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A total synthesis of (+)-oxybiotin from D-arabinose

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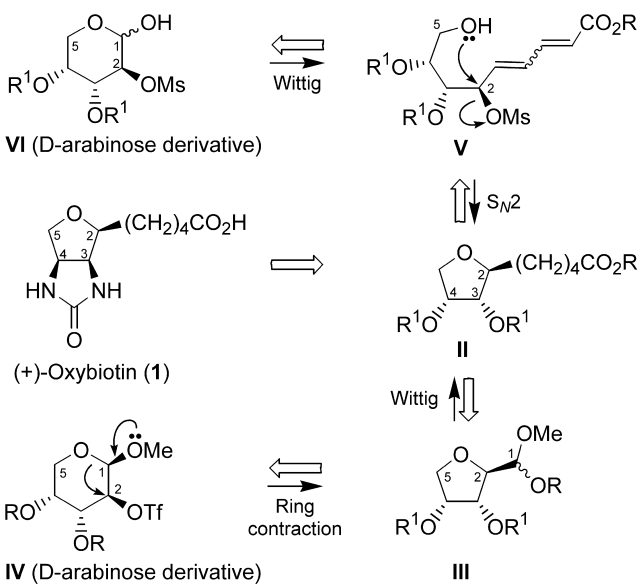
Abstract—A novel ten-step synthesis of (+)-oxybiotin, a biologically active analogue of (+)-biotin, has been achieved starting from D-arabinose.

1. Introduction

The oxygenated analogue of biotin in which an oxygen atom replaces sulphur was synthesized by Hofmann[1] and named oxybiotin.[2] The obtained racemic material showed 50% of biotin like growth-stimulatory activity.[3] Such results implied that the biologically active enantiomer should have the same absolute configuration as naturally occurring (+)-biotin. This assumption was confirmed by a total synthesis of enantiopure (+)-oxybiotin (**1**) that was achieved in 19 steps starting from D-glucose.[4] Recently we have reported a 14-step synthesis of (+)-**1** from D-xylose,[5] and now we describe a new ten-step synthesis of (+)-oxybiotin based on chirality transfer from D-arabinose.[6]

Retrosynthetic analysis of (+)-oxybiotin (**1**) is presented in Scheme 1. An examination of the target molecule **1** reveals a chiral tetrahydrofuran system containing three contiguous substituents including the C-3 and C-4 nitrogen functions incorporated into a *cis*-fused imidazolidinone ring. Our synthetic plan for the assembly of the C_3-C_4 domain involved an introduction of two nitrogen functions at C-3 and C-4 in a derivative of type **II** (with Walden inversion), followed by a subsequent closure of the imidazolidinone ring system. Further disconnection of **II** leads to a protected 2,5-anhydro-D-ribose derivative **III**, which should be accessible from an arabinopyranoside 2-triflate **IV** by a ring contraction process.

An alternative disconnection of the retron **II** leads to the open-chain intermediate **V**, which might be converted to a synthetic precursor of **II** by an intramolecular displacement of the allylic C-2 mesyloxy function by the C-5 hydroxyl group. The structure **V** can be finally correlated with a partially protected D-arabinose derivative **VI** via a simple Wittig reaction. Accordingly, the preparation of the postulated intermediates of type **III** and **VI** was first attempted.



Scheme 1. Retrosynthetic analysis (sugar numbering scheme).

2. Results and discussion

In 1989, Baer et al.[7] reported a facile formation of 2,5-anhydro-6-deoxy-L-talose derivatives by ring contraction

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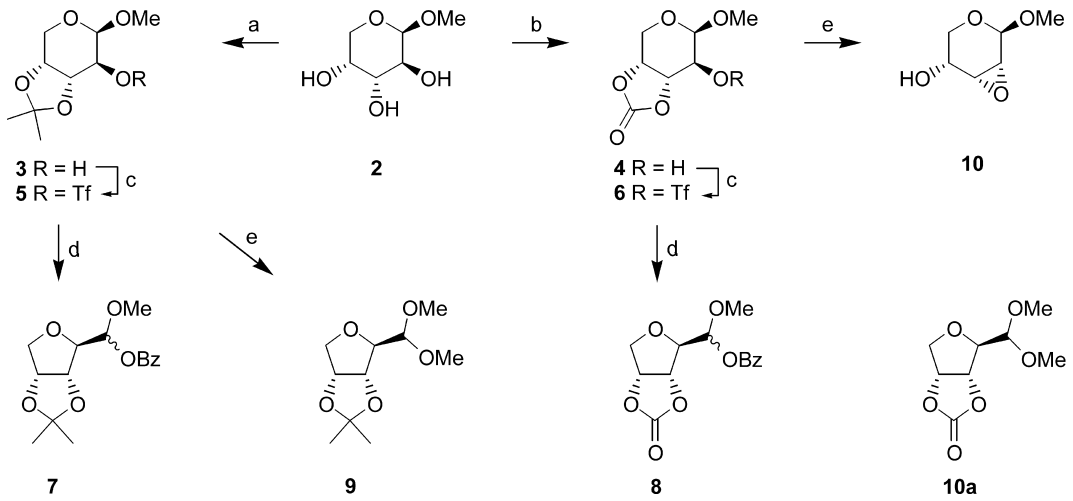
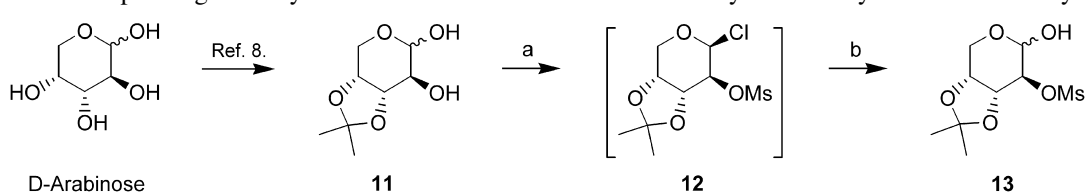


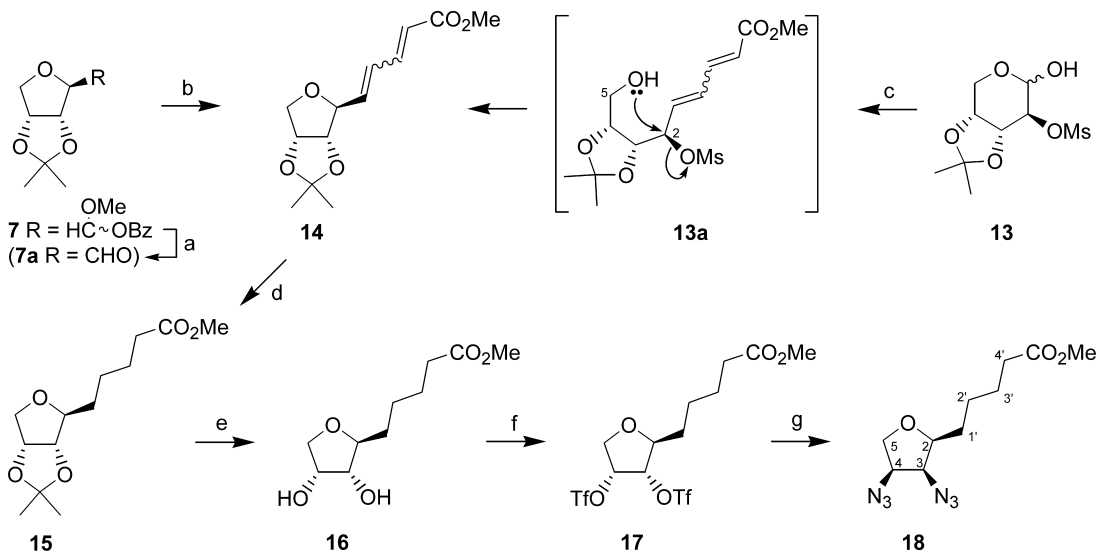
Scheme 2. (a) $Me_2C(OMe)_2$, TsOH, DMF, rt, 3.5 h, 89%; (b) Imd_2CO, C_6H_6, reflux, 1.5 h, 69%; (c) Tf_2O, Py, CH_2Cl_2, −10 °C, 0.5 h; (d) KOBz, DMF, rt, 20 h for **5**, 99% of **7** (two steps), 60–65°, 2 h for **6**, 80% of **8** (two steps); (e) $NaHCO_3$, MeOH, 50 °C, 4 h for **5**, 12% of **9**, 55–60 °C, 3 h for **6**, 77% of **10**.

in methyl 2-*O*-trifluoromethanesulfonyl-β-L-fucopyranoside under solvolytic conditions (KOBz/DMF, $NaHCO_3$/MeOH). It was therefore assumed that utilization of similar methodology in the D-arabinopyranose series would provide the postulated intermediate **III** from the retrosynthetic analysis scheme. The preparation of the 2-triflate esters **5** and **6** was first attempted starting from the 3,4-*O*-protected methyl β-D-arabinopyranosides **3** and **4** (Scheme 2). We adopted the Kiso–Hasegawa acetonation procedure[8] for the conversion of commercially available methyl β-D-arabinopyranoside (**2**) to the known[9] 3,4-*O*-isopropylidene derivative **3**. Compound **4**, in turn, was conveniently prepared by treatment of **2** with 1,1′-carbonyldiimidazole in boiling benzene. The melting point and NMR spectral data of thus obtained intermediate **4** were in reasonable agreement with those earlier reported for the L-configuration counterpart of **4**, obtained by treatment of the corresponding 3,4-*O*-thiocarbonyl derivative with bistributyltin oxide.[10] Both **3** and **4** readily reacted with triflic anhydride to afford the corresponding 2-*O*-triflate esters **5** (74%) and **6** (89%). Compound **5** was partially characterized from NMR spectroscopic data, but was rather unstable on storage similar to its fucopyranoside analogue.[7] It should be therefore used in the next synthetic step immediately after its brief isolation. On the contrary, the triflate **6** is a stable crystalline compound, which was fully characterized by the corresponding spectral (IR, NMR, MS) and analytical data. Similarly to L-fucopyranoside derivatives,[7] both arabinopyranosides **5** and **6** smoothly reacted with potassium benzoate in *N*,*N*-dimethylformamide to give the corresponding 2,5-anhydro-D-ribose derivatives **7** (99% from **2**; 2:1 mixture of C-1 epimers) and **8** (80% from **2**; 1:1 mixture of C-1 epimers). Compound **5** also reacted with sodium hydrogen carbonate in methanol (50 °C for 4 h)[7] to afford a low yield of the corresponding dimethyl acetal derivative **9** (12%), as a ring-contracted product. Conversely, the 3,4-*O*-carbonyl derivative **6**, under the similar reaction conditions, gave the known[11] epoxide **10** (77%) as a product of transesterification of the cyclic carbonate functionality in **6**, followed by a subsequent epoxide ring closure process. The dimethyl acetal derivative **10a**, an expected product of the presumed ring contraction process, could not be detected in the reaction mixture. In the light of their stereochemical and topological features, the 2,5-anhydro derivatives **7**–**9** fully correspond to the intermediate **III** from our retrosynthetic analysis. However, further work was continued with the isopropylidene derivative **7**, since only this intermediate was accessible from the starting material **2** in an almost quantitative yield.

Preparation of the 2-*O*-mesyl derivative **13**, a postulated intermediate in the alternative approach to **1**, started from 3,4-*O*-isopropylidene-D-arabinose (**11**), which was readily available from D-arabinose through a modified literature procedure[8] (Scheme 3). Treatment of **11** with mesyl chloride and triethylamine in dry dichloromethane gave the crystalline glycosyl chloride **12** as the only reaction product. Small vicinal coupling between H-1 and H-2 ($J_{1,2}$=3.7 Hz) is consistent with the *cis* arrangement of these protons and convincingly proved a β-configuration at the anomeric position. Although the compound **12** could be stored at −20 °C for weeks without change, it tended to decompose on prolonged standing at room temperature. Hence, the intermediate **12** was immediately treated with silver oxide in aqueous acetone, in the presence of a catalytic amount of silver triflate, to give the stable lactol **13** (94% from **11**). The synthesis of product **13** from methyl 3,4-*O*-isopropylidene-2-*O*-methanesulfonyl-β-D-arabinopyranoside, has already been described in the literature,[9] but in an overall yield of only 18% from two synthetic steps.



Scheme 3. (a) MsCl, Et_3N, CH_2Cl_2, −10 °C, 1 h; (b) Ag_2O, AgOTf, aq. Me_2CO, rt, 24 h, 95% from **11**.

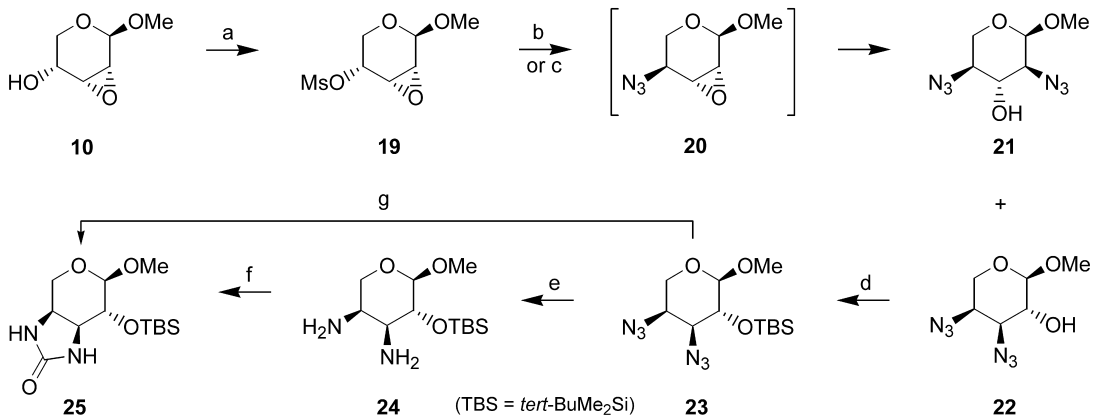


Scheme 4. (a) MeONa, MeOH, rt, 2 h; (b) Ph_3P:CHCH:$CHCO_2Me$, MeOH, rt, 2 h, 41% from **7**; (c) Ph_3P:CHCH:$CHCO_2Me$, Na_2CO_3, DMF, 135 °C, 2 h; (d) H_2, PtO_2, MeOH, rt, 24 h, 36% from **3**, 67% from **13**; (e) 9:1 TFA–H_2O, rt, 0.5 h, 95%; (f) Tf_2O, Py, CH_2Cl_2, 0 °C, 1.5 h; (g) NaN_3, HMPA, rt, 1.5 h, 68% from **16**.

Our sample **13** displayed a value of optical rotation {$[\alpha]_D=-116.5$ (*c* 1.5)} similar to that reported previously {$[\alpha]_D=-118.0$ (*c* 2.06)},[9] but its melting point was significantly lower (116–117 °C) with respect to the reported value (130–131 °C).[9] However, its IR, NMR (^1H and ^{13}C) and HR MS spectral data were fully consistent with structure **13**. The product **13** was mainly the β anomer since its chloroform solution mutarotated to a less negative equilibrium value {$[\alpha]_D=-116.5\rightarrow-106.4$ (24 h)}. The ^1H NMR spectral data also proved that the crystalline sample **13** consists of both α- and β-anomers, as established by integration of the corresponding proton signals [δ 3.83 (dd, $J_{5a,5b}$=14.1 Hz, $J_{4,5a}$=2.5 Hz, H-5aα), 3.97 (d, $J_{5a,5b}$= 13.3 Hz, H-5aβ). The initial 1:5 α/β anomeric ratio, recorded immediately after dissolution of the sample in $CDCl_3$, was changed to 1:3 after storing the solution at room temperature for 48 h.

Having obtained the key intermediates **7** and **13**, we next focused on their C_4-elongation at C-1 in order to elaborate the carboxybutyl (+)-oxybiotin side chain (Scheme 4). O-Debenzoylation of **7** with sodium methoxide in methanol produced the unstable aldehyde **7a**, which was not isolated but was further treated with 3-(carbomethoxy-2-propenylidene)triphenylphosphorane,[12] by using a one-pot procedure. The expected dienoate **14** was thus obtained as an inseparable mixture of corresponding *E*- and *Z*-isomers. Catalytic hydrogenation of **14** over PtO_2 in methanol finally furnished the saturated ester **15** in 36% overall yield with respect to **3**. In a different approach, the 3,4-*O*-isopropylidene-2-*O*-methanesulfonyl-D-arabinose (**13**) was treated with 3-(carbomethoxy-2-propenylidene)triphenylphosphorane in dry DMF, in the presence of sodium carbonate as a proton acceptor, to give directly the dienoates **14** (an inseparable mixture of *E*- and *Z*-isomers), as a result of the sequential Wittig reaction/intramolecular displacement process. Neither the acyclic intermediate **13a** nor the products of the competitive Michael addition could be detected in the reaction mixture. The ^1H and ^{13}C NMR spectra of the mixture of **14** thus obtained displayed essentially the same signals as the sample **14** prepared from the 2,5-anhydride **7**, but indicated somewhat different ratio of *E*- and *Z*-isomers. Conversely, the reaction of **13** with trimethyl-4-phosphono crotonate, in the presence of NaH in THF, at room temperature for 0.5 h, gave pure *E*,*E*-**14** (48%) as the only stereoisomer (not shown in the scheme). Finally, catalytic hydrogenation of **14**, over the Adams catalyst, gave the corresponding saturated ester **15** (67% from **13**). The four-step sequence based on the Wittig reaction of lactol **13** with 3-(carbomethoxy-2-propenylidene)triphenylphosphorane represents a more convenient route towards the key intermediate **15**, since it provided a considerably higher overall yield (63% from **11**) compared to the combined five-step sequence via the 2,5-anhydride **7** (36% from **2**). Hydrolytic removal of the isopropylidene protective group in **15** gave an excellent yield of the expected diol **16** (95%). Reaction of **16** with triflic anhydride in pyridine and dichloromethane gave the corresponding 3,4-ditriflate **17**, isolated by flash column chromatography in 51% yield. Subsequent treatment of **17** with sodium azide in HMPA afforded the corresponding 3,4-diazido derivative **18** as the only reaction product (47% from **16**). However, when the last two-step sequence was carried out without purification of the intermediate **17**, the desired product **18** was obtained in a considerably higher overall yield (68% from **16**).

Diazide **18** represents a final chiral intermediate for the completion of the synthesis of target **1**, since it has the correct absolute configuration at all the stereocentres. Therefore we next focused on the conversion of its vicinal diazido functionality into the imidazolidinone heterocyclic system. This requires previous conversion of **18** into the corresponding diamine **18a** (Scheme 6), followed by subsequent cyclization of the intermediate upon treatment with phosgene or its equivalent. However, in order to avoid wasting of the valuable intermediate **18**, the final imidazolidinone system building was first explored on the diazido derivative **23** as a model compound (Scheme 5).



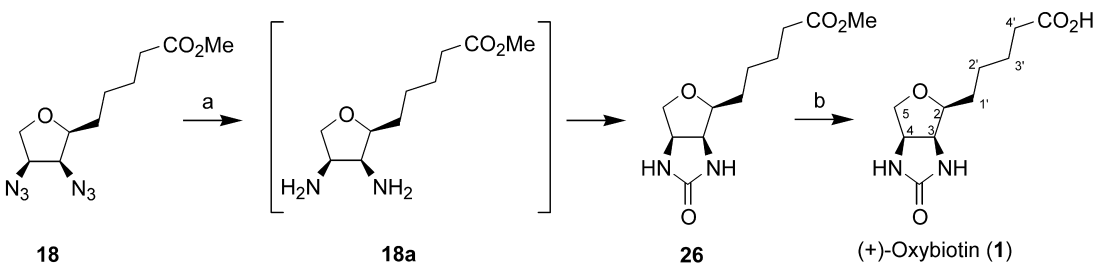
Scheme 5. (a) MsCl, Et_3N, CH_2Cl_2, −10 °C, 40 min, 97%; (b) NaN_3, DMF, 90–95 °C, 0.5 h, then 110–115 °C, 15 min 56% of **20**, 18% of **22**; (c) NaN_3, DMF, 140–145 °C, 3.5 h, **20**, 4% of **21**, 51% of **22**; (d) TBSCl, imidazole, DMF, rt, 24 h, 97%; (e) Ph_3P, THF, rt, 3 h, then aq. $NaHCO_3$, rt, 24 h, 63%; (f) $(Cl_3CO)_2CO$, Et_3N, CH_2Cl_2, 0°C, 2 h, 67%; (g) H_2, PtO_2, CH_2Cl_2, rt, 24 h, then $(Cl_3CO)_2CO$, Et_3N, 0°C, 2 h, then rt 22 h, 69% from **23**.

Methyl 2,3-anhydro-β-D-arabinopyranoside (**10**) was used as a convenient starting compound in this part of the work. Treatment of **10** with mesyl chloride and triethylamine in dichloromethane gave the corresponding 4-*O*-mesyl derivative **19** in an almost quantitative yield. Compound **19** readily reacted with sodium azide in DMF (90–95 °C) to afford the corresponding 4-azido derivative **20** (56%) accompanied with a small amount of the 3,4-diazido derivative **22** (18%). However, when the last reaction was carried out at an elevated temperature (140–145 °C), the desired compound **22** was isolated in 51% yield along with a minor quantity of the 2,4-diazido derivative **21** (4%). Major regioisomer **22** was treated with *tert*-butyldimethylsilyl chloride and imidazole to give the corresponding silyl ether **23** (97%), a convenient model-compound for optimising reaction conditions for the conversion of two vicinal azido functions into the imidazolidinone ring. The Staudinger reaction[13] of **23** provided the corresponding 3,4-diamino derivative **24** (63%), which was subsequently treated with triphosgene, under the conditions similar to those recently applied for the conversion of vicinal amino alcohols to oxazolidinones,[14] to give the imidazolidinone **25** in 67% yield (42% from **23**). However, the one-pot catalytic reduction of **23** followed by subsequent triphosgene treatment provided a significantly higher overall yield of **25** (69% from **23**).

Given this success in the model series, the last one-pot sequence was applied to **18**. The diazide **18** was first reduced over PtO_2 in dichloromethane and after 24 h, when the TLC indicated complete conversion of **18**, the reaction mixture was treated with triphosgene, whereby the imidazolidinone **26** was obtained in 66% yield. Treatment of **26** with an aqueous solution of sodium hydroxide, followed by neutralization with Amberlyst 15, gave an almost quantitative yield of (+)-oxybiotin (**1**, Scheme 6), with physical constants (mp and $[\alpha]_D$) in full agreement with those already reported.[4] Spectroscopic data of the final product thus obtained were consistent with structure **1**.

2.1. X-ray analysis

A single crystal X-ray diffraction analysis of compound **26** (Fig. 1) unambiguously confirmed its structure providing a proof that all intermediates generated by the multistep sequence **7→18** retained the required (*S*)-configuration at the C-2. The values of torsion angles C1′–C2–C3–N3=42.4(1)° and N3–C3–C4–N4=6.4(2)° are consistent with the all-*cis* geometry of **26**. The ureido ring, including the carbonyl oxygen, is essentially planar. The maximum deviation from the best plane of the ureido ring atoms is 0.066(2) Å for C-4. The bond distances [C6–O6=1.241(2), C6–N4=1.348(2) and C6–N3=1.350(2) Å] are comparable to those observed in the ureido system of (+)-biotin.[15] The five membered tetrahydrofuran ring adopts an envelope conformation, with O-1 above the best plane [0.608(1) Å] that contains the C-2, C-3, C-4 and C-5 ring atoms. The bicyclic moiety adopts an *endo* conformation with the O-1 oxygen atom proximal to the ureido ring [the nonbonded distance O1···C6=3.433(2) Å; torsion angles: N3–C3–C2–O1=−79.7(2)° and N4–C4–C5–O1=90.6(1)°]. Similar geometry of the bicyclic moiety was already observed in



Scheme 6. (a) (*i*) H_2, PtO_2, CH_2Cl_2, rt, 22 h, (*ii*) $(Cl_3CO)_2CO$, Et_3N, 0 °C, 2 h, then rt, 21 h, 66%; (b) NaOH, H_2O, rt, 24 h, then Amberlyst 15, rt, 1 h, 99%.

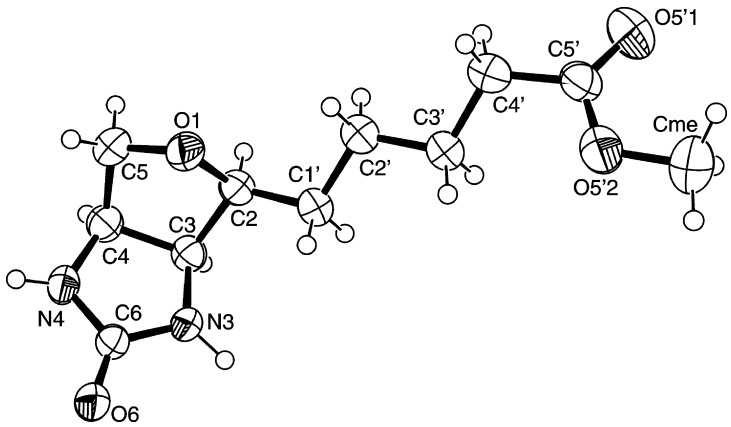


Figure 1. ORTEP drawing of the (+)-oxybiotin methyl ester (**26**) with non-H labelling scheme. The displacement ellipsoids were drawn at 50% probability.

the molecular structure of biotin.[15] The values of torsion angles C2–C1′–C2′–C3′=−176.4(1)°, C1′–C2′–C3′–C4′=179.3(2)° and C2′–C3′–C4′–C5′=171.8(2)° are consistent with an all-*trans* extended conformation of the valeryl side chain.

3. Conclusions

In conclusion, this paper reports a convenient ten-step synthesis of (+)-oxybiotin by chirality transfer from D-arabinose. Two independent routes towards the key intermediate **15** have been developed. The six-step sequence that involves the arabinopyranoside 2-triflate ring contraction process as a key step (Scheme 2) provided **15** in 32% overall yield with respect to the commercially available methyl β-D-arabinopyranoside (**2**). However, the alternative five-step sequence, based on the lactol **13** as a key intermediate (Scheme 3) furnished **15** in considerably higher overall yield (60% from D-arabinose). The intermediate **15** was finally converted to the target **1** by using the four-step sequence, which included the successive introduction of two azido groups at C-3 and C-4, with inversion of configuration at these positions, followed by a newly developed one-pot procedure for construction of the ureido system by using triphosgene, a safe and stable replacement of phosgene.[16] The overall yield of (+)-oxybiotin (**1**) from D-arabinose achieved via the lactol **13** as an intermediate was 22%. Finally, an X-ray diffraction analysis of **26** confirmed that its bicyclic moiety adopts an *endo* conformation, which is thought to be crucial for biological activity of (+)-biotin and analogues.[17]

4. Experimental

4.1. General methods

Melting points were determined on a Büchi 510 apparatus and were not corrected. Optical rotations were measured on a Polamat A (Zeiss, Jena) polarimeter. IR spectra were recorded with a Specord 75 IR spectrophotometer. NMR spectra were recorded on a Bruker AC 250 E instrument and chemical shifts are expressed in ppm downfield from tetramethylsilane. Low resolution mass spectra were recorded on Finnigan-MAT 8230 (CI) and VG AutoSpec (FAB) mass spectrometers. High-resolution mass spectra were taken on a Micromass LCT KA111 spectrometer. TLC was performed on DC Alufolien Kieselgel 60 F_{254} (E. Merck). Flash column chromatography was performed using ICN silica 32–63. All organic extracts were dried with anhydrous Na_2SO_4. Organic solutions were concentrated in a rotary evaporator under diminished pressure at a bath temperature below 35 °C.

4.1.1. Methyl 3,4-*O*-isopropylidene-β-D-arabinopyranoside (3). To a solution of **2** (1.37 g, 8.37 mmol) in dry DMF (12 mL) was added $Me_2C(OMe)_2$ (2.22 mL, 18.08 mmol) and TsOH×H_2O (0.015 g, 0.08 mmol). The mixture was stirred for 3.5 h at room temperature and then neutralized by stirring with Amberlite IRA-400 resin (3 g) at room temperature for 1 h. The mixture was filtered and the resin washed with MeOH. The combined organic solutions were evaporated to give pure **3** (1.52 g, 89%) as a colorless syrup, $[\alpha]_D$=−184.2 (*c*, 2.0 in $CHCl_3$), lit.[9] $[\alpha]_D$=−197.0 (*c*, 1.85 in $CHCl_3$), R_F=0.60 (EtOAc). ^{1}H NMR ($CDCl_3$): δ 1.35 and 1.52 (2×s, 3H each, Me_2C), 3.43 (s, 3H, OMe), 2.41 (d, 1H, exchangeable with D_2O, $J_{2,OH}$=7 Hz, OH), 3.74 (td, 1H, $J_{1,2}$=3.7 Hz, $J_{2,3}$=6.4 Hz, H-2), 3.92 (pseudo d, 2H, $J_{4,5}$=1.7 Hz, 2×H-5), 4.16 (t, 1H, $J_{3,4}$=6 Hz, H-3), 4.21 (m, 1H, H-4), 4.71 (d, 1H, H-1); ^{1}H NOE contact: OMe and H-5. ^{13}C NMR ($CDCl_3$): δ 25.94 and 27.92 (Me_2C), 55.61 (OMe), 59.24 (C-5), 70.12 (C-2), 72.95 (C-4), 76.00 (C-3), 98.84 (C-1), 109.14 (Me_2C).

4.1.2. Methyl 3,4-*O*-carbonyl-β-D-arabinopyranoside (4). A solution of **2** (0.149 g, 0.85 mmol) and *1*,*1*′-carbonyldiimidazole (0.157 g, 0.97 mmol) in dry benzene (3 mL) was stirred for 1.5 h at reflux. The mixture was evaporated and the residue was purified by flash column chromatography (3:2 EtOAc–CH_2Cl_2). Crystallization from CH_2Cl_2–hexane gave pure **4** (0.111 g, 69%) as colorless needles, mp 113–114 °C; lit.[10] mp 115–119 °C (L-enantiomer), $[\alpha]_D$=−142.7 (*c*, 0.79 in $CHCl_3$), R_F=0.31 (Et_2O). IR (KBr): ν_{max} 3410 (OH), 1800 (C=O). ^{1}H NMR (pyridine-d_5+D_2O): δ 3.33 (s, 3H, OMe), 4.18 (dd, 1H, $J_{1,2}$=3.7 Hz, $J_{2,3}$=7 Hz, H-2), 4.27 (s, 2H, 2×H-5), 5.10 (d, 1H, H-1), 5.28 (m, 2H, H-3 and H-4). ^{13}C NMR (pyridin-d_5): δ 55.82 (OMe), 58.30 (C-5), 69.14 (C-2), 76.41 and 78.37 (C-3 and C-4), 99.71 (C-1), 155.38 (C=O). FAB MS: *m*/*z* 191 (M^++H), 173 (M^+−OH), 159 (M^+−OMe).

4.1.3. Methyl 3,4-*O*-isopropylidene-2-*O*-trifluoromethanesulfonyl-β-D-arabinopyranoside (5). To a cooled (−10 °C) and stirred solution of **3** (1.34 g, 6.65 mmol) in dry CH_2Cl_2 (10 mL) and pyridine (2.66 mL, 32.92 mmol) was added a cooled (−10 °C) solution of Tf_2O (2.16 mL, 13.17 mmol) in dry CH_2Cl_2 (10 mL). The mixture was stirred at −10 °C for 0.5 h, then diluted with CH_2Cl_2 (20 mL) and washed successively with aq 5% HCl (2×25 mL) and 1% $NaHCO_3$ (25 mL). The organic solution was dried and evaporated. Flash column chromatography of the residue (1:1 CH_2Cl_2–cyclohexane) gave pure **5** (7.84 g, 70%) as a colorless solid. Recrystallization from CH_2Cl_2–hexane gave colorless crystals, mp 121–123 °C, $[\alpha]_D$=−176.6 (*c*, 0.5 in $CHCl_3$), R_F=0.50 (CH_2Cl_2). IR (KBr): ν_{max} 1415 (as. SO_2), 1225–1210 (sim. SO_2), 1125 (CF_3). ^{1}H NMR ($CDCl_3$): δ 1.37 and 1.53 (2×s, 3H each, Me_2C), 3.44 (s, 3H, OMe), 3.93 (dd, 1H, $J_{5a,5b}$=13.5 Hz, $J_{4,5a}$=2.6 Hz, H-5a), 4.03 (d, 1H, H-5b), 4.31 (dd, 1H, $J_{3,4}$=5.5 Hz, H-4), 4.38 (dd, 1H, $J_{2,3}$=7.6 Hz, H-3), 4.73 (dd, 1H, $J_{1,2}$=3.4 Hz, H-2), 4.88 (d, 1H, H-1). ^{13}C NMR ($CDCl_3$): δ 26.08 and 27.69 (Me_2C), 55.17 (C-5), 72.26 (C-3), 74.22 (C-4), 85.23 (C-2), 97.13 (C-1), 110.05 (Me_2C), 118.43 (q, $J_{C,F}$=319 Hz, CF_3). FAB MS: *m*/*z* 359 (M^++Na), 337 (M^++H).

4.1.4. Methyl 3,4-*O*-carbonyl-2-*O*-trifluoromethanesulfonyl-β-D-arabinopyranoside (6). A solution of **4** (0.326 g, 1.71 mmol) in dry CH_2Cl_2 (15 mL) and pyridine (0.7 mL, 8.66 mmol) was treated with Tf_2O (0.7 mL, 4.27 mmol) in dry CH_2Cl_2 (3 mL) under the above described conditions to give crude **6**. Flash column chromatography (CH_2Cl_2) afforded pure **6** (0.493 g, 89%) that crystallized from CH_2Cl_2–hexane in the form of colorless needles, mp 118–120 °C, $[\alpha]_D$=−148.2 (*c*, 0.89 in $CHCl_3$), R_F=0.47 (CH_2Cl_2). IR (KBr): ν_{max} 1800 (C=O), 1420 (as. SO_2), 1230–1210 (sim. SO_2), 1140 (CF_3). ^{1}H NMR ($CDCl_3$): δ 3.51 (s, 3H, OMe), 3.96 (dd, 1H, $J_{5a,5b}$=14.3 Hz, $J_{4,5a}$=2.7 Hz, H-5a), 4.17 (d, 1H, H-5b), 4.83 (dd, 1H, $J_{1,2}$=3.5 Hz, $J_{2,3}$=7.2 Hz, H-2), 4.89 (dd, 1H, $J_{3,4}$=6.9 Hz, H-4), 4.96 (t, 1H, H-3), 5.03 (d, 1H, H-1). ^{13}C NMR ($CDCl_3$): δ 56.46 (OMe), 56.86 (C-5), 73.12 (C-3), 75.29 (C-4), 81.55 (C-2), 96.03 (C-1), 118.32 (q, $J_{C,F}$= 320.4 Hz, CF_3SO_2), 152.65 (C=O). FAB MS: *m*/*z* 345 (M^++Na), 323 (M^++H). Anal. calcd for $C_8H_9F_3O_8S$: C, 29.82; H, 2.82; S, 9.95. Found: C, 30.06; H, 2.95; S, 10.33.

4.1.5. 2,5-Anhydro-1-*O*-benzoyl-3,4-*O*-isopropylidene-D-ribose methyl hemiacetal (7). *Procedure A*. To a solution of **5** (1.80 g, 5.35 mmol) in dry DMF (25 mL) was added KOBz (2.00 g, 12.49 mmol) and the resulting suspension was stirred at room temperature for 20 h. The solvent was evaporated and the residue partitioned between CH_2Cl_2 (50 mL) and water (50 mL). Organic phase was washed with water (2×50 mL), dried and evaporated. Flash column chromatography of the residue (4:1 CH_2Cl_2–toluene) gave pure **7** (1.31 g, 79%) as a colorless oil (an inseparable mixture of C-1 epimers).

Procedure B. A solution of **3** (5.50 g, 26.93 mmol) in CH_2Cl_2 (70 mL) and pyridine (11 mL, 136.14 mmol) was treated with Tf_2O (10.66 mL, 64.99 mmol) in CH_2Cl_2 (20 mL) according to procedure given in Section 4.1.4. to afford crude **5**. Treatment of crude **5** with KOBz (8.60 g, 53.40 mmol) in dry DMF (100 mL) for 20 h at room temperature, followed by the same workup as described above (Procedure A) gave **7** (8.20 g, 99%), as an inseparable 2:1 mixture of C-1 epimers, $[\alpha]_D$=−42.6 (*c*, 0.5 in $CHCl_3$), R_F=0.44 (CH_2Cl_2). IR (film): ν_{max} 1730 (C=O, ester), 1600 (Ph); ^{1}H NMR ($CDCl_3$): δ 1.38, 1.52 and 1.53 (3×s, 6H, CMe_2), 3.51 and 3.53 (2×s, 3H, OMe), 3.92–4.11 (m, 2H, 2×H-5), 4.21 and 4.29 (partially overlapped 2×dd, 1H, H-2), 4.82–5.05 (m, 2H, H-3 and H-4), 6.00 and 6.09 (2×d, 1H, H-1), 7.40–8.16 (m, 5H, Ph). FAB MS: *m*/*z* 331 (M^++Na), 309 (M^++H). HR MS (ES+): *m*/*z* 331.1157 (M^++Na). Calcd for $C_{16}H_{20}O_6Na$: 331.1158.

4.1.6. 2,5-Anhydro-1-*O*-benzoyl-3,4-*O*-carbonyl-D-ribose methyl hemiacetal (8). *Procedure A*. A mixture of **6** (0.203 g, 0.63 mmol) and KOBz (0.20 g, 1.25 mmol) in dry DMF (5 mL) was stirred for 2 h at 60–65 °C. After workup as described above (preparation of **7**) followed by chromatographic purification on a column of flash silica (9:1 CH_2Cl_2–toluene) gave pure **8** (0.161 g, 87%) as a colorless syrup (an inseparable mixture of C-1 epimers).

Procedure B. A solution of **4** (0.51 g, 2.68 mmol) in a mixture of CH_2Cl_2 (20 mL) and pyridine (2 mL, 24.75 mmol) was allowed to react with a solution of Tf_2O (1.32 mL, 8.05 mmol) in CH_2Cl_2 (5 mL) according to procedure B in Section 4.1.5 to afford crude **6**. A mixture of crude **6** and KOBz (0.861 g, 5.38 mmol) in dry DMF (20 mL), was stirred for 2 h at 60–65 °C. After workup as described above (preparation of **7**) followed by chromatographic purification on a column of flash silica (9:1 CH_2Cl_2–toluene) oily **8** was obtained (0.63 g, 80%), as a 1:1 mixture of C-1 epimers, $[\alpha]_D$=−16.7 (*c*, 0.70 in $CHCl_3$), R_F=0.54 (CH_2Cl_2). IR (film): ν_{max} 1810 (C=O, carbonate), 1730 (C=O, BzO), 1600 (Ph). ^{1}H NMR ($CDCl_3$): δ 3.51 and 3.52 (2×s, 3H, OMe), 4.09–4.23 (m, 2H, 2×H-5), 4.40 and 4.51 (2×d, 1H, $J_{1,2}$=3 Hz, H-2), 5.29 (m, 1H, H-4), 5.41 and 5.49 (2×d, 1H, $J_{3,4}$=7.1, 7 Hz, H-3), 6.06 and 6.13 (2×d, 1H, H-1), 7.40–8.15 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 57.61 and 57.66 (OMe), 73.76 and 74.04 (C-5), 80.54, 80.66 and 81.00 (C-3 and C-4), 83.91 and 84.04 (C-2), 97.28 and 97.39 (C-1), 128.50, 128.59, 128.71, 129.69, 129.81, 129.94, 133.84 and 133.94 (Ph), 154.00 (C=O, carbonate), 165.42 and 165.58 (C=O, BzO). FAB MS: *m*/*z* 317 (M^++Na), 295 (M^++H). HR MS (ES+): *m*/*z* 317.0640 (M^++Na). Calcd for $C_{14}H_{14}O_7Na$: 317.0637.

4.1.7. 2,5-Anhydro-3,4-*O*-isopropylidene-D-ribose dimethyl acetal (9). A suspension of **5** (3.90 g, 11.60 mmol) and $NaHCO_3$ (1.20 g, 14.29 mmol) in dry MeOH (35 mL), was stirred for 4 h at 50 °C. The mixture was cooled to ambient temperature, diluted with Et_2O (15 mL), filtered and evaporated to an oil. Flash column chromatography (17:3 toluene–Et_2O) of the residue gave pure **9** (0.29 g, 12%) as a colorless oil, $[\alpha]_D$=−21.0 (*c*, 1.02 in $CHCl_3$), R_F=0.36 (CH_2Cl_2). IR (film): ν_{max} 1100–1050 (C–O–C). ^{1}H NMR (1:1 $CDCl_3$–benzene-d_6): δ 1.22 and 1.46 (2×s, 3H each, Me_2C), 3.20 and 3.22 (2×s, 3H each, 2×OMe), 3.88 (dd, 1H, $J_{4,5a}$=4.2 Hz, $J_{5a,5b}$=9.9 Hz, H-5a), 3.94 (dd, 1H, $J_{4,5b}$=1.1 Hz, H-5b), 4.09 (bs, 2H, H-1 and H-2), 4.57 (ddd, 1H, $J_{3,4}$=6.3 Hz, H-4), 4.77 (d, 1H, H-3). ^{13}C NMR (1:1 $CDCl_3$–benzene-d_6): δ 24.60 and 26.42 (Me_2C), 54.68 and 55.66 (2×OMe), 74.06 (C-5), 81.32

(C-4), 81.48 (C-3), 84.46 (C-2), 104.98 (C-1), 112.07 (CMe_2). FAB MS: *m/z* 241 (M^++Na), 225 (M^++Na+H-Me), 217 (M^+−H). HR MS (ES+): *m/z* 241.1054 (M^++Na). Calcd for $C_{10}H_{18}O_5Na$: 241.1052.

4.1.8. Methyl 2,3-anhydro-β-D-ribopyranoside (10). To a solution of **6** (0.218 g, 0.68 mmol) in dry MeOH (5 mL) was added $NaHCO_3$ (0.07 g, 0.83 mmol) and the resulting suspension was stirred at 55–60 °C for 3 h, then filtered and evaporated. Flash column chromatography (9:1 CH_2Cl_2–EtOAc) of the residue gave pure **10** (0.076 g, 77%). Crystallization from CH_2Cl_2–hexane furnished colorless crystals, mp 51 °C, $[\alpha]_D$=−53.2 (*c*, 0.5 in $CHCl_3$); lit.[11] mp 46 °C, $[\alpha]_D$=−35.8 (*c*, 0.6 in $CHCl_3$), R_F=0.47 (Et_2O). IR (KBr): ν_{max} 3440–3300 (OH). ^{1}H NMR ($CDCl_3$): δ 2.64 (d, 1H, exchangeable with D_2O, $J_{4,OH}$=11.3 Hz, OH), 3.21 (d, 1H, $J_{2,3}$=3.8 Hz, H-2), 3.41 (dt, 1H, $J_{5a,5b}$=12.5 Hz, $J_{4,5a}$=1.3 Hz, $J_{3,5a}$=1 Hz, H-5a), 3.46 (s, 3H, OMe), 3.54 (bt, 1H, $J_{3,4}$=4.5 Hz, H-3), 3.77 (dd, 1H, $J_{4,5b}$=3 Hz, H-5b), 3.90 (m, 1H, H-4), 4.84 (s, 1H, H-1). ^{13}C NMR ($CDCl_3$): δ 51.68 (C-2 and C-3), 55.70 (OMe), 61.60 and 61.65 (C-4 and C-5), 95.34 (C-1). FAB MS: *m/z* 147 (M^++H).

4.1.9. 3,4-*O*-Isopropylidene-2-*O*-methanesulfonyl-β-D-arabinopyranosyl chloride (12). To a stirred and cooled (−10 °C) solution of **11**[8] (1.15 g, 6.05 mmol) in a mixture of dry CH_2Cl_2 (12 mL) and Et_3N (2.53 mL, 18.15 mmol) was added dropwise a solution of MsCl (1.17 mL, 15.12 mmol) in CH_2Cl_2 (3.5 mL). The mixture was stirred for 1 h at −10 °C, then diluted with CH_2Cl_2 (20 mL), and washed successively with cold (+4 °C) aq 5% HCl (2×40 mL) and 1% $NaHCO_3$ (20 mL). Organic phase was dried and evaporated to a pale yellow solid. Flash column chromatography (CH_2Cl_2) gave pure **12** (1.52 g, 88%). Recrystallization from CH_2Cl_2–hexane gave colorless crystals, mp 129–131 °C (decomposition), $[\alpha]_D$=−205.3 (*c*, 1.0 in $CHCl_3$), R_F=0.40 (CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 1.39 and 1.59 (2×s, 3H each, Me_2C), 3.19 (s, 3H, $MeSO_2$), 4.18–4.38 (m, 3H, 2×H-5 and H-4), 4.43 (dd, 1H, $J_{2,3}$=7.6 Hz, $J_{3,4}$=4.9 Hz, H-3), 4.75 (dd, 1H, $J_{1,2}$=3.7 Hz, H-2), 6.13 (d, 1H, H-1). ^{13}C NMR ($CDCl_3$): δ 26.13 and 27.86 (Me_2C), 38.75 ($MeSO_2$), 61.12 (C-5), 72.37 (C-3), 73.03 (C-4), 78.11 (C-2), 90.92 (C-1), 110.11 (Me_2C). CI MS: *m/z* 536 ($2M^+$−Cl), 287 (M^++H), 251 (M^+−Cl).

4.1.10. 3,4-*O*-Isopropylidene-2-*O*-methanesulfonyl-D-arabinopiranose (13). To a solution of **11** (3.00 g, 15.77 mmol) in dry CH_2Cl_2 (25 mL) and Et_3N (9.10 mL, 65.29 mmol) was added dropwise a solution of MsCl (4 mL, 51.58 mmol) in dry CH_2Cl_2 (12 mL). The mixture was stirred at −10 °C for 1 h. After workup as described above (procedure in Section 4.1.9), crude **12** was dissolved in Me_2CO (40 mL) and cooled to 0 °C. To the solution were added Ag_2O (3.70 g, 15.97 mmol), AgOTf (0.30 g, 1.17 mmol), and water (2 mL). The mixture was allowed to warm to room temperature and then stirred for the next 20 h. The reaction mixture was diluted with EtOAc (20 mL), filtered through a Celite pad and evaporated. Flash column chromatography (EtOAc) of the residue gave pure **13** (4.00 g, 95%), as a colorless syrup. Crystallization from a mixture of EtOAc–light petroleum furnished colorless crystals, mp 112–114 °C. Recrystallization from Et_2O gave an analytical sample **13**, mp 116–117 °C, $[\alpha]_D$=−116.5 (*c*, 1.5 in $CHCl_3$), lit.[9] mp 130–131 °C, $[\alpha]_D$=−118.0 (*c*, 2.06 in Me_2CO), R_F=0.70 (EtOAc). IR (KBr): ν_{max} 3420 (OH), 1360 (as. SO_2), 1190 (sim. SO_2). ^{1}H NMR ($CDCl_3$): δ 1.38 and 1.58 (2×s, 3H each, Me_2C), 3.18 (s, 3H, $MeSO_2$), 3.83 (dd, $J_{5a,5b}$=14.1 Hz, $J_{4,5a}$=2.5 Hz, H-5aα), 3.97 (d, 1H, $J_{5a,5b}$=13.3 Hz, H-5aβ), 4.14–4.33 (m, 2H, H-4αβ, H-5bαβ), 4.40 (dd, 1H, $J_{2,3}$=7.8 Hz, $J_{3,4}$=5.4 Hz, H-2α and H-3β), 4.56 (dd, 1H, $J_{1,2}$=3.3 Hz, H-2β), 4.61 (d, 1H, $J_{1,2}$=7.9 Hz, H-1α), 5.35 (d, 1H, H-1β). ^{13}C NMR ($CDCl_3$): δ 26.25 and 27.99 (Me_2C, α), 26.24 and 27.80 (Me_2C, β), 38.66 ($MeSO_2$, β), 39.06 ($MeSO_2$, α), 58.4 (C-5, β), 63.28 (C-5, α), 72.98 (C-3), 73.83 (C-4), 80.01 (C-2, β), 83.42 (C-2, α), 90.94 (C-1, β), 93.91 (C-1, α), 109.84 (Me_2C, β), 110.84 (Me_2C, α). FAB MS: *m/z* 518 ($2M^+$−H_2O), 269 (M^++H), 251 (M^+−OH). HR MS (ES+): *m/z* 286.0960 (M^++NH_4). Calcd for $C_9H_{20}NO_7S$: 286.0960.

4.1.11. *E,E*−2*S*-(4′-Methoxycarbonyl-1′,3′-butadienyl)-3*S*,4*R*-*O*-isopropylidene-tetrahydrofuran (14). To a stirred solution of **13** (0.54 g, 2.01 mmol) and trimethyl-4-phosphonocrotonate (0.46 g, 2.21 mmol) in dry THF (20 mL) was added NaH (0.136 g, 5.67 mmol) in portions during 5 min. The mixture was stirred at room temperature for 20 min then filtered, diluted with Et_2O (20 mL) and evaporated. Flash column chromatography (19:1 CH_2Cl_2–EtOAc) of the residue gave pure *E,E*-isomer **14** (0.246 g, 48%) as a colorless solid. Recrystallization from CH_2Cl_2–hexane gave an analytical sample *E,E*-**14** as colorless needles, mp 75 °C, $[\alpha]_D$=−108.2 (*c*, 0.88 in $CHCl_3$), R_F=0.29 (CH_2Cl_2). IR (KBr): ν_{max} 1710 (C=O, ester), 1650 and 1630 (CH=CH–CH=CH). ^{1}H NMR ($CDCl_3$): δ 1.32 and 1.51 (2×s, 3H each, Me_2C), 3.73 (s, 3H, CO_2Me), 3.83 (dd, 1H, $J_{5a,5b}$=10.7 Hz, $J_{4,5a}$=4.2 Hz, H-5a), 3.99 (dd, 1H, $J_{4,5b}$=1 Hz, H-5b), 4.58 (dd, 1H, $J_{2,3}$=1.7 Hz, $J_{3,4}$=6.2 Hz, H-4), 4.62 (ddd, 1H, $J_{2,2'}$=1.8 Hz, $J_{2,1'}$=4.6 Hz, H-2), 4.77 (dd, 1H, H-3), 5.88 (d, 1H, $J_{3',4'}$=15.4 Hz, H-4′), 5.97 (dd, 1H, $J_{1',2'}$=15.5 Hz, H-1′), 6.39 (ddd, 1H, $J_{2',3'}$=11 Hz, H-2′), 7.24 (dd, 1H, H-3′). ^{13}C NMR ($CDCl_3$): δ 24.91 and 26.48 (Me_2C), 51.53 (CO_2Me), 72.53 (C-5), 80.84 (C-4), 83.92 (C-2), 84.76 (C-3), 112.90 (Me_2C), 121.75 (C-4′), 128.83 (C-2′), 138.02 (C-1′), 143.23 (C-3′), 167.09 (CO_2Me). FAB MS: *m/z* 277 (M^++Na), 255 (M^++H). HR MS (ES+): *m/z* 277.1052 (M^++Na). Calcd for $C_{13}H_{18}O_5Na$: 277.1052. Anal. calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.52; H, 6.97.

4.1.12. 2*S*-(4′-Methoxycarbonyl-1′-butyl)-3*S*,4*R*-*O*-isopropylidene-tetrahydrofuran (15). *Procedure A*. To a solution of **7** (0.85 g, 2.76 mmol) in anhydrous MeOH (35 mL) was added 0.15 M NaOMe in MeOH (3.5 mL) and the mixture was stirred for 2 h at room temperature. 3-(methoxycarbonyl-2-propenylidene)triphenylphosphorane[14] (1.49 g, 4.14 mmol) was added to the solution and the reaction mixture was stirred at room temperature for additional 2 h and then evaporated. Chromatographic purification on a column of flash silica (7:3 light petroleum–Et_2O) afforded pure **14** (0.29 g) as an inseparable mixture of *E*- and *Z*-isomers. A solution of **14** (0.29 g, 1.14 mmol) in MeOH (20 mL) was hydrogenated over PtO_2 (0.03 g) for 24 h at room temperature. The mixture was filtered and the catalyst washed with MeOH. The organic

solution was evaporated. and the residue was purified by flash chromatography (9:1 CH_2Cl_2–EtOAc) to afford pure **15** (0.26 g, 36%) as a colorless oil.

Procedure B. To a solution of **13** (0.15 g, 0.56 mmol) in anhydrous DMF (6 mL) was added 3-(methoxycarbonyl-2-propenylidene)triphenylphosphorane[14] (0.28 g, 0.78 mmol) and anh Na_2CO_3 (0.50 g, 4.72 mmol). The mixture was stirred for 2 h at 110–120 °C, then poured in water (100 mL) and extracted with Et_2O (3×30 mL). The extracts were combined and evaporated. Flash column chromatography (7:3 light petroleum–ether) of the residue gave an inseparable mixture of *E*- and *Z*-isomers **14** (0.115 g, 81%). A solution of **14** (0.115 g, 1.14 mmol) in MeOH (6 mL) was hydrogenated over PtO_2 (0.01 g) by using the same methodology as described in the Procedure A, to afford pure **15** (0.127 g, 88%) as a colorless oil, $[\alpha]_D$=−30.7 (*c*, 0.90 in $CHCl_3$), R_F=0.32 (CH_2Cl_2). IR (KBr): ν_{max} 1735 (C=O, ester). ^{1}H NMR ($CDCl_3$): δ 1.24 and 1.41 (2×s, 3H each, Me_2C), 1.28–1.67 (m, 6H, 3×CH_2), 2.23 (t, 2H, C$H_2$$CO_2$Me), 3.58 (s, 3H, CO_2Me), 3.72, (dd, 1H, $J_{5a,5b}$=10.6 Hz, $J_{4,5a}$=4.2 Hz, H-5a), 3.81 (dd, 1H, $J_{4,5b}$=1.7 Hz, H-5b), 3.89 (m, 1H, $J_{2,3}$=1.7 Hz, H-2), 4.32 (dd, 1H, $J_{3,4}$=6.3 Hz, H-3), 4.69 (ddd, 1H, H-4). ^{13}C NMR ($CDCl_3$): δ 24.76 and 26.40 (*Me*$_2$C), 24.44, 25.09 and 30.18 (3×CH_2), 33.64 (*C*$H_2$$CO_2$Me), 51.24 ($CO_2$*Me*), 71.28 (C-5), 80.71 (C-4), 83.87 (C-2), 84.70 (C-3), 112.50 (Me$_2$*C*), 173.68 (*C*O_2Me). FAB MS (ES+): *m*/*z* 281 (M^++Na). HR MS (ES+): *m*/*z* 281.1363 (M^++Na). Calcd for $C_{13}H_{22}O_5Na$: 281.1365.

4.1.13. 2*S*-(4′-Methoxycarbonyl-1′-butyl)-3*S*,4*R*-dihydroxy-tetrahydrofuran (16). A solution of **15** (0.316 g, 1.22 mmol) in aq 90% TFA (2 mL) was stirred for 1 h at room temperature. The mixture was evaporated by co-distillation with toluene (3×5 mL) to a yellow oil. Flash column chromatography (EtOAc) of the residue gave pure **16** (0.253 g, 95%) as a colorless oil, $[\alpha]_D$=−39.4 (*c*, 1.0 in $CHCl_3$), R_F=0.26 (Et_2O). IR (film): ν_{max} 3380 (OH), 1370 (C=O, ester). ^{1}H NMR ($CDCl_3$): δ 1.38–1.65 (m, 6H, 3×CH_2), 2.35 (t, 2H, *C*$H_2$$CO_2$Me), 3.62 (s, 3H, CO_2Me), 3.6–3.8 (m, 5H, 2×OH, H-2, H-3 and H-5a), 4.04 (dd, 1H, $J_{5a,5b}$=9.9 Hz, $J_{4,5b}$=5.2 Hz, H-5b), 4.19 (m, 1H, $J_{4,5a}$=4.6 Hz, H-4). ^{13}C NMR ($CDCl_3$): δ 24.67, 25.19 and 32.74 (3×CH_2), 33.79 (*C*$H_2$$CO_2$Me), 51.52 ($CO_2$*Me*), 70.81 (C-4), 72.44 (C-5), 75.64 (C-2), 81.85 (C-3). CI MS: *m*/*z* 219 (M^++H). FAB MS (ES+): *m*/*z* 241 (M^++Na). HR MS (ES+): *m*/*z* 241.1057 (M^++Na). Calcd for $C_{10}H_{18}O_5Na$: 241.1052.

4.1.14. 2*S*-(4′-Methoxycarbonyl-1′-butyl)-3*S*,4*R*-*bis*-trifluoromethanesulfonyloxi-tetrahydrofuran (17). To a stirred and cooled (−10 °C) solution of **16** (0.43 g, 1.97 mmol) in a mixture of dry CH_2Cl_2 (17 mL) and pyridine (0.80 mL, 9.9 mmol) was added dropwise a cooled (−10 °C) solution of Tf_2O (0.69 mL, 4.21 mmol) in dry CH_2Cl_2 (7 mL). The mixture was stirred at 0 °C for 1.5 h, then diluted with CH_2Cl_2 (20 mL) and washed successively with aq 5% HCl (2×25 mL), 1% $NaHCO_3$ (25 mL) and water (25 mL). The organic solution was separated, dried and evaporated to a yellow oil. Flash column chromatography (CH_2Cl_2) of the residue gave pure **17** (0.48 g, 51%) as a colorless oil, $[\alpha]_D$=−35.9 (*c*, 2.25 in $CHCl_3$), R_F=0.68 (CH_2Cl_2). IR (film): 1730 (C=O, ester), 1420 (as. SO_2), 1240–1205 (sim. SO_2), 1130 (CF_3). ^{1}H NMR ($CDCl_3$): δ 1.37–1.83 (m, 6H, 3×CH_2), 2.31 (t, 2H, C$H_2$$CO_2$Me), 3.65 (s, 3H, CO_2Me), 4.03 (dd, 1H, $J_{5a,5b}$=11.2 Hz, $J_{4,5a}$=4.2 Hz, H-5a), 4.09 (m, 1 H, *J*=6.7 Hz, H-2), 4.32 (dd, 1H, $J_{4,5b}$=5.3 Hz, H-5b), 4.88 (t, 1H, $J_{3,4}$=6.1 Hz, H-3), 5.34 (m, 1H, H-4). ^{13}C NMR ($CDCl_3$): δ 24.40, 24.61 and 31.38 (3×CH_2), 33.59 (*C*$H_2$$CO_2$Me), 51.43 ($CO_2$*Me*), 69.24 (C-5), 79.23 (C-2), 81.42 (C-4), 83.66 (C-3), 118.19 (q, $J_{C,F}$=319.5 Hz, 2×CF_3SO_2), 173.69 (C=O). HR MS (EI): *m*/*z* 482.0163 (M^+). Calcd for $C_{12}H_{16}F_6O_9S_2$: 482.0140.

4.1.15. 2*S*-(4′-Methoxycarbonyl-1′-butyl)-3*S*,4*R*-diazido-tetrahydrofuran (18). *Procedure A*. To a solution of **17** (0.40 g, 0.83 mmol) in HMPA (4 mL) was added NaN_3 (1.50 g, 23.08 mmol) and the resulting suspension was stirred for 1.5 h at room temperature. The mixture was poured in water (30 mL) and extracted with 1:1 benzene–light petroleum (4×20 mL). Organic phase was washed with H_2O (2×20 mL), dried and evaporated to a yellow oil. Flash column chromatography (CH_2Cl_2) of the residue gave pure **18** (0.207 g, 93%) as a pale yellow oil.

Procedure B. A solution of **16** (0.56 g, 2.57 mmol) in dry CH_2Cl_2 (40 mL) and pyridine (2.08 mL, 25.74 mmol) was treated with Tf_2O (2.53 mL, 15.42 mmol) in dry CH_2Cl_2 (10 mL) under the same reaction conditions as described in procedure under Section 4.1.14. The workup as described above yielded crude **17**, which was immediately dissolved in HMPA (20 mL), and treated with NaN_3 (4.70 g, 72.31 mmol) according to the procedure 4.1.15A. Thus obtained crude mixture was purified by flash chromatography (4:1 light petroleum–EtOAc) to afford pure **18** (0.467 g, 68%) as a bright yellow oil, $[\alpha]_D$=+36.0 (*c*, 1.95 in $CHCl_3$), R_F=0.28 (CH_2Cl_2). IR (film): ν_{max} 2100 (N_3), 1740 (C=O, ester). ^{1}H NMR ($CDCl_3$): δ 1.29–1.78 (m, 6H, 3×CH_2), 2.33 (t, 2H, C$H_2$$CO_2$Me), 3.66 (s, 3H, CO_2Me), 3.78 (dd, 1H, $J_{5a,5b}$=9.1 Hz, $J_{4,5a}$=7.2 Hz, H-5a), 3.88 (m, 1H, $J_{1'a,2}$=5.8 Hz, $J_{1'b,2}$=7.3 Hz, $J_{2,3}$=3.4 Hz, H-2), 3.95–4.05 (m, 2H, $J_{3,4}$=7.7, $J_{4,5b}$=4 Hz, H-3 and H-5b), 4.25 (td, 1H, H-4). ^{13}C NMR ($CDCl_3$): δ 24.76, 25.47 and 29.68 (3×CH_2), 33.72 (*C*$H_2$$CO_2$Me), 51.46 ($CO_2$*Me*), 62.96 (C-4), 65.24 (C-3), 68.52 (C-5), 80.78 (C-2), 173.87 (*C*O_2Me). CI MS: *m*/*z* 269 (M^++H). FAB MS (ES+): *m*/*z* 291 (M^++Na). HR MS (ES+): *m*/*z* 291.1174 (M^++Na). Calcd for $C_{10}H_{16}N_6O_3Na$: 291.1182.

4.1.16. Methyl 2,3-anhydro-4-*O*-methanesulfonyl-β-D-ribopyranoside (19). To a stirred and cooled solution (−10 °C) of **10** (0.97 g, 6.65 mmol) in dry CH_2Cl_2 (20 mL) was added Et_3N (1.8 mL, 12.91 mmol) and a solution of MsCl (0.8 mL, 10.32 mmol) in CH_2Cl_2 (3 mL). Stirring was continued for 0.5 h at −10 °C and the mixture diluted with CH_2Cl_2 (10 mL), washed successively with aq 5% HCl (2×30 mL), satd aq $NaHCO_3$ (20 mL) and water (20 mL). The organic solution was dried and evaporated to yellow syrup. Flash column chromatography (19:1 CH_2Cl_2–EtOAc) of the residue gave pure **19** (1.45 g, 97%) as a solid, which upon crystallization from CH_2Cl_2–hexane gave colorless needles, mp 90 °C, $[\alpha]_D$=−19.2 (*c*, 0.5 in $CHCl_3$), R_F=0.52 (Et_2O). IR (KBr): ν_{max} 1350 (as. SO_2), 1190–1170 (sim. SO_2). ^{1}H NMR ($CDCl_3$): δ 3.16 (s, 3H, $MeSO_2$), 3.22 (d, 1H, $J_{2,3}$=3.7 Hz, H-2), 3.46 (s, 3H, OMe),

3.57–3.67 (m, 2H, $J_{3,4}$=4.3 Hz, $J_{4,5a}$=2.4 Hz, $J_{5a,5b}$=13.5 Hz, H-3 and H-5a), 3.92 (dd, 1H, $J_{4,5b}$=4.1 Hz, H-5b), 4.87 (s, 1H, H-1), 4.97 (td, 1H, H-4). ^{13}C NMR ($CDCl_3$): δ 38.72 ($MeSO_2$), 48.88 (C-3), 51.19 (C-2), 56.02 (OMe), 58.41 (C-5), 70.71 (C-4), 95.15 (C-1). FAB MS: *m/z* 247 (M^++Na), 225 (M^++H), 193 (M^+−OMe). Anal. calcd for $C_7H_{12}O_6S$: C, 37.49; H, 5.39; S, 14.30. Found: C, 37.65; H, 5.57; S, 14.56.

4.1.17. Methyl 2,3-anhydro-4-azido-4-deoxy-α-L-lyxopyranoside (20). To a solution of **19** (0.25 g, 1.12 mmol) in dry DMF (10 mL) was added NaN_3 (0.755 g, 11.62 mmol). The mixture was stirred at 90–95 °C for 0.5 h and then at 110–115 °C for additional 15 min. The mixture was evaporated and extracted with EtOAc (30 mL). Organic phase was filtered, washed with water (2×20 mL), dried and evaporated. The residue was purified by flash chromatography (3:2 light petroleum–EtOAc) to give pure **20** (0.107 g, 56%) as a colorless oil, $[\alpha]_D$=−91.8 (*c*, 0.8 in $CHCl_3$), R_F=0.66 (CH_2Cl_2). IR (film): ν_{max} 2120 (N_3). ^{1}H NMR ($CDCl_3$): δ 3.11 (d, 1H, $J_{2,3}$=3.7 Hz, H-3), 3.33 (dd, 1H, $J_{3,5b}\approx$0.7 Hz, H-2), 3.46 (s, 3H, OMe), 3.52 (dd, 1H, $J_{4,5a}$=9.1 Hz, $J_{5a,5b}$=11.4 Hz, H-5a), 3.62 (ddd, 1H, $J_{4,5b}$=5.8 Hz, H-5b), 3.75 (s, 1H, H-1), 4.79 (s, 1H, H-4). ^{13}C NMR ($CDCl_3$): δ 49.98 (C-3), 52.29 (C-4), 52.56 (C-2), 55.91 (OCH_3), 57.44 (C-5), 99.79 (C-1). FAB MS: *m/z* 194 (M^++Na), 172 (M^++H). Further elution of the column gave 3,4-diazido derivative **22** (0.042 g, 18%) as a minor product.

4.1.18. Methyl 3,4-diazido-3,4-dideoxy-α-L-arabinopyranoside (22) and methyl 2,4-diazido-2,4-dideoxy-α-L-xylopyranoside (21). To a solution of **19** (0.63 g, 2.83 mmol) in dry DMF (30 mL) was added NaN_3 (1.84 g, 28.31 mmol) and the resulting suspension was stirred at 140–145 °C for 3.5 h. The workup as described above, followed by flash column chromatography (4:1→3:2 light petroleum–EtOAc), gave two fractions. The first fraction contained pure **21** (0.025 g, 4%), which crystallized from CH_2Cl_2–hexane as colorless crystals, mp 124 °C, $[\alpha]_D$=−202.1 (*c*, 0.5 in $CHCl_3$), R_F=0.55 (9:1 CH_2Cl_2–EtOAc). IR (KBr): ν_{max} 3480 (OH), 2130 (N_3). ^{1}H NMR ($CDCl_3$): δ 3.01 (bd, 1H, exchangeable with D_2O, $J_{3,OH}$=2.4 Hz, OH), 3.26 (dd, 1H, $J_{1,2}$=3.5 Hz, $J_{2,3}$=10.1 Hz, H-2), 3.42 (s, 3H, OMe), 3.46–3.79 (m, 3H, $J_{3,4}$=8.9 Hz, $J_{4,5a}$=7 Hz, $J_{4,5b}$=3.6 Hz, 2×H-5 and H-4), 3.96 (bt, 1H, H-3), 4.78 (d, 1H, H-1). ^{13}C NMR ($CDCl_3$): δ 55.47 (OMe), 59.49 (C-5), 61.90 (C-4), 63.41 (C-2), 71.03 (C-3), 98.76 (C-1). CI MS: *m/z* 215 (M^++H). Anal. calcd for $C_6H_{10}N_6O_3$: C, 33.65; H, 4.71; N, 39.24. Found: C, 33.96; H, 5.06; N, 38.89. Pure **22** (0.306 g, 51%) was then eluted, which crystallized from CH_2Cl_2–hexane as colorless needless, mp 91 °C, $[\alpha]_D$=−17.0 (*c*, 0.5 in $CHCl_3$), R_F=0.37 (9:1 CH_2Cl_2–EtOAc). IR (KBr): ν_{max} 3450 (OH), 2170 and 2120 (N_3). ^{1}H NMR ($CDCl_3$): δ 2.90 (bs, 1H, exchangeable with D_2O, OH), 3.55 (s, 3H, OMe), 3.60 (dd, 1H, $J_{5a,5b}$=12.8 Hz, $J_{4,5a}$=1.6 Hz, H-5a), 3.62 (dd, 1H, $J_{2,3}$=9.8 Hz, $J_{3,4}$=3.8 Hz, H-3), 3.80 (dd, 1H, $J_{1,2}$=7.2 Hz, H-2), 3.81 (m, 1H, $J_{4,5b}$=2.2 Hz, H-4), 4.06 (dd, 1H, H-5b), 4.13 (d, 1H, H-1). ^{13}C NMR ($CDCl_3$): δ 55.47 (OMe), 59.49 (C-5), 61.90 (C-4), 63.41 (C-2), 71.03 (C-3), 98.76 (C-1). FAB MS: *m/z* 215 (M^++H), 172 (M^+−N_3). Anal. calcd for $C_6H_{10}N_6O_3$: C, 33.65; H, 4.72; N, 39.24. Found: C, 34.05; H, 4.72; N, 38.88.

4.1.19. Methyl 3,4-diazido-3,4-dideoxy-2-*O*-*tert*-butyldimethylsilyl-α-L-arabinopyranoside (23). To a stirred solution of **22** (0.27 g, 1.26 mmol) in dry DMF (11 mL) were added *tert*-$BuMe_2SiCl$ (0.81 g, 5.37 mmol) and imidazole (0.373 g, 5.48 mmol). The mixture was stirred for 24 h at room temperature and then evaporated. Flash column chromatography (9:1 light petroleum–EtOAc) of the residue gave pure **23** (0.403 g, 97%) as a colorless syrup, $[\alpha]_D$=−12.8 (*c*, 0.5 in $CHCl_3$), R_F=0.76 (CH_2Cl_2). IR (film): ν_{max} 2120 (N_3). ^{1}H NMR ($CDCl_3$): δ 0.11 and 0.16 (2×s, 3H each, Me_3CSiMe_2), 0.91 (s, 9H, Me_3CSiMe_2), 3.47 (s, 3H, OMe), 3.50 (dd, 1H, $J_{2,3}$=8.6 Hz, $J_{3,4}$=3.6 Hz, H-3), 3.58 (dd, 1H, $J_{4.5a}$=1.6 Hz, $J_{5a,5b}$=12.5 Hz, H-5a), 3.68 (dd, 1H, $J_{1,2}$=6.3 Hz, H-2), 3.88 (m, 1H, $J_{4,5b}$=3.3 Hz, H-4), 4.01 (dd, 1H, H-5b), 4.09 (d, 1H, H-1). ^{13}C NMR ($CDCl_3$): δ −5.08 and −4.48 (Me_3CSiMe_2), 18.09 (Me_3CSiMe_2), 25.64 (Me_3CSiMe_2), 56.69 (OMe), 59.49 (C-4), 63.20 (C-5), 65.66 (C-3), 70.93 (C-2), 104.58 (C-1). FAB MS (ES+): *m/z* 351 (M^++Na). HR MS (ES+): *m/z* 351.1593 (M^++Na). Calcd for $C_{12}H_{24}N_6O_3SiNa$: 351.1577.

4.1.20. Methyl 3,4-diamino-3,4-dideoxy-2-*O*-*tert*-butyldimethylsilyl-α-L-arabinopyranoside (24) and the corresponding oxalate (24×$H_2C_2O_4$). To a solution of **23** (0.229 g, 0.70 mmol) in dry THF (4 mL) was added Ph_3P (0.46 g, 1.75 mmol). The mixture was stirred for 3 h at room temperature. To the reaction mixture was added water (0.3 mL) and $NaHCO_3$ (0.06 g, 0.71 mmol), and the stirring at ambient temperature was continued for the next 24 h. The mixture was evaporated and the residue was purified on a column of flash silica (4:1 EtOAc–MeOH) to give pure **24** (0.121 g, 63%) as a colorless oil, $[\alpha]_D$=−26.6 (*c*, 0.4 in $CHCl_3$), R_F=0.18 (4:1 EtOAc–MeOH). IR (film): ν_{max} 3390–3300 (NH_2). ^{1}H NMR ($CDCl_3$): δ 0.06 and 0.07 (2×s, 3H each, Me_3CSiMe_2), 0.86 (s, 9H, Me_3CSiMe_2) 2.42 (bs, 4H, 2×NH_2), 2.76 (dd, 1H, $J_{2,3}$=7.7 Hz, $J_{3,4}$=3.9 Hz, H-3), 3.05 (m, 1H, $J_{4,5a}$=6 Hz, $J_{4,5b}$=4.5 Hz, H-4), 3.37 (dd, 1H, $J_{1,2}$=5.7 Hz, H-2), 3.41 (s, 3H, OMe), 3.52 (dd, 1H, $J_{5a,5b}$=11.8 Hz, H-5a), 3.71 (dd, 1H, H-5b), 4.06 (d, 1H, H-1). ^{13}C NMR ($CDCl_3$): δ −4.96 and −4.42 (Me_3CSiMe_2), 18.14 (Me_3CSiMe_2), 25.82 (Me_3CSiMe_2), 49.04 (C-4), 55.86 (C-3), 56.22 (OMe), 66.14 (C-5), 73.34 (C-2), 104.44 (C-1). A portion of **24** was converted to the corresponding oxalic acid salt (**24**×$H_2C_2O_4$) by using the following procedure: To a solution of **24** (0.055 g, 0.2 mmol) in dry EtOH (2 mL) was added a solution of oxalic acid (0.02 g, 0.22 mmol) in dry EtOH (1 mL). The mixture was stirred at room temperature for 4 h and then stored at +4 °C for 20 h to yield colorless crystals of pure **24**×$H_2C_2O_4$ (0.051 g, 70%). Recrystallization from EtOH gave an analytical sample as colorless needles, mp 164 °C, $[\alpha]_D$=−24.2 (*c*, 0.2 in H_2O). IR (KBr): ν_{max} 3450–2320 (NH_3^+), 1650 (C=O, oxalate). ^{1}H NMR (D_2O): δ 0.24 (s, 6H, Me_3CSiMe_2), 0.97 (s, 9H, Me_3CSiMe_2), 3.59 (s, 3H, OMe), 3.73 (m, 1H, H-2), 3.93–4.11 (m, 4H, H-3, H-4, and 2×H-5), 4.62 (d, 1H, $J_{1,2}$=4.4 Hz, H-1). Anal. calcd for $C_{14}H_{30}N_2O_7Si$: C, 45.88; H, 8.25, N, 7.64. Found: C, 46.08; H, 8.26, N, 7.32.

4.1.21. Methyl 3,4-dideoxy-3,4-carbonyldiamino-2-*O*-*tert*-butyldimethylsilyl-α-L-arabinopyranoside (25). *Procedure A*. To a stirred and cooled solution (0 °C) of **24** (0.051 g, 0.18 mmol) in dry CH_2Cl_2 (5 mL) was first added

Et_3N (0.08 mL, 0.57 mmol) and then a cooled solution (0 °C) of triphosgene (0.018 g, 0.06 mmol) in dry CH_2Cl_2 (1 mL) was added in three portions. The mixture was stirred for 2 h at 0 °C and evaporated. Flash column chromatography (EtOAc) of the residue, gave pure **25** (0.038 g, 67%), which crystallized from CH_2Cl_2–hexane.

Procedure B. A solution of **23** (0.15 g, 0.46 mmol) in dry CH_2Cl_2 (9 mL) was hydrogenated over PtO_2 (0.015 g, 0.66 mmol) for 24 h at room temperature, and then to the stirred and cooled (0 °C) mixture was added Et_3N (0.2 mL, 1.47 mmol) in one portion. A solution of triphosgene (0.047 g, 0.16 mmol) in dry CH_2Cl_2 (1.5 mL) was added dropwise while stirring the mixture at 0 °C for 1 h. After stirring at room temperature for additional 18 h, the suspension was filtered and the catalyst washed with CH_2Cl_2. The combined organic solution was evaporated and the residue purified by flash chromatography (EtOAc) to afford pure **25** (0.095 g, 69%) as colorless crystals. Recrystallization from CH_2Cl_2–hexane gave an analytical sample **25**, mp 111–112 °C, $[\alpha]_D=-3.2$ (*c*, 1.65 in $CHCl_3$), R_F=0.25 (EtOAc). IR (KBr): ν_{max} 1710 (C=O). ^{1}H NMR ($CDCl_3$): δ 0.08 and 0.10 (2×s, 3H each, Me_3CSiMe_2), 0.88 (s, 9H, Me_3CSiMe_2), 3.41 (s, 3H, OMe), 3.55 (t, 1H, $J_{2,3}=J_{3,4}$=8.3 Hz, H-3), 3.6 (dd, 1H, $J_{1,2}$=6 Hz, H-2), 3.73 (dd, 1H, $J_{4,5a}$=5.7 Hz, $J_{5a,5b}$=12.3 Hz, H-5a), 3.81 (dd, 1H, $J_{4,5b}$=6.4 Hz, H-5b), 4.07 (m, 1H, H-4), 4.20 (d, 1H, H-1), 4.92 (bs, 1H, NH-3), 5.50 (bs, 1H, NH-4). ^{13}C NMR ($CDCl_3$): δ −5.04 and −4.42 (Me_3CSiMe_2), 18.01 (Me_3CSiMe_2), 25.74 (Me_3CSiMe_2), 51.45 (C-4), 55.73 (OMe), 56.13 (C-3), 62.22 (C-5), 73.81 (C-2), 103.13 (C-1), 163.56 (C=O). FAB MS (ES+): *m*/*z* 301 (M^+-H). HR MS (ES+): *m*/*z* 325.1543 (M^++Na). Calcd for $C_{13}H_{26}N_2O_4SiNa$: 325.1560. Anal. calcd for $C_{13}H_{26}N_2O_4Si$: C, 51.66; H, 8.77; N, 9.27. Found: C, 51.94; H, 8.77; N, 9.88.

4.1.22. (+)-Oxybiotin methyl ester (26). A solution of **18** (0.086 g, 0.32 mmol) in dry CH_2Cl_2 (5 mL) was hydrogenated over PtO_2 (0.02 g) for 22 h at room temperature. A solution of triphosgene (0.033 g, 0.11 mmol) in dry CH_2Cl_2 (1 mL), was added dropwise while stirring the mixture at 0 °C for 1 h, and then at room temperature for 3 h. To the solution was added an additional amount of triphosgene (0.012 g, 0.04 mmol) and the mixture was stirred for 1 h at 0 °C and then at room temperature for 18 h. The suspension was filtered and the catalyst washed with CH_2Cl_2. The combined organic solution was concentrated and the residue purified by flash chromatography (9:1 EtOAc–MeOH) to afford pure **26** (0.051 g, 66%) as colorless solid. Recrystallization from CH_2Cl_2–hexane gave colorless crystals, mp 141 °C, $[\alpha]_D=+44.7$ (*c*, 0.5 in $CHCl_3$), R_F=0.29 (Me_2CO). IR (KBr): ν_{max} 3410–3120 (NH), 1750 (*CO*OMe), 1710 (NH*CO*NH). ^{1}H NMR ($CDCl_3$): δ 1.21–1.80 (m, 6H, 3×CH_2), 2.23 (t, 2H, CH_2CO_2Me), 3.40 (m, 1H, $J_{2,3}$=3.6 Hz, $J_{1'a,2}$=6.4 Hz, H-2), 3.49 (dd, 1H, $J_{5a,5b}$=10.1 Hz, $J_{4,5a}$=4.2 Hz, H-5a), 3.63 (s, 3H, CO_2Me), 3.86 (d, 1H, H-5b), 4.17 (dd, 1H, $J_{3,4}$=8.4 Hz, H-3), 4.34 (dd, 1H, H-4), 5.98 and 6.18 (2×bs, 1H each, 2×NH). ^{13}C NMR ($CDCl_3$): δ 24.81, 25.52 and 28.36 (3×CH_2), 33.67 (CH_2CO_2Me), 51.42 (CO_2Me), 57.52 (C-4), 58.98 (C-3), 75.23 (C-5), 82.58 (C-2), 163.62 (NH*C*ONH), 174.14 (*C*O_2Me). FAB MS: *m*/*z* 243 (M^++H). FAB MS (ES+): *m*/*z* 265 (M^++Na). HR MS (ES+): *m*/*z* 265.1168 (M^++Na). Calcd for $C_{11}H_{18}N_2O_4Na$: 265.1164.

4.1.23. (+)-Oxybiotin (1). A solution of **26** (0.068 g, 0.28 mmol) in 1 M aq NaOH (2 mL) was stirred for 24 h at room temperature. The mixture was diluted with water (3 mL) and neutralized by stirring with Amberlist-15 resin (3 g) at room temperature for 1 h. The mixture was filtered and the resin washed with water. The combined aqueous solution was evaporated by co-distillation with a mixture of 1:1 toluene–EtOH to give pure **1** (0.064 g, 99%) as a white powder. Recrystallization from water gave pure **18** as silky crystals, mp 187–188 °C, $[\alpha]_D=+57.8$ (*c*, 0.65 in 1 M NaOH); lit.[4] mp 187–188 °C, $[\alpha]_D=+57.7$. IR (KBr): ν_{max} 3430–2500 (CO*OH*), 1700 (NH*CO*NH), 1670 (*CO*OH). ^{1}H NMR (D_2O): δ 1.41–1.80 (m, 6H, 3×CH_2), 2.46 (t, 2H, CH_2CO_2H), 3.64–3.76 (m, 2H, $J_{2,3}$=4 Hz, $J_{4,5a}$=4.4 Hz, $J_{5a,5b}$=10.4 Hz, H-2 and H-5a), 3.94 (d, 1H, H-5b), 4.42 (dd, 1H, $J_{3,4}$=8.7 Hz, H-3), 4.45 (dd, 1H, H-4). ^{1}H NMR (Me_2SO-d_6): δ 1.18–1.58 (m, 6H, 3×CH_2), 2.20 (t, 2H, CH_2CO_2H), 3.33 (m, 1H, $J_{2,3}$=4 Hz, H-2), 3.39 (dd, 1H, $J_{4,5a}$=4.6 Hz, $J_{5a,5b}$=9.8 Hz, H-5a), 3.65 (d, 1H, H-5b), 4.07 (dd, 1H, $J_{3,4}$=8.7 Hz, H-3), 4.21 (dd, 1H, H-4), 6.36 and 6.40 (2×bs, 1H each, 2×NH). ^{13}C NMR (Me_2SO-d_6): δ 25.29, 25.99 and 28.33 (3×CH_2), 34.35 (CH_2CO_2H), 57.53 (C-4), 59.01 (C-3), 74.34 (C-5), 82.85 (C-2), 163.80 (NH*C*ONH), 176.09 (*C*O_2H). FAB MS: *m*/*z* 229 (M^++H), 211 (M^+-OH). FAB MS (ES+): *m*/*z* 251 (M^++Na). HR MS (ES+): *m*/*z* 251.1007 (M^++Na). Calcd for $C_{10}H_{16}N_2O_4Na$: 251.1008.

4.2. X-ray analysis[18]

A single transparent crystal of compound **26** selected for data collection was mounted on a Bruker PLATFORM three-circle goniometer equipped with SMART 1K CCD detector mounted at a crystal to detector distance of 5.4 cm. The data were collected using graphite monochromated MoKa X-radiation and frame widths of 0.3° in ω, with 10 s used to acquire each frame. More than a hemisphere of three-dimensional data were collected. Additional information regarding data collection and structure refinement is given in Table 1. The data were reduced using the Bruker program SAINT.[19] A semiempirical absorption-correction based upon the intensities of equivalent reflections was applied (program XPREP),[20] and the data were corrected for Lorentz, polarization, and background effects. The Bruker SHELXTL[20] system of programs was used for the refinement of the crystal structure. The positions of all non H-atoms were located by direct methods. The positions of hydrogen atoms were found from the inspection of the difference Fourier maps. The high value of the Flack parameter [1.8 (1.0)] indicates that the absolute configuration cannot reliably be resolved. The final refinement included atomic positional and displacement parameters for all atoms. The non H-atoms were refined anisotropically, while all H sites were refined with isotropic displacement parameters. The refinement converged at a final agreement index (R1) of 0.0376, calculated for 2143 unique observed reflections ($|F_o|>4\sigma F$) and a goodness-of-fit (S) of 0.945 (226 refined parameters).

Table 1. Crystallographic data and structure refinement of **26**

Crystallographic parameter	
Empirical formula	$C_{11}H_{18}N_2O_4$
Formula weight	242.3
Temperature (K)	293
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a=4.5903
	b=7.517
	c=36.0507
Volume (Å^3)	1243.94
Z	4
Density (calculated)	1.354 Mg/m^3
Absorption coefficient (mm^{-1})	0.10
F(000)	520
Crystal size	0.30 mm×0.20 mm×0.20 mm
2Θ max for data collection	56.43°
Index ranges	h: −6+5, k: −9+10, l: −47+27
Reflections collected	7228
Independent reflections	2786 [R(int)=0.0507]
Refinement method	Full matrix l.s. on F^2
Data/restraints/parameters	2786/0/226
Goodness-of-fit on F2	0.945
Final R indices [$F_o>4\sigma F_o$]	R1=0.0376
R indices (all data)	$R1$=0.0512, $wR2$=0.0905
Extinction coefficient	No
Largest diff. peak and hole	0.14 and −0.18 e A^{-3}

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