199. Total Synthesis of 2-(β-D-Ribofuranosyl)thiazole-4-carboxamide (Tiazofurin) and of Precursors of *ribo*-*C*-Nucleosides[1])

by **R. Mampuya Bimwala** and **Pierre Vogel***

Section de chimie de l'Université de Lausanne, 2, rue de la Barre, CH-1005 Lausanne

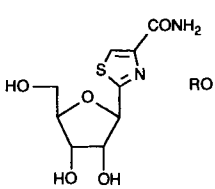
(3.X.89)

(1*R*,2*S*,4*R*)-2-Cyano-7-oxabicyclo[2.2.1]hept-5-en-2-yl (1*S'*)-camphanate (**5**) was transformed into (–)-methyl 2,5-anhydro-3,4,6-*O*-tris[(*tert*-butyl)dimethylsilyl]-D-allonate (**2**), (+)-1,3-diphenyl-2-{2',3',5'-*O*-tris[(*tert*-butyl)dimethylsilyl]-β-D-ribofuranosyl}imidazolidine (**3**), and the benzamide **20** of 1-amino-2,5-anhydro-1-deoxy-3,4,6-*O*-tris-[(*tert*-butyl)dimethylsilyl]-D-allitol. Compound **2** was converted efficiently into optically active tiazofurin (**1**).

Introduction. – *C*-Nucleosides have attracted a wide interest because of their biological activity [3]. One of them, 2-(β-D-ribofuranosyl)thiazole-4-carboxamide (= tiazofurin; **1**) [4–6], possesses significant antiviral activity against type-1 herpes virus, type-3 parainfluenza virus, and type-13 rhinovirus [6]. Tiazofurin is curative *in vivo* for *Lewis* lung carcinoma in mice [7] and has demonstrated *in vitro* activity against both human lymphoid [8] and lung tumor [9] cell lines, and *in vivo* activity against murine-implanted human ovarian cancers [10]. Recent findings have demonstrated efficacy in the treatment of acute myeloid leukemia [11].

We report here on the total syntheses of 2,5-anhydro-D-allose derivatives **2–4** that make use of the readily available, optically pure 7-oxabicyclo[2.2.1]hept-5-en-2-yl ester **5** derived from furan and 1-cyanovinyl (1*S*)-camphanate in 93% yield (taking into account the recovered dienophile) [12].

The OH groups of the *ribo*-*C*-nucleoside precursors **2–4** are protected as (*tert*-butyl)dimethylsilyl ethers. This makes these compounds as versatile as (if not more versatile than) the known corresponding [13] triesters [14] or tribenzyl ethers [15] in the construction of the heterocyclic moieties of the *C*-nucleosides around centre C(1). Indeed, the silyl polyethers are expected to be less prone than esters toward eliminations



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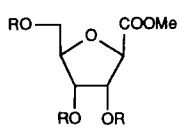
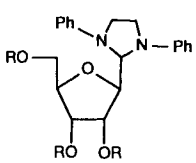
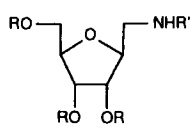


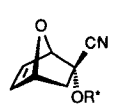
2 R = *t*-BuMe$_2$Si



3 R = *t*-BuMe$_2$Si



4 R' = H, R = *t*-BuMe$_2$Si
20 R' = PhCO, R = *t*-BuMe$_2$Si

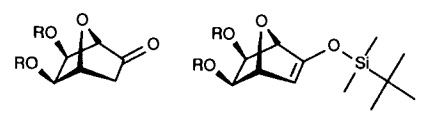


5 R* = (1*S*)-camphanoyl

[1]) Enantiomerically pure 7-oxabicyclo[2.2.1]hept-5-en-2-yl derivatives ('naked sugars' [1]) as synthetic intermediates, Part VIII. Part VII, see [2].

yielding furan derivatives [14]. Moreover, they are cleaved under conditions (*e.g.* Bu_4NF) that can be milder than those required for the cleavage of esters and benzyl ethers. The usefulness of the 2,5-anhydro-D-allonate derivative **2** will be illustrated by its efficient conversion into tiazofurin (**1**).

Results and Discussion. – Conversion of **5** into 7-oxanorbornanone derivative (+)-**6** has already been reported [16]. Treatment with 4 equiv. of Et_3N and *N*-[(*tert*-butyl)-dimethylsilyl]-*N*-methyltrifluoroacetamide gave the silyl enol ether (−)-**7** (90%). Ozonolysis of (−)-**7** (3% O_3 in O_2) at −78° in $MeOH/CH_2Cl_2$, followed by reduction of the ozonide and aldehydic intermediate with $NaBH_4$ (−78 to 20°), acidification (pH 2–3) with 1N HCl and esterification with diazomethane in Et_2O afforded the methyl 2,5-anhydro-allonate (−)-**8** (73%, based on (+)-**6**). The same sequence of reactions applied onto the isopropylidene protected derivative (±)-**9** [17] gave, *via* (±)-**10** (85%), the allonate (±)-**11** (42%, based on (±)-**9**).



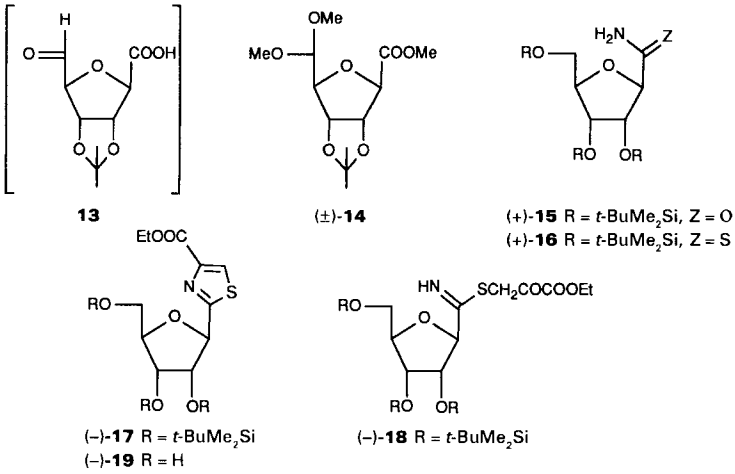
(+)-**6** R = *t*-$BuMe_2Si$ (±)-**9** R,R = Me_2C (−)-**7** R = *t*-$BuMe_2Si$ (±)-**10** R,R = Me_2C (−)-**8** R = *t*-$BuMe_2Si$ (±)-**11** R,R = Me_2C (±)-**12** R = *t*-$BuMe_2Si$

When the ozonolysis of (±)-**7** was followed by treatment with $NaBH_4$ and acidification with an excess of 10% HCl solution, the lactone (±)-**12** was obtained in 65% yield. The intermediate formyl-carboxylic acid **13** could be converted into the corresponding methyl 2,5-anhydro-D,L-allouronate dimethyl acetal (±)-**14** (64.5%) when the ozonolysis of (±)-**10** [17] was carried out in anhydrous MeOH (−78°) followed by treatment with Me_2S and workup with 2,2-dimethoxypropane, MeOH, and *Dowex-50 W*.

Silylation of the primary alcohol (−)-**8** with *t*-$BuMe_2SiCl$ and imidazole furnished **2** (96%). Treatment of **2** with NH_3/MeOH (20°) gave amide (+)-**15** quantitatively. Heating (+)-**15** with *Lawessons'* reagent (2,4-bis(4-methoxyphenyl)-1,3,2,λ^5,4,λ^5-dithiadiphosphetane-2,4-dithione [18]) in refluxing toluene afforded thioamide (+)-**16** (85%). However, treatment of (+)-**16** with ethyl 3-bromopyruvate in MeCN in the presence of AcONa gave the protected *C*-nucleoside (−)-**17** in modest yield only (34–45%), together with thioimidate (−)-**18**. All our attempts to improve the yield of (−)-**17** using acidic or other basic catalysts failed. We found, however, that the unprotected *C*-nucleoside (−)-**19** could be obtained in 58% yield in one step from (+)-**16** on treatment, first, with 50% aqueous HF solution in Me_3CN (20°, 3 d) and then with ethyl 3-bromopyruvate (20°). HF cleaves the silyl protective group and appears to be a catalyst of choice for the formation of the thiazole[2]). Treatment of (−)-**19** with NH_3/MeOH afforded tiazofurin (**1**) [4b] whose characteristics were identical in all respects with those reported for this *C*-nucleoside [4] [6].

Reduction of ester **2** with DIBAH (= diisobutylaluminium hydride, CH_2Cl_2, −78°) and treatment with *N*,*N*-diphenylethylenediamine (pH 3–4 (AcOH), 20°) afforded imidazolidine **3** (86%). The corresponding free amine **4** was obtained by reduction of (+)-**15** with 1.5 equiv. of $BH_3 \cdot Me_2S$ (boiling THF). Amine **4** was isolated as its benzamide **20**

[2]) CsF in DMF had been used in our laboratory to induce smooth H_2O elimination from 2,5-anhydro-4-deoxy-*N*-(4′,6′-diaminopyrimidin-5′-yl)-D-*ribo*-hexonamide to yield cordycepin C [19].



(78%) after treatment with benzoyl chloride. Analogous derivatives of **2** [14] and **4** [15] have been used as intermediates in the synthesis of a variety of *ribo-C*-nucleosides.

Conclusion. – Efficient total syntheses of optically pure *ribo-C*-nucleoside precursors based on the *Diels-Alder* adduct **5** of furan to 1-cyanovinyl (1*S*)-camphanate have been developed. Compared with analogous approaches of the groups of *Just* [20a], *Fourrey* [20b], *Noyori* [21], *Ohno* [22], *Kozikowski* [23], and *Gensler* [24], our method appears to be simpler, more versatile, and easier to apply to large-scale syntheses. Most interesting is the fact that the chiral auxiliary, (1*S*)-camphanic acid, is recovered at an early stage of the synthesis [17] [25]. Furthermore, since (1*R*)-camphanic acid is also commercially available, our method can be applied to obtain 2,5-anhydro-L-allose derivatives enantiomeric of **2**–**4**. This opens the possibility to prepare *C*-nucleosides derived from L-ribose.

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Experimental Part

General. See [25]. Silica gel used for column chromatography (FC = flash chromatography) and filtrations: *Merck 7734* or *9385*. None of the procedures reported here have been optimized.

*(–)-2,5-*exo,*6*exo-*{[(*tert*-*Butyl)dimethylsilyl]oxy}-7-oxabicyclo[2.2.1]hept-2-ene* ((–)-**7**). A mixture of (+)-(1*R*,4*R*,5*R*,6*S*)-5-*exo*,6-*exo*-bis{[(*tert*-butyl)dimethylsilyl]oxy}-7-oxabicyclo[2.2.1]heptan-2-one [16] ((+)-**6**; 1.7 g, 4.56 mmol), anh. DMF (50 ml), Et_3N (1.85 g, 18.25 mmol), and *N*-[(*tert*-butyl)dimethylsilyl]-*N*-methyltrifluoroacetamide (4.4 g, 18.25 mmol) was heated to 60° for 18 h under Ar (TLC control, AcOEt/petroleum ether 1:3, R_f ((–)-**7**) 0.6, vanillin as revelator). After solvent evaporation 50° 0.05 Torr, the residue was filtered through a short column of silica gel (50 g, AcOEt/petroleum ether 1:5): 2.0 g (90%), brownish oil. $[\alpha]_{589}^{27} = -14.8$, $[\alpha]_{578}^{27} = -15.4$, $[\alpha]_{546}^{27} = -17.8$, $[\alpha]_{436}^{27} = -33$, $[\alpha]_{365}^{27} = -57.7$ ($c = 18.3$ mg/ml, $CHCl_3$). UV (isooctane): 214 (2840). UV (95% EtOH): 211 (3030). IR (film): 2970, 2940, 2910, 2870, 1625, 1470, 1360, 1325, 1305, 1250, 1220, 1180, 1120, 1030, 1000, 910, 880, 830. ^{1}H-NMR (250 MHz, $CDCl_3$): 4.76 (*d*, $^3J = 2$, H–C(3)); 4.60 (*dd*, $^3J = 2$, $^3J = 1.5$, H–C(4)); 4.18 (*d*, $J = 1.5$, H–C(1)); 4.04, 3.95 (2*d*, $J = 5.5$, H–C(5), H–C(6)); 0.94–0.91 (3*s*, 3 *t*-Bu); 0.12 (*m*, 3 Me_2Si). MS (70 eV): 488 (17), 487 (41, M^+), 431 (3), 429 (14), 290 (5), 288 (47), 233 (5); 232 (11), 231 (54), 199 (6), 147 (6), 132 (10), 90 (26), 75 (13), 74 (22), 73 (100). Anal. calc. for $C_{24}H_{50}O_4Si_3$ (486.92): C 59.20, H 10.35, Si 17.30; found: C 59.15, H 10.32, Si 17.28.

*(−)-Methyl 2,5-Anhydro-3,4-bis-*O*-[(*tert*-butyl)dimethylsilyl]-*D*-allonate* ((−)-**8**). The crude (−)-**7** obtained above from 1.7 g of (+)-**6** (before filtration on silica gel) was dissolved in anh. CH_2Cl_2/MeOH 1:1 (100 ml) and cooled to −78°. A stream of O_3 (3% in O_2, 50 ml/h) was bubbled through the soln. for *ca.* 25 min until persistence of a blue colour (TLC control, AcOEt/petroleum ether 1:3). $NaBH_4$ (0.7 g, 18.2 mmol) was added portionwise and the mixture allowed to warm up to 20° under stirring. After 3 h at 20°, the soln. was cooled to 0° and acidified (pH 2–3) with aq. 1N HCl. A soln. of CH_2N_2 in Et_2O was added until persistence of the yellow colour. During the addition of CH_2N_2, the pH was adjusted to 2–3 by additions of 1N HCl. The solvent was evaporated and the residue taken in AcOEt (50 ml). The org. layer was washed with sat. aq. NH_4Cl soln., dried ($MgSO_4$), evaporated, and purified by column chromatography on silica gel (*Lobar*, column *C*, AcOEt/petroleum ether 1:4): 1.385 g (72.5%), colourless oil. $[\alpha]_{589}^{25} = -8.1$, $[\alpha]_{578}^{25} = -8.4$, $[\alpha]_{546}^{25} = -9.9$, $[\alpha]_{436}^{25} = -19.5$, $[\alpha]_{365}^{25} = -36.8$ ($c = 17$ mg/ml, $CHCl_3$). IR ($CHCl_3$): 3500, 3020, 2970, 2940, 2910, 2870, 1750, 1480, 1470, 1440, 1410, 1365, 1305, 1260, 1200, 1160, 1120, 1100, 1070, 1030, 1010, 990, 950, 940, 925, 910, 900, 875, 840. ^{1}H-NMR (360 MHz, $CDCl_3$): 4.39 (*d*, $J = 2.0$, H–C(2)); 4.22 (*dd*, $J = 4.0$, 2.0, H–C(3)); 4.18 (*dd*, $J = 7.0$, 4.0, H–C(4)); 4.07 (*m*, $J = 7.0$, 2.5, H–C(5)); 3.95, 3.60 (2*dd*, $^2J = 12.5$, $^3J = 2.5$, CH_2(6)); 3.80 (*s*, COOMe); 0.96, 0.92 (2*s*, 2 *t*-BuSi); 0.15–0.10 (2 Me_2Si). ^{13}C-NMR (90.55 MHz, $CDCl_3$): 172.6 (*s*, C(1)); 83.4 (*d*, ^1J(C,H) = 150, C(2)); 82.4 (*d*, ^1J(C,H) = 150, C(5)); 76.6 (*d*, ^1J(C,H) = 150, C(3)); 70.9 (*d*, ^1J(C,H) = 150, C(4)); 60.4 (*t*, ^1J = (C,H) = 150, C(6)); 52.5 (*q*, ^1J(C,H) = 150, CH_3); 25.8 (*q*, ^1J(C,H) = 125, 6 Me); 18.0 (*s*); −4.8 to −5.10 (4*q*, 4 Me). MS (70 eV): 421 (42, M^+), 363 (29), 303 (7), 231 (20), 213 (14), 171 (15), 147 (35), 133 (30), 117 (12). Anal. calc. for $C_{19}H_{40}O_6$ (420.70): C 54.25, H 9.58, Si 13.35; found: C 54.38, H 9.50, Si 13.32.

*(−)-Methyl 2,5-Anhydro-3,4,6-*O*-tris[(*tert*-butyl)dimethylsilyl]-*D*-allonate* (**2**). A mixture of (−)-**8** (415 mg, 0.844 mmol), imidazole (185 mg, 2.72 mmol), and (*tert*-butyl)dimethylsilyl chloride (480 mg, 3.18 mmol) in anh. DMF (10 ml) was heated to 50° for 5 h under Ar. After cooling to 20°, the soln. was poured into H_2O (100 ml) and the mixture extracted with Et_2O (100 ml, 3 times). The org. extracts were dried ($MgSO_4$) and evaporated. The residue was purified by filtration on a short column of silica gel (4 g, AcOEt/petroleum ether 1:3): 433 mg (96%), colourless oil. $[\alpha]_{589}^{25} = -10.4$, $[\alpha]_{578}^{25} = -10.6$, $[\alpha]_{546}^{25} = -12.2$, $[\alpha]_{436}^{25} = -21.4$, $[\alpha]_{365}^{25} = -35.1$. IR (film): 2950, 2820, 1750, 1465, 1430, 1380, 1360, 1250, 1200, 1150, 1120, 1080, 1000, 960, 930, 830. ^{1}H-NMR (250 MHz, $CDCl_3$): 4.36 (*d*, $J = 6.0$, H–C(2)); 4.20 (*dd*, $J = 6.0$, 4.0, H–C(3)); 4.09 (*t*, $J = 4.0$, H–C(4)); 3.98 (*q*, $J = 4.0$, H–C(5)); 3.74 (*s*, COOMe); 3.70 (*m*, $J = 4.0$, CH_2(6)); 0.91 (3 *t*-BuSi); 0.08 (3 Me_2Si). ^{13}C-NMR (90.55 MHz, $CDCl_3$); 172.5 (*s*, C(1)); 83.4 (*d*, ^1J(C,H) = 150, C(2)); 82.4 (*d*, ^1J(C,H) = 150, C(5)); 76.6 (*d*, ^1J(C,H) = 150, C(3)); 70.9 (*d*, ^1J(C,H) = 150, C(4)); 60.4 (*t*, ^1J(C,H) = 150, C(6)); 52.4 (*q*, ^1J(C,H) = 150, CH_3); 25.5 (*m*, 3 *t*-BuSi); 18.0 (*s*); −4.8 to −5.1 (*m*, 6 Me). MS (70 eV): 553 (12), 552 (27), 551 (47), 536 (13), 535 (28, $M^{+\cdot}$), 534 (48), 489 (5), 488 (8), 478 (13), 477 (29), 476 (55), 171 (8), 132 (12), 106 (19), 90 (41), 89 (20), 74 (19), 75 (17), 73 (100). Anal. calc. for $C_{25}H_{54}O_6Si_3$ (534.96): C 56.13, H 10.17, Si 15.75; found: C 56.04, H 10.20, Si 15.70.

*(±)-Methyl 2,5-Anhydro-3,4-*O*-isopropylidene-*D,L*-allonate* ((±)-**11**). Same procedure as for (−)-**8**, starting with *rac*-5-*exo*,6-*exo*-(isopropylidenedioxy)-7-oxabicyclo[2.2.1]heptan-2-one [17] ((±)-**9**; 2.0 g, 5.36 mmol): 0.48 g (41.5%) of (±)-**11**, colourless oil. IR (film): 3700–3100, 2980, 2960, 1740, 1435, 1380, 1330, 1270, 1230, 1210, 1110, 1080, 1050, 910, 860, 750. ^{1}H-NMR (360 MHz, $CDCl_3$): 4.84 (*dd*, $J = 6.0$, 3.0, H–C(3)); 4.74 (*dd*, $J = 6.0$, 2.0, H–C(4)); 4.58 (*d*, $J = 3.0$, H–C(2)); 4.38 (*m*, H–C(5)); 3.85 (*dd*, $^2J = 13.0$, $^3J = 2.5$); 3.52 (*dd*, $^2J = 13.0$, $^3J = 4.0$, CH_2(6)); 3.80 (*s*, MeOOC); 1.52, 1.32 (2*s*, Me_2C). ^{13}C-NMR (90.55 MHz, $CDCl_3$): 174 (*s*, C(1)); 113.9 (*s*); 87.75 (*d*, ^1J(C,H) = 150, C(2)); 84.95 (*d*, ^1J(C,H) = 150, C(5)); 84.90 (*d*, ^1J(C,H) = 150, C(3)); 82.8 (*d*, ^1J(C,H) = 150, C(4)); 63.5 (*t*, ^1J(C,H) = 150, C(6)); 53.0 (*q*, ^1J(C,H) = 150, COO*Me*); 27.5–25.7 (2*q*, ^1J(C,H) = 126, 2 Me). MS (70 eV): 217 (50, M^+), 187 (14), 185 (12), 173 (13), 143 (6), 127 (13), 85 (19), 83 (17), 81 (20), 71 (17), 69 (16), 59 (58), 55 (23), 43 (100). Anal. calc. for $C_{10}H_{16}O_6$ (232.22): C 51.72, H 6.90; found: C 51.63, H 6.83.

*2,5-Anhydro-3,4-*O*-bis[(*tert*-butyl)dimethylsilyl]-*D,L*-allono-1,6-lactone* ((±)-**12**). O_3 (3% in O_2, 50 ml/h) was bubbled through a soln. of (±)-**7** [17] (100 mg, 0.205 mmol) in anh. CH_2Cl_2/MeOH 1:4 (*vv*) maintained at −78° for 20 min. $NaBH_4$ (310 mg, 0.82 mmol) was added and the mixture allowed to warm up to 20° under stirring. After solvent evaporation, the residue was taken with 10% aq. HCl soln. (10 ml) and then extracted with Et_2O (10 ml, 3 times). The extracts were washed with sat. aq. NH_4Cl soln. (10 ml, twice) and dried ($MgSO_4$). After solvent evaporation, the crude product was recrystallized from AcOEt/hexane: 60 mg (75.3%), colourless crystals. M.p. 124–125°. IR ($CHCl_3$): 2960, 2940, 2860, 1750, 1465, 1360, 1250, 1160, 1120, 1100, 1060, 990, 940, 870, 840. ^{1}H-NMR (360 MHz, $CDCl_3$): 4.37 (*s*, H–C(2)); 4.32 (*d*, $J = 4.0$, H–C(5)); 4.15, 4.10 (2*dd*, $J = 8.0$, 4.0, H–C(3), H–C(4)); 4.0 (*dd*, $^2J = 12.0$, $^3J = 2.0$, H–C(6)); 3.68 (*d*, $^2J = 12.0$, H–C(6)); 0.92 (*s*, 2 *t*-BuSi); 0.12 (*s*, 2 Me_2Si). ^{13}C-NMR (90.55 MHz, $CDCl_3$): 172.5 (*s*, C(1)); 83.20 (*d*, ^1J(C,H) = 150, C(2)); 81.82 (*d*, ^1J(C,H) = 150, C(5)); 70.20 (*d*, ^1J(C,H) = 150, C(4)); 59.80 (*t*, ^1J(C,H) = 150, C(6)); 25.74 (*m*, 3 *t*-BuSi); 174.6 (*s*); −4.8 to −5.1 (*m*, 6 Me). MS (70 eV): 149 (10), 133 (16), 115 (9), 81 (14), 75 (100), 69 (26), 59 (21), 58 (12), 57 (78), 56 (41), 55 (20). Anal. calc. for $C_{18}H_{36}O_5Si_2$ (388.66): C 55.63, H 9.34; found: C 54.04, H 9.74.

*Methyl 2,5-Anhydro-3,4-O-isopropylidene-*D,L*-allouronate Dimethyl Acetal* ((±)-**14**). O_3 (3% in O_2, 50 ml/h) was bubbled through a soln. of (±)-**10** [17] (827 mg, 2.77 mmol) in anh. MeOH maintained at −78° for 20 min. After addition of Me_2S (0.7 ml, 8.85 mmol), the soln. was allowed to warm up to 20°. After solvent evaporation, the residue was dissolved in 2,2-dimethoxypropane (5 ml) and anh. MeOH (1 ml). The soln. was cooled to 0° and *Dowex 50 W* added until pH 2–3. The mixture was stirred at 5° for 12 days (TLC control, AcOEt/petroleum ether 1:3, vanilin and 2,4-dinitrophenylhydrazine as revelators). After filtration, the solvent was evaporated and the residue purified by column chromatography (*Lobar*, column *B*, AcOEt/petroleum ether 1:3): 494 mg (64.5%), colourless oil. IR (film): 2990, 2960, 2840, 1750 (br.), 1450, 1380, 1210, 1110, 870. ^{1}H-NMR (360 MHz, $CDCl_3$): 4.90 (*dd*, J = 6.0, 3.0, H–C(3)); 4.78 (*d*, J = 6.0, H–C(4)); 4.48 (*d*, J = 3.0, H–C(2)); 4.28 (*d*, J = 3.0, H–C(6)); 4.20 (*d*, J = 3.0, H–C(5)); 3.75 (*s*, COOMe); 3.44, 3.32 (2*s*, $(MeO)_2C$); 1.48, 1.28 (2*s*, Me_2C). ^{13}C-NMR (90.55 MHz, $CDCl_3$): 170.7 (*s*, C(6)); 112.9 (*s*); 105.2 (*d*, ^1J(C,H) = 150, C(1)); 85.3, 84.8, 83.8, 81.1 (4*d*, ^1J(C,H) = 150, C(2), C(3), C(4), C(5)); 56.0, 56.0, 52.1 (3*q*, ^1J(C,H) = 150, 3 MeO); 26.7, 24.9 (2*q*, ^1J(C,H) = 125, 2 Me). MS (70 eV): 294 (75), 278 (2), 262 (6), 248 (19), 245 (16), 231 (3), 230 (22), 199 (10), 130 (5), 75 (100). Anal. calc. for $C_{12}H_{20}O_7$ (276.29): C 52.17, H 7.30; found: C 51.97, H 7.29.

*(+)-2,5-Anhydro-3,4,6-*O*-tris[(*tert*-butyl)dimethyl]-*D*-allonamide* ((+)-**15**). A sat. soln. of NH_3 in anh. MeOH (50 ml) was added to a soln. of (−)-**2** (1.2 g, 2.24 mmol) in anh. MeOH (5 ml). After stirring at 20° for 3 h, the solvent was evaporated, yielding 1.16 g (100%), colourless oil. $[\alpha]_{589}^{25} = +22.8$, $[\alpha]_{578}^{25} = +24.2$, $[\alpha]_{546}^{25} = +26.8$, $[\alpha]_{436}^{25} = +43.1$, $[\alpha]_{365}^{25} = +65.3$ (c = 16.5 mg/ml $CHCl_3$). IR ($CHCl_3$): 3480, 3330, 3000–2840, 1675, 1575, 1470, 1380, 1350, 1250, 1150, 1120, 1060, 990, 960, 900, 860, 830. ^{1}H-NMR (250 MHz, $CDCl_3$): 7.55, 5.44 (2 br. *s*, $CONH_2$); 4.26 (*s*, H–C(2)); 4.24 (*d*, J = 4.0, H–C(3)); 4.11 (*dd*, J = 4.0, 2.5, H–C(4)); 4.09 (*m*, H–C(5)); 3.98, 3.70 (2*dd*, ^2J = 10.0, ^3J = 2.5, CH_2(6)); 0.92, 0.91, 0.90 (3*s*, 3 *t*-BuSi); 0.19, 0.12, 0.12, 0.09, 0.06, 0.06 (4*s*, 3 Me_2Si). ^{13}C-NMR (90.55 MHz, $CDCl_3$): 174.0 (*s*, $CONH_2$); 84.7, 81.5, 76.5, 69.9 (4*d*, ^1J(C,H) = 150, C(2), C(3), C(4), C(5)); 60.4 (*t*, ^1J(C,H) = 150, C(6)); 25.7 (*m*, 3 *t*-BuSi); 18.0 (*s*); −4.8 to −5.0 (*m*, 6 Me). MS (70 eV): 463 (10), 402 (26, M^+), 171 (4), 145 (2), 144 (4), 133 (5), 115 (7), 89 (26), 81 (12), 75 (46), 73 (100), 59 (12), 57 (21), 56 (33). Anal. calc. for $C_{24}H_{53}NO_5Si_3$ (519.95): C 55.44, H 10.27, N 2.69, Si 16.20; found: C 55.65, H 10.20, N 2.57, Si 16.41.

*(+)-2,5-Anhydro-3,4,6-*O*-tris[(*tert*-butyl)dimethylsilyl]-*D*-allonthioamide* ((+)-**16**). A mixture of (+)-**15** (550 mg, 1.056 mmol) and 2,4-bis(4-methoxyphenyl)-1,3,2λ^5,4λ^5-dithiadiphosphetane-2,4-dithione (214 mg, 0.528 mmol) was heated to 80° for 5 min. After cooling to 20°, anh. toluene (5 ml) was added and the mixture heated under reflux for 50 min. The solvent was evaporated and the residue purified by column chromatography on silica gel (*Lobar*, column *B*, AcOEt/petroleum ether 1:4): 478 mg (84.6%), colourless oil. $[\alpha]_{589}^{27} = +9.5$, $[\alpha]_{578}^{27} = +9.8$, $[\alpha]_{546}^{27} = +10.3$, $[\alpha]_{436}^{27} = +12.2$, $[\alpha]_{365}^{27} = +20.3$ (c = 17.7 mg/ml, $CHCl_3$). UV (isooctane): 271 (6076). UV (MeCN): 271 (5960). IR ($CHCl_3$): 3440, 3280, 3180, 2950, 2850, 1595, 1460, 1420, 1360, 1250, 1180, 1120, 1050, 1030, 990, 870, 830. ^{1}H-NMR (250 MHz, $CDCl_3$): 9.22, 7.78 (2 br. *s*, $CSNH_2$); 4.65 (*s*, H–C(2)); 4.37 (*d*, J = 4.0, H–C(3)); 4.06 (*m*, H–C(4)); 4.02 (*m*, H–C(5)); 4.00, 3.70 (2*d*, ^2J = 10.0, CH_2(6)); 0.92 (3 *t*-BuSi); 0.12 (3 Me_2Si). ^{13}C-NMR (90.55 MHz, $CDCl_3$); 174.0 (*s*, C(1)); 90.2, 81.1, 78.9, 68.9 (4*d*, ^1J(C,H) = 150, C(2), C(3), C(4), C(5)); 60.2 (*t*, ^1J(C,H) = 150, C(6)); 18.01 (*s*); 25.8 (*m*, 3 *t*-BuSi); −4.1 to −5.0 (3 Me_2Si). MS (70 eV): 553 (2), 537 (60), 536 (100, M^+), 520 (6), 519 (8), 480 (13), 479 (22), 478 (44), 446 (2). Anal. calc. for $C_{24}H_{53}NO_4SSi_3$ (536.02): C 53.78, H 9.97, S 5.98, N 2.61, Si 15.72; found: C 53.60, H 9.85, N 2.68, Si 15.58.

*Ethyl 2-{2′,3′,5′-*O*-Tris[(*tert*-butyl)dimethylsilyl]-β-*D*-ribo-furanosyl}thiazole-4-carboxylate* ((−)-**17**). *Method A.* Freshly distilled $BrCH_2COCOOEt$ (0.035 ml, 0.28 mmol) was added to a stirred soln. of (+)-**16** (50 mg, 0.094 mmol) and AcONa (8.5 mg, 0.103 mmol) in anh. MeCN (0.3 ml) cooled to 0° under Ar. The temp. was allowed to rise to 20°, and the solvent was evaporated. After the addition of AcOH (0.2 ml) and AcONa (8.5 mg, 0.103 mmol), the mixture was heated to 90° for 2 days. After cooling to 20°, the mixture was neutralized with sat. aq. $NaHCO_3$ soln. (0.5 ml) and extracted with Et_2O/H_2O (5 ml, 4 times). The org. extracts were dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel (*Lobar*, column *A*, AcOEt/petroleum ether 1:4): 20–25 mg (34–45%) of (−)-**17**, colourless oil. $[\alpha]_{589}^{28} = -17.0$, $[\alpha]_{578}^{28} = -18.0$, $[\alpha]_{546}^{28} = -20.6$, $[\alpha]_{436}^{28} = -38.29$, $[\alpha]_{365}^{28} = -64.86$. UV (isooctane): 206 (1250), 237 (510). UV (95% EtOH): 207 (1116), 238 (474). IR ($CHCl_3$): 2860–2960, 1710, 1460, 1360, 1255, 1160, 960, 830. ^{1}H-NMR (250 MHz, $CDCl_3$): 8.15 (*s*, H–C(5)); 5.15 (*d*, J = 4.5, H–C(1′)); 4.40 (*q*, J = 7.0, CH_3CH_2O); 4.30 (*t*, J = 4.5, H–C(2′)); 4.20 (*t*, J = 4.5, H–C(3′)); 4.12 (*m*, H–C(4′)); 3.95, 3.68 (2*dd*, ^2J = 13.0, ^3J = 2.5, CH_2(5′)); 1.40 (*t*, J = 7.0, CH_3CH_2O); 0.92 (3 *t*-BuSi); 0.12 (3 Me_2Si). ^{13}C-NMR (90.55 MHz, $CDCl_3$): 173 (*s*); 148 (*s*); 127.6 (*d*, ^1J(C,H) = 190, C(5)); 86.5, 81.0, 79.3, 73.8 (4*d*, ^1J(C,H) = 150, C(1′), C(2′), C(3′), C(4′)); 63.4 (*t*, ^1J(C,H) = 130, CH_3CH_2O); 61.2 (*t*, ^1J(C,H) = 150, C(5′)); 25.8 (*q*, 3 *t*-BuSi); 18.10 (*s*, 14.33 (*q*, ^1J(C,H) = 130, CH_3CH_2O); −3.0 to −4.5 (3 Me_2Si). MS (70 eV): 633 (0.5), 632 (0.3, M^+), 556 (2), 520 (28), 519 (44), 518 (100), 462 (13), 460 (69).

Method B. A mixture of (−)-**19** (33.5 mg, 0.116 mmol), imidazole (50 mg, 0.695 mmol), and (*tert*-butyl)dimethylsilyl chloride (104.7 mg, 0.695 mmol) in anh. DMF (2 ml) was heated to 50° for 4 h under Ar. After

cooling to 20°, the soln. was poured into H_2O (20 ml) and the mixture extracted with Et_2O (20 ml, 3 times). The org. extracts were combined, dried ($MgSO_4$), and evaporated. Without further purification, (−)-**17** (68.3 mg, 93.2%) was obtained pure. The product was identical in all respects with that prepared by *Method A*.

(−)-Ethyl 3-{{2′,5′-Anhydro-3′,4′,6′-O-tris[(tert-butyl)dimethylsilyl]-D-allonimidoyl}thio}-2-oxopropanoate ((−)-**18**). Freshly distilled $BrCH_2COCOOEt$ (0.140 ml, 1.12 mmol) was added to a stirred soln. of (+)-**16** (200 mg, 0.376 mmol) and AcONa (32 mg, 0.388 mmol) in anh. MeCN (1.5 ml) cooled to 0° under Ar. The temp. was allowed to rise to 20°. After 4 h, the mixture was neutralized with sat. aq. $NaHCO_3$ soln. (3 ml) and extracted with Et_2O/H_2O (10 ml, 4 times). The org. extracts were combined, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography on silica gel (*Lobar*, column *B*, AcOEt/petroleum ether 1:5). A first fraction yielded 157 mg (66.3%; m.p. 71–73°) of (−)-**18** (mixture of 2 isomers). A second fraction afforded 20 mg (2.8%) of (−)-**17**. (−)-**18**: $[\alpha]_{589}^{25} = -6.3$, $[\alpha]_{578}^{25} = -7.0$, $[\alpha]_{546}^{25} = -8.0$, $[\alpha]_{436}^{25} = -14.7$, $[\alpha]_{365}^{25} = -22.7$ (c = 19.5 mg/ml, $CHCl_3$). UV (isooctane): 226 (2064), 255 (2553). UV (MeCN): 220 (2097), 254 (2371). IR (KBr): 2960, 2950, 2900, 2860, 1740, 1600, 1470, 1390, 1360, 1250, 1000, 960, 940, 830. ^{1}H-NMR (250 MHz, C_6D_6): 5.05 (2*d*, J = 5.5, J = 5.0, H–C(2′)); 4.6, 4.5 (2*dd*, J = 5.0, J = 5.1, H–C(3′)); 4.1 (br. *s*, NH); 4.3 (*m*, H–C(5′)); 4.2 (*m*, H–C(4′)); 3.92 (2*q*, J = 7, CH_3CH_2O); 3.75 (br. *m*, CH_2(6′)); 3.65, 3.53, 3.12, 3.10 (4*d*, J = 12, 1 H); 1.05–0.98 (6*s*, 3 *t*-BuSi); 0.94, 0.80 (2*t*, J = 7, CH_3CH_2O); 0.25–0.10 (8*s*, 3 Me_2Si). ^{13}C-NMR (90.55 MHz, $CDCl_3$): 178 (*s*); 170.5 (*s*); 105.5 (*s*); 86.05, 81.6, 81.5, 73.7 (4*d*, ^1J(C,H) = 150, C(2′), C(3′), C(4′), C(5′)); 63.5 (*t*, ^1J(C,H) = 130, CH_3CH_2O); 62.8 (*t*, ^1J(C,H) = 150, C(6′)); 38.5 (*t*, SCH_2(3)); 25.9 (*q*, *t*-BuSi); 18.5 (*s*); 14.2 (*q*, ^1J(C,H) = 130, CH_3CH_2O); −4.0 (Me_2Si). MS (70 eV): 678 (0.2), 653 (16), 652 (42), 651 (72), 650 (100, $M^{+\cdot}$), 634 (4), 595 (6), 594 (16), 593 (28), 592 (50), 576 (3). Anal. calc. for $C_{29}H_{59}NO_7SSi_3$ (650.12): C 53.58, H 9.15, N 2.15, S 4.93, Si 12.96; found: C 53.40, H 9.07, N 2.16, S 4.77, Si 11.37.

(−)-Ethyl 2-(β-D-Ribofuranosyl)thiazole-4-carboxylate ((−)-**19**). A mixture of (+)-**16** (115 mg, 0.215 mmol), MeCN (2 ml), and 50% aq. HF soln. (0.09 ml, 0.087 mmol) was allowed to stand at 20° for 3 days. The solvent was evaporated under high vacuum. The residue was dissolved in anh. MeCN (2 ml). After cooling to 0°, $BrCH_2COCOOEt$ (125 mg, 0.645 mmol) was added dropwise. After stirring at 20° for 1 h (TLC control, $MeOH/CH_2Cl_2$ 1:4, R_f ((−)-**19**) 0.5), the soln. was cooled to 0° and neutralized with a few drops of a sat. aq. soln. $NaHCO_3$. The residue was purified by column chromatography on silica gel ($MeOH/CHCl_3$ 1:9): 35 mg (58%), colourless oil. $[\alpha]_{589}^{26} = -7.8$, $[\alpha]_{578}^{26} = -8.13$, $[\alpha]_{546}^{26} = -9.4$, $[\alpha]_{436}^{26} = -17.73$, $[\alpha]_{365}^{26} = -34.0$ (c = 15 mg/ml, $CHCl_3$). UV (MeOH): 205 (8631), 237 (3736). IR ($CHCl_3$): 3650, 3300, 3000, 2960, 2940, 2860, 1710, 1420, 1360, 1255, 1090, 1050, 1020, 1010, 900. ^{1}H-NMR (250 MHz, (D_6)DMSO): 8.31 (*s*); 5.44 (*d*, J = 6.0); 5.05 (*d*, J = 5.0, H–C(1′)); 4.98 (*t*, H–C(2′)); 4.40 (*q*, J = 9, CH_3CH_2); 4.0 (*m*, 1 H); 3.90 (*m*, CH_2(5′)); 3.50 (*m*, 3 H); 1.42 (*t*, J = 7, CH_3CH_2O). ^{13}C-NMR (90.55 MHz, (D_6)DMSO): 172.2 (*s*); 160.9 (*s*); 146.5 (*s*); 127.2 (*d*, ^1J(C,H) = 190, C(5)); 84.7, 82.1, 76.9, 71.4 (4*d*, ^1J(C,H) = 150, C(1′), C(2′), C(3′), C(4′)); 62.3 (*t*, ^1J(C,H) = 150, CH_3CH_2O); 61.3 (*t*, ^1J(C,H) = 150, C(5′)); 14.0 (*q*, ^1J(C,H) = 130, CH_3CH_2O). MS (70 eV): 291 (13.6), 290 (100, $M^{+\cdot}$), 289 (5), 233 (3), 200 (24), 186 (12), 171 (4), 158 (3), 154 (4).

2-(β-D-Ribofuranosyl)thiazole-4-carboxamide (**1**). Thiazole (−)-**19** (33.5 mg, 0.116 mmol) was treated with sat. NH_3/MeOH at 20° for 30 h. After evaporation, the residue was purified by column chromatography on silica gel (25 g, $MeOH/CHCl_3$ 3:7): 27.3 mg (90.6%), colourless crystals. M.p. 144–145°. $[\alpha]_{589}^{25} = -3.0$, $[\alpha]_{578}^{25} = -4.2$, $[\alpha]_{546}^{25} = -6.4$, $[\alpha]_{436}^{25} = -7.8$, $[\alpha]_{365}^{25} = -9.1$ (c = 6 mg/ml EtOH; [4a]: $[\alpha]_D^{22} = -9$ (c = 0.5, EtOH); $[\alpha]_D^{22} = -4.5$, $[\alpha]_{578}^{22} = -5.5$, $[\alpha]_{546}^{22} = -6.5$, $[\alpha]_{436}^{22} = -11.3$, $[\alpha]_{365}^{22} = -18.5$ (c = 2 mg/ml, MeOH); [4b]: $[\alpha]_D^{22} = -4.7$ (c = 2, MeOH)). UV (MeOH): 205 (9689), 236 (3629). IR (KBr): 3480, 3400, 2960, 1670, 1470, 1360, 1255, 1090, 1050, 1020, 1090, 890. ^{1}H-NMR (250 MHz, (D_6)DMSO): 8.31 (*s*); 7.69, 7.56 (2 br. *s*, $CONH_2$); 5.38 (*d*, J = 6.0, 1 H); 5.09 (*d*, J = 5.0, H–C(1′)); 4.95 (*d*, J = 5.0, 1 H); 4.86 (*t*, J = 5.0, 1 H); 4.59 (*t*, J = 5.0, 1 H); 4.04 (*m*, 1 H); 3.86 (*m*, 2 H, CH_2(5′)); 3.50 (*m*). ^{13}C-NMR (90.55 MHz, (D_6)DMSO): 172.2 (*s*); 162.4 (*s*); 150.3 (*s*); 124.4 (*d*, ^1J(C,H) = 150, C(5)); 85.1, 81.9, 76.9, 71.4 (4*d*, ^1J(C,H) = 150, C(1′), C(2′), C(3′), C(4′)); 61.9 (*t*, ^1J(C,H) = 150, C(5′)). MS (70 eV): 261 (100), 260 (4, $M^{+\cdot}$), 171 (7), 157 (3), 140 (2), 102 (16), 87 (3), 85 (52).

(+)-1,3-Diphenyl-2-{2′,3′,5′-O-tris[(tert-butyl)dimethylsilyl]-β-D-ribo-furanosyl}imidazolidine (**3**). A soln. of DIBAH (0.38 ml, 0.4 mmol) in toluene was added dropwise to a stirred soln. of **2** (185 mg, 0.346 mmol) in anh. CH_2Cl_2 (5 ml) cooled to −78° under Ar. After stirring at −78° for 2 h, AcOH (0.2 ml) was added dropwise until pH 3–4, and then *N,N*-diphenylethylenediamine (90 mg, 0.424 mmol) was added. The mixture was stirred at 20° for 3 h, H_2O (10 ml) added, and the mixture extracted with $CHCl_3$ (10 ml, 3 times). The org. extracts were dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography on silica gel (*Lobar*, column *B*, AcOEt/petroleum ether 1:5): 208 mg (86.2%), colourless oil. $[\alpha]_{589}^{25} = +5.7$, $[\alpha]_{578}^{25} = +5.92$, $[\alpha]_{546}^{25} = +6.31$, $[\alpha]_{436}^{25} = +8.55$, $[\alpha]_{365}^{25} = +9.13$ (c = 10.3 mg/ml, $CHCl_3$). UV (isooctane): 204 (5416), 254 (4079), 295 (580). UV (MeCN): 256 (9942), 295 (1347). IR (film): 2980–2850, 1595, 1500, 1470, 1390, 1360, 1310, 1250, 1150, 1075, 1000, 860, 830, 770, 740, 690. ^{1}H-NMR (250 MHz, $CDCl_3$): 7.30–6.80 (*m*, 10 arom. H); 5.58 (*s*, H–C(1)); 4.38 (*m*,

H–C(1′)); 4.10 (*m*, H–C(2′)); 3.94 (*m*, H–C(3′), H–C(5′)); 3.84 (*m*, H–C(4′)); 3.60 (*m*, CH_2(3), CH_2(4)); 3.45 (*m*, H–C(5′)); 0.92 (*s*, 3 *t*-BuSi); 0.12 (*s*, 3 Me_2Si). ^{13}C-NMR (90.55 MHz, $CDCl_3$): 130 (*s*); 129.2, 128.9, 128.9, 128.8 (4*d*, ^1J(C,H) = 160); 86.9 (*d*, ^1J(C,H) = 150, C(1′)); 81.2 (*d*, ^1J(C,H) = 150, C(2′)); 76.5 (*d*, ^1J(C,H) = 150, C(3′)); 72.8 (*d*, ^1J(C,H) = 150, C(4′)); 60.4 (*t*, ^1J(C,H) = 150, C(5′)); 50.0 (*d*, ^1J(C,H) = 130, C(1)); 47.3 (*t*, ^1J(C,H) = 130, C(3), C(4)); 25.8 (*m*, 3 *t*-BuSi); 18.0 (*s*); −4.8 to −5.2 (*m*, 6 Me). MS (70 eV): 700 (33), 699 (36, $M^{+\cdot}$), 224 (29), 223 (100), 147 (2), 91 (4), 75 (5), 74 (4), 73 (5), 72 (2). Anal. calc. for $C_{38}H_{66}N_2O_4Si_3$ (699.29): C 65.28, H 9.51, N 4.01, Si 12.05; found: C 64.08, H 9.44, N 4.01, Si 12.0.

*1-Benzamido-2,5-anhydro-1-deoxy-3,4,6-*O*-tris[(*tert*-butyl)dimethylsilyl]-*D*-allitol* ((−)-**20**). A mixture of (+)-**15** (120 mg, 0.231 mmol) and BH_3·MeS (0.065 ml, 0.693 mmol) in anh. THF (3 ml) was heated under reflux for 3 h (TLC control, petroleum ether/AcOEt 3:1). The solvent was evaporated and the residue taken up with THF/MeOH 6:1. *Dowex 50 W* was added (pH *ca.* 2–3) and the mixture stirred at 20° for 30 min. After filtration, the solvent was evaporated, the residue taken up with pyridine (1 ml), anh. benzene (2 ml), and benzoyl chloride (0.1 ml), and the soln. heated to 70° for 1 h. Benzoyl chloride and benzene in excess were evaporated (20°/0.05 Torr), and the residue was extracted with toluene (20 ml)/H_2O (20 ml, 3 times). The org. phases were washed with sat. aq. Na_2CO_3 soln. (20 ml), dried ($MgSO_4$), and evaporated. The residue was purified on silica gel (6 g, AcOEt/petroleum ether 1:3): 110 mg (78.05%), colourless crystals. M.p. 82–84°. $[\alpha]_{589}^{25} = -19.8$, $[\alpha]_{578}^{25} = -20.6$, $[\alpha]_{546}^{25} = -23.6$, $[\alpha]_{436}^{25} = -42.1$, $[\alpha]_{365}^{25} = -59.7$ (c = 15 mg/ml, $CHCl_3$). UV (isooctane): 223 (12372), 269 (1343). UV (MeCN): 224 (10877). IR ($CHCl_3$): 3450, 3000, 2960, 2930, 2900, 2860, 1650, 1520, 1470, 1250, 1100, 840. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.8, 7.4 (5 arom. H); 6.5 (br. *m*, NH); 4.08 (*m*, H–C(2)); 4.02 (*d*, J = 4.0, H–C(4)); 3.92 (*q*, J = 3.5, H–C(5)); 3.82 (*dd*, J = 6.1, 6.0, H–C(3)); 3.76, 3.45 (2*ddd*, ^2J = 13.0, ^3J = 6.5, ^3J = 5.0, CH_2(1)); 3.72 (*dd*, ^2J = 12.0, ^3J = 3.0, CH_2(6)); 0.92, 0.91, 0.90 (3*s*, 3 *t*-BuSi); 0.19, 0.12, 0.09, 0.06 (4*s*, 3 Me_2Si). ^{13}C-NMR (90.55 MHz, $CDCl_3$): 171 (*s*); 191.3 (*s*); 129.7, 128.9, 128.9, 128.8, 128.8 (5*d*, ^1J(C,H) = 160); 86.9, 80.6, 74.05, 73.0 (4*d*, ^1J(C,H) = 150, C(2), C(3), C(4), C(5)); 62.9 (*t*, ^1J(C,H) = 150, C(6)); 41.8 (*t*, ^1J(C,H) = 130, C(1)); 25.8 (*m*, 3 *t*-BuSi); 18.4 (*s*); −4.3 to −5.2 (*m*, 6 Me). MS (70 eV): 613 (5), 612 (20), 611 (45), 610 (68, $M^{+\cdot}$), 609 (17), 608 (6), 555 (11), 553 (55), 552 (100), 299 (6), 281 (6), 105 (30), 77 (11), 75 (20), 74 (16), 73 (60). Anal. calc. for $C_{31}H_{59}O_5NSi_3$ (610.08): C 61.03, H 9.75, N 2.30, Si 13.81; found: C 62.79, H 9.81, N 2.15, Si 13.26.

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