A Convenient Synthesis of a *N*-Protected L-carbamoylpolyoxamic Acid Derivative: Total Synthesis of (+)-Polyoxin J and (+)-Polyoxin L[1]

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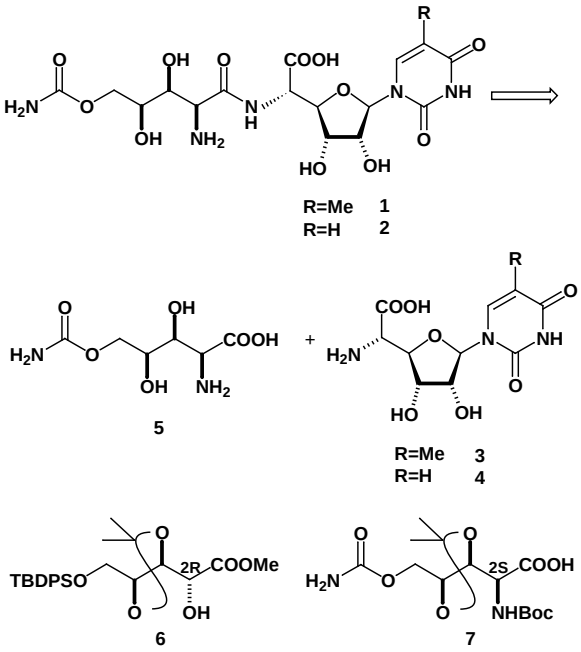
Abstract: A convenient synthesis of the *N*-protected L-carbamoylpolyoxamic acid derivative **7** from 4-*O*-*tert*-butyldiphenylsilyl-2,3-isopropylidene-L-threose (**8**) using vinylmagnesium bromide and its application to the total syntheses of the peptidyl nucleoside antibiotics, polyoxins J (**1**) and L (**2**), are described.

Key words: total synthesis, diastereoselective vinylation, polyoxamic acid, polyoxin J, polyoxin L

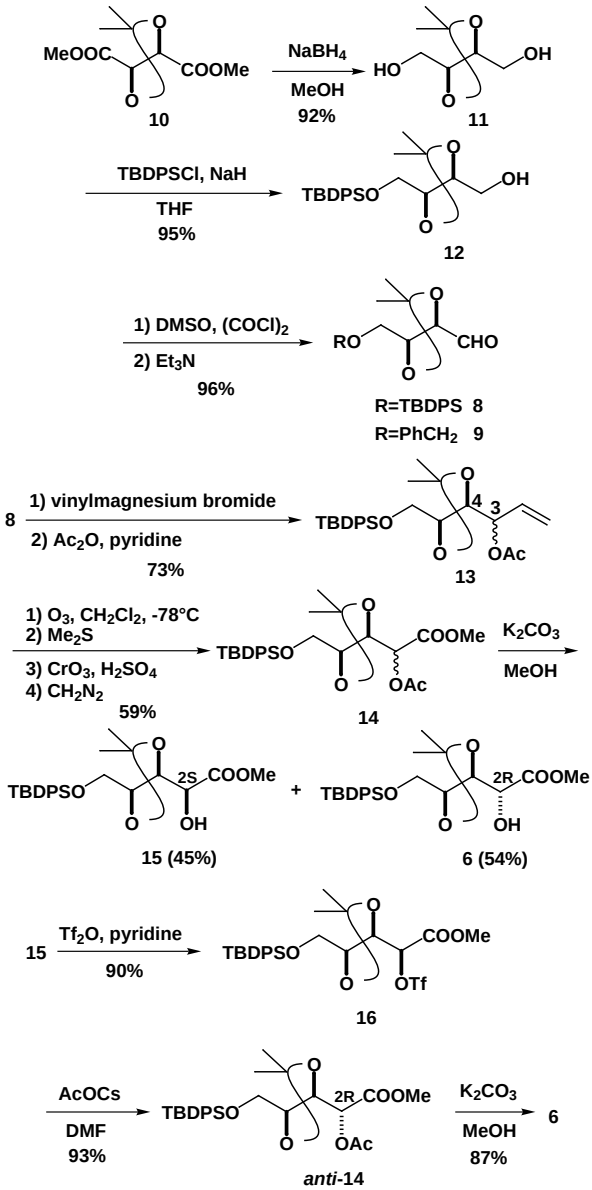
Polyoxins J (**1**) and L (**2**) are a class of peptidyl nucleoside antibiotics isolated from the culture broths of *Streptomyces cacao*i var *asoensis*.[2] All members of the polyoxin family possess the 1-(5'-amino-5'-deoxy-β-D-allofuranuronosyl)pyrimidines such as thymine polyoxin C (**3**) and uracil polyoxin C (**4**) as a basic component. The biological activity of the polyoxins are very characteristic because of their specific action against phytopathogenic fungi and the human fungal pathogen (e.g. *Candida albicans*), and lack of activity against other microorganisms, plants, fish, and mammals.[2b] The site of action of the polyoxins was reported to be responsible for cell wall chitin biosynthesis.[3] Based on the structure of polyoxins, the appearance of biological activity was reported to be due to the gross structural similarity of the polyoxins to UDP-*N*-acetylglucosamine, a substrate for chitin synthetase, which is the polymerizing enzyme responsible for the synthesis of chitin, a polysaccharide corresponding to the β-1,4-poly-*N*-acetylglucosamine.[2b] In the preceeding paper, [4] we reported a short path synthesis of ethyl (methyl-2,3-*O*-isopropylidene-α-L-talofuranoside)uronate from methyl 2,3-*O*-isopropylidene-dialdo-D-ribofuranoside using 1-ethoxyvinyllithium and its application to the total syntheses of thymine polyoxin C (**3**) and uracil polyoxin C (**4**). Four total syntheses[5] of **1** have been reported, these methods involving coupling of the congener of polyoxamic acid **5** with thymine polyoxin C (**3**).[5b,5d,6] A variety of chemical syntheses 5-*O*-carbamoyl-polyoxamic acid derivatives have been reported over years,[7,5d] one of the most important intermediate for the general synthesis of them appeared to be (2*R*)-hydroxy ester such as **6**. We now describe a convenient synthesis of the *N*-protected L-carbamoylpolyoxamic acid derivative **7** via **6** from 4-*O*-*tert*-butyldiphenylsilyl-2,3-isopropylidene-L-threose (**8**) derived from dimethyl L-tartrate and its application to the total syntheses of polyoxins J (**1**) and L (**2**) (Scheme 1). The key reaction step is the addition of vinylmagnesium bromide to **8**.



Scheme 1

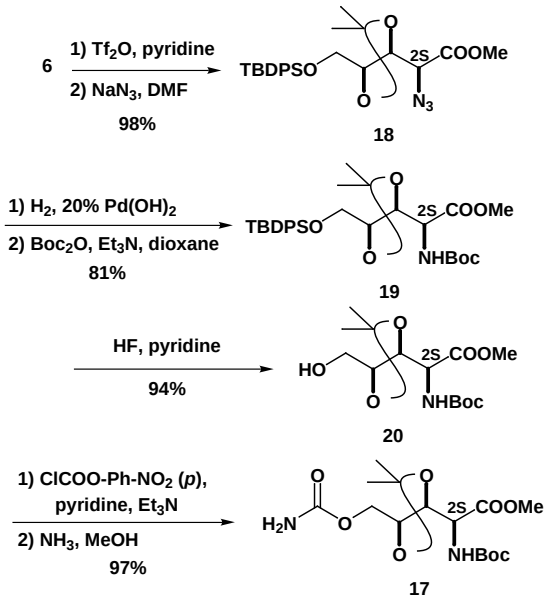
In seeking a practical route to **7**, use of dimethyl L-tartrate with its inherent C-2 axis symmetry appeared to be the most promising. A useful synthesis of **5** utilizing L-tartaric acid has been described by Mukaiyama et al.,[7f] the crucial step being the stereoselective addition of titanium silylacetylide species to 4-*O*-benzyl-2,3-isopropylidene-L-threose (**9**). Our own strategy for the introduction of the α-hydroxy ester functionality involves the addition of vinylmagnesium bromide to 4-*O*-*tert*-butyldiphenylsilyl-2,3-isopropylidene-L-threose (**8**) followed by oxidative cleavage of the terminal double bond as key steps. Reduction of the commercially available acetonide **10** with $NaBH_4$ gave the diol **11** (92%), which was treated with *t*-$BuPh_2SiCl$ (TBDPSCl) in the presence of NaH[8] to afford the monosilyl ether **12** (95%). Swern oxidation of **12** provided the aldehyde **8** (96%) which reacted with vinylmagnesium bromide followed by acetylation to give a 53:47 diastereomeric mixture of the acetates **13** in 73% overall yield. Ozonolysis of **13** followed by treatment with Jones reagent and CH_2N_2 afforded a diastereomeric mixture of α-acetoxy esters **14** in 59% overall yield. This mixture was hydrolysed to the diastereomeric mixture of α-hydroxy esters **15** and **6**, which were separated to the less polar alcohol (2*S*)-**15** {45%, $[\alpha]_D$ +4.0 (*c* = 0.80, $CHCl_3$)}

and the more polar one (2*R*)-**6** {54%, $[\alpha]_D$ –21.3 (*c* = 0.95, $CHCl_3$)}. Conversion of (2*S*)-**15** into (2*R*)-**6** was effected by treating **15** with trifluoromethanesulfonic anhydride (Tf_2O) to form first the triflate **16** (90%). Reaction of triflate **16** with cesium acetate provided the (2*R*)-acetoxy ester-**14** {93%, $[\alpha]_D$ –15.2 (*c* = 1.34, $CHCl_3$)}. Hydrolysis of (2*R*)-**14** gave the inverted (2*R*)-hydroxy ester (**6**) {87%, $[\alpha]_D$ –21.8 (*c* = 1.25, $CHCl_3$)} which is consistent with the above mentioned (2*R*)-hydroxy ester **6** (Scheme 2).



Scheme 2

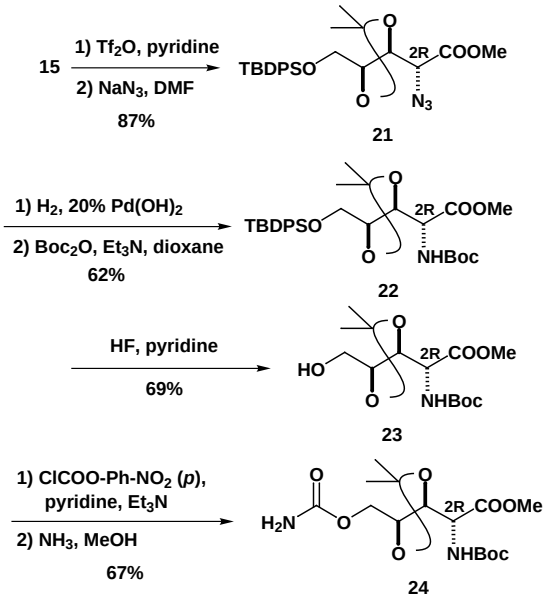
In order to determine the stereochemistry, the α-hydroxy ester **6** was converted to the reported *N*-protected 5-*O*-carbamoyl-(2*S*)-polyoxamic acid derivative **17**.[7c] Triflation of **6** followed by treatment with NaN_3 afforded the diastereomerically pure (2*S*)-azide ester **18** {98% overall yield, $[\alpha]_D$ –16.2 (*c* = 1.02, $CHCl_3$)} which was subjected to hydrogenation and subsequent *N*-Boc derivation to provide the (2*S*)-*N*-Boc ester **19** {81% overall yield, $[\alpha]_D$+1.4 (*c* = 0.51, $CHCl_3$)}. Desilylation of **19** with HF in pyridine gave the alcohol **20** {94%, $[\alpha]_D$+15.3 (*c* = 1.0, $CHCl_3$)} which was subjected to carbamoylation by the reported procedure[9] to furnish the desired *N*-protected carbamoylpolyoxamic acid ester **17** (Scheme 3) {97% overall yield, $[\alpha]_D$ –2.7 (*c* = 1.05, CH_2Cl_2)}. Physical data ($[\alpha]_D$ and NMR) of the prepared **17** were identical with those {$[\alpha]_D$ –3.6 (*c* = 1.5, CH_2Cl_2) and NMR} of the reported (2*S*,3*S*,4*S*)-**17**.[7c]



Scheme 3

The stereochemistry of **15** was also confirmed by comparison with the reported *N*-protected 5-*O*-carbamoyl-(2*R*)-polyoxamic acid derivative **24**.[7c] Triflation of **15** followed by treatment with NaN_3 afforded the diastereomerically pure (2*R*)-azide ester **21** {87% overall yield, $[\alpha]_D$ –21.4 (*c* = 0.98, $CHCl_3$)} which was subjected to hydrogenation and subsequent *N*-Boc derivatization to provide the (2*R*)-*N*-Boc ester **22** {62% overall yield, $[\alpha]_D$ –26.2 (*c* = 1.02, $CHCl_3$)}. Desilylation of of **22** with HF in pyridine gave the alcohol **23** {69%, $[\alpha]_D$ –40.9 (*c* = 0.75, $CHCl_3$)} which was subjected to carbamoylation to afford the *N*-protected carbamoylpolyoxamic acid ester **24** (Scheme 4) {67% overall yield, $[\alpha]_D$ –28.8 (*c* = 0.55, CH_2Cl_2)}. Physical data ($[\alpha]_D$ and NMR) of the **24** prepared were identical with those {$[\alpha]_D$ –26.5 (*c* = 1.8, CH_2Cl_2) and NMR} of the reported (2*R*,3*S*,4*S*)-**24**.[7c] Thus, the configurations of the newly generated chiral centers of α-hydroxy esters **6** and **15** were found to be *R* and *S*, respectively.

In the nucleophilic addition of vinylmagnesium bromide to the aldehyde **8**, a low diastereoselectivity (53:47) was observed. For the purpose of improving the diastereoselectivity, effect of coexisting metal halides in addition to **8** was examined (Scheme 5) and the results are shown in the Table. The *anti*-selective addition of a nucleophile to



Scheme 4

8 is explainable by the Felkin–Anh model[10] as depicted in the Figure. The β-chelation of metal ion enhances the Felkin selectivity. The addition of nucleophile to **8** may be controlled by the above mentioned reason since the $TBDPSOCH_2$-group is located *trans* to the reacting formyl group on the dioxolane ring. The addition of vinyl magnesium bromide to **8** in the presence of $ZnBr_2$ followed by acetylation raised *anti*-selectivity and afforded (3,4)-*anti*-**13** (Table, Entries 4, 5 and 6). When this reaction was carried out at –78 °C, ratio of *anti/syn* was enhanced up to 8:1. On the contrary, without $ZnBr_2$ the addition was non-selective to give a 53:47 mixture of (3,4)-*anti*- and (3,4)-*syn*-**13** (Table, Entry 1). For large scale preparation of (2*R*)-**6**, the 5:1 mixture of (3,4)-*anti*-**13** (Table, Entry 6) was converted to **6** [52% overall yield from (3,4)-*anti*-**13**] as the main product by the same way as stated above. From the point view of synthetic effectiveness (diastereoselectivity and conversion yield), the present synthetic route to the desired α-azide ester (2*S*)-**18** by way of (2*S*)-**15** and (2*R*)-**6** seemed to be useful because both (2*S*)-**15** and (2*R*)-**6** were finally converted to the important intermediate **18** for the synthesis of *N*-protected L-carbamoyl-polyoxamic acid derivative **7**.

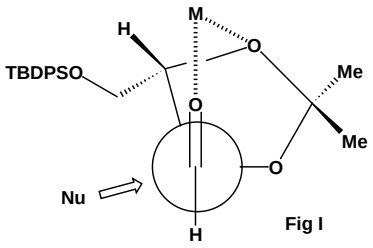
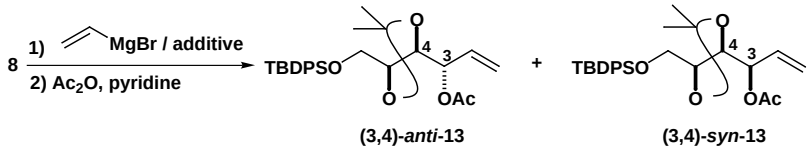


Figure Felkin–Anh model for the *anti*-selective addition of a nucleophile to **8**

For the conversion of ester group in **17** to carboxylic acid under mild conditions, it was transesterified with benzyl alcohol into the benzyl ester **25** {$[\alpha]_D$ –16.4 (*c* = 1.01, $CHCl_3$)} in the presence of Ti(OPr-*i*)$_4$ in 82% yield. Catalytic deprotection of benzyl group in **25** gave the desired *N*-protected (2*S*)-carbamoylpolyoxamic acid derivative **7** {$[\alpha]_D$ +1.03 (*c* = 0.775, acetone)} in quantitative yield, which is consistent with the reported values.[7c] Successful coupling of thymine polyoxin C (**3**)[4] with the desired *N*-protected (2*S*)-**7** was carried out by the *N*,*N*-dicyclohexylcarbodiimide-*N*-hydroxysuccinimide (DCC-HOSu) active ester method [5a] in DMSO and *N*,*N*-diisopropylethylamine as the base. Thus, the treatment of polyoxamic acid derivative **7** with DCC-HOSu gave the active ester **26** which was condensed with **3** to afford the dipeptide **27** (82% from **7**). Removal of the *N*-Boc and *O*-isopropylidene protecting groups upon acid hydrolysis provided polyoxin J (**1**) (Scheme 6) {mp 195–200 °C (dec), $[\alpha]_D$ +35.7 (*c* = 0.68, H_2O)} in 86% yield. The physical properties of the **1** prepared were identical with those of synthetic polyoxin J (**1**) {$[\alpha]_D$ +33.0 (*c* = 0.75,



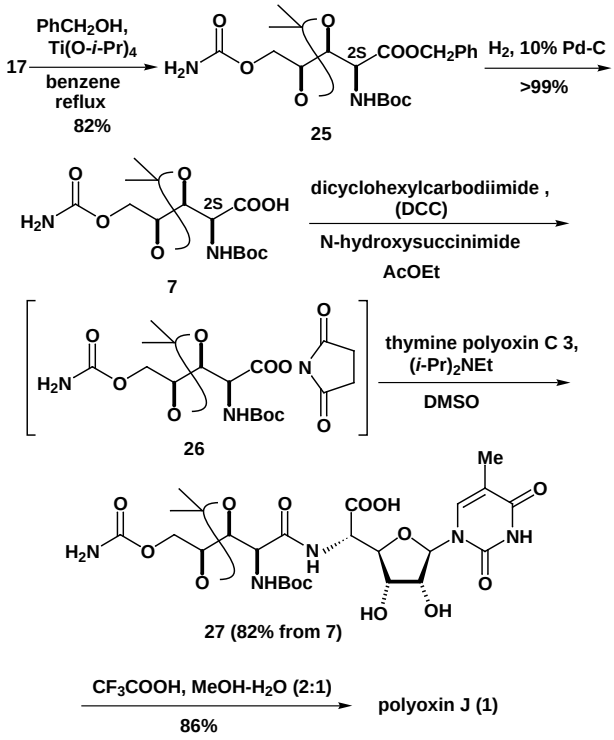
(3,4)-*anti*-13 (3,4)-*syn*-13

Table Reaction of **8** and Vinylmagnesium Bromide in the Presence of Additive

Entry	Substrate **8** (g)	Additive	Reaction Conditions	Yield of 13 (%)	Ratio of *anti*/*syn*[a]
1	9.53	none	0°C, 2 h	73	53:47
2	0.4	Et_2AlCl	–40 to 0°C, 3 h	50	2:1
3	0.4	$TiCl_4$/Ti(OPr-i)$_4$ (1:1)	0°C, 2 h	69	4:3
4	0.4	$ZnBr_2$	–40 to 0°C, 2 h	80	5:1
5	2	$ZnBr_2$	–78 to 0°C, 2 h	50	8:1
6	12	$ZnBr_2$	–78 to 0°C, 4 h	70	5:1

[a] The *anti*/*syn* ratio was determined by NMR analysis of an integral value based on acetoxy groups [δ = 2.05 (s), 2.07 (s)].

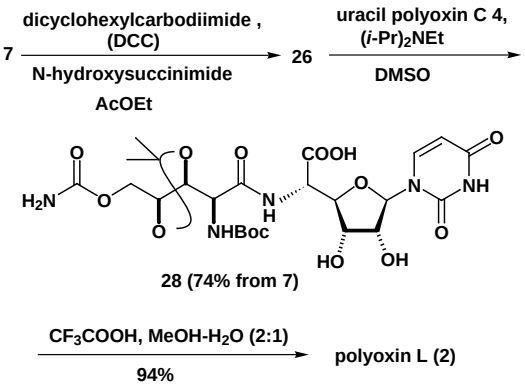
H_2O),[5a] mp 200–210 °C(dec.),[5b] $[\alpha]_D$ +35.0 (*c* = 0.8, H_2O),[5b] and NMR,[5b] mp 200 °C(dec.),[5c] $[\alpha]_D$ +30.3 (*c* = 0.10, H_2O)[5c]}.



Scheme 5

Likewise, condensation of the active ester **26** with uracil polyoxin C (**4**) afforded the dipeptide **28** (74% from **7**) which was converted to polyoxin L (**2**) (Scheme 7) {mp 180–183°C (dec), ($[\alpha]_D$ +35.0 (*c* = 1.215, H_2O)} in 94% yield. The physical properties of the **2** prepared were in good agreement with the literature of natural polyoxin L (**2**)[11] {$[\alpha]_D$ +34.4 (*c* = 1, H_2O)} and constitutes its first total synthesis. The work described herein can be applicable to the synthesis of other components of polyoxin families.[1a]

All melting points were measured on a Yanaco MP-S3 micro melting point apparatus and are uncorrected. NMR spectra were measured on a Jeol EX-400 spectrometer and spectra were taken as 5-10% (w/v) solutions in $CDCl_3$ with TMS as an internal reference. IR spectra were measured on a Jasco FT/IR-300 spectrometer. FAB-MS were obtained with a Jeol JMS-DX 303 instrument [matrix: DDT/NBA; a 1:1 (v/v) mixture of dithiothreitol (DTT) and *m*-nitrobenzyl alcohol (NBA)[12]]. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. A11 the reactions were carried out in an atmosphere of argon. A11 evaporations were performed under reduced pressure.



Scheme 6

(+)-2,3-*O*-Isopropyridene-L-threitol (11)

To a solution of **10** (12.61 g, 57.8 mmol) in MeOH (100 ml) was added $NaBH_4$ (4.72 g, 126 mmol) at 0 °C and the mixture was stirred for 30 min. The mixture was diluted with H_2O (500 mL), extracted with EtOAc (3 × 300 mL) and dried ($MgSO_4$). Evaporation of organic solvent gave an oily product which was chromatographed on silica gel (300 g) with hexane/EtOAc (1:1) as eluent to **11** as a colorless oil; yield:8.64 g (92%); $[\alpha]_D^{25}$ +3.8 (*c* = 2.1, EtOH).

IR (neat): ν = 3410 cm^{-1}.

^1H NMR: δ = 1.43 (s, 6 H), 2.40 (br s, 2 H), 3.66–3.73 (m, 2 H), 3.76–3.83 (m, 2 H), 3.98–4.02 (m, 2 H).

MS (FAB): *m*/*z* = 163 (M^++1).

4-*O*-*tert*-Butyldiphenylsilyl-2,3-*O*-Isopropyridene-L-threitol (12)

To a solution of **11** (19.14 g, 118 mmol) in THF (200 mL) was added a 50% suspension of NaH in mineral oil (5.66 g, 118 mmol) at 0 °C and the mixture was stirred for 30 min. *tert*-Butyldiphenylsilyl chloride (33.1 g, 118 mmol) was then added and the mixture was stirred for 10 min. The mixture was diluted with H_2O (300 mL), extracted with EtOAc (3 × 300 mL) and dried ($MgSO_4$). Evaporation of organic solvent gave an oily product which was chromatographed on silica gel (200 g) using hexane/EtOAc (4:1) as eluent to **12** as a colorless oil; yield: 44.96 g (95%); $[\alpha]_D^{24}$ –0.09 (*c* = 1.1, $CHCl_3$).

Anal. calcd for $C_{23}H_{32}SiO_4$ (400.6): C, 68.96; H, 8.05. Found C, 68.73; H, 8.07.

IR (neat): ν = 3464 cm^{-1}.

^1H NMR: δ = 1.06 (s, 9 H), 1.39 (s, 3 H), 1.41 (s, 3 H), 3.65 (dd, 1 H, *J* = 4.5, 12 Hz), 3.74 (dd, 1 H, *J* = 6, 10.5 Hz), 3.80 (dd, 1 H, 4, 12 Hz), 3.82 (dd, 1 H, *J* = 4, 10.5 Hz), 3.97 (ddd, 1 H, *J* = 4, 6, 8 Hz), 4.07 (dt, 1 H, *J* = 4, 8 Hz), 7.37–7.46 (m, 6 H), 7.65–7.68 (m, 4 H).

MS (FAB): *m*/*z* = 401 (M^++1).

4-*O*-*tert*-butyldiphenylsilyl-2,3-isopropylidene-L-threose (8)

To a solution of DMSO (7.09 mL, 100 mmol) in CH_2Cl_2 (80 mL) was added oxalyl chloride (4.23 mL, 50 mmol) at –78 °C and the mixture was stirred for 30 min. A solution of **12** (10 g, 25 mmol) in CH_2Cl_2 (20 ml) was the added and the mixture was stirred for 50 min. Et_3N (27.67 mL, 200 mmol) was added and the mixture was stirred at r.t., for 15 min. The mixture was diluted with H_2O (300 mL), extracted with EtOAc (3 × 300 mL) and dried ($MgSO_4$). Evaporation of organic solvent gave an oily product which was chromatographed on silica gel (100 g) with hexane/EtOAc (9:1) as eluent to give **8** as a colorless oil; yield: 9.53 g (96%); $[\alpha]_D^{24}$ –2.89 (*c* = 1.07, $CHCl_3$).

^1H NMR: δ = 1.06 (s, 9 H), 1.42 (s, 3 H), 1.49 (s, 3 H), 3.81 (dd, 1 H, *J* = 4.5, 11 Hz), 3.86 (dd, 1 H, *J* = 4.5, 11 Hz), 4.18 (dt, 1 H, *J* = 4.5, 7 Hz), 4.43 (dd, 1 H, *J* = 1.5, 7 Hz), 7.37–7.47 (m, 6 H), 7.66–7.71 (m, 4 H), 9.79 (d, 1 H, *J* = 1.5 Hz).

MS (FAB): *m*/*z* = 399 (M^++1).

Reaction of 8 and Vinylmagnesium Bromide (Table, Entry 1)
To a solution of **8** (9.53 g, 23.9 mmol) in THF (90 mL) at 0 °C was added vinylmagnesium bromide (1 M in THF, 95.6 mL (95.6 mmol)). The mixture was stirred at 0 °C for 2 h, diluted with 1 M aq HCl (150 mL) and extracted with EtOAc (2 × 300 mL). The extract was washed with brine (100 mL), dried ($MgSO_4$) and concentrated. To a solution of the crude product in pyridine (60 mL, 742 mmol) at 0 °C was added Ac_2O (27 mL, 286 mmol). The mixture was stirred for 12 h, diluted with H_2O (200 mL) and extracted with EtOAc (2 × 300 mL). The organic layer was washed with 10% aq HCl (100 mL), brine (100 mL), dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel (200 g) with hexane/EtOAc (9:1) as eluent to give a mixture of (3,4)-*anti*-**13** and (3,4)-*syn*-**13** (*anti*/*syn* = 53:47) as a colorless oil; yield: 8.16 g (73%).

Anal. calcd for $C_{27}H_{37}SiO_6$ (468.7): C, 69.20; H, 7.74. Found C, 69.04; H, 8.11.

IR (neat): ν = 1747 cm^{-1}.

^1H NMR: δ = 1.07 (s, 18 H), 1.42 (s, 12 H), 2.05 (s, 3 H), 2.07 (s, 3 H), 3.70 (dd, 1 H, *J* = 4, 11 Hz), 3.72 (dd, 1 H, *J* = 4, 11 Hz), 3.81 (dd, 1 H, *J* = 4, 11 Hz), 3.82 (dd, 1 H, *J* = 4, 11 Hz), 3.95 (dt, 1 H, *J* = 4, 8 Hz), 3.98 (dt, 1 H, *J* = 4, 8 Hz), 4.18 (dd, 1 H, *J* = 6.5, 8 Hz), 4.20 (dd, 1 H, *J* = 4, 8 Hz), 5.24 (dd, 1 H, *J* = 1, 10.5 Hz), 5.28 (dd, 1 H, *J* = 1, 10.5 Hz), 5.30 (dd, 2 H, *J* = 1, 17 Hz), 5.38 (dd, 1 H, *J* = 5.5, 6.5 Hz), 5.45 (dd, 1 H, *J* = 4, 6.5 Hz), 5.75 (ddd, 1 H, *J* = 5.5, 10.5, 17 Hz), 5.83 (ddd, 1 H, *J* = 6.5, 10.5, 17 Hz), 7.36–7.45 (m, 12 H), 7.66–7.71 (m, 8 H).

MS (FAB): *m*/*z* = 453 ($M^+ - CH_3$).

Ozonolysis of a Mixture of (3,4)-*anti*-13 and (3,4)-*syn*-13
Ozone was passed through a solution of a mixture of (3,4)-*anti*-**13** and (3,4)-*syn*-**13** (*anti* **:** *syn* = 53:47, 8.16 g, 17.4 mmol) in CH_2Cl_2 (80 mL) at –78°C for 4.5 h followed by the addition of Me_2S (16 mL, 188 mmol). The mixture was stirred at r.t. for 30 min and evaporated. The residue was dissolved in acetone (80 mL) and Jones reagent (8.16 mL, 26.1 mmol) was added at –20 °C. The mixture was stirred for 30 min at the same temperature and treated with isopropyl alcohol (5 mL). The mixture was diluted with H_2O (100 mL) and extracted with Et_2O (3 × 200 ml). After evaporation, the residue was chromatographed on silica gel (200 g) with $CHCl_3$/MeOH (4:1) as eluent to give an amorphous product (7.54 g). A solution of the amorphous product in Et_2O (50 mL) was treated with an excess of CH_2N_2 in Et_2O at 0°C. The mixture was stirred at r.t. for 30 min and evaporated. The residue was chromatographed on silica gel (200 g) using hexane/EtOAc (14:1) as eluent to give a mixture of (2*R*)-**14** and (2*S*)-**14** as a colorless oil; yield: 5.13 g (59%).

Anal. calcd for $C_{27}H_{36}SiO_7$ (500.7): C, 64.77; H, 7.25. Found C, 64.77; H, 7.35.

IR (neat): ν = 1754 cm^{-1}.

^1H NMR: δ = 1.06 (s, 9 H), 1.07 (s, 9 H), 1.38(s, 3 H), 1.40 (s, 3 H), 1.43 (s, 3 H), 1.44 (s, 3 H), 2.15 (s, 3 H), 2.18 (s, 3 H), 3.70–3.80 (m, 2 H), 3.71 (s, 3 H), 3.72 (dd, 1H, *J* = 4, 11 Hz), 3.78 (s, 3 H), 3.81 (dd, 1 H, *J* = 4, 11 Hz), 4.08 (ddd, 1 H, *J* = 4.5, 5.5, 7.5 Hz), 4.34 (dt, 1 H, *J* = 4, 8 Hz), 4.42 (dd, 1 H, *J* = 3, 8 Hz), 4.52 (dd, 1 H, *J* = 3, 8 Hz), 5.18 (d, 1 H, *J* = 3 Hz),. 5.25 (d, 1 H, *J* = 3 Hz), 7.37–7.46 (m, 12 H), 7.66–7.7 (m, 8 H).

MS (FAB): *m*/*z* = 485 ($M^+ - CH_3$).

Methyl 5-*O*-*tert*-Butyldiphenysilyl-3,4-*O*-isopropylidene-L-xylonate (15)
and Methyl 5-*O*-*tert*-Butyldiphenysilyl-3,4-*O*-isopropylidene-L-lyxonate (6)
To a solution of a mixture of (2*R*)-**14** and (2*S*)-**14** (2.57 g, 5.13 mmol) in MeOH (20 mL) was added K_2CO_3 (0.78 g, 5.64 mmol) at 0 °C and the mixture was stirred for 40 min at 0 °C. The mixture was diluted with H_2O (100 mL) and extracted with Et_2O (2 × 100 mL). The organic layer was dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel (100 g) with hexane/EtOAc (14:1) as eluent to afford **15** (1.07 g, 45%) and **6** (1.26 g, 54%) as colorless oils.

15
$[\alpha]_D^{23}$ +4.0 (*c* = 0.8, $CHCl_3$).

Anal.calcd for $C_{25}H_{34}SiO_6.5\ H_2O$ (467.6): C, 64.21; H, 7.54. Found C, 64.39; H, 7.43.

IR (neat): ν = 3501, 1748 cm^{-1}.

^1H NMR: δ = 1.07 (s, 9 H), 1.38 (s, 3 H), 1.42 (s, 3 H), 3.02 (d, 1 H, *J* = 9 Hz), 3.77 (dd, 1 H, *J* = 4, 10.5 Hz), 3.85 (s, 3 H), 3.88 (dd, 1 H, *J* = 6, 10.5 Hz), 4.26 (dd, 1 H, *J* = 1, 9 Hz), 4.30 (ddd, 1 H, *J* = 4, 6, 8 Hz), 4.32 (dd, 1 H, *J* = 1, 8 Hz), 7.37–7.47 (m, 6 H), 7.66–7.72 (m, 4H).

MS (FAB): *m*/*z* = 443 ($M^+ - CH_3$).

6
$[\alpha]_D^{24}$ –21.3 (*c* = 0.95, $CHCl_3$).

Anal. calcd for $C_{25}H_{34}SiO_6.0.5\ H_2O$ (467.6): C, 64.21; H, H, 7.54. Found C, 64.71; H, 7.54.

IR (neat): ν = 3464, 1744 cm^{-1}.

^1H NMR: δ = 1.07 (s, 9 H), 1.40 (s, 3 H), 1.41 (s, 3 H), 3.06 (d, 1 H, *J* = 6 Hz), 3.70 (dd, 1 H, *J* = 4, 11 Hz), 3.75 (s, 3 H), 3.80 (dt, 1 H, *J* = 4.5, 11 Hz), 4.23 (ddd, 1 H, *J* = 4, 4.5, 8 Hz), 4.31 (dd, 1 H, *J* = 4, 8 Hz), 4.39 (dd, 1 H, *J* = 4, 6 Hz), 7.36–7.47 (m, 6 H), 7.66–7.71 (m, 4 H).

MS (FAB): *m*/*z* = 443 ($M^+ - CH_3$).

Conversion of 15 into (2*R*)-14
To a solution of **15** (371 mg, 0.81 mmol) in CH_2Cl_2 (4 mL) at 0 °C was added pyridine (0.65 mL, 8.1 mmol) and Tf_2O (0.2 mL, 1.21 mmol) and the mixture was stirred for 20 min. It was then diluted with H_2O (20 mL), extracted with Et_2O (2 × 20 mL). The organic layer was washed with 1 M aq HCl (10 mL), brine and dried ($MgSO_4$). After evaporation, the residue was chromatographed on silica gel (20 g) with hexane/EtOAc (19:1) as eluent to afford **16** (428 mg, 90%) as a colorless oil. To a solution of a part of **16** (124 mg, 0.21 mmol) in DMF (1 mL) was added CsOAc (81 mg, 0.42 mmol) and the mixture was stirred for 1 h. It was diluted with H_2O (20 mL), extracted with Et_2O (2 × 20 mL). The organic layer was washed with brine and dried ($MgSO_4$). After evaporation, the residue was chromatographed on silica gel (20 g) with hexane/EtOAc (19:1) as eluent to afford (2*R*)-**14** (97 mg, 81% overall yield from **15**) as a colorless oil; $[\alpha]_D^{24}$ –15.2 (*c* = 1.34, $CHCl_3$).

Anal. clcd for $C_{27}H_{36}SiO_7{\cdot}H_2O$ (518.7): C, 62.52; H, 7.38. Found C, 62.55; H, 7.32.

IR (neat):ν = 1754 cm^{-1}.

^1H NMR: δ = 1.06 (s, 9 H), 1.38 (s, 3 H), 1.43 (s, 3 H), 2.15 (s, 3 H), 3.71 (s, 3 H), 3.72 (dd, 1 H, *J* = 4, 11 Hz), 3.81 (dd, 1 H, *J* = 4, 11 Hz) 4.34 (dt, 1 H, *J* = 4, 8 Hz),4.42 (dd, 1 H, *J* = 3, 8 Hz), 5.25 (d, 1 H, *J* = 3 Hz), 7.37–7.46 (m, 6 H), 7.66–7.70 (m, 4 H).

Methyl 5-*O*-*tert*-Butyldiphenysilyl-3,4-*O*-isopropylidene-L-lyxonate (6)
To a solution of **14** (91 mg, 0.18 mmol) in MeOH (2 mL) was added K_2CO_3 (0.78 g, 5.64 mmol) at 0 °C and the mixtutre was stirred for 1 h. The mixture was diluted with H_2O (10 mL) and extracted with Et_2O (2 × 20 mL). The organic layer was dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel (30 g) with hexane/EtOAc (9:1) as eluent to afford **6** (72 mg, 87%) as a color-

less oil; $[\alpha]_D^{21}$ –21.8 (*c* = 1.25, $CHCl_3$). Pyhsical data (IR and NMR) were identical with those of the above mentioned **6**.

Methyl 2-Azido-5-*O*-*tert*-butyldiphenysilyl-2-deoxy-3,4-*O*-isopropylidene-L-xylonate (18)

To a solution of **6** (395 mg, 0.86 mmol) in CH_2Cl_2 (4 mL) at 0 °C was added pyridine (0.7 mL, 8.6 mmol) and Tf_2O (0.21 mL, 1.29 mmol) and the mixture was stirred for 20 min. It was diluted with H_2O (20 mL), extracted with Et_2O (2 × 20 mL). The organic layer was washed with 1 M aq HCl (10 mL), brine, dried ($MgSO_4$) and concentrated. To a solution of the crude product in DMF (4 mL) was added NaN_3 (84 mg, 1.29 mmol) at 0 °C and the mixture was stirred at r.t. for 30 min. It was diluted with H_2O (30 mL) and extracted with Et_2O (2 × 20 mL). The organic layer was dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel (25 g) with hexane/EtOAc (19:1) as eluent to give **18** as a colorless oil; yield 409 mg (98%); $[\alpha]_D^{24}$ –16.2 (*c* = 1.02, $CHCl_3$).

Anal. calcd for $C_{25}H_{33}N_3O_5Si$•0.5 H_2O (492.7): C, 60.95; H, 6.96; N, 8.53. Found C, 60.88; H, 6.68; N, 8.35.

IR (neat): ν = 2118, 1752 cm^{-1}.

^1H NMR: δ = 1.06 (s, 9 H), 1.38 (s, 3 H), 1.49 (s, 3 H), 3.74 (dd, 1 H, *J* = 6.5, 10.5 Hz), 3.82 (d, 1 H, *J* = 2 Hz), 3.86 (dd, 1 H, *J* = 4, 10.5 Hz), 3.87 (s, 3 H), 4.24 (ddd, 1 H, *J* = 4, 6.5 8 Hz), 4.52 (dd, 1 H, *J* = 2, 8 Hz), 7.37–7.47 (m, 6 H), 7.64–7.68 (m, 4 H).

MS (FAB): *m*/*z* = 484 (M^++1).

Methyl 5-*O*-*tert*-Butyldiphenysilyl-2-*(tert*-butoxycarbonyl)amino-2-deoxy-3,4-*O*-isopropylidene-L-xylonate (19)

A mixture of **18** (561 mg, 1.16 mmol) and 20% $Pd(OH)_2$ on carbon (81 mg) in MeOH (6 mL) was subjected to catalytic hydrogenation at r.t. for 12 h and the mixture was filtered with the aid of Celite. The filtrate was evaporated to give the crude product. To a solution of the crude product in dioxane (6 mL) was added Et_3N (0.24 g, 2.32 mmol) and di-*tert*-butyl dicarbonate (0.39 g, 1.74 mmol) at r.t. and the mixture was stirred for 75 min. The mixture was diluted with H_2O (10 mL), extracted with Et_2O (50 mL), dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (30g) with hexane/EtOAc (19:1) as eluent to provide **19** as a colorless oil; yield: 521 mg (81%); $[\alpha]_D^{26}$ +1.4 (*c* = 0.51, $CHCl_3$).

Anal. calcd for $C_{30}H_{43}NO_7Si$ (557.8): C, 64.60; H, 7.77; N, 2.51. Found C, 64.31; H, 8.15; N, 2.89.

IR (KBr): ν = 3446, 2937, 2864, 1750, 1720 cm^{-1}.

^1H NMR: δ = 1.07 (s, 9 H), 1.38 (s, 3 H), 1.42 (s, 3 H), 1.45 (s, 9 H), 3.80 (s, 3 H), 3.77–3.86 (m, 2 H), 3.96 (dt, 1 H, *J* = 4, 8 Hz), 4.48 (d, 1 H, *J* = 10 Hz), 4.59 (d, 1 H, *J* = 8 Hz), 5.31 (d, 1 H, *J* = 10 Hz), 7.36–7.46 (m, 6 H), 7.68–7.73 (m, 4 H).

MS (FAB): *m*/*z* = 558 (M^++1).

Methyl 2-*(tert*-Butoxycarbonyl)amino-2-deoxy-3,4-*O*-isopropylidene-L-xylonate (20)

To a solution of **19** (1.15 g, 2.06 mmol) in pyridine (10 mL) at 0 °C was added aq 48% HF (2 mL) and the mixture was stirred at r.t. for 3 h. It was diluted with H_2O (50 mL), extracted with EtOAc (2 x 100 mL). The organic layer was washed with 1 M aq HCl (10 mL), 7% aq $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (30 g) with hexane/EtOAc (3:1) as eluent to give **20** as a colorless oil; yield: 620 mg (94%); $[\alpha]_D^{24}$ +15.3 (*c* = 1.0, $CHCl_3$).

Anal. calcd for $C_{14}H_{25}NO_7$ (319.4): C, 52.66; H, 7.89; N, 4.39. Found C, 52.23; H, 8.36; N, 4.28.

IR (neat): ν = 3448, 2984, 2936, 1749, 1712 cm^{-1}.

^1H NMR: δ = 1.39 (s, 3 H), 1.40 (s, 3 H), 1.45 (s, 9 H), 2.33 (t, 1 H, *J* = 6 Hz), 3.79 (s, 3 H), 3.80 (m, 2 H), 3.90 (dt, 1 H, *J* = 4, 8.5 Hz), 4.36 (dd, 1 H, *J* = 2, 8.5 Hz), 4.45 (dd, 1 H, *J* = 2, 9 Hz), 5.39 (d, 1 H, *J* = 9 Hz).

MS (FAB): *m*/*z* = 320 (M^++1).

Methyl 5-*O*-(Aminocarbonyl)-2-*(tert*-butoxycarbonyl)amino-2-deoxy-3,4-*O*-isopropylidene-L-xylonate (17):

To a solution of **20** (176 mg, 0.55 mmol) in THF (0.6 mL)/Et_2O (1.5 mL) at –20 °C was added pyridine (0.29 mL, 3.58 mmol), Et_3N (0.1 mL, 0.72 mmol) and 4-nitrophenyl chloroformate (167 mg, 0.825 mmol) and the mixture was stirred for 1 h at the same temperature. After the mixture was stored in a refrigerator for 3 days, it was diluted with H_2O (50 mL), extracted with EtOAc (2 × 20 mL). The organic layer was washed with 1 M aq HCl (10 ml), 7% aq $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated. To a solution of the crude residue in MeOH (8 mL) was added an cxcess of 8% NH_3 in MeOH at 0 °C and the mixture was stirred for 30 min. The mixture was evaporated to give the crude product, which was chromatographed on silica gel (20 g) with hexane/EtOAc (3:1) as eluent to affod **17** as a colorless oil; yield: 194 mg (97%); $[\alpha]_D^{22}$ –2.7 (*c* = 1.05, CH_2Cl_2).

Anal. calcd for $C_{15}H_{26}N_2O_8$ (362.4): C, 49.72; H, 7.23; N, 7.73. Found C, 50.26; H, 7.57; N, 7.84.

IR (KBr): ν = 3455, 2984,1727, 1609 cm^{-1}.

^1H NMR: δ = 1.38 (s, 3 H), 1.42 (s, 3 H), 1.45 (s, 9 H), 3.79 (s, 3 H), 4.02 (dt, 1 H, *J* = 5, 8 Hz), 4.23–4.30 (m, 3 H), 4.50 (dd, 1 H, *J* = 1.5, 9.5 Hz), 4.80 (br s, 2 H), 5.25 (d, 1 H, *J* = 9.5 Hz).

MS (FAB): *m*/*z* = 363 (M^++1).

Methyl 2-Azido-5-*O*-*tert*-butyldiphenysilyl-2-deoxy-3,4-*O*-isopropylidene-L-lyxonate (21)

To a solution of **15** (381 mg, 0.83 mmol) in CH_2Cl_2 (4 mL) at 0 °C was added pyridine (0.67 mL, 8.3 mmol) and Tf_2O (0.21 mL, 1.25 mmol) and the mixture was stirred for 20 min. It was diluted with H_2O (20 mL), extracted with Et_2O (2 × 20 mL). The organic layer was washed with 1 M aq HCl (10 mL), brine, dried ($MgSO_4$) and concentrated. To a solution of the crude product in DMF (2 mL) was added NaN_3 (81 mg, 1.25 mmol) at 0 °C and the mixture was stirred at r.t. for 20 min. It was diluted with H_2O (30 mL) and extracted with Et_2O (2 × 20 mL). The organic layer was dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel (25 g) with hexane/EtOAc (19:1) as eluent to give **21** as a colorless oil; yield 348 mg (87%); $[\alpha]_D^{23}$ –21.4 (*c* = 0.98, $CHCl_3$).

Anal. calcd for $C_{25}H_{33}N_3O_5Si$ (483.6): C, 62.09; H, 6.88; N, 8.69. Found C, 62.07; H, 6.85; N, 8.50.

IR (neat): ν = 2112, 1749 cm^{-1}.

^1H NMR: δ = 1.08 (s, 9 H), 1.43 (s, 6 H), 3.68 (dd, 1 H, *J* = 4, 11 Hz), 3.75 (s, 3 H), 3.83 (dd, 1 H, *J* = 4, 11 Hz), 4.21 (d, 1 H, *J* = 4.5 Hz), 4.24 (ddd, 1 H, *J* = 4, 4, 7.5 Hz), 4.46 (dd, 1 H, *J* = 4.5, 7.5 Hz), 7.37–7.46 (m, 6 H), 7.67–7.71 (m, 4 H).

MS (FAB): *m*/*z* = 484 (M^++1).

Methyl 5-*O*-*tert*-Butyldiphenysilyl-2-*(tert*-butoxycarbonyl)amino-2-deoxy-3,4-*O*-isopropylidene-L-lyxonate (22)

A mixture of **21** (354 mg, 0.73 mmol) and 20% $Pd(OH)_2$ on carbon (51 mg) in MeOH (4 mL) was subjected to catalytic hydrogenation at r.t. for 12 h and the mixture was filtered with the aid of Celite. The filtrate was evaporated to give the crude product. To a solution of the crude product in dioxane (4 mL) was added Et_3N (0.20 g, 1.47 mmol) and di-*tert*-butyldicarbonate (0.26 g, 1.1 mmol) at r.t. and the mixture was stirred for 75 min. The mixture was diluted with H_2O (10 mL), extracted with Et_2O (50 mL), dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (30g) with

hexane/EtOAc (14:1) as eluent to provide **22** as a colorless oil; yield: 253 mg (62%); $[\alpha]_D^{27}$ –26.2 (*c* = 1.02, $CHCl_3$).

Anal. calcd for $C_{30}H_{43}NO_7Si$ (557.8): C, 64.60; H, 7.77; N, 2.51. Found C, 64.44; H, 8.09; N, 2.57.

IR(KBr): ν = 3436, 2930, 1746, 1713 cm^{-1}.

^1H NMR: δ = 1.07 (s, 9 H), 1.36 (s, 3 H), 1.38 (s, 3 H), 1.42 (s, 9 H), 3.68–3.73 (m, 1 H), 3.73 (s, 3 H), 3.76–3.82 (m, 1 H), 4.21–4.28 (m, 2 H), 4.45–4.51 (m, 1 H), 5.29 (br s, 1 H), 7.36–7.49 (m, 6 H), 7.68–7.72(m, 4 H).

MS (FAB): *m*/*z* = 558 (M^++1).

Methyl 2-*(tert*-Butoxycarbonyl)amino-2-deoxy-3,4-*O*-isopropylidene-L-lyxonate (23)

To a solution of **22** (133 mg, 0.24 mmol) in pyridine (2 mL) at 0 °C was added aq 48% HF (0.6 mL) and the mixture was stirred for 4 h. It was diluted with H_2O (10 mL), extracted with EtOAc (2 x 20 mL). The organic layer was washed with 1 M aq HCl (10 mL), 7% aq $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (20 g) with hexane/EtOAc (2:1) as eluent to give **23** as a colorless oil; yield: 52 mg (69%); $[\alpha]_D^{26}$ –40.9 (*c* = 0.75, $CHCl_3$).

Anal. calcd for $C_{14}H_{25}NO_7.H_2O$ (337.4): C, 49.84; H, 8.07; N, 4.15. Found C, 49.53; H, 7.84; N, 4.10.

IR (neat): ν = 3443, 2984, 2936, 1714, 1518 cm^{-1}.

^1H NMR: δ = 1.36 (s, 3 H), 1.39 (s, 3 H), 1.44 (s, 9 H), 2.40 (br s,, 1 H), 3.78 (s, 3 H), 3.68–3.84 (m, 2 H), 4.08 (dd, 1 H, *J* = 4, 8 Hz), 4.23 (dt, 1 H, *J* = 4, 8 Hz), 4.51 (br s, 1 H), 5.44 (br s, 1 H).

MS (FAB): *m*/*z* = 320 (M^++1).

Methyl 5-*O*-(Aminocarbonyl)-2-*(tert*-butoxycarbonyl)amino-2-deoxy-3,4-*O*-isopropylidene-L-lyxonate (24)

To a solution of **23** (38 mg, 0.12 mmol) in THF (0.4 mL)/Et_2O (1 mL) at –20 °C was added pyridine (0.063 mL, 0.78 mmol), Et_3N (0.034 mL, 0.24 mmol) and 4-nitrophenyl chloroformate (36 mg, 0.18 mmol) and the mixture was stirred for 1 h at the same temperature. After the mixture was stored in a refrigerator for 3 days, it was diluted with H_2O (10 mL), extracted with EtOAc (2 × 20 mL). The organic layer was washed with 1 M aq HCl (1 mL), 7% aq $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated. To a solution of the crude residue in MeOH (1 mL) was added an cxcess of 8% NH_3 in MeOH at 0 °C and the mixture was stirred for 30 min. The mixture was evaporated to give the crude product, which was chromatographed on silica gel (20 g) with hexane/EtOAc (2:1) as eluent to affod **24** as a colorless oil; yield: 29 mg (67%); $[\alpha]_D^{26}$ –28.8 (*c* = 0.55, CH_2Cl_2).

Anal. calcd for $C_{15}H_{26}N_2O_8$ (362.4): C, 49.72; H, 7.23; N, 7.73. Found C, 50.04; H, 7.53; N, 7.34.

IR (KBr): ν = 3440, 3363, 2927,1749, 1690, 1523, 1431 cm^{-1}.

^1H NMR: δ = 1.36 (s, 3 H), 1.38 (s, 3 H), 1.43 (s, 9 H), 3.78 (s, 3 H), 4.02 (dd, 1 H, *J* = 4, 8 Hz), 4.15 (dd, 1 H, *J* = 5, 11 Hz), 4.24 (dd, 1 H, *J* = 5.5, 11 Hz), 4.34 (m, 1 H), 4.60 (dd, 1 H, *J* = 4, 9 Hz), 4.94 (br s, 2 H), 5.43 (d, 1 H, *J* = 9 Hz).

MS (FAB): *m*/*z* = 363 (M^++1).

Reaction of 8 and Vinylmagnesium Bromide in the Presence of Et_2AlCl (Table, Entry 2)

To a solution of Et_2AlCl [1.08 M in hexane. 1.85 mL (2.0 mmol)] was added vinylmagnesium bromide (1 M in THF, 2 mL, 2 mmol), and the mixture was stirred at –78 °C for 10 min. A solution of **8** (400 mg, 1 mmol) in THF (4 mL) was added to the above mixture at 0 °C, and the mixture was stirred at 0 °C for 3 h. The mixture was diluted with H_2O (50 mL) and extracted with EtOAc (3 × 20 mL). The extract was washed with brine (20 mL), dried ($MgSO_4$) and concentrated. To a solution of the crude product in pyridine (1 mL, 12.9 mmol) at 0 °C was added Ac_2O (0.5 mL, 5.3 mmol). The mixture was stirred at r.t. for 6 h, diluted with H_2O (50 mL) and extracted with EtOAc (30 mL). The organic layer was washed with brine (20 mL), dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel (20 g) with hexane/EtOAc (9:1) as eluent to give a mixture of (3,4)-*anti*-**13** and (3,4)-*syn*-**13** (*anti* **:** *syn* = 2:1) as a colorless oil; yield: 233 mg (50%).

Reaction of 8 and Vinylmagnesium Bromide in the Presence of $TiCl_4$ and $Ti(O\text{-}i\text{-}Pr)_4$ (Table, Entry 3)

To a solution $TiCl_4$ (0.22 mL, 2 mmol) and $Ti(OPr\text{-}i)_4$ (0.59 mL, 2 mmol) in THF (10 mL) at –40 °Cwas added vinylmagnesium bromide (1 M in THF, 2 mL, 2 mmol), and the mixture was stirred at –40 °Cfor 10 min. A solution of **8** (400 mg, 1 mmol) in THF (4 mL) was added to the above mixture at 0 °C, and the mixture was stirred at –40 °Cfor 10 min and stirred at 0 °C for 2 h. The mixture was diluted with H_2O (50 mL) and extracted with EtOAc (3 × 30 mL). The extract was washed with brine (20 mL), dried ($MgSO_4$) and concentrated. To a solution of crude product in pyridine (1 mL, 12.9 mmol) at 0 °Cwas added Ac_2O (0.5 mL, 5.3 mmol). The mixture was stirred at room temperature for 6 h, diluted with H_2O (50 mL) and extracted with EtOAc (30 mL). The organic layer was washed with brine (20 mL), dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel (20 g) with hexane/EtOAc (9:1) as eluent to give a mixture of (3,4)-*anti*-**13** and (3,4)-*syn*-**13** (*anti* **:** *syn* = 4:3) as a colorless oil; yield: 322 mg (69%).

Reaction of 8 and Vinylmagnesium Bromide in the Presence of $ZnBr_2$ (Table, Entry 4)

To a mixture of $ZnBr_2$ (450 mg, 2 mmol) in THF (5 mL) at –40 °Cwas added vinylmagnesium bromide (1 M in THF, 2 mL, 2 mmol), and the mixture was stirred at –40 °C for 10 min. A solution of **8** (400 mg, 1 mmol) in THF (4 mL) was added to be above mixture at –40 °C, and the mixture was stirred at –40 °C for 10 min and stirred at 0 °C for 2 h. The mixture was diluted with H_2O (50 mL) and extracted with EtOAc (3 × 30 mL). The extract was washed with brine (20 mL), dried ($MgSO_4$) and concentrated. To a solution of the crude product in pyridine (1 mL, 12.9 mmol) at 0 °C was added Ac_2O (0.5 mL, 5.3 mmol). The mixture was stirred at r.t. for 6 h, diluted with H_2O (50 mL) and extracted with EtOAc (30 mL). The organic layer was washed with brine (20 mL), dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel (20 g) with hexane/EtOAc (9:1) as eluent to give a mixture of (3,4)-*anti*-**13** and (3,4)-*syn*-**13** (*anti* **:** *syn* = 5:1) as a colorless oil; yield: 375 mg (80%).

Major product; (3,4)-*anti*-**13**

^1H NMR: δ = 1.07 (s, 9 H), 1.40 (s, 3 H), 1.42 (s, 3 H), 2.05 (s, 3 H), 3.72 (dd, 1 H, *J* = 4, 11 Hz), 3.82 (dd, 1 H, *J* = 4, 11 Hz), 3.98 (dt, 1 H, *J* = 4, 8 Hz), 4.20 (dd, 1 H, *J* = 4, 8 Hz), 5.28 (dd, 1 H, *J* = 1, 10.5 Hz), 5.30 (dd, 1 H, *J* = 1, 17 Hz), 5.45 (dd, 1 H, *J* = 4, 6.5 Hz), 5.83 (ddd, 1 H, *J* = 6.5, 10.5, 17 Hz), 7.37–7.43 (m, 6 H), 7.67–7.71 (m, 4 H).

Reaction of 8 and Vinylmagnesium Bromide in the Presence of $ZnBr_2$ (Table, Entry 5)

To a mixture of $ZnBr_2$ (2.25 g, 10 mmol) in THF (40 mL) at –78 °C was added vinylmagnesium bromide (1 M in THF, 11 mL, 11 mmol), and the mixture was stirred at –78°C for 30 min. A solution of **8** (2.0 g, 5 mmol) in THF (10 mL) was added to the above mixture at –78 °C, and the mixture was stirred at –78 °C for 10 min and stirred at 0 °Cfor 2 h. The mixture was diluted with H_2O (100 mL) and extracted with EtOAc (100 mL). The extract was washed with brine (50 mL), dried ($MgSO_4$) and concentrated. The crude product was dissolved in pyridine (4 mL, 49.5 mmol) at 0 °C and treated

with Ac_2O (3 mL, 31.8 mmol). The mixture was stirred at r.t. for 12 h, diluted with H_2O (50 mL) and extracted with EtOAc (100 mL). The organic layer was washed with brine (20 mL), dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel (50 g) with hexane/EtOAc (9:1) as eluent to give a mixture of (3,4)-*anti*-**13** and (3,4)-*syn*-**13** (*anti* **:** *syn* = 8:1) as a colorless oil; yield:1.18 g (50%).

Reaction of 8 and Vinylmagnesium Bromide in the Presence of $ZnBr_2$ (Table, Entry 6)

i) To a mixture of $ZnBr_2$ (10 g, 44.4 mmol) in THF (200 mL) at –78 °C was added vinylmagnesium bromide (1 M in THF, 45 mL, 45 mmol), and the mixture was stirred at –78°C for 30 min. A solution of **8** (12 g, 30.1 mmol) in THF (30 mL) was added at –78 °C, and the mixture was stirred at –78 °C for 1 h and stirred at 0 °C for 3 h. The mixture was diluted with H_2O (300 mL) and extracted with EtOAc (3 × 300 mL). The extract was washed with brine (200 mL), dried ($MgSO_4$) and concentrated. To a solution of the crude product in pyridine (5 mL, 63.3 mmol) at 0 °C was added Ac_2O (5 mL, 49 mmol). The mixture was stirred at r.t. for 6 h, diluted with H_2O (200 mL) and extracted with EtOAc (3 × 100 mL). The organic layer was washed with brine (200 mL), dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel (200 g) with hexane/EtOAc (15:1) as eluent to give a mixture of (3,4)-*anti*-**13** and (3,4)-*syn*-**13** (*anti* **:** *syn* = 5:1) as a colorless oil; yield: 9.9 g (70%).

ii) Ozone was passed through a solution of a mixture of (3,4)-*anti*-**13** and (3,4)-*syn*-**13** (*anti* **:** *syn* = 5:1, 9.9 g, 21.2 mmol) in CH_2Cl_2 (50 mL) at –78 °C for 3 h followed by the addition of Me_2S (4 mL, 47 mmol). The mixture was stirred at r.t. for 1 h and evaporated. The residue was dissolved in acetone (20 mL) and Jones reagent (22 mL) was added at –20 °C. The mixture was stirred for 2 h at the same temperature and treated with isopropyl alcohol (10 mL). The mixture was diluted with H_2O (100 mL) and extracted with Et_2O (3 × 200 mL). After evaporation, the residue was dissolved in Et_2O (50 mL) and treated with an excess of CH_2N_2 in Et_2O at 0 °C. The mixture was stirred at r.t. for 2 h and evaporated. The crude residue of (2*R*)-**14** and (2*S*)-**14**) was dissolved in MeOH (30 mL), K_2CO_3 (2.9 g, 21 mmol) was added at 0 °C and the mixture was stirred for 30 min at r.t. The mixture was diluted with brine (100 mL) and extracted with EtOAc (3 × 100 mL). The organic layer was dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel (200 g) with hexane/EtOAc (10:1) as eluent to afford **15** [0.98 g, overall yield 10% from (3,4)-*syn*-**13**] and **6** [5.1 g, overall yield 52% from (3,4)-*anti*-**13**] as colorless oils. NMR spectra of both **15** and **6** were identical with those of the above mentioned (2*S*)-**15** and (2*R*)-**6**, respectively.

Benzyl 5-*O*-(Aminocarbonyl)-2-*(tert*-butoxycarbonyl)amino-2-deoxy-3,4-*O*-isopropylidene-L-xylonate (25)

A mixture of **17** (1.217 g, 3.36 mmol), benzyl alcohol (7.26 g, 67 mmol) and and Ti(OPr-*i*)$_4$ (0.473 mL, 1.68 mmol) in benzene (40 mL) was refluxed with stirring for 12 h. The mixture was diluted with H_2O (10 mL), extracted with EtOAc (2 × 20 mL). The organic layer was washed with 1 M aq HCl (1 mL), 7% aq $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (50 g) with hexane/EtOAc (2:1) as eluent to give **25** as a colorless oil; yield: 1.205 g (82%); $[\alpha]_D^{28}$ –16.4 (*c* = 1.01, $CHCl_3$).

Anal. calcd for $C_{21}H_{30}N_2O_8$ (438.5): C, 57.52; H, 6.90; N, 6.29. Found C, 57.76; H, 7.34; N, 6.47.

IR (KBr): ν = 3452, 3377, 2983,1721, 1604, 1503 cm^{-1}.

^{1}H NMR: δ = 1.36 (s, 3 H), 1.41 (s, 3 H), 1.44 (s, 9 H), 4.02 (dt, 1 H, *J* = 5, 8 Hz), 4.20 (dd, 1 H, *J* = 5, 11 Hz), 4.27 (dd, 1 H, *J* = 5, 11 Hz), 4.30 (dd, 1 H, *J* = 2, 8 Hz), 4.56 (dd, 1 H, *J* = 2, 10 Hz), 4.83 (br s, 2 H), 5.16 (d, 1 H, *J* = 12.5 Hz), 5.29 (d, 1 H, *J* = 12.5 Hz), 5.30 (d, 1 H, *J* = 10 Hz), 7.35 (m, 5 H).

^{13}C NMR ($CDCl_3$) : δ = 26.7, 26.8, 28.2, 53.1, 64.0, 67.4, 74.8, 78.2, 109.9, 128.0, 128.3, 128.5, 135.2, 155.8, 156.2, 170.0.

MS (FAB): *m*/*z* = 439 (M^++1).

5-*O*-(Aminocarbonyl)-2-*(tert*-butoxycarbonyl)amino-2-deoxy-3,4-*O*-isopropylidene-L-xylonic acid (7)

A mixture of **25** (86 mg, 0.196 mmol) and 10% Pd/C (50 mg) in MeOH (6 mL) was subjected to catalytic hydrogenation at r.t. for 30 min and the mixture was filtered with the aid of Celite. The filtrate was evaporated to give **7** as a colorless oil; yield: 68 mg (>99%); $[\alpha]_D^{28}$ +1.03 (*c* = 0.775, acetone).

IR (KBr): ν = 3445, 3367, 2929, 1724, 1602 cm^{-1}.

^{1}H NMR: δ = 1.40 (s, 3 H), 1.42 (s, 3 H), 1.45 (s, 9 H), 4.02 (dt, 1 H, *J* = 5, 8 Hz), 4.26 (dd, 1 H, *J* = 5, 11.5 Hz), 4.31 (dd, 1 H, *J* = 5, 11.5 Hz), 4.36 (d, 1 H, *J* = 8 Hz), 4.52 (d, 1 H, *J* = 9.5 Hz), 5.35 (d, 1 H, *J* = 9.5 Hz), 5.39 (br s, 2 H).

MS (FAB): *m*/*z* = 349 (M^+ + 1).

^{13}C NMR data of **7** were already given in Ref. 5d.

Coupling Between 7 and Thymine Polyoxin C (3)

A mixture of **7** (68 mg, 0.196 mmol), *N*-hydroxysuccinimide (23 mg, 0.196 mmol), *N*,*N*-dicyclohexylcarbodiimide (41 mg, 0.196 mmol) in EtOAc (2 mL) was stirred at 0 °Cfor 1 h. The mixture was evaporated to give a crude residue which was dissolved in DMSO (1 mL). A solution of thymine polyoxin C **3** (59 mg, 0.196 mmol) and *i*-Pr_2NEt (0.034 mL, 0.196 mmol) in DMSO (2 mL) was added to the above DMSO Solution and the mixture was stirred for 24 h at r.t. The mixture was directly chromatographed on silica gel (10 g) with $CHCl_3$/MeOH (4:1) as eluent to give **27** as a colorless amorphous product; yield: 101 mg (82%); mp 170–172 ° C (dec.); $[\alpha]_D^{25}$ –7.7 (*c* = 0.505, MeOH).

IR (KBr): ν = 3433, 1701, 1512 cm^{-1}.

^{1}H NMR (CD_3OD/D_2O): δ = 1.36 (s, 3 H), 1.41 (s, 3 H), 1.45 (s, 9 H), 1.91 (d, 3 H, *J* = 1 Hz), 4.05 (m 1 H), 4.18 (m, 1 H), 4.24–4.35 (m, 5 H), 4.42 (m, 1 H), 4.64 (d, 1 H, *J* = 3.5 Hz), 5.73 (d, 1 H, *J* = 6 Hz), 7.52 (d, 1 H, *J* = 1 Hz).

MS (FAB): *m*/*z* = 632 (M^+ + 1), 654 (M^+ + Na), 670 (M^+ + K).

^{13}C NMR data of **27** were already given Ref. 5d.

Polyoxin J (1)

To a solution of **27** (170 mg, 0.27 mmol) in MeOH (6 mL) and H_2O (3 mL) at 0 °Cwas added CF_3SO_3H (3 mL) and the mixture was stirred for 24 h at r.t. The mixture was evaporated to give a residue, which was chromatographed on silica gel (10 g) with $CHCl_3$/MeOH (2:1) as eluent to give an amorphous product. It was dissolved in H_2O (2 mL) and filtered with the aid of Celite (100 mg) and activated carbon (50 mg). The filtrate was evaporated to afford **1** as an amorphous product; yield: 113 mg (86%); mp 195–200 °C(dec.); $[\alpha]_D^{28}$ +35.7 (*c* = 0.68, H_2O).

IR (KBr): ν = 3433, 2985, 1701, 1515 cm^{-1}.

^{1}H NMR (D_2O): δ = 1.77 (d, 3 H, *J* = 1 Hz), 3.94–4.02 (m, 3 H), 4.08 (m, 1 H), 4.10–4.16 (m, 2 H), 4.20 (t, 1 H, *J* = 5 Hz), 4.37 (t, 1 H, *J* = 5 Hz), 4.45 (d, 1 H, *J* = 3 Hz), 5.71 (d, 1 H, *J* = 5 Hz), 7.41 (d, 1 H, *J* = 1 Hz).

MS (FAB): *m*/*z* = 492 (M^+ + 1), 514 (M^+ + Na), 530 (M^+ + K).

HRMS (FAB, matrix: glycerol): *m*/*z* calcd for $C_{17}H_{26}N_5O_{12}$ (M^+ + 1) 492.1578; found 492.1575.

^{13}C NMR data of **1** were already given Ref. 5d.

Coupling Between 7 and Uracil Polyoxin C (4)

A mixture of **7** (160 mg, 0.46 mmol), *N*-hydroxysuccinimide (53 mg, 0.46 mmol), *N*,*N*-dicyclohexylcarbodiimide (95 mg, 0.46 mmol) in EtOAc (4 mL) was stirred at 0 °C for 1 h. The mixture was evaporated and the crude residue was dissolved in DMSO (1 mL). A solution of uracil polyoxin C **4** (132 mg, 0.46 mmol) and *i*-Pr_2NEt (0.081 mL, 0.46 mmol) in DMSO (2 mL) was added to the above DMSO Solution and the mixture was stirred for 24 h at r.t. The mixture was directly chromatographed on silica gel (10 g) with $CHCl_3$/MeOH (4:1) as eluent to give **28** as a colorless amorphous product; yield: 209 mg (74%); mp 176–178 °C (dec.); $[\alpha]_D^{25}$ –3.2 (*c* = 1.22, MeOH).

IR (KBr): ν = 3423, 2985, 1701, 1507 cm^{-1}.

^{1}H NMR (CD_3OD): δ = 1.26 (s, 3 H), 1.30 (s, 3 H), 1.35 (s, 9 H), 3.95 (m 1 H), 4.05 (m, 1 H), 4.12–4.24 (m, 4 H), 4.35 (m, 2 H), 4.58 (m, 1 H), 5.68 (d, 1 H, *J* = 8 Hz), 5.76 (d, 1 H, *J* = 5 Hz), 7.55 (d, 1 H, *J* = 8 Hz).

MS (FAB): *m*/*z* = 618 (M^+ + 1), 640 (M^+ + Na), 656 (M^+ + K).

Polyoxin L (2)

To a solution of **28** (157 mg, 0.254 mmol) in MeOH (6 mL) and H_2O (3 mL) at 0 °Cwas added CF_3SO_3H (3 mL) and the mixture was stirred for 24 h at r.t. The mixture was evaporated to give a residue, which was chromatographed on silica gel (10 g) with $CHCl_3$/MeOH (2:1) as eluent to give an amorphous product. It was dissolved in H_2O (2 mL) and filtered with the aid of Celite (100 mg) and activated carbon (50 mg). The filtrate was evaporated to afford **2** as an amorphous product; yield: 113 mg (94%); mp 180–183°C (dec.); $[\alpha]_D^{22}$ +35.0 (*c* = 1.215, H_2O).

IR (KBr): ν = 3348, 1685, 1617, 1469 cm^{-1}.

^{1}H NMR (D_2O): δ = 3.96–4.04 (m, 3 H), 4.08 (d, 1 H, *J* = 5 Hz), 4.15 (t, 1 H, *J* = 3.5 Hz), 4.17 (d, 1 H, *J* = 5 Hz), 4.21 (t, 1 H, *J* = 5.5 Hz), 4.37 (t, 1 H, *J* = 5.5 Hz), 4.52 (d, 1 H, *J* = 3.5 Hz), 5.69 (t, 1 H, *J* = 5.5 Hz), 5.76 (d, 1 H, *J* = 8 Hz), 7.52 (d, 1 H, *J* = 8 Hz).

^{13}C NMR (D_2O) : δ = 55.9, 64.8, 68.0, 69.0, 69.3, 69.6, 72.4, 83.6, 88.9, 102.1, 141.7, 151.2, 158.5, 165.5, 166.8, 169.5.

MS (FAB): *m*/*z* = 478 (M^+ + 1).

HRMS (FAB, matrix: glycerol): *m*/*z* calcd for $C_{16}H_{24}N_5O_{12}$ (M^+ + 1) 478.1421; found 478.1418.

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