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A New Access to Enantiomerically Pure Deoxy Aminohexoses: Methyl 4-Amino-4,6-Dideoxygulopyranoside and *epi*-Tolyposamine

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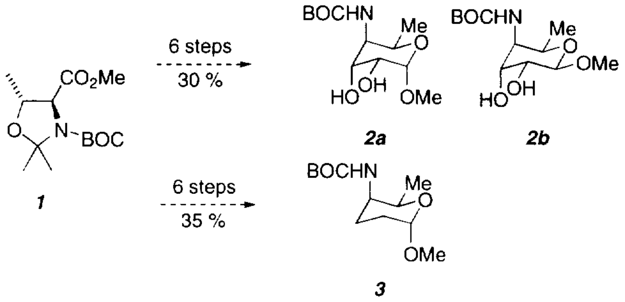
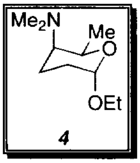
Abstract: New efficient synthetic routes have been developed starting from the fully protected L-threonine derivative 1 for some deoxy-4-aminohexoses: methyl 4-amino-4,6-dideoxy gulopyranoside 2 and *epi*-tolyposamine 3. The title compounds were synthesized using an improved Horner-Emmons reaction of the threonine derived aldehyde 7. A new method for selective removal of the aminal protection is also reported. © 1997 Elsevier Science Ltd.

Cell surface glycoconjugates (glycoproteins, proteoglycans, glycosphingolipids, and glycosyl phosphadityl inositols) play an important role in biological recognition, carrying encoded biological information that is recognized by other cells, viruses, bacteria, and toxins. The recognition event is important for the regulation of cell-substratum adhesion and cell proliferation, for the binding and uptake of extracellular components and for the regulation of extracellular matrix formation.[1] For example, inflammatory response involves cell adhesion, and in some cases too many leukocytes are recruited, destroying normal tissue.[2] This occurs in disorders such as psoriasis and rheumatoid arthritis, in septic shock, and in organ transplants. If adhesion could be prevented, the excessive recruitment of white blood cells would also be prevented. 6-Deoxyaminohexoses have been identified as key components of many antibiotics and are found on the cell walls of many bacteria.[3-6] Under such conditions they may function as anti-inflammatory agents. Similar cell adhesion processes are involved in cancer metastasis. On this basis the title compounds are interesting as glycomimics in pharmaceutical applications.

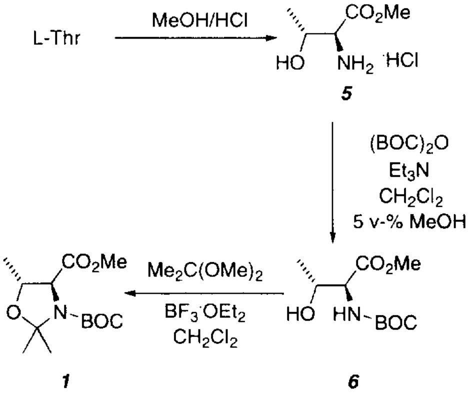
During a program on the study of amino acids as starting materials for natural products in enantiopure form,[7] efficient synthetic routes were developed for di- and tetradeoxy-4-aminohexoses in the D-series of sugars. In this paper, we wish to report efficient short syntheses for two representative congeners of the title compounds, i.e. methyl *N*-BOC 4-amino-4,6-dideoxy-D-gulopyranoside **2** and methyl *N*-BOC-D-*epi*-tolyposamine glycoside **3** (Scheme 1).



Scheme 1.



The methyl 4-amino-4,6-dideoxy-D-gulopyranoside **2** was synthesized in 6 steps from fully protected L-threonine with an overall yield of 30 %. Stevens *et al.* have synthesized the related ossamine **4** from penta-acetyl D-glucose in 13 steps.[8] In our modification the N-BOC D-*epi*-tolyposamine was synthesized in 6 steps starting from fully protected L-threonine[9] in an overall yield of 35 %.



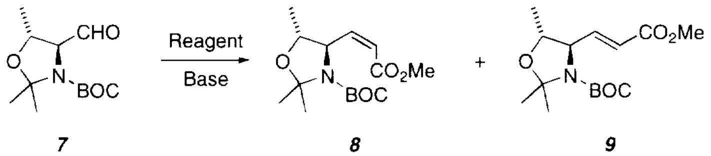
Scheme 2.

The fully protected L-threonine 1 was prepared by an improvement of a literature route.[9,10] In our modification, L-threonine was first esterified followed by BOC-protection and ketal protection. The ketal protection was performed under Lewis acid conditions, instead of Brønsted acid, in an apolar solvent. This led to a dramatically shorter reaction time and markedly improved the yield (overall yield over three steps 84 %) (Scheme 2).

***Cis*- and *trans*-enoates 8 and 9** were envisioned as key building blocks for the synthesis of deoxyaminohexoses. The *E*/*Z* ratio of the olefinic products formed in Horner-Emmons reactions depends not only on the metal cation, solvent, and temperature, but also on the esters of the phosphonate.[11] The Horner-Emmons olefination leads preferentially to the thermodynamically more stable *E*-olefins, but the selectivity can be changed to favor the kinetic *Z*-product. Modifications of Horner-Wadsworth-Emmons olefination are available to produce both enoates selectively.[12,13] Still and Gennari have reported a *cis*-selective Horner-Wadsworth-Emmons olefination for aliphatic and alicyclic aldehydes.[12] These conditions also work for heterocyclic aldehydes.[13,14] Electron-withdrawing esters, *e.g.* bis-1,1,1-trifluoroethyl methyl phosphonoacetate, destabilize oxaphosphetane intermediate, and the elimination of the initial adduct is faster than adduct equilibration, which favors *Z*-selectivity.[12]

The fully protected L-threonine methyl ester 1 was reduced (DIBAL-H) to the corresponding aldehyde derivative 7 in high yield (83 %).[9] The aldehyde 7 was subjected to Horner-Wadsworth-Emmons type olefination reactions under a variety of conditions, in order to obtain the *E*- and *Z*-enoates 8 and 9, respectively, with high selectivity. The results of these experiments are collected in Table 1.

Table 1. *Z*- And *E*-olefination of the aldehyde 7



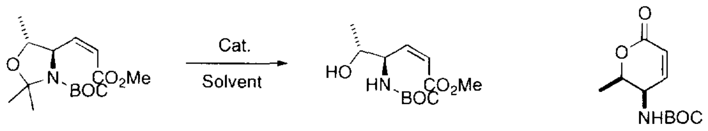
Entry	Reagent[a]	Solvent	Base	18-Crown-6[b]	Temperature	Yield	(8/9)
1	**A**	MeOH	-	-	rt	69 %	1:2
2	**B**	PhMe	K_2CO_3	-	rt	81 %	1:6
3	**B**	PhMe	K_2CO_3	200	rt	84 %	1:19
4	**B**	MeCN	K_2CO_3	-	rt	80 %	1:4
5	**B**	MeCN	K_2CO_3	200	-20 → 0 °C	N/D	1:10
6	**C**	PhMe	K_2CO_3	-	rt	91 %	3:1
7	**C**	PhMe	K_2CO_3	200	-20 → 0 °C	98 %	17:1
8	**C**	MeCN	K_2CO_3	-	rt	96 %	6:1
9	**C**	MeCN	K_2CO_3	200	-20 → 0 °C	95 %	9:1
10	**C**	THF	KHMDS	500	-78 °C	90 %	10:1

[a] **A** = $CH_3O_2CCHPPh_3$; **B** = $CH_3O_2CCH_2P(O)(OCH_3)_2$; **C** = $CH_3O_2CCH_2P(O)(OCH_2CF_3)_2$.
[b] amount of 18-crown-6 in mol-%.

Wittig reaction with methoxycarbonylmethylidene triphenylphosphorane (entry 1) gave the poorest yield and selectivity. Trimethyl phosphonoacetate gave, as expected, mainly the *E*-isomer (entries 2-5). Toluene proved to be a better solvent in both the presence and absence of crown ether. Methyl bistrifluoroethyl phosphonoacetate gave mainly the *Z*-isomer under all conditions tested (entries 6-9). For the *Z*-isomer, toluene was a better solvent when crown ether was present, but acetonitrile gave better selectivity when no crown ether was used (entries 6 and 8). The most selective conditions for the formation of both enoates *8* and *9* were obtained by using potassium carbonate in toluene in the presence of 18-crown-6 at 0 °C (ratio of *Z*:*E*-isomers with trimethyl phosphonoacetate was 1:19, and with methyl bistrifluoroethyl phosphonoacetate 17:1, entries 3 and 7). Both phosphonates gave good yields (80 % - 100 %) in all conditions tested. The presence of 18-crown-6 shortened the reaction times, which permitted reactions to be run at a lower temperature, which led to improved selectivities when methyl bistrifluoroethyl phosphonoacetate was used. Trimethyl phosphonoacetate gave better selectivities at room temperature. Use of KHDMS in THF with 18-crown-6 gave the *Z*-isomer in ratio 10:1 (entry 10). Thus, potassium carbonate in toluene allows the employment of less 18-crown-6 while giving higher selectivities than the traditional KHMDS.[12]

Cleavage of the aminal protection. In the synthesis of methyl 4-amino-4,6-dideoxy gulopyranoside *2*, we decided to introduce the C-3 and C-2 oxygens after the formation of the lactone ring, in order to utilize the inherent facial selectivity of the cyclic array. After considerable experimentation (Table 2), neat acetic acid was found to cleave selectively the aminal protection without simultaneous cleavage of the acid labile carbamate. Lactonization of the open chain intermediate was also effected under these conditions (overall yield of *11* from *8* 68 %). Most of the methods tested produced mixtures of the open chain product *10* and the lactone *11*.

Table 2. Cleavage of the aminal protection with and without cyclization



8 *10* *11*

Entry	Solvent	Catalyst	Transketalisation	Temperature	10/11[a]
1	MeOH	p-TsOH	-	reflux	4:1
2	MeOH	CSA	-	reflux	4:1
3	MeOH	p-TsOH	glycol	reflux	4:1
4	MeOH	CSA	glycol	reflux	4:1
5	CH_2Cl_2	$BF_3 \cdot OEt_2$	dithiol	rt	3:4
6	AcOH	-	-	50-80 °C[b]	0:1
7	80% AcOH	-	-	rt	3:1
8	HCO_2H	-	-	rt[c]	4:1

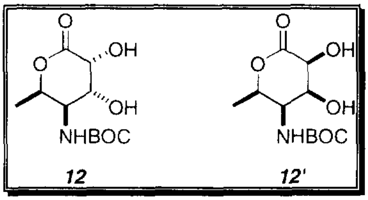
[a] according to crude NMR
[b] no reaction at rt
[c] cleavage of the carbamate was also detected

Acidic methanolysis[15] produced mixtures of compounds *10* and *11* giving mainly the open chain product *10* (ratio 4:1). The reaction did not proceed to completion even after refluxing for several days. Increasing the acidity of the acid by changing the p-toluenesulfonic acid to camphorsulfonic acid showed no improvement. Transketalization (entries 3 and 4) did not have any effect on the reaction, presumably because the five membered ring in compound **8** is more stable than the five membered ring in the ketal protected glycol due to entropic effects.

Lewis acid ($BF_3{\cdot}OEt_2$) catalyzed transketalization in methylene chloride with a dithiol[16] instead of Brønsted acid catalyzed deketalization/transketalization, also produced a mixture of compounds **10** and **11**, but now compound **11** was formed as the major isomer (ratio 3:4).

In glacial acetic acid at 50 - 80 °C (optimally 60 - 70 °C), only compound **11** was produced (entry 6). At room temperature hardly any reaction was detected and at higher temperatures a side product (completely deprotected compound) was formed in considerable amount. When the reaction was run in 80 % acetic acid the open chain intermediate **10** was formed with appreciable selectivity (entry 7). Lowering the pK_a of the acid (formic acid instead of acetic acid) accelerated the deketalization reaction, but also led to cleavage of the acid labile carbamate before cyclization. Only compound **10** was obtained in low yield (entry 8).

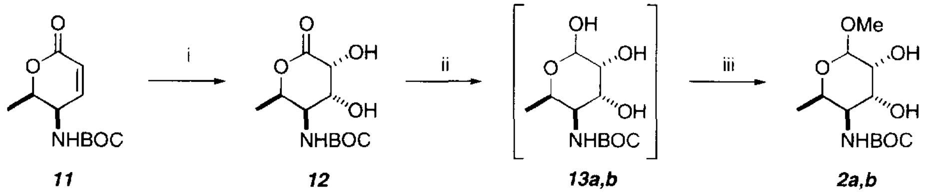
Methyl 4-amino-4,6-dideoxygulopyranoside 2. Dihydroxylation of the double bond of **11** with a catalytic amount of osmium tetroxide[17,18] produced stereoselectively the diol lactone **12** (73 % yield). This was predicted by molecular modeling to be the *syn,anti,syn*-isomer, in line with the results by Kishi et al.[17] Minimum energy conformations of the two possible isomers showed that both structures are distorted.[18] According to calculations with an algorithm based on the modified Altona-Haasnoot equation,[19] there should be at least two different couplings in the all *syn* isomer ($^3J_{3,4}$ = 8.5 Hz; $^3J_{2,3}$ = 3.6 Hz), while in the *syn,anti,syn* isomer the two couplings are of the same magnitude (3.4 Hz and 3.1 Hz). This was indeed proven to be correct by NMR. The proton at position three gives a quartet with a coupling constant *ca.* 3 Hz. An apparent quartet of H-3 with coupling constant 3 Hz is not compatible with structure **12'**.



12 **12'**

In compound **11**, the dihedral angle between C(4)-NHBOC and C(3)-H is considerably smaller (approximately 35°) than an ideal value of 60°. This is manifested in a steric interaction between the substituents, which forces the allylic NHBOC-group to adopt a pseudoaxial position (allylic $A^{1,2}$ strain[20]). At the axial position the allylic NHBOC-group can form a stabilizing hydrogen bond with the ring oxygen.[21] The pseudoaxial NHBOC-group effectively shields the upper face and only the lower face is attacked. Also stereoelectronic effects favor the adoption of an *anti* orientation by the allylic NHBOC-group, in order to maximize the electron donation.[20,22]

Lactone 12 was converted to the corresponding methyl glycoside 2 by reduction with DIBAL-H followed by acidic methanolysis (60 % yield). (The α-anomer was crystallized from ethyl acetate. The β-anomer was isolated from the mother liquid by preparative TLC.)

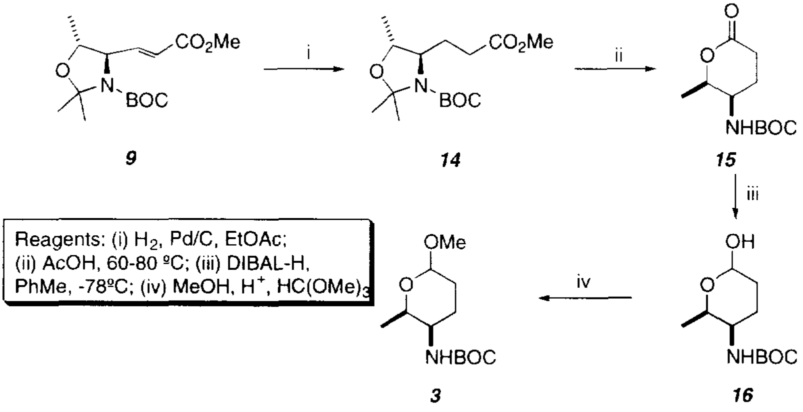


Reaction conditions:
(i) OsO_4, NMMO; (ii) DIBAL-H, PhMe, -78 °C; (iii) MeOH, CSA.

Scheme 3

D-*epi*-Tolyposamine 3. An adaptation of the route developed for dideoxy aminohexoses also gives access to D-*epi*-tolyposamine. Thus, the enoate was prepared with the potassium carbonate (K_2CO_3, MeCN, rt, 80 %) method giving a 1:4 mixture of isomers (*Z*:*E*). The double bond of the *E*-enoate 9 was hydrogenated under standard conditions (H_2, Pd/C, EtOAc) in excellent yield (99 %) before lactonization. The aminal protection was removed as described above and the lactone 15 was obtained in 74 % yield.

Reduction of the lactone 15 with DIBAL-H (quantitative) and treatment of lactol 16 with acidic methanol in the presence of trimethyl orthoformate as water scavenger produced the α-anomer of the methyl glycoside 3 in 71 % yield.



Reagents: (i) H_2, Pd/C, EtOAc; (ii) AcOH, 60-80 ºC; (iii) DIBAL-H, PhMe, -78ºC; (iv) MeOH, H^+, $HC(OMe)_3$

Scheme 4

Conclusions

Efficient synthetic routes utilizing non-carbohydrate starting materials were developed for the D-series of di- and tetra-6-deoxy-4-aminohexoses: methyl *N*-BOC 4-amino-4,6-dideoxy-D-gulopyranoside **2** and *N*-BOC-D-*epi*-tolyposamine methyl glycoside **3**. Both aminohexoses were synthesized from the fully protected L-threonine derivative **1**. Improved Horner-Emmons reaction of the derived aldehyde **7** as well as new methods for the selective removal of the aminal protection were developed. An adaptation of the route described also gives access to other di-, tri- and tetra-6-deoxy-4-aminohexoses derived from L-threonine. Analogously, the L-series of di-, tri-, and tetra-6-deoxy-4-aminohexoses can be obtained from D-threonine.

Experimental

General procedures. Methanol was dried by distilling from magnesium methoxide. Methylene chloride was distilled prior to use from calcium hydride. Toluene was distilled from phosphorus pentoxide and stored under Ar over metallic sodium. Acetonitrile was distilled prior to use from phosphorus pentoxide. Boron trifluoride diethyl etherate was treated with a small quantity of ethyl ether and then distilled under reduced pressure from calcium hydride and stored under Ar. Triethylamine was distilled from sodium and stored under Ar. Trimethyl orthoformate and trifluoroacetic acid were fractionally distilled and stored under Ar. All other reagents and solvents except those noted were used as obtained from the supplier, without further purification. All air or moisture sensitive reactions were carried out under Ar with magnetic stirring. Reactions were monitored by TLC (on silica gel 60 F_{254} plates from Merck). The chromatograms were visualized by UV light and staining with phosphomolybdic acid (PMA) unless otherwise noted. Reaction temperatures refer to bath temperatures. After extractive work-up, organic extracts were dried over Na_2SO_4 or $MgSO_4$, filtered, and evaporated on a rotary evaporator (water aspirator). Static evaporation with an oil pump followed. Melting points were determined on a Kofler-type hot plate apparatus, and are given uncorrected. NMR spectra were recorded on a Bruker AM-200 spectrometer operating at 200.1 MHz (for ^1H). Optical rotations were determined on a Perkin-Elmer 243B digital polarimeter in a 1 dm/1mL cell.

Methyl (4*S*, 5*R*)-2,2,5-trimethyl-3-(*tert*-butoxycarbonyl)-oxazolidine-4-carboxylate **1**. *(a) L-Threonine methyl ester* **5**. Acetyl chloride (68 ml, 0.95 mol, 200 mol-%) was added dropwise to ice-cold methanol (300 ml). After the addition of L-threonine (0.48 mol, 100 mol-%), the reaction mixture was warmed in an oil bath to 50°C and stirred at this temperature until most of the acid had reacted. Evaporation of the solvent gave crude **5** as a yellow oil, which was used in the next step without further purification. TLC(EtOAc:MeOH, 1:1), ninhydrin, $R_f = 0.45$. ^1H NMR (d_4-MeOH+$CDCl_3$) δ 4.38 (m, 1H), 4.00 (s, 3H), 3.87 (d, 1H), 1.48 (d, 3H).

(b) N-(tert-butoxycarbonyl)-L-threonine methyl ester **6**. The crude ester hydrochloride **5** (0.48 mol, 105 mol-%) was dissolved in 5 ml of dry methanol, and methylene chloride (300 ml) was added. The solution was cooled in an ice bath while triethylamine (78.5 ml, 0.57 mol, 125 mol-%) was added dropwise, followed by di-tert-butyl dicarbonate (98.9 g, 0.45 mol, 100 mol-%). The reaction mixture was then allowed to warm to rt (strong evolution of carbon dioxide) and stirred until observed to be complete by TLC. The reaction was quenched with citric acid (3x100 ml), and the organic phase was washed with brine (100 ml). The organic layer was dried and evaporated to give the product **5** as a

yellow oil, which was used without purification in the next step. TLC(EtOAc:MeOH, 1:1), ninhydrin, R_f = 0.90. ^{1}H NMR (d_4-MeOH+$CDCl_3$) δ 5.51 (d, 1H), 4.11 (m, 1H), 3.60, 3.55 (s, 3H), 1.70 (m, 1H), 1.49, 1.35 (s, 9H), 1.07 (d, 3H).

(c) Methyl (4S, 5R)-2,2,5-trimethyl-3-(tert-butoxycarbonyl)-oxazolidine-4-carboxylate *1*. 2,2-Dimethoxy propane (105 ml, 0.86 mol, 200 mol-%) was added to the *N*-BOC-aminoacid methyl ester *6* (0.43 mol, 100 mol-%) dissolved in methylene chloride (180 ml) at rt, and boron trifluoride diethyl etherate was added (2.8 ml, 0.02 mol, 5 mol-%). The reaction mixture was then stirred at rt for 20 min, and washed with brine (200 ml). The organic layer was dried overnight, and concentrated, and the product was distilled *in vacuo* (80 °C/0.15 mmHg) to give pure *1* (110 g, 84 % over three steps). TLC(EtOAc:hexane, 1:1), R_f = 0.60. $[\alpha]_D$ = -52.0° (*c* 1.0, EtOH). lit.[9] $[\alpha]_D$ = -57° (*c* 1.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 4.12 (m, 1H), 3.92 (dd, 1H), 3.74 (s, 3H), 1.62 (s, 3H), 1.57 (s, 3H), 1.46, 1.38 (s, 9H), 1.37 (d, 3H). ^{13}C NMR ($CDCl_3$) δ 171.0 (C), 150.7 (C), 94.9 (C), 80.0 (C) 73.6 (CH), 66.0 (CH), 52.0 (CH_3), 28.0(3 CH_3), 26.3 (CH_3), 23.7 (CH_3), 18.6 (CH_3).

(4*S*, 5*R*)-2,2,5-Trimethyl-3-(*tert*-butoxycarbonyl)-4-formyloxazolidine *7*. Compound *1* (15 g, 54.5 mmol, 100 mol-%) was dissolved in dry toluene (55 ml) and cooled to -84 °C. Diisobutylaluminum hydride (DIBAL-H, 1.0 M in toluene, 93 ml, 93 mmol, 170 mol-%) was slowly added to maintain the internal temperature below -74 °C. After the addition, the mixture was stirred at -84 °C for another five minutes and quenched by slow addition of cold (-84 °C) methanol (22 ml) keeping the internal temperature below -74 °C. The resulting white emulsion was poured into ice-cold 1*N* HCl (330 ml) with stirring over 15 minutes and the aqueous mixture was then extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give the crude product as a colorless oil. Distillation *in vacuo* (70 °C, 0.09 mmHg) gave compound *7* (11 g, 83 %). TLC(EtOAc:hexane, 1:2.5), R_f = 0.55. ^{1}H NMR (C_6D_6, T = 330 K) δ 9.32 (d, 1H, *J* = 3.5 Hz), 3.80 (dq, 1H, *J* = 5.9 Hz, 8.2 Hz), 3.67 (dd, 1H, *J* = 3.5 Hz, *J* = 8.2 Hz), 1.63 (s, 3H), 1.52 (s, 3H), 1.38 (s, 9H), 1.14 (d, 3H, *J* = 5.9 Hz). ^{13}C NMR (C_6D_6, T = 330 K) δ 196.5 (C), 151 (C), 80.9 (C), 71.6 (CH), 70.6 (CH), 28.3 (3 CH_3), 26.9 (CH_3), 25.5 (CH_3), 18.1 (CH_3).

(4*S*, 5*R*)-2,2,5-Trimethyl-3-(*tert*-butoxycarbonyl)-4-(*Z*-methoxycarbonylethenyl)-oxazolidine *8*. Potassium carbonate (23.5 g, 170 mmol, 600 mol-%) and 18-crown-6 (15 g, 56.6 mmol, 200 mol-%) were mixed with toluene (100 ml), and stirred at rt for 1 h. After cooling to -20 °C, aldehyde *7* (6.88 g, 28.3 mmol, 100 mol-%) in toluene (20 ml) and bis-1,1,1-trifluoroethyl methyl phosphonoacetate *11* (9.0 g, 28.3 mmol, 100 mol-%) were added. The reaction mixture was allowed to warm to 0°C and stirred for 40 minutes. Quenching with 5 w-% citric acid, washing with brine, and drying over $MgSO_4$, followed by concentration gave the crude product, which was purified by flash column chromatography (10% EtOAc in hexane) to give compound *8* as white needles (8.3 g, 98 %). Mp = 76-78 °C. TLC(EtOAc:hexane, 1:2.5), R_f = 0.56. ^{1}H NMR ($CDCl_3$) δ 5.99 (dd, 1H, *J* = 8.4 Hz, 11.5 Hz), 5.85 (d, 1H, *J* = 11.5 Hz), 5.07 (dd, 1H, *J* = 8.4 Hz, 6.2 Hz), 3.82 (q, 1H, *J* = 6.2 Hz), 3.68 (s, 3H), 1.58 (s, 3H), 1.49 (s, 3H), 1.32 (s, 9H), 1.31 (d, 3H, *J* = 6.2 Hz). ^{13}C NMR ($CDCl_3$) δ 166.1 (C), 151.8 (C), 148.9 (CH), 120.3 (CH), 94.3 (C), 79.9 (C) 75.1 (CH), 60.8 (CH), 51.2 (CH_3), 28.2 (3 CH_3), 26.5 (CH_3), 25.7 (CH_3), 18.0 (CH_3). Anal. Calcd. for $C_{15}H_{25}NO_5$: C 60.2, H 8.4, N 4.7; found C 60.1, H 8.6, N 4.7.

(4*S*, 5*R*)-2,2,5-Trimethyl-3-(*tert*-butoxycarbonyl)-4-(*E*-methoxycarbonylethenyl)-oxazolidine *9*. Potassium carbonate (6.5 g, 47.2 mmol, 200 mol-%) was suspended in acetonitrile (65 ml) and cooled to -20 °C. The aldehyde *7* (5.74 g, 23.6 mmol, 100 mol-%) in acetonitrile (5 ml) and trimethyl phosphonoacetate (5.2 ml, 28.3 mmol, 120 mol-%) were added sequentially. The reaction mixture was allowed to warm to rt during stirring overnight. Quenching with 5 w-% citric acid, washing with brine, drying over $MgSO_4$, and concentration gave the crude product, which was purified with flash column (10 % EtOAc in hexane) to give compound *9* as a colorless oil (5.7 g, 80 %). TLC(EtOAc:hexane 1:2.5), R_f = 0.54. ^{1}H NMR ($CDCl_3$) δ 6.74 (dd, 1H, *J* = 7.2 Hz, 15.0 Hz), 5.90 (d, 1H, *J* = 15.0 Hz), 3.86 (m, 2H), 3.73 (s, 3H), 1.59 (s, 3H), 1.51 (s, 3H), 1.37 (s, 9H), 1.27 (d, 3H, *J* =

5.9 Hz). ^{13}C NMR ($CDCl_3$) δ 166.2 (C), 151.8 (C), 146.9 (CH), 121.9 (CH), 94.4 (C), 80.3 (C) 74.5 (CH), 65.3 (CH), 51.4 (CH_3), 28.2 (3 CH_3), 26.6 (CH_3), 25.7 (CH_3), 17.3 (CH_3). Anal. Calcd. for $C_{15}H_{25}NO_5$: C 60.2, H 8.4, N 4.7; found C 59.9, H 8.2, N 4.8.

(4*S*, 5*R*)-2,2,5-Trimethyl-3-(*tert*-butoxycarbonyl)-4-methoxycarbonylethyl-oxazolidine *14*. The *E*-enoate *9* (3.59 g, 12 mmol) was dissolved in EtOAc (40 ml), and 10% Pd/C (180 mg, 5 w-%) was added under inert atmosphere. After rinsing with hydrogen gas, the mixture was stirred for 1h at rt. Filtration and concentration of the mixture gave compound *14* as a colorless oil in (3.85 g, 99 %). TLC(EtOAc, hexane 1:2.5, PMA) R_f = 0.65. ^{1}H NMR ($CDCl_3$) δ 3.87 (q, 1H, *J* = 6.1 Hz), 3.62 (s, 3H), 3.44 (bm, 1H), 2.27 (bm, 2H), 2.00 (bm, 2H),1.54 (s, 3H), 1.42 (s, 9H), 1.41 (s, 3H), 1.25 (d, 3H, *J* = 6.1 Hz). ^{13}C NMR ($CDCl_3$) δ 173.2 (C), 152.1 (C), 93.8 (C), 79.8 (C) 75.0 (CH), 62.8 (CH), 51.4 (CH_3), 29.9 (CH_2), 28.3 (3 CH_3), 27.9 (CH_3), 27.1 (CH_2), 26.7 (CH_3) 20.1 (CH_3). Anal. Calcd. for $C_{15}H_{27}NO_5$: C 59.8, H 9.0, N 4.7; found C 60.2, H 9.3, N 4.7.

(5S, 6R)-3,4,5,6-tetrahydro-5-(*N*-*tert*-butoxycarbonyl)amino-6-methyl-2-pyrone *15*. Compound *14* (3.0 g, 10 mmol) dissolved in glacial acetic acid (30 ml) was stirred at 60 °C for six days. Acetic acid was evaporated and the precipitate was dissolved in EtOAc. After washing with saturated sodium carbonate solution the organic layer was dried and concentrated. Purification with flash column chromatography (1:1, EtOAc, hexane) gave compound *15* (1.7 g, 74 %). Mp = 95.5 °C, $[\alpha]_D$ = +68.5° (*c* 0.73, EtOH). TLC(EtOAc:hexane, 1:1), ninhydrin, R_f = 0.33. ^{1}H NMR ($CDCl_3$) δ 5.01 (bd, 1H, *J* = 7.7 Hz), 4.49 (dq, 1H, *J* = 2.5 Hz, 6.5 Hz), 3.98 (bm, 1H, *J* = 2.5 Hz, 7.7 Hz, 4.2 Hz, 7.2 Hz), 2.53 (t, 2H, *J* = 7.2 Hz), 2.16 (dq, 1H, *J* = 7.2 Hz, 14.0 Hz), 1.92 (ddt, 1H, *J* = 7.2 Hz, 14.0 Hz, 4.2 Hz), 1.40 (s, 9H), 1.31 (d, 3H, *J* = 6.5 Hz). ^{13}C NMR ($CDCl_3$) δ 171.2 (C), 155.5 (C), 79.9 (C) 76.4 (CH), 46.6 (CH), 28.2 (3 CH_3), 26.0 (CH_2), 25.5 (CH_2), 16.8 (CH_3). Anal. Calcd. for $C_{11}H_{19}NO_4$: C 57.6, H 8.3, N 6.1; found C 57.3, H 8.0, N 5.9.

(5*S*, 6*R*)-5,6-Dihydro-5-(*N*-*tert*-butoxycarbonyl)amino-6-methyl-2-pyrone *11*. Compound *8* (5.7 g, 19 mmol) dissolved in glacial acetic acid (56 ml) was stirred at 60 °C for six days. Acetic acid was evaporated and the precipitate was dissolved to EtOAc. After washing with saturated sodium carbonate solution the organic layer was dried and concentrated. Purification by flash column chromatography (1:2.5, EtOAc, hexane) gave compound *11* (2.94 g, 68 %). Mp = 127 °C, $[\alpha]_D$ = -192.5° (*c* 1.05, EtOH). TLC(EtOAc:hexane 1:1), R_f = 0.55. ^{1}H NMR ($CDCl_3$) δ 6.87 (dd, 1H, *J* = 6.4 Hz, 9.7 Hz), 6.02 (dd, 1H, *J* = 9.7 Hz, 0.6 Hz), 5.01 (d, 1H, *J* = 9.7 Hz), 4.58 (dq, 1H, *J* = 3.2 Hz, 6.5 Hz), 4.27 (dddd, 1H, *J* = 3.2 Hz, 6.4 Hz, 9.7 Hz, 0.6 Hz), 1.39 (s, 9H), 1.34 (d, 3H, *J* = 6.5 Hz). ^{13}C NMR ($CDCl_3$) δ 163.7 (C), 155.3 (C), 143.7 (CH), 122.4 (CH), 80.2 (C) 76.1 (CH), 45.2 (CH), 28.1 (3 CH_3), 16.0 (CH_3). Anal. Calcd. for $C_{11}H_{17}NO_4$: C 58.1, H 7.5, N 6.2; found C 58.0, H 7.5, N 6.0.

(4*S*, 5*R*)-4-(*N*-*tert*-butoxycarbonyl)amino-5-hydroxy-*Z*-hex-2-enoic acid methyl ester *10*. A solution of compound *8* (205 mg, 6.8 mmol) in 80 % acetic acid (2 ml) was stirred for six days at rt. Acetic acid was evaporated and the precipitate was dissolved in EtOAc. After washing with saturated sodium carbonate solution, the organic layer was dried and concentrated. Purification by flash column chromatography (1:2.5, EtOAc, hexane) gave compound *10* (90 mg, 51 %). TLC(EtOAc:hexane, 1:1) R_f = 0.55. ^{1}H NMR ($CDCl_3$) δ 6.24 (dd, 1H, *J* = 8.2 Hz, 11.5 Hz), 5.89 (dd, 1H, *J* = 1.0 Hz, 11.5 Hz), 5.24 (bd, 1H, *J* = 8.2 Hz), 5.05 (ddt, 1H, *J* = 1.0 Hz, 3.2 Hz, 8.2 Hz), 4.06 (bm, 1H, *J*= 3.2 Hz, 6.4 Hz), 3.71 (s, 3H), 2.57 (bs, 1H), 1.42 (s, 9H), 1.23 (d, 3H, *J* = 6.4 Hz). ^{13}C NMR ($CDCl_3$) δ 166.3 (C), 156.0 (C), 148.8 (CH), 120.4 (CH), 79.9 (C), 70.3 (CH), 54.2 (CH), 51.5 (CH_3), 28.3 (3 CH_3), 20.1 (CH_3).

(5*S*, 6*R*)-3,4,5,6-Tetrahydro-3,4-dihydroxy-5-(*N*-*tert*-butoxycarbonyl)amino-6-methyl-2-pyrone *12*. To a solution of compound *11* (1.00 g, 4.4 mmol, 100 mol-%) in a mixture of water and acetone (1:8, 75 ml), 4-methylmorpholine *N*-oxide (1.04 g, 8.8 mmol, 200 mol %) and osmium tetroxide in t-butanol (2.76 ml, 0.22 mmol, 5 mol-%) were added. The resulting mixture was stirred overnight at rt. A saturated solution of sodium bisulfite (20 ml) was added and the mixture was stirred for 15 minutes, diluted with brine (50 ml), and extracted with ethyl acetate. The organic solvent was evaporated and the residue was purified by flash column chromatography (20 % EtOAc in hexane) to give compound ***12*** (0.84 g, 73 %). Mp = 112 °C. $[\alpha]_D$ = +52° (*c* 0.79, EtOH). TLC(EtOAc:hexane, 1:1), ninhydrin R_f = 0.25. ^1H NMR (d_4-acetone) δ 6.56 (bd, 1H, *J* = 9.5 Hz), 4.97 (dq, 1H, *J* = 3.4 Hz, 6.8 Hz), 4.89 (d, 1H, *J* = 3.4 Hz), 4.58 (bd, 1H, *J* = 3.4 Hz), 4.41 (t, 1H, *J* = 3.4 Hz), 4.19 (q, 1H, *J* = 3.4 Hz), 4.04 (dt, 1H, *J* = 3.4 Hz, 9.5 Hz), 1.41 (s, 9H), 1.27 (d, 3H, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$) δ 174.4 (C), 155.5 (C), 80.7 (C), 75.5 (CH), 69.5 (CH), 67.7 (CH), 52.9 (CH), 28.3 (3 CH_3), 16.2 (CH_3). Anal. Calcd. for $C_{11}H_{19}NO_6$: C 50.6, H 7.3, N 5.4; found C 50.4, H 7.3, N 5.2.

2,3,4,6-Tetradeoxy-4-(*N-tert*-butoxycarbonyl)amino galactopyranoside *16*. Compound ***15*** (200 mg, 0.87 mmol, 100 mol-%) was dissolved in dry toluene (2 ml) and cooled to -84 °C. Diisobutylaluminum hydride (DIBAL-H, 0.53 M in toluene, 2.8 ml, 1.48 mmol, 170 mol-%) was added slowly, with the temperature maintained below -65 °C. After stirring for another 5 min at -84 °C, cold methanol (1.8 ml, -84 °C) was added, and then an ice-cold solution of 1.0 M NH_4Cl (10 ml). Stirring was continued for 15 min at rt. The white solution was extracted with EtOAc and the organic extract was washed with 1 M NH_4Cl solution until both layers were clear. The combined organic layers were dried and evaporated to give a colorless liquid (201 mg, 100%). TLC(EtOAc:hexane, 1:1), ninhydrin $R_{f\alpha,\beta}$ = 0.37, 0.19. This crude mixture was used without purification in the next reaction. Attempts to separate the anomers from each other would be in vain because of the equilibration.

Data for ***16α***: ^1H NMR (D_6-acetone) δ 5.65 (bd, 1H), 5.05 (bd, 1H), 4.21 (dq, 1H), 3.52 (bm, 1H), 1.95 (m, 1H), 1.50 (m, 1H), 1.75 (m, 1H), 1.40 (m, 1H), 1.40 (s, 9H), 0.94 (d, 3H).

Data for ***16β*** ^1H NMR (D_6-acetone) δ 5.34 (bd, 1H), 4.67 (dd, 1H), 3.63 (dq, 1H), 3.47 (bm, 1H), 1.70 (m, 1H), 1.65 (m, 1H), 1.50 (m, 1H), 1.40 (m, 1H), 1.36 (s, 9H), 1.01 (d, 3H).

^{13}C NMR(α and β) ($CDCl_3$) δ 155.9 (C), 96.3 (CH), 91.7 (CH), 83.3 (C) 79.2 (CH), 73.4 (CH), 65.5 (CH), 63.0 (CH), 48.0 (CH_2), 47.2 (CH_2), 31.9 (CH_2), 28.4 (3 CH_3), 27.6 (CH_2), 20.8 (CH_3) 17.5 (CH_3). HRMS(α and β) (M-18): Calcd. $C_{11}H_{19}NO_3$: 213.1365; found 213.1363.

Methyl 2,3,4,6-tetradeoxy-4-(*N-tert*-butoxycarbonyl)amino-α-galactopyranoside *3*. Compound ***16*** (201 mg, 0.87 mmol, 100 mol-%) was dissolved in dry methanol (5 ml). Pyridinium *p*-toluenesulfonate (20 mg, 0.08 mmol, 9 mol-%) was added, followed by trimethyl orthoformate (93 ml, 0.87 mmol, 100 mol-%). The reaction mixture was stirred at rt for 40 minutes, then diluted with water (1 ml) and acidified with 5 w-% citric acid. Extraction with EtOAc and washing of the organic layer with saturated sodium bicarbonate solution and brine gave, after drying and concentration, the crude product. This was purified by flash column chromatography (20 % EtOAc in hexane) to give compound ***3*** (125 mg, 58 %) along with recovered starting material. (The yield of compound ***3*** based on recovered starting material 71 %.) $[\alpha]_D$ = +58.5° (*c* 1.62, EtOH). TLC(EtOAc:hexane, 1:1), ninhydrin, R_f = 0.46. ^1H NMR ($CDCl_3$) δ 5.24 (d, 1H, *J* = 3.5 Hz), 3.83 (dq, 1H, *J* = 6.4 Hz, 3.8 Hz), 3.65 (ddd, 1H, *J* = 3.8 Hz, 6.6 Hz, 10.3 Hz), 3.31 (s, 3H), 1.98 (m, 1H) 1.95-1.65 (m, 3H), 1.47 (s, 9H), 1.12 (d, 3H, *J* = 6.4 Hz). ^{13}C NMR ($CDCl_3$) δ 157.0 (C), 89.9 (CH), 81.3 (CH), 73.5 (C), 64.1 (CH), 54.9 (CH_3), 31.7 (CH_2), 28.3 (3 CH_3), 26.3 (CH_2), 20.6 (CH_3). Anal. Calcd. for $C_{12}H_{23}NO_4$: C 58.8, H 9.5, N 5.7; found C 59.0, H 9.7, N 5.3.

Methyl 4,6-dideoxy-4-(*N-tert*-butoxycarbonyl)amino-gulopyranoside *2a, 2b*. Compound ***12*** (110 mg, 0.42 mmol, 100 mol-%) was dissolved in dry toluene (2 ml) and cooled to -84 °C. Diisobutylaluminum hydride (DIBAL-H, 1.0 M in toluene, 1.5 ml, 1.47 mmol, 350 mol-%) was added slowly keeping the internal temperature below -65 °C. After stirring of the reaction mixture for another 5 min at -84 °C, cold methanol (1.0 ml, -84 °C) was added, and then ice-cold 1.0 M NH_4Cl (10 ml). Stirring was continued for 15 min at rt. The white solution was extracted with isopropanol/EtOAc (1/4) and the organic extract was washed with 1 M NH_4Cl solution until both layers were clear. The combined organic layers were dried and evaporated to give a residue containing ***13a*** and ***13b***. (TLC: 20% MeOH, CH_2Cl_2) ninhydrin R_f= 0.66. This mixture was dissolved in dry methanol (5 ml), and camphorsulfonic acid (11 mg, 0.05 mmol, 11 mol-%) was added. The mixture was stirred at rt for 8 h. Dilution with water (1 ml) and acidification with 5 w-% citric acid, followed by extraction with EtOAc, and washing of the organic layer with saturated sodium bicarbonate solution and brine gave, after drying and evaporation, the crude product. Purification by flash column chromatography (5% MeOH in CH_2Cl_2) gave the product **2** (50 mg, 43 %) as a 3:1 mixture of α- and β-anomers, along with recovered starting material. (Yield of **2** based on recovered starting material 60 %.) The α-anomer was crystallized from ethyl acetate and pure β-anomer was isolated by preparative TLC. TLC(EtOAc) $R_f = 0.25$ and 0.32.

Data for **2a**: Mp = 133-136°C, $[\alpha]_D = +54^\circ$ (*c* 0.72, EtOH). ^1H NMR (d_4-MeOH) δ 5.11 (d, 1H, *J* = 5.2 Hz), 4.21 (t, 1H, *J* = 5.6 Hz), 4.12 (q, 1H, *J* = 6.3 Hz), 3.96 (t, 1H, *J* = 5.6 Hz), 3.87 (t, 1H, *J* = 5.9 Hz), 3.49 (s, 3H), 1.54 (s, 9H), 1.32 (d, 3H, *J* = 6.3 Hz). ^{13}C NMR (d_4-MeOH) δ 163.1 (C), 91.9 (CH), 83.6 (CH), 73.3 (C), 72.8 (CH), 69.9 (CH), 67.0 (CH), 57.6 (CH_3), 29.3 (3 CH_3), 22.1 (CH_3).

Data for **2b**: $[\alpha]_D = +13^\circ$ (*c* 0.95, EtOH) ^1H NMR (d_4-MeOH) δ 4.63 (bs, 1H), 4.38 (dd, 1H, *J* = 4.8 Hz, 8.4 Hz), 4.12 (dq, 1H, *J* = 6.8 Hz, 1.7 Hz), 3.88 (dd, 1H, *J* = 8.4 Hz, 1.7 Hz), 3.87 (d, 1H, *J* = 4.8 Hz), 3.41 (s, 3H), 1.49 (s, 9H), 1.27 (d, 3H, *J* = 6.8 Hz). ^{13}C NMR (d_4-acetone) δ 157.4 (C), 96.3 (CH), 80.7 (CH), 75.2 (C), 71.3 (CH), 66.0 (CH), 64.2 (CH_3), 57.5 (CH), 29.1 (3 CH_3), 23.3 (CH_3). Anal. Calcd. for $C_{12}H_{23}NO_4$: C 58.8, H 9.5, N 5.7; found C 59.0, H 9.7, N 5.4.

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References and Notes:

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1. a) Höök, M.; Woods, A.; Johansson, S.; Kjellen, L.; Couchman, J.R. in *Functions of the proteoglycans,* Wiley, Chichester (Ciba Fundation Symposium 124), **1986,** p 143-157. b) Ginsberg, V.; Robbins, P. W. in *Biology Of Carbohydrates*, Jai Press, London, **1991**. c) Roberts, D. D.; Mecham, R. P. *Cell Surface and Extracellular Glycoconjugates Structure and Function*, Academic Press, San Diego, **1993**.
2. Borman, S. *Chem. Engng. News* **1992**, *December 7*, 25.
3. Leet, J.E.; Schroeder, D.R.; Hofstead, S.J.; Golik, J.; Colson, K.L.; Huang, S.; Klohr, S.E.; Doyle, T.W.; Matson, J.A. *J. Am. Chem. Soc.* **1992**, *114*, 7946.
4. Nakamura, T.; Fukatsu, S.; Seki, S.; Niida, T. *Chem. Lett.* **1978**, 1293.
5. Lown, J. W. *Chem. Soc. Rev.* **1993**, 165.
6. Baumann, H.; Tzianabos, J.-R.; Kasper, D. L.; Jennings, H. J. *Biochem.* **1992**, *31*, 4081.
7. (a) Koskinen, A.M.P. *Pure Appl. Chem.* **1993**, *65*, 1465. (b) Koskinen, A.M.P. *Pure Appl. Chem.* **1995**, *67*, 1031.
8. Stevens, C. L.; Gutowski, G. E.; Bryant, C. P.; Glinski, R. P. *Tetrahedron Lett.* **1969**, 1181.
9. Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361.
10. (a) Koskinen, A. M. P.; Krische, M. J.; *Synlett* **1990**, 665. (b) For ketal protection of the analogous serine derived ester under Lewis acidic conditions, see: Moriwaki, T.; Hamano, S.; Saito, S.; Torri, S. *Chem. Lett.* **1987**, 2085.
11. Thompson, S. K.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 3386.
12. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
13. (a) Jako, I.; Uiber, P.; Mann, A.; Taddei, M.; Wermuth, C: *Tetrahedron Lett.* **1990**, *31*, 1011. (b) Koskinen, A. M. P.; Chen, J. *Tetrahedron Lett.* **1991**, *32*, 6977. (c) We have earlier shown that

potassium carbonate is eminent for base sensitive Horner-Emmons couplings: Koskinen, A.M.P.; Koskinen, P.M. *Synlett* **1993**, 501.

14. Boeckman, R. K.; Weider, C. H.; Perni, R. B.; Napier, J. J. *J. Am. Chem. Soc.* **1989**, *111*, 8036.
15. Wagner, R.; Tilley, J. W. *J. Org. Chem.* **1990**, *55*, 6289.
16. Satoh, T.; Uwaya, S.; Yamakawa, K. *Chem. Lett.* **1983**, 667.
17. Cha, J.K.; Christ, W.J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247.
18. Molecular modeling was performed using the MacroModel v. 4.5 program suite. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liscamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.
19. Haasnoot, C. A. G.; De Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.
20. Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, J. *Science* **1993**, *231*, 1108.
21. Baggett, N.; Brimacombe, J.S.; Foster, A.B.; Stacey, M.; Whiffen, D.M. *J. Chem. Soc.* **1960**, 2574.
22. With the goal of allowing facile access to kedarosamine [Leet, J. E.; Golik, J.; Hofstead, S. J.; Matson, J. A.; Lee, A. Y.; Clardy, J. *Tetrahedron Lett.* **1992**, *33*, 6107; Vuljanic, T.; Kihlberg, J.; Somfai, P. *Tetrahedron Lett.* **1994**, *35*, 6937], the epoxidation of the unsaturated lactone ***11*** was also examined with several epoxidation reagents. Due to the electron deficiency of the double bond, the nucleophilic epoxidation reagent t-BuOO$^-$Li$^+$ and dimethyl dioxirane were the only ones that reacted to any noticeable degree with lactone ***11***.[23,24] Unfortunately both methods gave very low yields.
23. Meth-Cohn, O.; Moore, C.; Taljaard, H.C. *J. Chem. Soc., Perkin I* **1988**, 2663.
24. Adam, W.; Hadjiarapoglou, L.; Nestler, B. *Tetrahedron Lett.* **1990**, *31*, 331.

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