Diastereoselective Synthesis of the Monosaccharide Kedarosamine and Incorporation in an Analogue of the Enediyne Kedarcidin Chromophore

Tatjana Vuljanic,† Jan Kihlberg,*,‡ and Peter Somfai*,†

Organic Chemistry 2, Center for Chemistry and Chemical Engineering, Lund Institute of Technology, Lund University, P.O. Box 124, S-221 00 Lund, Sweden, and Organic Chemistry, Umeå University, S-901 87 Umeå, Sweden

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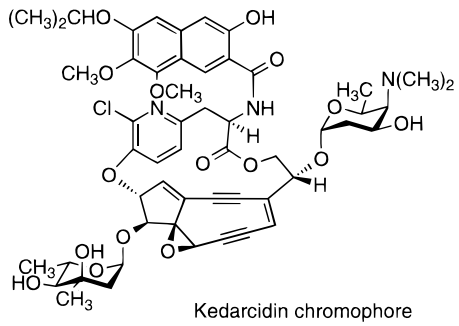
Kedarcidin chromophore, as with most enediyne antitumor antibiotics, contains unusual monosaccharide moieties. Synthesis of one of these moieties, the 2,4,6-trideoxy-4-dimethylaminohexose kedarosamine, from D-threonine and incorporation into an analogue of kedarcidin chromophore (**1**) is described herein. Conversion of D-threonine into allyl ketone **7** and stereoselective reduction by using tetramethylammonium triacetoxyborohydride for intramolecular hydride delivery were key steps in the preparation of kedarosamine. A thioglycoside derivative of kedarosamine (**12**) was found to be less efficient as a glycosyl donor, whereas a 1-*O*-acetate (**15**) gave the desired α-glycoside exclusively in 60−80% yield when treated with borontrifluoride etherate. Use of a Cbz instead of a Fmoc protecting group for the C-4 amino group of kedarosamine was essential for the successful preparation of analogue **1**. Finally, dimethylation of the amino group at C-4 of kedarosamine was found to require careful adjustment of the reaction conditions in order to avoid byproduct formation.

Introduction

Kedarcidin is a noncovalent complex between a reactive enediyne chromophore and a carrier protein that was isolated from the fermentation broth of the actinomycete strain L585-6, itself derived from a soil sample collected in India.[1,2] The chromophore exhibits potent in vivo antitumor activity against P388 leukemia and B16 melanoma in murine models and it also shows substantial activity against Gram-positive bacteria. The apoprotein stabilizes the chromophore but also possesses selective proteolytic activity and has been shown to cleave histones to small peptide fragments.[3] Kedarcidin chromophore[2,4] (Figure 1) binds to the minor grove in DNA and cleaves the duplex DNA site specifically in a single-stranded manner.[5] The damage is generally believed to be initiated by hydrogen atom abstraction from the deoxyribose moiety of DNA by the biradical formed after Bergman rearrangement of the enediyne moiety of the chromophore. Subsequent reactions then lead to cleavage of the phosphodiester backbone of DNA.

The enediyne antibiotics[6] pose an interesting synthetic challenge because of their complex structure and their biological activity. Some of the enediynes have already been synthesized,[7−10] but the kedarcidin chromophore has



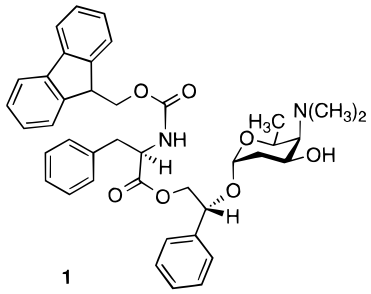


Figure 1.

* Corresponding author. For Prof. Jan Kihlberg: phone, +46-90-786 68 90; fax, +46-90-13 88 85; e-mail, jan.kihlberg@chem.umu.se.
† Lund University.
‡ Umeå University.
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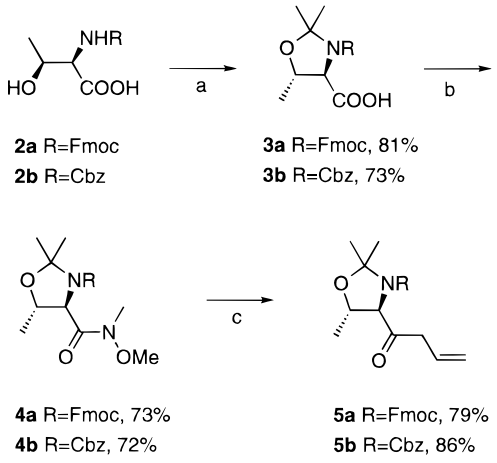
Scheme 1[a]



[a] Reagents and conditions: (a) $CH_2(OMe)_2$, pTsOH, benzene, reflux; (b) (i) cyanuric chloride, pyridine, CH_2Cl_2, (ii) Me(MeO)NH·HCl, pyridine, CH_2Cl_2; (c) allylmagnesium bromide, THF, −78 °C.

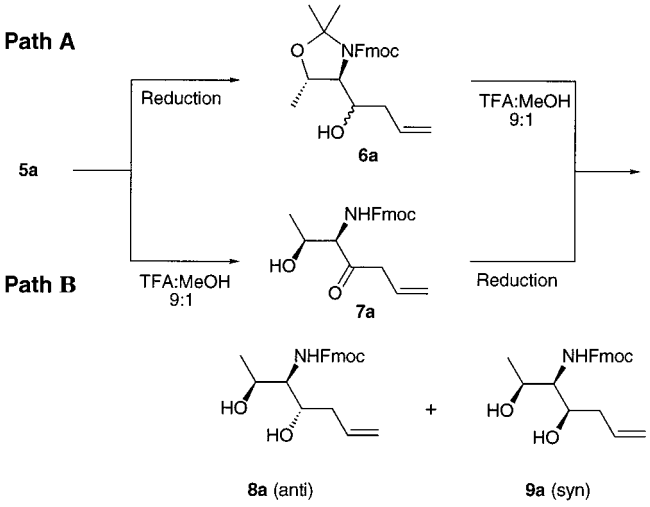
not yet been prepared. We focused our interest on the synthesis of the unusual aminodeoxysugar kedarosamine,[11,12] as well as on procedures whereby this monosaccharide could be attached to the rest of the chromophore. Analogue **1** was chosen as a target since the aglycon has similar structural features as the kedarcidin chromophore in the region of the aminodeoxysugar moiety. Furthermore, after removal of the Fmoc protecting group from **1,** it should be possible to incorporate the 2-hydroxynaphthoate moiety found in the kedarcidin chromophore.

Results and Discussion

Synthesis of kedarcidin chromophore analogue **1** was first initiated starting from *N*-9-fluorenylmethoxycarbonyl (Fmoc) protected D-threonine **2a** (Scheme 1). The hydroxyl and amino functionalities in **2a** were protected with an isopropylidene group to give **3a**, since it was found that both hydrogen atoms on the α-amino group had to be removed in order not to interfere with a subsequent Grignard reaction (vide infra). The protected acid (**3a**) was converted with cyanuric chloride into the corresponding acid chloride,[13] which was immediately transformed, without any purification, into amide **4a**.[14] Ketone **5a** was then obtained in 73% yield by addition of allylmagnesium bromide to amide **4a**. Ketone **5a** was found to be labile since it isomerized to the corresponding α,β-unsaturated ketone upon storing at −25 °C for 3 months.

Conversion of ketone **5a** into the desired *anti*-diol **8a** requires a key stereoselective reduction and cleavage of the isopropylidene protective group. It is well-known that the choice of protecting group on nitrogen can tune the stereochemical outcome in nucleophilic additions to α-amino aldehydes,[15] and this has also been shown for

Table 1. Reduction of the Ketone 5a To Give the Anti and Syn Unsaturated Diols 8a and 9a by Pathways A and B



entry	reducing agent, solvent	path A **8a:9a**[a]	path A % yield[b]	path B **8a:9a**[a]	path B % yield[b]
1	$NaBH_4$, MeOH	1:9	46		*c*
2	$NaBH_3CN$, MeOH		*c*	1:1	62
3	$Zn(BH_4)_2$, ether	17:1	30[d]	1:1	40
4	$Zn(BH_4)_2$, THF	2:1	60		*c*
5	DIBAL, hexane	2:1	90	1:1	16
6	$Et_3SiH/TiCl_4$, CH_2Cl_2		0		0
7	$Me_4NBH(OAc)_3$, CH_3CN:HOAc 1:1		*c*	>300:1	73

[a] The ratio between **8a** and **9a** was determined by HPLC. [b] Combined yields of **8a** and **9a** after purification by flash chromatography. [c] The reduction was not attempted. [d] A byproduct, in which the carbonyl group in **5a** had been reduced to a hydroxyl group and the isopropylidene group partially cleaved, leaving an isopropyl group attached to the oxygen atom, was isolated in 29% yield.

the reduction of α-amino ketones by Dondoni et al.[16] Thus the conversion of **5a** to **8a** was attempted both by reduction of **5a** to give **6a** followed by methanolysis of the isopropylidene group (Table 1, path A), and by performing the reduction on **7a** obtained after removal of the protective group (Table 1, path B). Nonchelation-controlled reduction of **5a** and **7a** was expected to give a diastereomeric mixture, with the undesired syn isomer **9a** predominating, as was recently reported for similar systems.[17] In agreement with this expectation, reduction of **5a** with $NaBH_4$ selectively gave the syn isomer, whereas reduction of **7a** with $NaBH_3CN$ was nonselective (Table 1, entries 1 and 2). In contrast, 1,2-chelation-controlled reduction of **5a** and **7a** should give the desired anti isomer **8a**. Accordingly, reduction of the fully protected **5a** with $Zn(BH_4)_2$[18,19] in diethyl ether was found to be highly anti selective, but it proceeded in low yield due to accompanying reductive opening of the isopropylidene group (Table 1, entry 3). The reductive opening was assumed to reflect a too strong chelation of Zn^{2+} to the substrate, and ether was therefore replaced by the stronger donor THF. Isopropylidene opening was then suppressed, but a significant loss in diastereoselectivity

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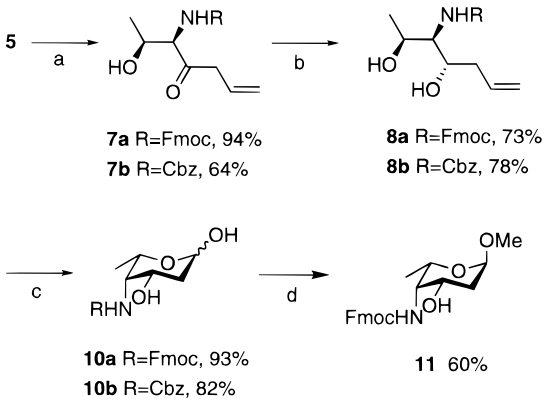
Scheme 2[a]

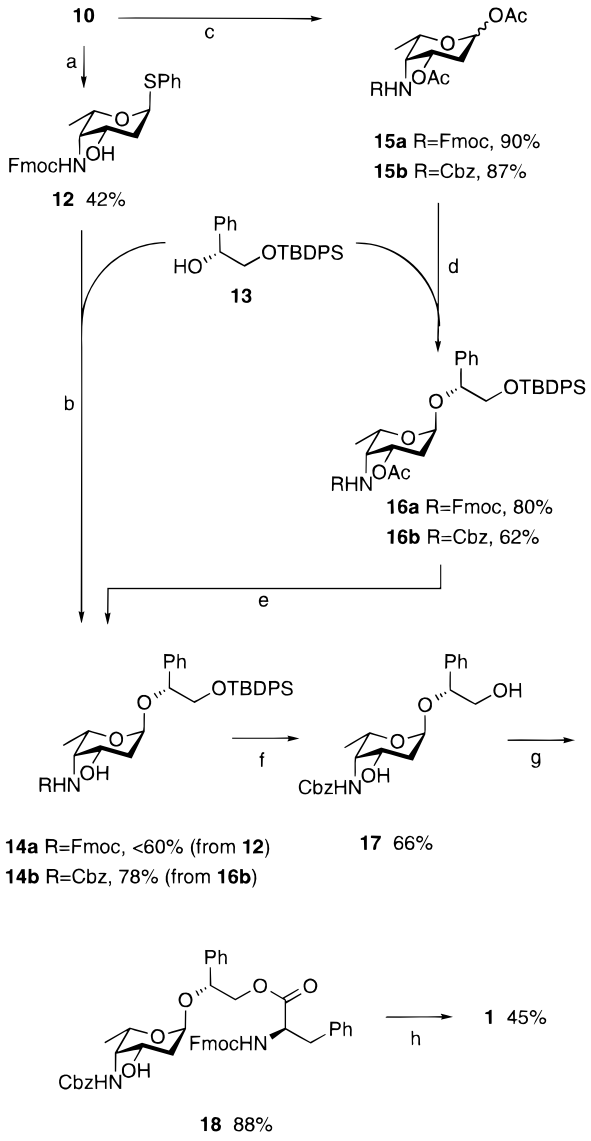


[a] Reagents and conditions: (a) TFA:MeOH 9:1; (b) $Me_4NBH(OAc)_3$, CH_3CN:HOAc 1:1, −28 °C; (c) O_3, Me_2S, MeOH, −78 °C; (d) pTsOH, MeOH.

in the reduction was also observed (Table 1, entry 4). Reduction of **5a** with DIBAL afforded a high yield, but it was nonselective (Table 1, entry 5). For β-hydroxy ketone **7a**, reductions with either $Zn(BH_4)_2$ or DIBAL were not stereoselective, which could result from competing 1,2- and 1,3-chelation to the Fmoc-amino and hydroxyl groups, respectively. Almost complete anti selectivity has been reported in the reduction of *N*-benzyloxycarbonyl-protected α-amino ketones with triethylsilane and titanium tetrachloride,[20] but in our hands, **5a** and **7a** could not be reduced with these reagents (Table 1, entry 6). Evans et al. have described high anti stereoselectivity, based on intramolecular hydride delivery, in reductions of β-hydroxy ketones with tetramethylammonium triacetoxyborohydride.[21] Application of this protocol to ketone **7a** resulted in a smooth formation of the desired *anti*-alcohol **8a** in 73% yield and as a single diastereomer (Table 1, entry 7).

The unsaturated diol **8a** was subjected to ozonolysis to give **10a** which was then treated with acidic methanol to give an anomeric mixture of methyl glycosides (α:β, 4:1) from which the α-anomer (**11**) was isolated in 60% yield (Scheme 2). The stereochemistry of the newly formed stereocenters at C-1 (methyl glycoside formation) and C-3 (ketone reduction) was conclusively determined for compound **11** using COSY and NOESY NMR spectroscopy. In this analysis the possibility for **11** and its stereoisomers to exist in different chairlike conformations was taken into account. The NOE interaction observed between H-3 and H-5 confirmed the (*S*)-configuration at C-3. The presence of a NOE between H-5 and the methyl glycoside and the absence of NOE interactions between H-1 and H-3, and H-1 and H-5, which were expected for the β-glycoside, confirmed the anomeric configuration as α. Conversion of methyl glycoside **11** into methyl α-kedarosaminide has been described previously by us.[12] The ^1H and ^{13}C NMR data of the obtained methyl α-kedarosaminide were found to be in good agreement with data reported for methyl α-kedarosaminide isolated from natural sources[22] and synthesized by Hornyak et al.[11] This further corroborated the assignment of the (*S*)-configuration at C-3 in **11**.

Scheme 3[a]



[a] Reagents and conditions: (a) PhSH, $BF_3{\cdot}Et_2O$, toluene:CH_2Cl_2 4:1; (b) NIS, 2,6-di-*tert*-butylpyridine, *N*-methylpyrrolidinone; (c) Ac_2O, pyridine; (d) $BF_3{\cdot}Et_2O$, toluene, 0 °C; (e) 0.02 M NaOMe; (f) $QF{\cdot}xH_2O$, THF; (g) Fmoc-D-Phe-OH, DEAD, PPh_3, THF; (h) HCHO, 10% Pd/C, H_2, MeOH:H_2O 2:1.

Stereoselective glycosylation with 2-deoxysugars as glycosyl donors has been shown to be problematic, and several different methods have been employed to accomplish the coupling.[23−26] Conversion of **10a** into the corresponding phenyl thioglycoside (**12**, Scheme 3) was attempted since similar glycosyl donors have been shown to perform well in glycosylations. However, only a disappointing 42% yield of **12** was obtained. The subsequent coupling of **12** with the acceptor **13** [obtained from (*R*)-phenyl-1,2-ethanediol] promoted by NIS[23] and 2,6-di-*tert*-butylpyridine gave a modest yield of glycoside

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14a (<60%). The overall yield of glycoside **14a** was thus 25% from **10a**. Preliminary studies with glycosyl imidates[27] were unsuccessful, whereas use of a 1-*O*-acetate was more promising (Scheme 3). Acetate **15a** was prepared from **10a** as an α/β-mixture (1:1.4, 90%) and glycosylation of the acceptor **13**, using $BF_3{\cdot}Et_2O$ as a promotor, gave the glycoside **16a** in 80% yield.[28] This glycosylation method might require some tuning when used on the sensitive aglycon from the kedarcidin chromophore.

Attempted removal of the TBDPS-protecting group in **16a** with QF,[25] to allow attachment of the D-phenylalanine moiety in **1**, resulted in facile removal of the Fmoc group[29] and concomitant migration of the acetyl group from O-3 to the amino group at C-4. Cleavage of the Fmoc group in **16a** under basic conditions also resulted in acetyl migration to the amino group. Furthermore, all attempts to remove the acetyl group prior to the Fmoc group failed, thus preventing introduction of the two methyl groups at the C-4 amino group. Probably, the close proximity between the Fmoc group and the acetate moiety in **16a** resulted in steric hindrance and allowed a facile $O \rightarrow N$ acetyl migration, thereby rendering the selective cleavage of either protecting group problematic. The difficulties encountered during these functional group manipulations prevented transformation of **16a** into kedarcidin chromophore analogue **1**. However, since the synthesis of the glycosyl donor **15a** and the subsequent glycosylation of **13** proceeded in good overall yield and with excellent selectivity, we decided to pursue the developed strategy toward **1**. To avoid further difficulties, a Cbz protecting group, which is more base stable than the Fmoc group, was employed for the amino group of kedarosamine.

Cbz-protected threonine **2b** was converted into **15b** by using the same procedures, in comparable yields, as described for the Fmoc series (Schemes 1−3). However, ozonolysis and reductive workup (Me_2S) of unsaturated diol **8b** gave a considerable amount of a hydroperoxide (in addition to the expected **10b**), which could be reduced to **10b** by using ferric sulfate. This hydroperoxide formation was observed only in trace amounts in the Fmoc series. It was also noted that removal of the isopropylidene group from **5b** and coupling of acetate **15b** with alcohol **13** gave somewhat lower yields as compared to the Fmoc series, probably due to some cleavage of the Cbz moiety under acidic conditions. Types of glycosyl donors other than the 1-*O*-acetate **15b** were also prepared from **10b**, i.e. 1-*O*-silylates[30] and imidates,[27] but in our hands these were obtained in unsatisfactory yields. After coupling of kedarosamine 1-*O*-acetate **15b** with alcohol **13,** the acetyl group in **16b** was removed with sodium methoxide in methanol to give **14b** (Scheme 3). No concomitant cleavage of the Cbz moiety was observed under these conditions, in contrast to the result obtained with the Fmoc-protected **16a**, and glycoside **14b** was obtained in an overall yield of 42% from hemiacetal **10b**.

Removal of the TBDPS group in **14b**, to give **17**, was carried out with moist QF, since dry reaction conditions caused some cleavage of the Cbz moiety. Regioselective esterification of **17** at the primary hydroxyl group with Fmoc-D-Phe-OH using the Mitsunobu procedure[31] gave **18**. Finally, removal of the Cbz group in **18** followed by reductive methylation of the resulting primary amine was performed in a one-pot procedure to give the desired kedarcidin chromophore analogue **1** in 45% yield from **18**.[28] The reductive methylation was performed in methanol/water and was found to be sensitive to the amount of water present and the concentration of formaldehyde. If water was omitted, or not added in sufficient amounts, extensive byproduct formation occurred and the desired product could not be isolated.[12]

In conclusion, a diastereoselective synthesis of the monosaccharide kedarosamine, one of the carbohydrate moieties of the enediyne kedarcidin chromophore, has been developed starting from D-threonine. Stereoselective reduction of ketone **7** with tetramethylammonium triacetoxyborohydride was a critical step in this synthesis. Various procedures for anomeric activation were investigated in an effort to couple kedarosamine to an aglycon that resembles kedarcidin chromophore in the region of the aminodeoxy sugar moiety. Of these procedures boron trifluoride etherate-promoted activation of a 1-*O*-acetate was found to be preferred and the desired α-glycoside was obtained in 60−80% yield, depending on the protective group used for the C-4 amino group. Acetyl group migration from O-3 to the amino group of kedarosamine prevented preparation of kedarcidin chromophore analogue **1** in the Fmoc series. However, the target analogue **1** was reached when the Fmoc protective group was replaced by a Cbz group. We anticipate that the results presented herein will facilitate studies directed toward elucidation of the biological role of the carbohydrate moieties of enediyne antitumor antibiotics.

Experimental Section

General Methods. All starting materials were commercially available and were used without further purification. Solvents were dried by distillation from sodium benzophenone (THF, toluene), CaH_2 (CH_2Cl_2), or $CuSO_4$ (HOAc) or by passing through aluminum oxide (CH_3CN). Reactions in these solvents were performed under a nitrogen atmosphere. TLC was carried out on aluminum sheets precoated with silica gel 60 F_{254} (0.2 mm, E. Merck) and the spots were visualized with UV light and cerium sulfate/phosphomolybdic acid in 10% sulfuric acid. Flash column chromatography was performed on silica gel (Matrex 60 Å, 35−70 μm, Grace Amicon). ^1H and ^{13}C NMR spectra were recorded at ambient temperature at 400 and 100 MHz, respectively, and the ^1H and ^{13}C chemical shifts are reported relative to residual $CHCl_3$ (δ_H 7.27 ppm) and to $CDCl_3$ (δ_C 77.0 ppm).

(4*R*,5*S*)-3-(9-Fluorenylmethoxycarbonyl)-2,2,5-trimethyl-4-ozaxolidinecarboxylic Acid (3a). A mixture of Fmoc-D-Thr-OH (3.42 g, 10.0 mmol), 2,2-dimethoxypropane (3.08 mL, 25.0 mmol), and *p*-toluenesulfonic acid (26.3 mg, 0.140 mmol) in benzene (90 mL) was heated under reflux for 3 h and then slowly distilled until a volume of 60 mL had been collected. Ether was added to the cooled reaction mixture and the solution was washed with brine. The aqueous layer was extracted with ether, and the combined organic extracts were dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (heptane:ethyl acetate:acetic acid 80:20:5) which afforded **3a** (3.10 g, 81%):

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(28) The conformation of the hexopyranose ring was determined for compounds **11**, **16a,** and **1** by using NOESY NMR spectroscopy. Thus, NOEs were observed between H-3 and H-5 in these three compounds. An additional NOE was also observed between NH and the axial H-2 in **16a**. These NOEs are only compatible with the $^1C_4$ conformation for the hexose moiety, as shown in Figure 1 and Schemes 2 and 3.

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(31) Mitsunobu, O. *Synthesis* **1981**, 1−28.

R_f 0.27 (chloroform:methanol:acetic acid 92:3:5); $[\alpha]^{23}_D$ +71.3° (*c* 1.0, $CHCl_3$). Two rotamers in a ratio of 1:1.1 were detected by NMR. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.12 (bs, 2H), 7.77−7.26 (m, 16H), 4.67 (m, 2H), 4.42 (m, 2H), 4.09 (m, 2H), 3.91 (m, 2H), 1.68 (bs, 3H), 1.59 (bs, 3H), 1.47 (bs, 3H), 1.33 (m, 3H), 1.10 (bs, 3H), 1.06 (bs, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.6, 175.0, 152.8, 151.8, 144.0, 143.8, 143.6, 143.4, 141.5, 141.4, 141.2, 127.7, 127.0, 124.9, 124.8, 124.4, 124.3, 119.9, 95.9, 95.0, 74.4, 73.6, 67.2, 66.7, 66.0, 65.2, 47.4, 47.2, 26.6, 26.6, 26.4, 24.2, 23.9, 19.3, 19.0, 18.8; HRMS (CI) calcd for $C_{22}H_{24}NO_5$ (M + H) 382.1654, found 382.1655.

(4*R*,5*S*)-3-(Benzyloxycarbonyl)-2,2,5-trimethyl-4-oza-xolidinecarboxylic Acid (3b). The synthesis was carried out as described for **3a** to give **3b** in 73% yield after purification by flash chromatography (heptane:ethyl acetate:acetic acid 80:10:5): R_f 0.28 (heptane:ethyl acetate:acetic acid 80:20:5); $[\alpha]^{23}_D$ +49.8° (*c* 1.0, $CHCl_3$). Two rotamers in a ratio of 1:1.4 were detected by NMR. Minor rotamer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.1 (bs, 1H), 7.45−7.36 (m, 5H), 5.31 (AB-type d, 1H, J = 12.2 Hz), 5.24 (AB-type d, 1H, J = 12.3 Hz), 4.37 (m, 1H), 4.16 (d, 1H, J = 7.7 Hz), 1.68 (s, 3H), 1.66 (s, 3H), 1.54 (d, 3H, J = 6.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.2, 152.9, 135.8, 128.6, 128.2, 95.1, 73.7, 67.8, 66.1, 27.7, 25,0, 19.0. Major rotamer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.1 (bs, 1H), 7.45−7,36 (m, 5H), 5.19 (AB-type d, 1H, J = 12.4 Hz), 5.15 (AB-type d, 1H, J = 12.4 Hz), 4.33 (m, 1H), 4.12 (d, 1H, J = 7.5 Hz), 1.79 (s, 3H), 1.69 (s, 3H), 1.54 (d, 3H, J = 6.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.1, 151.6, 136.0, 128.4, 128.0, 127.7, 95.8, 74.3, 67.8, 65.4, 26.5, 23.9, 19.1. HRMS (CI) calcd for $C_{15}H_{20}NO_5$ (M + H) 294.1341, found 294.1339.

9-Fluorenylmethyl (4*R*,5*S*)-4-(*N*-Methoxy-*N*-methyl-carbamoyl)-2,2,5-trimethyl-3-oxazolidinecarboxylate (4a). A mixture of cyanuric chloride (164 mg, 0.882 mmol) in CH_2Cl_2 (10 mL) was slowly added to a solution of **3a** (1.02 g, 2.66 mmol) and pyridine (0.215 mL, 2.66 mmol) in CH_2Cl_2 (10 mL). A white precipitate was formed immediately. The slurry was stirred for an additional 50 min and was then filtered into a mixture of *N*,*O*-dimethylamine hydrochloride (286 mg, 2.93 mmol), pyridine (0.473 mL, 5.86 mmol), and 3 Å molecular sieves in CH_2Cl_2 (200 mL). After 50 min the molecular sieves were filtered off and the solution was washed with saturated NH_4Cl. The aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried with Na_2SO_4, filtered, and concentrated. The crude product which contained **3a** and **4a** in an approximative ratio of 1:1 was dissolved in CH_2Cl_2 and taken through the same reaction and work up cycle to give, after purification by flash chromatography (heptane:ethyl acetate 1:1), **4a** (0.793 g, 73%) and recovered **3a** (0.253 g, 25%). Compound **4a** had R_f 0.56 (heptane:ethyl acetate 1:2); $[\alpha]^{23}_D$ +23.8° (*c* 1.0, $CHCl_3$); two rotamers in a ratio of 1:1.3 were detected by NMR. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78−7.30 (m, 8H major, 8H minor), 4.70−4.63 (m, 2H, major), 4.61 (ABX-type dd, 1H, J = 6.2 and 11.1 Hz, minor), 4.47 (ABX-type dd, 1H, J = 5.5 and 11.1 Hz, minor), 4.29 (m, 1H, minor), 4.26 (t, 1H, J = 4.6 Hz, major), 4.22−4.14 (m, 1H major, 1H minor), 4.14−4.07 (m, 1H, minor), 3.79 (s, 3H, major), 3.38 (s, 3H, minor), 3.24 (s, 3H, major), 3.09 (s, 3H, minor), 1.67 (s, 3H, minor), 1.66 (s, 3H, minor), 1.38 (d, 3H, J = 6.2 Hz, minor), 1.33 (d, 3H, J = 6.1 Hz, major), 1.17 (s, 3H, major), 1.04 (s, 3H, major); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3, 169.7, 152.65, 152.0, 144.3, 143.9, 143.9, 143.7, 141.6, 141.4, 141.3, 141.2, 127.6, 127.6, 127.5, 127.2, 127.0, 127.0, 125.0, 124.8, 124.6, 124.4, 119.9, 119.9, 119.8, 119.8, 95.7, 94.7, 75.1, 74.2, 66.7, 66.2, 63.1, 63.0, 61.09, 60,8, 47.5, 47.2, 32.4, 32.3, 27.3, 26.9, 24.4, 24.4, 20.2, 18.9; HRMS (CI) calcd for $C_{24}H_{29}N_2O_5$ (M + H) 425.2076, found 425.2068.

Benzyl (4*R*,5*S*)-4-(*N*-Methoxy-*N*-methylcarbamoyl)-2,2,5-trimethyl-3-oxazolidinecarboxylate (4b). The synthesis was carried out as discribed for **4a** to give **4b** (72%) and recovered **3b** (27%) after purification by flash chromatography (heptane:ethyl acetate:triethylamine 67:33:5). Compound **4b** had R_f 0.31 (heptane:ethyl acetate:triethylamine; 67:33:5); $[\alpha]^{23}_D$ +32.0° (*c* 1.0, $CHCl_3$). Two rotamers in a ratio of 1:2 were detected by NMR. Minor rotamer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38−7.30 (m, 5H), 5.21 (AB-type d, 1H, J = 12.3 Hz), 5.13 (AB-type d, 1H, J = 11.6 Hz), 4.58 (d, 1H, J = 7.2 Hz), 4.23 (dq, 1H, J = 6.2 and 6.3 Hz), 3.83 (s, 3H), 3.27 (s, 3H), 1.64 (s, 3H), 1.61 (s, 3H), 1.41 (d, 3H, J = 6.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.8, 151.6, 136.1, 128.5, 128.2, 128.1, 94.8, 74.3, 67.4, 63.3, 61.2, 28.0, 25.0, 19.0. Major rotamer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38−7.30 (m, 5H), 5.10 (AB-type d, 1H, J = 10.8 Hz), 4.97 (AB-type d, 1H, J = 11.6 Hz), 4.40 (d, 1H, J = 7.3 Hz), 4.16 (dq, 1H, J = 6.1 and 6.2 Hz), 3.24 (s, 3H), 3.04 (s, 3H), 1.72 (s, 3H), 1.69 (s, 3H), 1.37 (d, 3H, J = 6.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.9, 152.7, 136.0, 129.0, 128.3, 127.9, 95.3, 74.7, 67.3, 62.6, 60.4, 31.9, 26.7, 23.9, 18.9. HRMS (CI) calcd for $C_{17}H_{25}N_2O_5$ (M + H) 337.1763, found 337.1762.

9-Fluorenylmethyl (4*R*,5*S*)-2,2,5-Trimethyl-4-(1-oxobut-3-enyl)-3-oxazolidinecarboxylate (5a). Allylmagnesium bromide (1 M solution in ether, 4.71 mL, 4.71 mmol) was added to a solution of **4a** (1.00 g, 2.36 mmol) in THF (30 mL) at −78 °C during 30 min. After stirring at −78 °C for 2.5 h the reaction was quenched by addition of saturated aqueous NH_4-Cl. The resultant mixture was allowed to reach room temperature and then the layers were separated. The organic phase was washed with saturated aqueous NH_4Cl and brine. The aqueous layers were extracted with CH_2Cl_2 and the combined organic extracts were dried with Na_2SO_4, filtered, and concentrated. Purification of the residue by flash column chromatography (heptane:ethyl acetate 4:1) afforded **5a** (0.709 g, 79%): R_f 0.74 (heptane:ethyl acetate 1:1); $[\alpha]^{23}_D$ +32.0° (*c* 1.0, $CHCl_3$); two rotamers in a ratio of 1:1 were detected by NMR. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78−7.31 (m, 16H), 5.90 (ddt, 1H, J = 6.8, 10.1, and 17.1 Hz), 5.73 (ddt, 1H, J = 6.9, 10.0, and 17.1 Hz), 5.20 (d, 1H, J = 10.04 Hz), 5.12 (bd, 2H, J = 12.2 Hz), 5.01 (bd, 1H, 17.3 Hz), 4.79 (dd, 1H, J = 4.08 and 10.72 Hz), 4.69 (dd, 1H, J = 6.05 and 10.94 Hz), 4.66 (dd, 1H, J = 3.9 and 10.2 Hz), 4.35 (dd, 1H, J = 5.0 and 10.9 Hz), 4.22 (m, 1H), 4.22 (t, 1H, J = 5.5 Hz), 3.99−3.81 (m, 3H), 3.76 (d, 1H, J = 7.4 Hz), 3.28 (dd, 1H, J = 6.8 and 17.5 Hz), 3.10 (dd, 1H, J = 6.5 and 17.5 Hz), 2.86 (d, 2H, J = 6.6 Hz), 1.58 (s, 6H), 1.33 (d, 3H, J = 6.0 Hz), 1.29 (d, 3H, J = 5.8 Hz), 1.04 (s, 3H), 0.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 204.5, 204.3, 152.8, 151.6, 144.0, 143.8, 143.6, 143.3, 141.6, 141.5, 141.4, 130.0, 129.7, 127.7, 127.2, 124.8, 124.7, 124.4, 124.3, 120.0, 119.9, 119.1, 118.9, 95.6, 94.6, 73.5, 73.0, 71.2, 71.0, 66.4, 66.4, 47.4, 47.3, 44.9, 43.8, 26.6, 24.5, 19.32 18.6; HRMS (CI) calcd for $C_{25}H_{28}NO_4$ (M + H) 406.2018, found 406.2017.

Benzyl (4*R*,5*S*)-2,2,5-Trimethyl-4-(1-oxobut-3-enyl)-3-oxazolidinecarboxylate (5b). The synthesis was carried out as described for **5a** to give **5b** in 86% yield after purification by flash chromatography (heptane:ethyl acetate 10:1). Compound **5b** had R_f 0.55 (heptane:ethyl acetate 3:1); $[\alpha]^{23}_D$ +20.8° (*c* 1.0, $CHCl_3$); two rotamers in a ratio of 1:1.6 were detected by NMR. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37−7.27 (m, 5H major, 5H minor), 5.95 (ddt, 1H, J = 6.8, 10.2, and 17.1 Hz, minor), 5.69 (ddt, 1H, J = 6.8, 10.2, and 17.1 Hz, major), 5.24−4.93 (m, 4H major, 4H minor), 4.17 (d, 1H, J = 8.0 Hz, minor), 4.08−4.00 (m, 2H major, 1H minor), 3.43 (ABX-type dd, 1H, J = 17.5 and 6.5 Hz, minor), 3.25 (ABX-type dd, 1H, J = 17.4 and 6.9 Hz, minor), 3.11 (ABX-type dd, 1H, J = 17.6 and 6.7 Hz, major), 3.02 (ABX-type dd, 1H, J = 17.7 and 6.8 Hz, major), 1.95 (s, 3H, major), 1.64 (s, 3H, major), 1.59 (s, 3H, minor), 1.57 (s, 3H, minor), 1.38 (d, 3H major, 3H minor, J = 5.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 204.8, 204.6, 152.8, 151.5, 135.9, 135.6, 129.8, 129.4, 128.6, 128.4, 128.3, 128.2, 128.0, 128.0, 119.2, 119.2, 95.6, 94.7, 73.6, 73.2, 71.3, 71.1, 67.6, 67.2, 45.4, 44.3, 27.6, 26.5, 25.3, 24.4, 19.0, 18.7; HRMS (CI) calcd for $C_{18}H_{24}NO_4$ (M + H) 318.1705, found 318.1710.

(2*S*,3*R*)-3-(9-Fluorenylmethoxycarbonylamino)-2-hydroxyhept-6-en-4-one (7a). TFA (27 mL) was added to a solution of **5a** (80 mg, 0.197 mmol) in MeOH (3 mL). After 15 min, EtOAc and saturated $NaHCO_3$ were added followed by addition of solid $NaHCO_3$ until pH 7 was obtained. The layers were then separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried with Na_2-SO_4, filtered, and concentrated. Purification of the residue by flash chromatography (heptane:ethyl acetate 3:1) afforded **7a** (67.8 mg, 94%): R_f 0.47 (heptane:ethyl acetate 1:1); $[\alpha]^{23}_D$

+16.4° (*c* 0.44, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.78−7.31 (m, 8H), 5.91 (ddt, 1H, *J* = 17.1, 10.1, and 6.9 Hz), 5.66 (d, 1H, *J* = 8.5 Hz), 5.22 (d, 1H, *J* = 10.0 Hz), 5.16 (d, 1H, *J* = 17.4 Hz), 4.48 (d, 2H, *J* = 6.7 Hz), 4.39 (m, 1H), 4.31 (d, 1H, *J* = 8.6 Hz), 4.23 (t, 1H, *J* = 6.6 Hz), 3.40−3.28 (m, 2H), 2.20 (d, 1H, *J* = 3.4 Hz), 1.21 (d, 3H, *J* = 6.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.9, 156.8, 143.7, 141.4, 129.6, 127.8, 127.1, 125.0, 120.0, 119.5, 67.0, 66.7, 63.8, 47.2, 45.1, 19.5; HRMS (CI) calcd for $C_{22}H_{24}NO_4$ (M + H) 366.1705, found 366.1710.

(2*S*,3*R*)-3-Benzyloxycarbonylamino-2-hydroxyhept-6-en-4-one (7b). The synthesis was carried out as described for **7a** to give **7b** in 64% yield after purification by flash chromatography (heptane:ethyl acetate 2:1). Compound **7b** had R_f 0.68 (heptane:ethyl acetate 1:2); $[\alpha]^{23}_D$ +7.4° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35−7.29 (m, 5H), 5.95−5.84 (m, 2H), 5.20−5.12 (m, 4H), 4.36−4.32 (m, 2H), 3.39 (ABX-type dd, 1H, *J* = 6.8 and 17.5 Hz), 3.32 (ABX-type dd, 1H, *J* = 7.0 and 17.5 Hz), 2.90 (bd, 1H, *J* = 2.9 Hz), 1.20 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 206.9, 156.8, 135.0, 129.6, 128.6, 128.3, 128.2, 128.0, 119.4, 67.4, 67.3, 66.8, 63.9, 45.2, 19.5; HRMS (CI) calcd for $C_{15}H_{20}NO_4$ 278.1392, found 278.1392.

(2*S*,3*R*,4*S*)-3-(9-Fluorenylmethoxycarbonylamino)hept-6-en-2,4-diol (8a). Tetramethylammonium triacetoxyborohydride (1.42 g, 5.40 mmol) was dissolved in HOAc (10 mL) and CH_3CN (10 mL). The solution was stirred for 30 min and then cooled to −28 °C followed by addition of **7a** (395 mg, 1.08 mmol) in CH_3CN (7.5 mL). After stirring for 4 h at −28 °C the reaction mixture was diluted with EtOAc and poured into saturated aqueous $NaHCO_3$. Solid $NaHCO_3$ was added to the resulting mixture until pH 7 was obtained. The layers were then separated and the organic layer was washed with saturated aqueous $NaHCO_3$ and with water. The combined aqueous layers were extracted four times with EtOAc. The combined organic extracts were dried with Na_2SO_4, filtered, and concentrated. Purification of the residue by flash chromatography (heptane:ethyl acetate 2:1) gave **8a** (291 mg, 73%): R_f 0.54 (heptane:ethyl acetate 1:2); $[\alpha]^{23}_D$ +6.3° (*c* 0.79, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.86−7.38 (m, 8H), 5.91 (dddd, 1H, *J* = 6.6, 7.8, 9.6, and 17.4 Hz), 5.62 (d, 1H, *J* = 9.2 Hz), 5.29−5.25 (m, 2H), 4.56 (dd, 1H, *J* = 7.0 and 10.7 Hz), 4.51 (dd, 1H, *J* = 6.8 and 10.7 Hz), 4.44 (bq, 1H, *J* = 6.4 Hz), 4.31 (t, 1H, *J* = 6.9 Hz), 3.93 (dt, 1H, *J* = 4.4 and 8.8 Hz), 3.55 (ddd, 1H, *J* = 1.1, 4.4, and 9.2 Hz), 2.50−2.35 (m, 2H), 1.26 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.7, 143.9, 143.8, 141.4, 141.3, 134.0, 127.6, 127.0, 127.0, 125.0, 125.0, 120.0, 120.0, 119.0, 73.2, 66.6, 65.7, 57.5, 47.3, 39.0, 20.0; HRMS (CI) calcd for $C_{22}H_{26}NO_4$ (M + H) 368.1862, found 368.1862.

(2*S*,3*R*,4*S*)-3-(Benzyloxycarbonylamino)hept-6-en-2,4-diol (8b). The synthesis was carried out as described for **8a** to give **8b** as white crystals in 78% yield after purification by flash chromatography (heptane:ethyl acetate 1:1) and crystallization from ethyl acetate/heptane. Compound **8b** had R_f 0.42 (heptane:ethyl acetate 1:2); mp 87−91 °C; $[\alpha]^{23}_D$ +4.5° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.38−7.30 (m, 5H), 5.83 (m, 1H), 5.63 (d, 1H, *J* = 9.2 Hz), 5.20−5.10 (m, 4H), 4.36 (bq, 1H, *J* = 6.4 Hz), 3.87 (m, 1H), 3.49 (ddd, 1H, *J* = 9.2, 4.4, and 1.2 Hz), 2.93 (bs, 1H), 2.68 (bs, 1H), 2.44−2.28 (m, 2H), 1.19 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.7, 136.4, 134.0, 128.5, 128.2, 128.0, 119.0, 73.3, 67.9, 65.7, 57.5, 39.4, 20.0; HRMS (CI) calcd for $C_{15}H_{22}NO_4$ (M + H) 280.1549, found 280.1552.

2,4,6-Trideoxy-4-(9-fluorenylmethoxycarbonylamino)-L-*lyxo*-hexopyranose (10a). Ozone was bubbled through a solution of **8a** (345 mg, 0.938 mmol) in MeOH (60 mL) at −78 °C for 10 min. The resulting solution was stirred for an additional 3 h, then Me_2S (15 mL) was added and the mixture was allowed to attain room temperature. After 2.5 h the solvent was removed and the residue was purified by flash chromatography (heptane:ethyl acetate 1:2) to give **10a** (324 mg, 93%): R_f 0.11 (heptane:ethyl acetate 1:2); $[\alpha]^{23}_D$ −23.8° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.70−7.32 (m, 16H), 5.37 (bs, 1H), 5.28 (d, 1H, *J* = 8.9 Hz), 5.08 (d, 1H, *J* = 8.9 Hz), 4.79 (m, 1H), 4.62 (dd, 1H, *J* = 10.6 and 4.6 Hz), 4.55−4.48 (m, 3H), 4.36−4.23 (m, 5H), 3.96−3.89 (m, 1H), 3.85 (bdd, 1H, *J* = 9.6 and 3.6 Hz), 3.66 (bq, 1H, *J* = 6.4 Hz), 3.24 (d, 1H, *J* = 5.7 Hz), 2.58−2.47 (m, 3H), 2.13 (m, 1H), 2.02 (dd, 1H, *J* = 13.9 and 5.2 Hz), 1.42 (dt, 1H, *J* = 12.2 and 10.4 Hz), 1.23 (d, 3H, *J* = 6.5 Hz), 1.15 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.4, 143.8, 143.8 141.4, 127.8, 127.1, 125.0, 125.0, 120.0, 94.5, 92.34, 69.5, 67.0, 66.9, 65.7, 64.6, 55.1, 54.0, 47.3, 47.2, 36.2, 33.0, 17.2, 17.0; MS (CI) *m*/*z* (rel intensity) 369 (M^+, 3), 352 (1), 333 (3), 316 (5), 239 (4), 207 (16), 195 (16), 179 (100).

4-Benzyloxycarbonylamino-2,4,6-trideoxy-L-*lyxo*-hexopyranose (10b). Ozone was bubbled through a solution of **8b** (364 mg, 1.31 mmol) in MeOH (20 mL) at −78 °C for 30 min. The resulting solution was stirred for an additional 1 h, Me_2S (6 mL) was added, and the solution was allowed to reach room temperature and then stirred overnight. After concentration the crude product was purified by flash chromatography (heptane:ethyl acetate 1:3) to give **10b** (183 mg) and a byproduct. To a solution of the byproduct in CH_2Cl_2 (2 mL) was added 2.2 M aqueous $FeSO_4$ (2 mL) and the mixture was stirred for 5 d. The layers were then separated and the aqueous layer was extracted twice with EtOAc. The combined organic extracts were dried with Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (heptane:ethyl acetate 1:4) to give **10b** (117 mg). The total yield of **10b** was thus 300 mg (82%). Compound **10b** had R_f 0.19 (heptane:ethyl acetate 1:4); $[\alpha]^{23}_D$ −26.0° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.43−7.38 (m, 10H), 5.83 (d, 1H, *J* = 9.3 Hz), 5.41 (d, 1H, *J* = 9.3 Hz), 5.37 (d, 1H, *J* = 3.5 Hz), 5.20 (d,1H, *J* = 12.1 Hz), 5.19 (d, 1H, *J* = 12.1 Hz), 5.15 (d, 1H, *J* = 12.2 Hz), 5.13 (d, 1H, *J* = 12.2 Hz), 4.73 (dd, 1H, *J* = 9.8 and 1.7 Hz), 4.34−4.27 (m, 2H), 3.94−3.84 (m, 3H), 3.58 (q, 1H, *J* = 6.5 Hz), 2.12 (m, 1H), 1.98 (dd, 1H, *J* = 13.3 and 4.9 Hz), 1.64 (dt, 1H, *J* = 13.3 and 3.5 Hz), 1.50 (dt, 1H, *J* = 12.2 and 10.0 Hz), 1.24 (d, 3H, *J* = 6.3 Hz), 1.19 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.2, 136.0, 136.0, 128.5, 128.5, 128.2, 128.2, 128.0, 128.0, 94.4, 92.2, 69.5, 68.8, 67.3, 67.2, 65.6, 64.6, 55.1, 54.0, 33.1, 33.0, 17.1, 17.0; HR FABMS calcd for $C_{14}H_{19}NNaO_5$ (M + Na) 304.1161, found 304.1156.

Methyl 2,4,6-Trideoxy-4-(9-fluorenylmethoxycarbonylamino)-α-L-*lyxo*-hexopyranoside (11). The hemiacetal **10a** (252 mg, 0.68 mmol) was dissolved in a solution of *p*-toluenesulfonic acid in MeOH (0.5 M, 12 mL) and stirred for 2 d. Saturated aqueous $NaHCO_3$ and ethyl acetate were added to the methanolic solution. The layers were then separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried with Na_2SO_4, filtered, and concentrated. The crude product was obtained as an anomeric mixture of methyl glycosides (α/β = 4:1). Purification of the residue by flash chromatography (heptane:ethyl acetate:methanol; 14:2:1) afforded **11** (156 mg, 60%): $[\alpha]^{23}_D$ −62.1° (*c* 0.78, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.80−7.32 (m, 8H), 5.08 (d, 1H, *J* = 9.3 Hz), 4.76 (d, 1H, *J* = 3.6 Hz), 4.51 (ABX-type dd, 1H, *J* = 10.7 and 7.0 Hz), 4.45 (ABX-type dd, 1H, *J* = 10.7 and 6.6 Hz), 4.25 (bt, 1H, *J* = 6.7 Hz), 4.20−4.14 (m, 1H), 4.04 (bq, 1H, *J* = 6.5 Hz), 3.88 (dd, 1H, *J* = 9.3 and 3.0 Hz), 3.32 (s, 3H), 2.46 (bs, 1H), 1.97 (dd, 1H, *J* = 13.4 and 5.1 Hz), 1.69 (ddd, 1H, *J* = 13.2, 12.1, and 3.4 Hz),1.17 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.6, 144.3, 144.1, 141.8, 128.2, 128.0, 127.5, 127.5, 125.5, 125.4, 125.1, 120.5, 120.5, 99.2, 67.4, 66.5, 64.7, 55.4, 55.4, 47.7, 33.5, 17.5; HR FABMS calcd for $C_{22}H_{25}NNaO_5$ (M + Na) 406.1630, found 406.1639.

Phenyl 2,4,6-Trideoxy-4-(9-fluorenylmethoxycarbonylamino)-1-thio-α-L-*lyxo*-hexopyranoside (12). Thiophenol (7.6 μL, 74.0 μmol), followed by $BF_3{\cdot}Et_2O$ (12.8 μL, 101 μmol), was added to a solution of **10a** (25 mg, 67.7 μmol) in CH_2Cl_2 (0.6 mL) at −78 °C. After stirring for 3 h at −78 °C the solution was poured into CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (toluene:ethyl acetate 3:2) to give **12** (13 mg, 42%): R_f 0.56 (heptane:ethyl acetate 1:2); $[\alpha]^{23}_D$ −5.7° (*c*

0.035, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.80−7.29 (m, 13H), 5.62 (d, 1H, J = 6.0 Hz), 5.07 (d, 1H, J = 8.8 Hz), 4.60 (bq, 1H, J = 6.3 Hz), 4.53 (dd, 1H, J = 7.0 and 10.6 Hz), 4.47 (dd, 1H, J = 6.6 and 10.6 Hz), 4.25 (t, 1H, J = 6.7 Hz), 4.41 (m, 1H), 3.96 (m, 1H), 2.61 (bs, 1H), 2.17 (dd, 1H, J = 6.0 and 13.8 Hz), 2.02 (ddd, 1H, J = 6.0, 12.0, and 13.8 Hz), 1.17 (d, 3H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.2, 143.8, 143.62, 141.3, 141.3, 134.7, 131.3, 129.0, 127.8, 127.3, 127.1, 125.0, 125.0, 120.0, 84.1, 67.0, 65.7, 55.2, 47.2, 33.6, 17.0; HR FABMS calcd for $C_{27}H_{27}NNaO_4S$ (M + Na) 484.1559, found 484.1550.

1,3-Di-*O*-acetyl-2,4,6-trideoxy-4-(9-fluorenylmethoxycarbonylamino)-L-*lyxo*-hexopyranose (15a). A solution of **10a** (30.0 mg, 81 μmol) in pyridine (1 mL) and acetic acid (1 mL) was stirred overnight. The solvents were then removed, and the residue was purified by flash chromatography (heptane:ethyl acetate 5:2) to give **15a** (33.2 mg, 90%) as an α/β mixture (1.4:1) which had R_f 0.60 (heptane:ethyl acetate 2:1). α-anomer: $[\alpha]^{23}_D$ −23.5° (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.88−7.39 (m, 8H), 6.31 (bs, 1H), 5.32 (ddd, 1H, J = 3.6, 6.8, and 10.8 Hz), 5.08 (d, 1H, J = 9.8 Hz), 4.55 (ABX-type dd, 1H, J = 7.2 and 10.7 Hz), 4.50 (dd, 1H, J = 6.8 and 10.7 Hz), 4.34 (t, 1H, J = 7.8 Hz), 4.32 (dq, 1H, J = 1.4 and 6.3 Hz), 4.23 (bdd, 1H, J = 2.9 and 9.8 Hz), 2.20 (s, 3H), 2.07−2.01 (m, 2H), 1.24 (d, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.5, 169.2, 156.7, 143.8, 143.7, 141.4, 141.3, 127.8, 127.1, 125.0, 124.9, 120.1, 120.0, 91.4, 67.4, 66.9, 66.8, 51.4, 47.2, 28.9, 21.1, 21.0, 16.9; FABMS *m/z* (rel intensity) 479 (4), 460 (84), 393 (3), 349 (5), 329 (20), 199 (13), 176 (100), 173 (15), 154 (12), 136 (10), 92 (7), 23 (21). β-anomer: $[\alpha]^{23}_D$ −31.0° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.88−7.38 (m, 8H), 5.81 (dd, 1H, J = 2.6 and 10.22 Hz), 5.18 (d, 1H, J = 9,9 Hz), 5.06 (ddd, 1H, J = 3.9, 4.9, and 12.6 Hz), 4.54 (dd, 1H, J = 7.3 and 10.7 Hz), 4.48 (dd, 1H, J = 6.8 and 10.7 Hz), 4.34 (t, 1H, J = 7.0 Hz), 4.16 (dd, 1H, J = 3.6 and 10.0 Hz), 3.89 (dq, 1H, J = 1.4 and 6.4 Hz), 2.23 (s, 3H), 2.14 (ddd, 1H, J = 2.7, 5.1, and 12.6 Hz), 2.07 (s, 3H), 1.85 (dt, 1H, J = 10.3 and 12.6 Hz), 1.31 (d, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.2, 168.8, 156.6, 143.9, 143.7, 141.3, 127.7, 127.0, 125.1, 125.0, 120.1, 120.0, 91.8, 70.8, 69.0, 66.8, 50.7, 47.2, 30.5, 21.0, 20.9, 16.8; HR FABMS calcd for $C_{25}H_{27}KNO_7$ (M + K) 492.1425, found 492.1443.

1,3-Di-*O*-acetyl-4-benzyloxycarbonylamino-2,4,6-trideoxy-L-*lyxo*-hexopyranose (15b). The synthesis was carried out as described for **15a** to give **15b** in 87% yield as an α/β mixture (1:1.3) after purification by flash chromatography (heptane:ethyl acetate 2:1). R_f 0.63 (heptane:ethyl acetate 1:2). α-anomer: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.38−7.31 (m, 5H), 6.19 (dd, 1H, J = 2.2 Hz), 5.22 (ddd, 1H, J = 3.6, 6.3, and 11.4 Hz), 5.15 (d, 1H, J = 12.3 Hz), 5.07 (d, 1H, J = 12.3 Hz), 5.04 (d, 1H, J = 10.0 Hz), 4.22 (dq, 1H, J = 1.4 and 6.5 Hz), 4.15 (dd, 1H, J = 3.1 and 10.0 Hz), 2.10 (s, 3H), 2.06−1.98 (m, 2H), 1.96 (s, 3H), 1.17 (d, 3H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.4, 169.3, 156.6, 136.4, 128.5, 128.2, 128.0, 91.4, 69.0, 67.4, 66.9, 51.4, 28.8, 21.5, 20.9, 16.9. β-anomer: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.38−7.31 (m, 5H), 5.70 (dd, 1H, J = 2.6 and 10.2 Hz), 5.17 (d, 1H, J = 12.3 Hz), 5.12 (d, 1H, J = 10.0 Hz), 5.07 (d, 1H, J = 12.3 Hz), 4.98 (ddd, 1H, J = 3.7, 5.0, and 12.6 Hz), 4.07 (dd, 1H, J = 3.7 and 10.0 Hz), 3.79 (dq, 1H, J = 1.4 and 6.4 Hz), 2.11 (s, 3H), 1.95 (s, 3H), 1.95−1.90 (m, 1H), 1.74 (dt, 1H, J = 10.3 and 12.6 Hz), 1.24 (d, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.2, 168.8, 156.6, 136.5, 128.5, 128.1, 127.9, 91.7, 70.6, 66.9, 66.8, 50.6, 30.4, 20.9, 20.8, 16.8. HR FABMS calcd for $C_{18}H_{23}NNaO_7$ (M + Na) 388.1372, found 388.1364.

(*R*)-2-(*tert*-Butyldiphenylsilyloxy)-1-phenylethyl 3-*O*-Acetyl-2,4,6-trideoxy-4-(9-fluorenylmethoxycarbonylamino)-α-L-*lyxo*-hexopyranoside (16a). $BF_3{\cdot}Et_2O$ (170 μL, 1.35 mmol) was added to a solution of **15a** (614 mg, 0.35 mmol) and **13** (561 mg, 1.49 mmol) in toluene (30 mL) at 0 °C. After stirring for 1 h the solution was poured into EtOAc and washed with saturated aqueous $NaHCO_3$. The organic layer was separated, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (heptane:ethyl acetate 7:1 + 5% pyridine) to give **16a** (1.042 g, 80%): R_f 0.51 (heptane:ethyl acetate 2:1); $[\alpha]^{23}_D$ −65.8° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.78−7.17 (m, 18H), 5.41 (ddd, 1H, J = 3.8, 5.1, and 12.3 Hz), 5.04 (d, 1H, J = 9.8 Hz), 4.78 (d, 1H, J = 3.4 Hz), 4.76 (dd, 1H, J = 4.0 and 7.8 Hz), 4.50 (dq, 1H, J = 1.1 and 6.5 Hz), 4.43 (dd, 1H, J = 7.5 and 10.6 Hz), 4.39 (dd, 1H, J = 6.8 and 10.6 Hz), 4.26 (t, 1H, J = 7.0 Hz), 4.08 (dd, 1H, J = 2.9 and 9.8 Hz), 3.90 (dd, 1H, J = 7.9 and 10.8 Hz), 3.67 (dd, 1H, J = 4.0 and 10.8 Hz), 1.99−1.90 (m, 1H), 1.77 (dt, 1H, J = 3.9 and 12.8 Hz), 1.12 (d, 3H, J = 6.5 Hz), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3, 156.7, 143.9, 143.8, 141.3, 138.15, 135.6, 135.5, 133.3, 133.2, 129.7, 129.7, 129.0, 128.4, 128.2, 128.2, 127.8, 127.7, 127.7, 127.0, 125.3, 125.1, 125.0, 120.0, 120.0, 93.9, 78.3, 68.0, 67.6, 66.7, 64.7, 51.8, 47.2, 30.1, 26.8, 21.1, 19.2, 17.0; HR FABMS calcd for $C_{47}H_{51}NNaO_7Si$ (M + Na) 792.3333, found 792.3348.

(*R*)-2-(*tert*-Butyldiphenylsilyloxy)-1-phenylethyl 3-*O*-Acetyl-4-benzyloxycarbonylamino-2,4,6-trideoxy-α-L-*lyxo*-hexopyranoside (16b). $BF_3{\cdot}Et_2O$ (4 × 37 μL, 4 × 0.293 mmol) was added in portions to a solution of **15b** (107 mg, 0.293 mmol) and **13** (121 mg, 0.322 mmol) in toluene (5 mL) at 0 °C. After stirring for 2 h, the solution was poored into EtOAc and washed with saturated aqueous $NaHCO_3$. The organic layer was separated, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (heptane:ethyl acetate 9:1 + 5% pyridine) to give **16b** (124 mg, 62%): R_f 0.42 (heptane:ethyl acetate 2:1); $[\alpha]^{23}_D$ −82.4° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.70−7.24 (m, 20H), 5.41 (ddd, 1H, J = 3.9, 5.0, and 12.3 Hz), 5.17 (d, 1H, J = 12.3 Hz), 5.09 (d, 1H, J = 12.3 Hz), 5.04 (d, 1H, J = 9.9 Hz), 4.77−4.74 (m, 2H), 4.50 (dq, 1H, J = 1.3 and 6.4 Hz), 4.09 (dd, 1H, J = 3.2 and 9.9 Hz), 3.89 (dd, 1H, J = 7.9 and 10.8 Hz), 3.66 (dd, 1H, J = 4.1 and 10.8 Hz), 1.99 (s, 3H), 1.92 (dd, 1H, J = 5.3 and 13.2 Hz), 1.73 (dt, 1H, J = 3.8 and 12.9 Hz), 1.13 (d, 3H, J = 6.4 Hz), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3, 156.7, 138.2, 136.59, 135.5, 135.5, 133.3, 133.2, 129.7, 129.7, 128.5, 128.4, 128.3, 128.1, 127.9, 127.7, 127.7, 127.4, 93.9, 78.2, 68.0, 67.9, 66.7, 64.7, 51.8, 30.1, 26.78, 21.0, 19.1, 17.0; HR FABMS calcd for $C_{40}H_{47}NNaO_7Si$ (M + Na) 704.3020, found 704.3008.

(*R*)-2-(*tert*-Butyldiphenylsilyloxy)-1-phenylethyl 4-Benzyloxycarbonylamino-2,4,6-trideoxy-α-L-*lyxo*-hexopyranoside (14b). A solution of **16b** (194 mg, 0.284 mmol) in 0.02 M methanolic NaOMe (2.5 mL) was stirred for 5 h. The solution was then neutralized by addition of Doulite C436, and the mixture was stirred for 1 h and then filtrated and concentrated. The crude product was purified by flash chromatography (heptane:ethyl acetate 5:1 + 5% pyridine) to give **14b** (142 mg, 78%): R_f 0.20 (heptane:ethyl acetate 2:1); $[\alpha]^{23}_D$ −87.4° (*c* 0.95, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.78−7.31 (m, 20H), 5.21 (d, 2H, J = 3.0 Hz), 5.16 (d, 1H, J = 9.1 Hz), 4.83 (dd, 1H, J = 3.6 and 8.3 Hz), 4.79 (d, 1H, J = 3.5 Hz), 4.53 (bq, 1H, J = 6.5 Hz), 4.41 (m, 1H), 3.95 (m, 1H), 3.95 (dd, 1H, J = 8.3 and 10.8 Hz), 3.72 (dd, 1H, J = 3.9 and 10.8 Hz), 2.59 (bs, 1H), 2.04 (dd, 1H, J = 5.1 and 13.4 Hz), 1.65 (dt, 1H, J = 3.5 and 12.6 Hz), 1.22 (d, 3H, J = 6.5 Hz), 1.12 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.3, 138.2, 136.1, 135.5, 133.3, 133.3, 129.7, 128.6, 128.4, 128.3, 128.3, 128.1, 128.1, 128.0, 127.7, 127.7, 127.4, 94.1, 78.1, 68.2, 67.3, 66.4, 64.5, 55.2, 33.1, 26.8, 19.1, 17.2; HR FABMS calcd for $C_{38}H_{45}NNaO_6Si$ (M + Na) 662.2914, found 662.2923.

(*R*)-2-Hydroxy-1-phenylethyl 4-Benzyloxycarbonylamino-2,4,6-trideoxy-α-L-*lyxo*-hexopyranoside (17). $QF{\cdot}3H_2O$ (63.1 mg, 0.200 mmol) was added to a solution of **14b** (128 mg, 0.200 mmol) in THF (5 mL), and the solution was stirred overnight. The solution was concentrated and the crude product was purified by flash chromatography (heptane:ethyl acetate 1:3 + 5% pyridine) to give **17** (53.0 mg, 66%): R_f 0.60 (chloroform:methanol 9:1); $[\alpha]^{23}_D$ −140.9° (*c* 0.80, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) 7.38−7.30 (m, 10H), 5.17−5.10 (m, 2H), 5.12 (d, 1H, J = 9.1 Hz), 4.79 (d, 1H, 3.8 Hz), 4.71 (dd, 1H, J = 3.8 and 8.2 Hz), 4.31 (m, 2H), 3.96 (bd, 1H, J = 7.2 Hz), 3.75 (bt, 1H, J = 9.9 Hz), 3.69 (m, 1H), 2.73 (bs, 1H), 2.29 (bs, 1H), 1.97 (dd, 1H, J = 5.1 and 13.3 Hz), 1.60 (ddd, 1H, J = 4.0, 12.2, and 13.3 Hz), 1.24 (d, 3H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.3, 137.6, 136.0, 128.6, 128.6, 128.4,

128.3, 128.1, 127.1, 94.8, 79.0, 67.3, 67.2, 66.2, 65.1, 55.1, 33.0, 17.2; HR FABMS calcd for $C_{22}H_{27}NNaO_6$ (M + Na) 424.1736, found 424.1750.

(*R*)-2-(4-Benzyloxycarbonylamino-2,4,6-trideoxy-α-L-*lyxo*-hexopyranosyloxy)-2-phenylethyl *N*-(9-Fluorenylmethoxycarbonyl)-D-phenylalaninate (18). Triphenylphosphine (53 mg, 0.202 mmol) in THF (1 mL), followed by DEAD (32 μL, 0.202 mmol), was added to a solution of **17** (40.5 mg, 0.101 mmol) in THF (1 mL). After stirring of the resulting mixture for 40 min, a solution of *N*-(9-flourenylmethoxycarbonyl)-D-phenylalanine in THF (1 mL) was added. After stirring for an additional 70 min, the mixture was concentrated and the crude product was purified by flash chromatography (heptane:ethyl acetate 1:1) to give **18** (68.3 mg, 88%): R_f 0.33 (heptane:ethyl acetate 1:2); $[\alpha]^{23}_D$ −76.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78−7.01 (m, 23H), 5.23 (d, 1H, *J* = 8.4 Hz), 5.15−5.08 (m, 2H), 5.06 (d, 1H, *J* = 9.4 Hz), 4.83 (dd, 1H, *J* = 3.4 and 8.0 Hz), 4.69−4.64 (m, 2H), 4.49 (dd, 1H, *J* = 7.1 and 10.5 Hz), 4.34 (dd, 1H, *J* = 6.9 and 10.5 Hz), 4.26 (dd, 1H, *J* = 3.6 and 11.5 Hz), 4.20 (q, 1H, *J* = 7.1 Hz), 3.89 (bd, 1H, *J* = 6.8 Hz), 3.11 (ABX-type dd, 1H, *J* = 5.8 and 13.8 Hz), 3.03 (ABX-type dd, 1H, *J* = 5.7 and 13.8 Hz), 2.65 (bd, 1H, *J* = 2.6 Hz), 1.93 (dd, 1H, *J* = 4.7 and 13.4 Hz), 1.54 (dt, 1H, *J* = 3.9 and 12.7 Hz), 1.17 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.3, 158.2, 155.4, 143.8, 143.7, 141.3, 136.8, 136.0, 135.4, 129.2, 128.8, 128.7, 128.6, 128.3, 128.1, 127.7, 127.3, 127.2, 127.1, 125.1, 125.0, 120.0, 94.5, 74.8, 68.6, 67.3, 66.9, 66.2, 65.0, 55.0, 54.8, 47.2, 38.4, 32.8, 17.1; HR FABMS calcd for $C_{46}H_{46}N_2NaO_9$ (M + Na) 793.3101, found 793.3099.

(*R*)-2-(2,4,6-Trideoxy-4-(dimethylamino)-α-L-*lyxo*-hexopyranosyloxy)-2-phenylethyl *N*-(9-Fluorenylmethoxycarbonyl)-D-phenylalaninate (1). A freshly prepared solution of formalin in H_2O:MeOH (88 μL, 4.7 M, 10:1) and 10% Pd/C (6 mg) were added to a solution of **18** (16.0 mg, 20.8 μmol) in MeOH:H_2O (2.25 mL, 4:1), and the resulting mixture was hydrogenated at atmospheric pressure. After 24 h, additional 10% Pd/C (6 mg) and formalin solution (88 μL) were added. The hydrogenation was then continued for an additional 3 d, after which the catalyst was removed by filtration and washed with CH_2Cl_2. The combined organic phases were washed with H_2O, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (heptane:ethyl acetate:methanol 4:16:1) to give **1** (6.2 mg, 45%). R_f 0.22 (heptane:ethyl acetate 1:4); $[\alpha]^{23}_D$ −79.8° (*c* 0.47, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80−7.03 (m, 18H), 5.27 (d, 1H, *J* = 8.3 Hz), 4.91 (t, 1H, *J* = 6.0 Hz), 4.83 (bs, 1H), 4.71 (dt, 1H, *J* = 5.5 and 8.3 Hz), 4.48 (dd, 1H, *J* = 7.2 and 10.5 Hz), 4.36−4.30 (m, 2H), 4.28−4.23 (m, 2H), 4.22 (t, 1H, *J* = 6.8 Hz), 4.03 (dt, 1H, *J* = 5.3 and 10.5 Hz), 3.14 (ABX-type dd, 1H, *J* = 5.4 and 13.9 Hz), 3.05 (ABX-type dd, 1H, *J* = 5.3 and 13.9 Hz), 2.58 (s, 6H), 2.53 (dd, 1H, *J* = 3.5 and 4.6 Hz), 1.96 (ddd, 1H, *J* = 2.3, 5.4, and 13.8 Hz), 1.75 (ddd, 1H, *J* = 3.8, 10.3, and 13.8 Hz), 1.42 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1, 155.4, 143.8, 143.7, 141.3, 137.2, 135.5, 129.3, 128.7, 128.6, 127.7, 127.2, 127.2, 127.1, 125.1, 125.0, 120.0, 120.0, 94.0, 74.8, 68.7, 68.3, 66.9, 63.9, 63.3, 54.7, 47.2, 44.9, 38.2, 35.5, 18.1; HR FABMS calcd for $C_{40}H_{44}N_2NaO_7$ (M + Na) 687.3046, found 687.3049.

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Supporting Information Available: Copies of the ^{1}H and ^{13}C NMR spectra of compounds **1, 3a,b**−**5a,b**, **7a,b**, **8a,b**, **10a,b**, **11**, **12**, **14b**, **15a,b**, **16a,b**, **17**, and **18** (46 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering instructions.

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