** (Q = acetyl, R = H) in 60% yield. $[\alpha]_D = +192$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35 (s, 3H), 1.53 (s, 3H), 2.0 (s, 3H), 2.88 (dd, *J* = 10.0, 4.4 Hz, 1H), 3.75 (d, *J* = 13.2 Hz, 1H), 3.87 (ddd, *J* = 10.0, 5.6, 2.0 Hz, 1H), 3.95 (d, *J* = 13.2 Hz, 1H), 4.13 (dd, *J* = 12.0, 5.6 Hz, 1H), 4.39 (dd, *J* = 12.0, 2.0 Hz, 1H), 4.58 (t, *J* = 4.0 Hz, 1H), 5.79 (d, *J* = 4.0 Hz, 1H), 7.23−7.36 (m, 5H). NMR ^{13}C (400 MHz, $CDCl_3$) δ: 20.8, 26.4, 26.6, 51.8, 60.6, 63.6, 76.7, 77.8, 104.6, 112.0, 127.1, 128.0, 128.3, 139.8, 170.9. FAB-HRMS *m*/*z* 322.1654 $[M + H]^+$ calcd for $C_{17}H_{24}N_1O_5$: 322.1701.

Synthesis of 2-*epi*-(−)-Jaspine B.

(2*S*,3*R*,4*R*,5*S*)-5-Allyl-*N*-benzyl-4-(benzyloxy)-tetrahydro-2-(methyl-*tert*-butyldimethylsilyloxy)furan-3-amine (8). To a solution of *trans*-**6** (1 g, 2.64 mmol) and NaH (0.127 g, 5.29 mmol) in 30 mL of THF at 0 °C was added benzyl bromide (0.90 g, 5.29 mmol). The reaction mixture was stirred for 2 h at reflux and then quenched with 5 mL of water. The organic phase was extracted three times with ethyl acetate (50 mL) and processed as usual. Flash chromatography on silica gel (eluent: hexane/ethyl acetate 5/1) gave 1.15 g of **8** in 93% yield. $[\alpha]^{25}_D = +48.1$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.05 (s, 3H), 0.06 (s, 3H), 0.88 (s, 9H), 2.22 (m, 2H), 3.14 (dd, *J* = 7.6, 5.2 Hz, 1H), 3.61 (dd, *J* = 5.6, 2.8 Hz, 1H), 3.65 (m, 1H), 3.67 (s, 2H), 3.73−3.79 (m, 2H), 4.09 (td, *J* = 6.4, 2.8 Hz, 1H), 4.33 (d, *J* = 11.2 Hz, 1H), 4.54 (d, *J* = 11.6 Hz, 1H), 5.03−5.08 (m, 2H), 5.80 (m, 1H), 7.21−7.36 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: −5.4, −5.3, 18.4, 26.0, 39.0, 52.5, 59.0, 63.2, 71.5, 80.0, 81.3, 83.1, 117.2, 127.0, 127.8, 128.0, 128.1, 128.3, 128.4, 134.5, 138.0, 140.5. FAB-HRMS *m*/*z* 468.2968 $[M + H]^+$ calcd for $C_{28}H_{42}N_1O_3Si_1$: 468.2954.

(2*S*,3*R*,4*R*,5*S*)-*N*-Benzyl-4-(benzyloxy)-tetrahydro-2-(methyl-*tert*-butyldimethylsilyloxy)-5-tetradecylfuran-3-amine (10). In an oven-dried two-neck 100 mL round flask, equipped with a magnetic stir bar and a rubber septum and reflux column, was added catalytic amount of second generation Hoveyda−Grubbs catalyst (0.219 g, 0.350 mmol) in 30 mL of toluene. The reaction mixture was stirred for 10 min, and then compound **8** (0.820 g, 1.75 mmol) and 1-trideceno (1.91 g, 10.5 mmol) were added. The reaction mixture was stirred at reflux for 1 h, the solids were filtered off, and the liquid mother solution was evaporated under reduced pressure. The residue was dissolved in 20 mL of methanol and treated with $Pd(OH)_2$ (0.10 mg) under a hydrogen atmosphere for 1 h. The solids were filtered off, and the filtrate was concentrated under reduced pressure. Flash chromatography on silica gel (eluent: hexane/ethyl acetate 7/1) gave 0.77 g of **10** in 70% yield. $[\alpha]^{25}_D = +10.5$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.04 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 0.89 (t, *J* = 6.8 Hz, 3H), 1.25 (broad-s, 24H), 1.63 (broad, 2H), 3.15 (dd, *J* = 7.6, 5.6 Hz, 1H), 3.57 (dd, *J* = 5.6, 3.2 Hz, 1H), 3.65 (m, 1H), 3.68 (s, 2H), 3.73−3.78 (m, 2H), 4.0 (m, 1H), 4.36 (d, *J* = 11.6 Hz, 1H), 4.56 (d, *J* = 11.2 Hz, 1H), 7.26−7.37 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: −5.4, −5.3, 14.1, 18.4, 22.7, 25.8, 26.0, 29.3, 29.5, 29.6, 29.7, 31.9, 34.6, 52.4, 59.0, 63.3, 71.5, 80.5, 81.8, 82.9, 126.9, 127.8, 127.9, 128.1, 128.3, 128.4, 137.9, 140.6. FAB-HRMS *m*/*z* 623.4734 $[M + H]^+$ calcd for $C_{39}H_{65}N_1O_3Si_1$: 623.4741

(2*S*,3*R*,4*R*,5*S*)-3-(Benzylamino)-4-(benzyloxy)-tetrahydro-5-tetradecylfuran-2-yl)methanol (11). A solution of amine **10** (0.630 g, 1.03 mmol) and TBAF (0.39 g, 1.51 mmol) in 10 mL of THF was allowed to react for 1 h. When consumption of starting material was completed, the reaction mixture was quenched by addition 10 mL of water, and the organic phase was extracted three times with ethyl acetate (50 mL) and concentrated under reduced pressure. The reaction was highly quantitative, and compound **11** was submitted to the next reaction. $[\alpha]_D = +77.5$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, *J* = 6.4 Hz, 3H), 1.25 (broad-s, 26H), 3.03 (apparent-t, *J* = 8.0 Hz, 1H), 3.5 (dd, *J* = 5.2, 1.6 Hz, 1H), 3.67 (d, *J* = 12.8 Hz, 1H), 3.71 (d, *J* = 10.4 Hz, 1H), 3.75 (s, 2H), 4.05 (m, 1H), 4.34 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 7.26−7.35 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 22.7, 25.8, 29.4, 29.4, 29.5,29.6, 29.7, 32.0, 34.9, 52.5, 62.0, 63.9, 71.3, 79.8, 80.0, 83.4, 127.1, 127.9,128.0, 128.1, 128.4, 128.5, 137.7, 140.0.

(2*S*,3*R*,4*R*,5*S*)-*N*-Benzyl-4-(benzyloxy)-tetrahydro-2-(methyl-*N*-phthalimidyl)-5-tetradecylfuran-3-amine (12). To a solution of amine **12** (0.350 g, 0.686 mmol) and triphenylphosphine (0.361 g, 1.37 mmol) in 20 mL of THF at 0 °C were added *N*-hydroxyphthalimide (0.145 g, 0.896 mmol) and subsequently DEAD (0.25 g, 1.24 mmol). The resultant solution was warmed to room temperature and allowed to react for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: 4:1 hexane/ethyl acetate) to give 0.37 g of **12** in 81% yield. $[\alpha]^{25}_D = +31.7$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88 (t, *J* = 6.8 Hz, 3H), 1.22 (broad-s, 6H), 1.25 (broad-s, 18H), 1.95 (broad, 2H), 3.04 (dd, *J* = 9.2, 5.52 Hz, 1H), 3.50 (dd, *J* = 5.6, 2.4 Hz, 1H), 3.68 (d, *J* = 13.2 Hz, 1H), 3.77 (d, *J* = 13.2 Hz, 1H) 3.92 (t, *J* = 5.6 Hz, 1H), 4.0 (t, *J* = 7.2 Hz, 1H), 4.24 (dd, *J* = 11.6, 6.0 Hz, 1H), 4.33 (d, *J* = 11.6 Hz, 1H), 4.46 (dd, *J* = 10.8, 2.0 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 7.22−7.35 (m, 10H), 7.72 (m, 2H), 7.81 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 22.7, 25.6, 29.3, 29.4, 29.5, 29.6, 29.7, 31.9, 34.6, 52.5, 60.5, 71.4, 78.7, 79.3, 80.1, 83.4, 123.3, 127.1, 127.9, 128.0, 128.1, 128.3, 128.4, 129.0, 134.1, 137.7, 140.3, 163.3. FAB-HRMS *m*/*z* 655.4285 $[M + H]^+$ calcd for $C_{41}H_{54}N_2O_5$: 655.4211.

(3*R*,4*R*,5*S*)-*N*-Benzyl-4-(benzyloxy)-tetrahydro-5-tetradecylfuran-3-amine (13). To a boiled solution of phthalimide **12** (50 mg, 0.076 mmol) and catalytic amounts of AIBN (15 mg) in 30 mL of toluene was added slowly (30 min) Bu_3SnH (19 mg, 0.061 mmol) dissolved in 20 mL of toluene. The reaction mixture was stirred for 2 h and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 5/1) to give 31 mg of **13** in 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, *J* = 6.4 Hz, 3H), 1.25 (broad, 19H), 1.42 (broad, 2H), 1.62 (broad, 4H), 3.26 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.55−3.61 (m, 2H), 3.71 (d, *J* = 13.2 Hz, 1H), 3.75 (d, *J* = 13.2 Hz, 1H), 3.99 (dd, *J* = 8.43.99 (dd, *J* = 8.4, 6.4 Hz, 1H), 4.42 (d, *J* = 11.6 Hz, 1H), 4.57 (d, *J* = 11.6 Hz, 1H), 7.22−7.35 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 22.2, 22.7, 25.2, 25.9, 29.3, 29.6, 29.7, 31.9, 34.3, 34.5, 52.3, 59.2, 70.8, 71.7, 80.9, 82.9, 127.0, 127.9, 128.1, 128.4, 128.5, 137.8, 140.2. FAB-HRMS *m*/*z* 479.3763 $[M + H]^+$ calcd for $C_{32}H_{49}N_1O_2$: 479.3801

2-*epi*-(−)-Jaspine B (7). To a solution of amine **13** (20 mg, 0.041 mmol) and acetic acid (two drops) in 3 mL of methanol was added an excess of $Pd(OH)_2$ (40 mg) under a hydrogen atmosphere. The reaction was stirred for 3 days, solids were filtered off, the filtrate was evaporated, and the residue was purified by column chromatography to give **7** in 80% yield. $[\alpha]^{25}_D = -8.2$ (*c* 1.0, $CHCl_3$); [lit.[8b] $[\alpha]^{25}_D = -9.6$ (*c* 1.1, $CHCl_3$)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, *J* = 6.8 Hz, 3H), 1.25 (s, 26H) 3.61−3.75 (m, 5H), 4.03 (t, *J* = 6 Hz, 1H), 4.14 (dd, *J* = 9.6, 6.4, Hz, 1H,). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 20.7, 21.8, 25.5, 29.6, 31.8, 32.9, 51.8, 66.0, 73.0, 84.3

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, NMR data, and copies of ^{1}H and ^{13}C spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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