(1-Ethoxyvinyl)lithium in the Total Synthesis of Thymine Polyoxin C and Uracil Polyoxin C[1)]

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A short path synthesis of the ethyl (methyl 2,3-*O*-isopropylidene-β-D-allofuranosid)uronate (5) and ethyl (methyl 2,3-*O*-isopropylidene-α-L-talofuranosid)uronate (6) from methyl 2,3-*O*-isopropylidene-β-D-ribopentodialdo-1,4-furanoside (3) using (1-ethoxyvinyl)lithium and its application to the total synthesis of the pyrimidine nucleosides, thymine polyoxin C (1) and uracil polyoxin C (2), are described.

Key words total synthesis; (1-ethoxyvinyl)lithium; α-hydroxy ester; thymine polyoxin C; uracil polyoxin C

Polyoxins are an important class of peptidyl nucleoside antibiotics isolated from the culture broths of *Streptomyces cacaoi* var. *asoensis*, and are potent competitive inhibitors of chitin synthetase of a variety of phytopathogenic fungi.[2)] They do not exhibit toxicity to bacteria, plants, or animals because chitin synthetase is inhibited. Recent studies suggest that polyoxins inhibit chitin synthetase of *Candida albicans*, a medically important human fungal pathogen.[3)] Such results indicate the usefulness of a new synthetic route to polyoxins or their analogs. All members of the polyoxin family possess the 1-(5-amino-5-deoxy-β-D-allofuranuronosyl)pyrimidines thymine polyoxin C (**1**) and uracil polyoxin C (**2**) as basic components.

A variety of chemical syntheses of amino acid nucleosides (**1** and **2**) have been reported over the years,[4)] and one of the most important intermediates for their general synthesis appears to be methyl 2,3-*O*-isopropylidene-α-L-talofuranosyluronic acid ester (A). For the synthesis of α-hydroxy ester from aldehyde, the reaction of aldehyde and 1-ethoxyvinyl carbanion followed by oxidative cleavage of the generated allyl alcohol (B) seem to be the most promising. We now report the short path synthesis of A from readily available methyl 2,3-*O*-isopropylidene-β-D-ribopentodialdo-1,4-furanoside (**3**)[4j)] derived from D-ribose by the addition of (1-ethoxyvinyl)lithium and its application to the total synthesis of thymine polyoxin C (**1**) and uracil polyoxin C (**2**).

D-Ribose was converted into methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (**4**) (67%). Swern's oxidation of **4** afforded the corresponding aldehyde (**3**) (90%). The reaction of the aldehyde (**3**) with (1-ethoxyvinyl)lithium[5)] followed by ozonolysis and subsequent treatment with Me_2S gave the diastereomeric mixture of α-hydroxy esters which were separated into the major α-hydroxy ester (**5**; 31% from **3**, $[\alpha]_D$ −52.3° (c=1.00, $CHCl_3$)) and the minor one (**6**; 10% yield from **3**, $[\alpha]_D$ −44.2° (c=1.46, $CHCl_3$)). The low diastereoselectivity (2:1) against **3** using vinylmagnesium bromide was also reported.[6)] An improvement of the diastereoselectivity against **3** using another carbanion in the presence of coexisting metal halide is being attempted. In spite of the low diastereoselectivity (3:1), the formation of the major product (**5**) was explained by taking into account the Felkin Ahn model (non-chelation) or β-chelation as shown in Chart 2. For the purpose of conversion of **5** into **6**, treatment of **5** with trifluoromethanesulfonic anhydride (Tf_2O) afforded the triflate (**7**) (83%) which was treated with benzoic acid in the presence of cesium fluoride (CsF)[7)] to provide the α-benzoyloxy ester (**8**) (86%). Alcoholysis of **8** gave the inverted α-hydroxy ester (**6**) (65%) which is consistent with the minor one (**6**). To determine the stereochemistry of **6**, the α-hydroxy ester (**6**) was converted to the reported (5*S*)-azide methyl ester (**9**).[4j)] Transesterification of **6** into the methyl ester (**10**) with MeOH in the presence of titanium(IV) isopropoxide ($Ti(O\text{-}isoPr)_4$) was achieved in 84% yield. Triflation of **10** followed by treatment of the triflate (**11**) (74%) with sodium azide (NaN_3) afforded the diastereomerically pure α-azide ester (**9**) (95%, $[\alpha]_D$

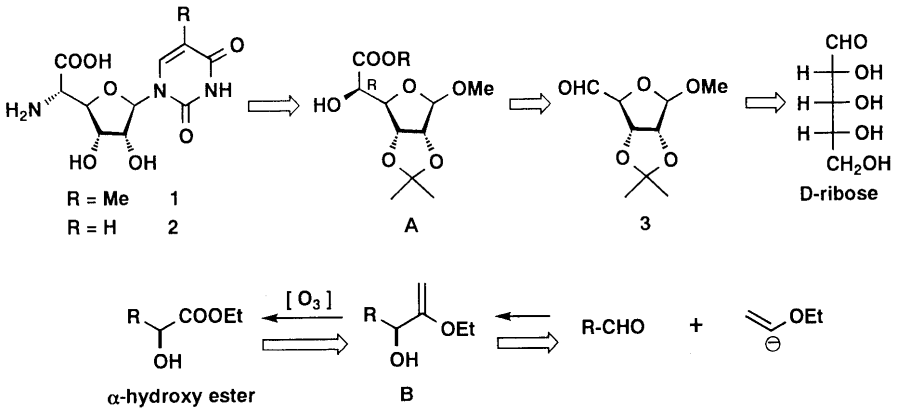

Chart 1

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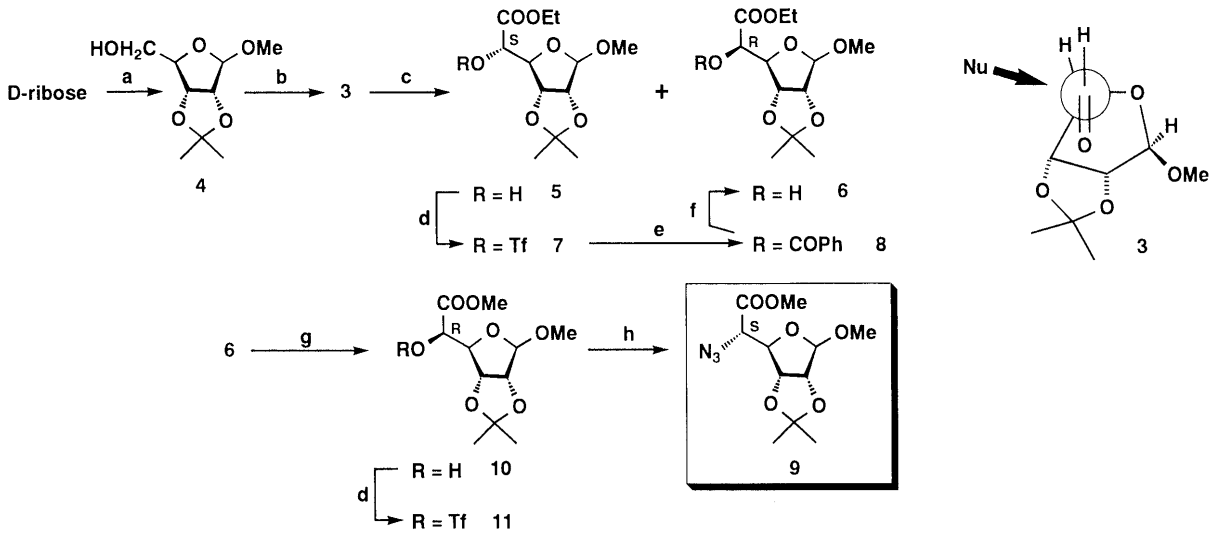
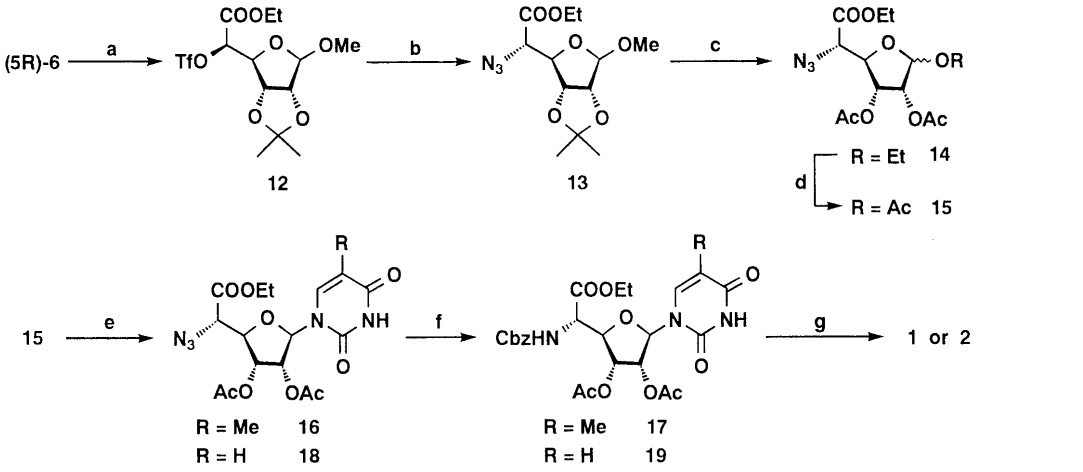


a; MeOH / acetone / *conc.* HCl b; DMSO / $(COCl)_2$ / Et_3N, -78 °C c; 1) Ethyl vinyl ether / *t*-BuLi, THF, -78 °C 2) O_3 / CH_2Cl_2 3) Me_2S / CH_2Cl_2 d; Tf_2O, pyridine / CH_2Cl_2 e; PhCOOH, CsF / DMF f; EtONa / EtOH g; MeOH, Ti(O-*i*Pr)$_4$ / PhH, reflux h; NaN_3 / DMF

Chart 2



a; Tf_2O, pyridine / CH_2Cl_2 b; NaN_3 / DMF c; 1) Dowex 50W H^+ / EtOH, reflux 2) Ac_2O / pyridine d; Ac_2O, AcOH, *conc.* H_2SO_4 / CH_2Cl_2 e; for 16: 5-methyl-2,4-bis(trimethylsilyloxy)pyrimidine, TMSOTf / CH_2Cl_2, reflux e; for 18: 2,4-bis(trimethylsilyloxy)pyrimidine, TMSOTf / CH_2Cl_2, reflux f; for 17: 1) H_2, 20% $Pd(OH)_2$-C / MeOH 2) CbzCl, 7% $NaHCO_3$ aq. / dioxane f; for 19: 1) H_2, 5% Pd-$BaSO_4$ / MeOH 2) CbzCl, 7% $NaHCO_3$ aq. / dioxane g; 1) $LiOH \cdot H_2O$ / THF 2) 0.1 N HCl 3) H_2, 10% Pd-C / MeOH

Chart 3

$-53.3°$ ($c=1.41$, $CHCl_3$)) whose spectral data were identical with those ($[\alpha]_D$ $-55.3°$ ($c=0.89$, $CHCl_3$), ^{1}H-NMR) of the reported (5*S*)-**9**.[4j] Thus, the stereochemistry due to the C-5 position of α-hydroxy esters (**5**) and (**6**) was found to be *S*- and *R*-configurations, respectively.

Conversion of ethyl ester group into methyl ester group is not always essential for the total synthesis of the target molecules (**1**) and (**2**). Treatment of the (*R*)-α-hydroxy ethyl ester (**6**) with Tf_2O in pyridine gave the triflate (**12**) (64%) which was reacted with NaN_3 in dimethyl formamide (DMF) to afford the (*S*)-α-azide ethyl ester (**13**) (86%, $[\alpha]_D$ $-49.1°$ ($c=1.17$, $CHCl_3$)). The (*S*)-α-azide ethyl ester (**13**) was subjected to the deisopropylidenation (Dowex 50W H^+, EtOH reflux) to provide the diol, which was acetylated directly (Ac_2O, pyridine) to yield the diastereomeric mixture of diacetate (**14**) (87%). Anomeric acetolysis smoothly gave the triacetate (**15**) (88%) in which no C-5 epimerization could be detected. Reaction of the triacetate (**15**) with 5-methyl-2,4-bis(trimethylsilyloxy)-pyrimidine[8] under the conditions reported by Vorbrüggen *et al.*[9] (trimethylsilyl trifluoromethanesulfonate (TMSOTf), 1,2-dichloroethane, reflux) gave exclusively the β-nucleoside (**16**) (84%). Hydrogenation of the azide (**16**) in the presence of 20% $Pd(OH)_2$–C afforded the α-amino acid ester which was treated with benzyl chloroformate (CbzCl) in the presence of 7% aqueous $NaHCO_3$ to provide the (5*S*)-**17** (90% from **16**). Alkaline hydrolysis of **17** followed by hydrogenation gave thymine polyoxin C (**1**) (75% from **17**). The synthetic material (**1**, $[\alpha]_D$ $+8.5°$

($c=0.53$, H_2O), mp 190—192 °C, ^{1}H-NMR) was identical with authentic material ($[\alpha]_D$ +8.2° ($c=0.7$, H_2O),[3a] $[\alpha]_D$ +8.0° ($c=0.37$, H_2O),[4c] mp 190—194 °C,[4c] mp 180—190 °C,[4f] ^{1}H-NMR[4c,d]). Likewise, reaction of the key triacetate (**15**) with 2,4-bis(trimethylsilyloxy)pyrimidine[8] under similar conditions afforded exclusively the β-nucleoside (**18**) (84%). Hydrogenation of the azide (**18**) in the presence of 5% Pd–$BaSO_4$ followed by protection of the amino group with CbzCl in the presence of 7% aqueous $NaHCO_3$ gave the (5*S*)-**19** (74% from **18**). Alkaline hydrolysis of **19** followed by hydrogenation afforded uracil polyoxin C (**2**, 72% from **19**, $[\alpha]_D$ +15.9° ($c=0.58$, H_2O), mp 247—250 °C, ^{1}H-NMR) which was identical with authentic material (**2**, $[\alpha]_D$ +15.8° ($c=0.205$, H_2O),[2a] mp 240—247 °C,[2a] ^{1}H-NMR[4j]). The syntheses described herein demonstrate the utility of (1-ethoxyvinyl)lithium for the short path synthesis of α-hydroxy esters (**5** and **6**) from the aldehyde (**3**), which contribute to the total syntheses of thymine polyoxin C (**1**) and uracil polyoxin C (**2**).

Experimental

All melting points were measured on a Yanaco MP-S3 micro melting point apparatus and are uncorrected. NMR spectra were measured on a JEOL EX-400 spectrometer and spectra were taken as 5—10% (W/V) solutions in $CDCl_3$ with Me_4Si as an internal reference. IR spectra were measured on a JASCO FT/IR-300 spectrometer. FAB-MS were obtained with a JEOL JMS-DX 303 instrument. High-resolution mass spectra (HRMS, FAB-MS) were recorded on a JEOL JMS-HX 100 mass spectrometer. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. All the reactions were carried out in an atmosphere of argon. All evaporations were performed under reduced pressure.

Methyl 2,3-*O*-Isopropylidene-β-D-ribofuranoside (4) To a solution of D-ribose (24.7 g, 0.165 mol) in a mixed solvent (acetone (95 ml), and MeOH (95 ml)) was added concentrated HCl (2.5 ml) and the solution was allowed to reflux for 14 h. The reaction mixture was cooled, neutralized with pyridine, poured into H_2O, and extracted with Et_2O. The organic layer was dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel (300 g) with hexane/EtOAc (4 : 1) to give **4** as a colorless oil (22.6 g, 67% yield). **4**: *Anal.* Calcd for $C_9H_{16}O_5$: C, 52.93; H, 7.90. Found C, 52.51; H, 8.00. FAB-MS *m/z*: 205($M^+ + 1$). IR(neat): 3452 cm^{-1}. NMR δ: 1.32 (s, 3H), 1.49 (s, 3H), 3.44 (s, 3H), 3.61 (dd, 1H, $J=3$, 13 Hz), 3.79 (dd, 1H, $J=3$, 13 Hz), 4.43 (m, 1H), 4.59 (d, 1H, $J=6$ Hz), 4.83 (d, 1H, $J=6$ Hz), 4.98 (s, 1H).

Methyl 2,3-*O*-Isopropylidene-β-D-ribopentodialdo-1,4-furanoside (3) To a solution of dimethyl sulfoxide (DMSO) (14.9 ml, 0.21 mol) in CH_2Cl_2 (100 ml) was added oxalyl chloride (8.9 ml, 0.11 mol) at −78 °C and the reaction mixture was stirred for 0.5 h. A solution of **4** (10.7 g, 0.053 mol) in CH_2Cl_2 (10 ml) was added to the above reaction mixture and the whole mixture was stirred for 0.5 h. Et_3N (58 ml, 0.42 mol) was added to the above reaction mixture and the whole mixture was stirred at r.t. for 15 min. The reaction mixture was diluted with 0.1 N HCl and extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel (200 g) with hexane/EtOAc (4 : 1) to afford **3** as colorless crystals (9.56 g, 90% yield). **3**: mp 66—67 °C. *Anal.* Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found C, 53.21; H, 6.96. FAB-MS *m/z*: 203($M^+ + 1$). IR (neat): 1740, 1589 cm^{-1}. NMR δ: 1.32 (s, 3H), 1.48 (s, 3H), 3.44 (s, 3H), 4.46 (s, 1H), 4.49 (d, 1H, $J=6$ Hz), 5.94 (d, 1H, $J=6$ Hz), 5.08 (s, 1H), 9.57 (s, 1H)

Ethyl (Methyl 2,3-*O*-Isopropylidene-β-D-allofuranosid)uronate (5) and Ethyl (Methyl 2,3-*O*-Isopropylidene-α-L-talofuranosid)uronate (6) To a solution of ethyl vinyl ether (4.75 ml, 49.4 mmol) in THF (20 ml) at −78 °C was added *tert*-BuLi (1.7 M in pentane, 29.1 ml (49.5 mmol)) and the reaction mixture was stirred for 20 min. This mixture was added to a solution of **3** (2 g, 9.89 mmol) in THF (10 ml) at −78 °C and the whole mixture was stirred for 1 h. The reaction mixture was diluted with H_2O and extracted with Et_2O. The extract was dried ($MgSO_4$) and concentrated. The residue was dissolved in CH_2Cl_2 (10 ml) and ozone was passed through the above solution at −78 °C for 1.5 h followed by the addition of Me_2S (3 ml). The whole reaction mixture was stirred at r.t. for 0.5 h and diluted with H_2O, extracted with Et_2O. The organic layer was dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel (60 g) with hexane/EtOAc (10 : 1—9 : 1) to give **6** (less polar) as a colorless oil and **5** (more polar) as a colorless oil. **5**: yield: 842 mg (31%). *Anal.* Calcd for $C_{12}H_{20}O_7$: C, 52.16; H, 7.30. Found C, 52.09; H, 7.43. FAB-MS *m/z*: 277 ($M^+ + 1$). IR (neat): 3444, 1749 cm^{-1}. $[\alpha]_D^{26}$ −52.3° ($c=1.0$, $CHCl_3$). NMR δ: 1.31 (s, 3H), 1.32 (t, 3H, $J=7.3$ Hz), 1.47 (s, 3H), 3.43 (s, 3H), 3.91 (d, 1H, $J=3.9$ Hz), 4.26 (m, 2H, $J=7.3$ Hz), 4.29 (d, 1H, $J=4.4$ Hz), 4.53 (d, 1H, $J=4.4$ Hz), 4.60 (d, 1H, $J=5.9$ Hz), 4.91 (d, 1H, $J=5.9$ Hz), 5.00 (s, 1H). **6**: yield: 283 mg (10%). *Anal.* Calcd for $C_{12}H_{20}O_7$: C, 52.16; H, 7.30. Found C, 52.27; H, 7.49. FAB-MS *m/z*: 277 ($M^+ + 1$). IR (neat): 3446, 1738 cm^{-1}. $[\alpha]_D^{28}$ −44.2° ($c=1.46$, $CHCl_3$). NMR δ: 1.31 (t, 3H, $J=7$ Hz), 1.32 (s, 3H), 1.48 (s, 3H), 3.42 (s, 3H), 4.23 (s, 1H), 4.24 (s, 1H), 4.25 (q, 2H, $J=7$ Hz), 4.60 (d, 1H, $J=6$ Hz), 4.79 (s, 1H), 4.90 (d, 1H, $J=6$ Hz), 4.94 (s, 1H).

Ethyl (Methyl 5-Deoxy-5-trifluoromethanesulfonyloxy-2,3-*O*-isopropylidene-β-D-allofuranosid)uronate (7) To a solution of **5** (548 mg, 1.98 mmol) in a mixed solvent (pyridine (1.6 ml, 19.8 mmol) and CH_2Cl_2 (16 ml)) at 0 °C was added trifluoromethanesulfonic anhydride (0.63 ml, 3.96 mmol). After stirring for 20 min, the reaction mixture was diluted with H_2O and extracted with Et_2O. The organic layer was washed with 1 N HCl and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (20 g) with hexane/EtOAc (15 : 1) to provide **7** (675 mg, 83% yield) as a colorless oil. **7**: *Anal.* Calcd for $C_{13}H_{19}F_3O_9S$: C, 38.24; H, 4.70. Found C, 38.60; H, 4.63. FAB-MS *m/z*: 407 ($M^+ - 1$). IR (neat): 2941, 1759, 1423 cm^{-1}. $[\alpha]_D^{24}$ −57.3° ($c=1.21$, $CHCl_3$). NMR δ: 1.33 (s, 3H), 1.34 (t, 3H, $J=7$ Hz), 1.48 (s, 3H), 3.38 (s, 3H), 4.32 (q, 2H, $J=7$ Hz), 4.55 (dd, 1H, $J=1.5$, 6.3 Hz), 4.61 (d, 1H, $J=5.9$ Hz), 4.87 (dd, 1H, $J=1.5$, 5.9 Hz), 5.02 (s, 1H), 5.10 (d, 1H, $J=5.9$ Hz).

Ethyl (Methyl 5-Benzoyloxy-5-deoxy-2,3-*O*-isopropylidene-α-L-talofuranosid)uronate (8) To a solution of **7** (825 mg, 2.02 mmol) in DMF (16 ml) at r.t. was added cesium fluoride (CsF, 1.53 g, 10 mmol) and benzoic acid (1.23 g, 10 mmol), and the reaction mixture was allowed to stir at 60 °C for 15 h. After cooling, the reaction mixture was diluted with H_2O and extracted with Et_2O. The organic layer was washed with sat. $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel (20 g) with hexane/EtOAc (15 : 1) to provide **8** (658 mg, 86% yield) as a colorless oil. **8**: *Anal.* Calcd for $C_{19}H_{24}O_8$: C, 59.99; H, 6.34. Found C, 59.98; H, 6.21. FAB-MS *m/z*: 379 ($M^+ - 1$), 365 ($M^+ - CH_3$), 349 ($M^+ - OCH_3$). IR (neat): 2985, 2937, 1765, 1730, 1602 cm^{-1}. $[\alpha]_D^{24}$ −48.5° ($c=1.29$, $CHCl_3$). NMR δ: 1.29 (t, 3H, $J=7.3$ Hz), 1.32 (s, 3H), 1.52 (s, 3H), 3.33 (s, 3H), 4.27 (q, 2H, $J=7.3$ Hz), 4.68 (d, 1H, $J=5.9$ Hz), 4.80 (dd, 1H, $J=1.5$, 5.4 Hz), 4.90 (dd, 1H, $J=1.5$, 5.9 Hz), 5.08 (s, 1H), 5.34 (d, 1H, $J=5.4$ Hz), 7.48 (t, 2H, $J=7.9$ Hz), 7.60 (t, 1H, $J=7.3$ Hz), 8.20 (d, 2H, $J=8.3$ Hz).

Ethyl (Methyl 2,3-*O*-Isopropylidene-α-L-talofuranosid)uronate (6) To a solution of **8** (658 mg, 1.73 mmol) in EtOH (6 ml) at 0 °C was added 0.1 N-EtONa/EtOH (19 ml, 1.9 mmol), prepared beforehand in another flask; the reaction mixture was then stirred for 1.5 h, acidified with 1 N HCl and extracted with Et_2O. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel (20 g) with hexane/EtOAc (10 : 1) to provide **6** (312 mg, 65% yield) as a colorless oil.

Methyl (Methyl 2,3-*O*-Isopropylidene-α-L-talofuranosid)uronate (10) Titanium(IV) isopropoxide (0.17 ml, 0.57 mmol) was added to a mixture of **6** (198 mg, 0.71 mmol) in a mixed solvent (PhH (6 ml), MeOH (2.94 ml)) and the whole mixture was refluxed for 16 h. It was diluted with H_2O (20 ml), extracted with Et_2O. The organic layer was dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel (20 g) with hexane/EtOAc (10 : 1) to give **10** (158 mg, 84% yield) as a colorless oil. **10**: *Anal.* Calcd for $C_{11}H_{18}O_7$: C, 50.37; H, 6.92. Found C, 50.27; H, 7.03. FAB-MS *m/z*: 263 ($M^+ + 1$). IR (neat): 3419, 1747 cm^{-1}. $[\alpha]_D^{28}$ −56.7° ($c=1.47$, $CHCl_3$). NMR δ: 1.32 (s, 3H), 1.47 (s, 3H), 3.42 (s, 3H), 3.79 (s, 3H), 4.26 (s, 1H), 4.26 (d, 1H, $J=2$ Hz), 4.60 (d, 1H, $J=5.9$ Hz), 4.78 (d, 1H, $J=2$ Hz), 4.90 (d, 1H, $J=5.9$ Hz), 4.94 (s, 1H).

Methyl (Methyl 5-Deoxy-5-trifluoromethanesulfonyloxy-2,3-*O*-isopropylidene-α-L-talofuranosid)uronate (11) To a solution of **10** (85 mg, 0.326 mmol) in a mixed solvent (pyridine (0.26 ml, 2.6 mmol) and CH_2Cl_2 (2 ml)) at 0 °C was added trifluoromethanesulfonic anhydride (0.11 ml, 0.671 mmol). After stirring for 20 min, the reaction mixture was diluted

with H_2O and extracted with Et_2O. The organic layer was washed with 1 N HCl and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (10 g) with hexane/EtOAc (15 : 1) to give **11** (95 mg, 74% yield) as a colorless oil. **11**: FAB-MS *m/z*: 395 ($M^+ + 1$). IR (neat): 2942, 1756, 1421 cm^{-1}. $[\alpha]_D^{24}$ −15.0° ($c = 1.19$, $CHCl_3$). NMR δ: 1.33 (s, 3H), 1.49 (s, 3H), 3.37 (s, 3H), 3.89 (s, 3H), 4.60 (d, 2H, $J = 6$ Hz), 4.85 (dd, 1H, $J = 2, 6$ Hz), 5.05 (s, 1H), 5.19 (d, 1H, $J = 6$ Hz).

Methyl (Methyl 5-Azido-5-deoxy-2,3-*O*-isopropylidene-β-D-allofuranosid)uronate (9) To a solution of **11** (84 mg, 0.215 mmol) in DMF (1 ml) was added NaN_3 (15 mg, 0.237 mmol) at 0 °C and the reaction mixture was stirred at r.t. for 25 min. It was diluted with H_2O and extracted with Et_2O. The organic layer was dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel (10 g) with hexane/EtOAc (20 : 1) to give **9** (58 mg, 95% yield) as a colorless oil. **9**: *Anal.* Calcd for $C_{11}H_{17}N_3O_6$: C, 45.99; H, 5.97; N, 14.63. Found C, 46.35; H, 6.02; N, 14.21. FAB-MS *m/z*: 288 ($M^+ + 1$). IR (neat): 2939, 2112, 1747, 1438 cm^{-1}. $[\alpha]_D^{24}$ −53.3° ($c = 1.41$, $CHCl_3$). NMR δ: 1.33 (s, 3H), 1.49 (s, 3H), 3.34 (s, 3H), 3.82 (d, 1H, $J = 9$ Hz), 3.84 (s, 3H), 4.45 (dd, 1H, $J = 1$, 9 Hz), 4.59 (d, 1H, $J = 6$ Hz), 4.87 (dd, 1H, $J = 1$, 6 Hz), 4.98 (s, 1H).

Ethyl (Methyl 5-Deoxy-5-trifluoromethanesulfonyloxy-2,3-*O*-isopropylidene-α-L-talofuranosid)uronate (12) To a solution of **6** (82 mg, 0.3 mmol) in a mixed solvent (pyridine (0.22 ml, 2.2 mmol) and CH_2Cl_2 (2 ml)) at 0 °C was added trifluoromethanesulfonic anhydride (0.1 ml, 0.61 mmol). After stirring for 15 min, the reaction mixture was diluted with H_2O and extracted with Et_2O. The organic layer was washed with 1 N HCl and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (10 g) with hexane/EtOAc (15 : 1) to afford **12** (78 mg, 64% yield) as a colorless oil. **12**: *Anal.* Calcd for $C_{13}H_{19}F_3O_9S$: C, 38.24; H, 4.70. Found C, 38.20; H, 4.29. FAB-MS *m/z*: 407 ($M^+ - 1$). IR (neat): 2941, 1749, 1421 cm^{-1}. $[\alpha]_D^{28}$ −8.9° ($c = 0.46$, $CHCl_3$). NMR δ: 1.33 (s, 3H), 1.34 (t, 3H, $J = 7$ Hz), 1.49 (s, 3H), 3.37 (s, 3H), 4.34 (q, 2H, $J = 7$ Hz), 4.60 (dd, 1H, $J = 2.5$, 5.9 Hz), 4.60 (d, 1H, $J = 5.9$ Hz), 4.85 (dd, 1H, $J = 2$, 5.9 Hz), 5.05 (s, 1H), 5.15 (d, 1H, $J = 5.9$ Hz).

Ethyl (Methyl 5-Azido-5-deoxy-2,3-*O*-isopropylidene-β-D-allofuranosid)uronate (13) To a solution of **12** (625 mg, 1.53 mmol) in DMF (7 ml) was added NaN_3 (119 mg, 1.84 mmol) at 0 °C and the reaction mixture was stirred at r.t. for 1 h. It was diluted with H_2O and extracted with Et_2O. The organic layer was dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel (20 g) with hexane/EtOAc (20 : 1) to give **13** (395 mg, 86% yield) as a colorless oil. **13**: *Anal.* Calcd for $C_{12}H_{19}N_3O_6$: C, 47.83; H, 6.36; N, 13.95. Found C, 47.95; H, 6.36; N, 13.68. FAB-MS *m/z*: 300 ($M^+ - 1$). IR (neat): 2987, 2110, 1743, 1446 cm^{-1}. $[\alpha]_D^{28}$ −49.1° ($c = 1.17$, $CHCl_3$). NMR δ: 1.33 (s, 3H), 1.34 (t, 3H, $J = 7$ Hz), 1.52 (s, 3H), 3.35 (s, 3H), 3.79 (d, 1H, $J = 9$ Hz), 4.30 (q, 2H, $J = 7$ Hz), 4.45 (dd, 1H, $J = 1$, 9 Hz), 4.60 (d, 1H, $J = 6$ Hz), 4.86 (dd, 1H, $J = 1$, 6 Hz), 4.98 (s, 1H).

Ethyl (Ethyl 5-Azido-5-deoxy-2,3-di-*O*-acetyl-D-allofuranosid)uronate (14) To a solution of **13** (168 mg, 0.558 mmol) in EtOH (8 ml) was added Dowex 50W H^+ resin (530 mg), and the reaction mixture was refluxed for 14 h. The solution was filtered with the aid of Celite, the Celite was washed with EtOH and CH_2Cl_2, and the whole filtrate was evaporated. A mixture of the residue and Ac_2O (1.35 ml, 14.3 mmol) in pyridine (5.4 ml, 54.4 mmol) was stirred at r.t. for 1 h. The reaction mixture was poured into ice (10 g), allowed to stir for 0.5 h, and extracted with Et_2O. The organic layer was washed with 2 N HCl, 7% aqueous $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (10 g) with hexane/EtOAc (7 : 1) to give **14** (174 mg, 87% yield) as a colorless oil. **14**: *Anal.* Calcd for $C_{14}H_{21}N_3O_8$: C, 46.79; H, 5.89; N, 11.70. Found C, 47.04; H, 5.65; N, 11.14. FAB-MS *m/z*: 358 ($M^+ - 1$). IR (neat): 2981, 2113, 1754 cm^{-1}. α-anomer: NMR δ: 1.23 (t, 3H, $J = 7$ Hz), 1.33 (t, 3H, $J = 7$ Hz), 2.11 (s, 3H), 2.12 (s, 3H), 3.57—3.64 (m, 1H), 3.75—3.83 (m, 1H), 4.28 (q, 2H, $J = 7$ Hz), 4.36 (d, 1H, $J = 3$ Hz), 4.46 (t, 1H, $J = 3.4$ Hz), 4.96 (dd, 1H, $J = 4.4$, 7.3 Hz), 5.29 (d, 1H, $J = 4.4$ Hz), 5.34 (dd, 1H, $J = 3.9$, 7.3 Hz). β-anomer: NMR δ: 1.21 (t, 3H, $J = 7$ Hz), 1.34 (t, 3H, $J = 7$ Hz), 2.05 (s, 3H), 2.11 (s, 3H), 3.45—3.51 (m, 1H), 3.75—3.83 (m, 1H), 3.95 (d, 1H, $J = 6.4$ Hz), 4.25—4.32 (m, 2H), 4.47 (t, 1H, $J = 6.4$ Hz), 5.00 (s, 1H), 5.23 (d, 1H, $J = 4.9$ Hz), 5.55 (dd, 1H, $J = 4.9$, 6.4 Hz).

Ethyl (5-Azido-5-deoxy-1,2,3-tri-*O*-acetyl-D-allofuranosid)uronate (15) To a solution of **14** (210 mg, 0.586 mmol) in a mixed solvent (CH_2Cl_2 (1.6 ml), AcOH (1.6 ml)) at 0 °C was added Ac_2O (0.5 ml, 5.3 mmol) followed by a catalytic amount of H_2SO_4 (1 drop). The reaction mixture was allowed to stir at 0 °C for 1 h and at r.t. for a further 1 h. It was then poured into ice, allowed to stir for 0.5 h, and extracted with Et_2O. The organic layer was washed with 7% aqueous $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel (10 g) with hexane/EtOAc (7 : 1) to provide **15** (192 mg, 88% yield) as a colorless oil. **15**: *Anal.* Calcd for $C_{14}H_{19}N_3O_9$: C, 45.04; H, 5.13; N, 11.26. Found C, 45.08; H, 4.72; N, 10.99. FAB-MS *m/z*: 374 ($M^+ + 1$). IR (neat): 2986, 2116, 1747 cm^{-1}. α-anomer: NMR δ: 1.33 (t, 3H, $J = 7$ Hz), 2.08 (s, 3H), 2.12 (s, 6H), 4.29 (q, 2H, $J = 7$ Hz), 4.39 (d, 1H, $J = 2.9$ Hz), 4.62 (t, 1H, $J = 2.9$ Hz), 5.24 (dd, 1H, $J = 4.9$, 6.8 Hz), 5.37 (dd, 1H, $J = 2.4$, 6.8 Hz), 6.44 (d, 1H, $J = 4.9$ Hz). β-anomer: NMR δ: 1.33 (t, 3H, $J = 7.3$ Hz), 2.03 (s, 3H), 2.13 (s, 6H), 4.25 (q, 2H, $J = 7.3$ Hz), 4.29 (d, 1H, $J = 4.9$ Hz), 4.60 (dd, 1H, $J = 4.9$, 6.8 Hz), 5.36 (d, 1H, $J = 4.9$ Hz), 5.55 (dd, 1H, $J = 4.9$, 6.8 Hz), 6.16 (s, 1H).

1-(Ethyl 2′,3′-Di-*O*-acetyl-5′-azido-5′-deoxy-β-D-allofuranosyluronate)-thymine (16) A mixture of thymine (260 mg, 2.07 mmol), 1,1,1,3,3,3-hexamethyldisilazane (6.2 ml, 36.9 mmol) and trimethylsilyl chloride (0.66 ml, 5.12 mmol) was refluxed for 16 h, then cooled and evaporated. The residue was dissolved in 1,2-dichloroethane (10 ml), and the resulting clear solution was used for subsequent reactions. To a solution of **15** (104 mg, 0.28 mmol) in $ClCH_2CH_2Cl$ (5.2 ml) was added the above solution and the reaction mixture was allowed to stir for 5 min. After adding trimethylsilyl trifluoromethanesulfonate (0.3 ml, 1.68 mmol), the reaction mixture was allowed to stir at 100 °C for 1 h and then quenched by adding 7% aqueous $NaHCO_3$. The reaction mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel (10 g) with hexane/EtOAc (1 : 1) to give **16** (103 mg, 84% yield) as a colorless oil. **16**: HRMS (FAB-MS): Calcd for $C_{17}H_{21}N_5O_9$ ($M^+ + 1$) 440.1418. Found 440.1422. IR (KBr): 3022, 2116, 1749, 1693, 1469 cm^{-1}. $[\alpha]_D^{21}$ −66.9° ($c = 1.12$, $CHCl_3$). NMR δ: 1.35 (t, 3H, $J = 7$ Hz), 1.96 (d, 3H, $J = 1$ Hz), 2.08 (s, 3H), 2.12 (s, 3H), 4.33 (q, 2H, $J = 7$ Hz), 4.46 (t, 1H, $J = 2.9$ Hz), 4.50 (d, 1H, $J = 3.4$ Hz), 5.33 (dd, 1H, $J = 5.9$, 7.3 Hz), 5.42 (dd, 1H, $J = 2.9$, 5.9 Hz), 6.21 (d, 1H, $J = 7.3$ Hz), 7.32 (d, 1H, $J = 1$ Hz), 9.25 (br, 1H).

1-(Ethyl 2′,3′-Di-*O*-acetyl-5′-carbobenzyloxyamino-5′-deoxy-β-D-allofuranosyluronate)thymine (17) A mixture of **16** (101 mg, 0.23 mmol) and 20% $Pd(OH)_2$–C (30 mg) in EtOH (2 ml) was subjected to catalytic hydrogenation at ordinary temperature and the reaction mixture was filtered with the aid of Celite. The filtrate was evaporated to give the residue. A mixture of the residue, benzyl chloroformate (0.12 ml, 0.8 mmol), and 7% aqueous $NaHCO_3$ (0.7 ml) in dioxane (3 ml) was stirred at r.t. for 1 h, and diluted with H_2O. The reaction mixture was extracted with EtOAc, and the organic layer was dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel (10 g) with hexane/EtOAc (1 : 1) to afford **17** (113 mg, 90% overall yield) as a colorless oil. **17**: FAB-MS *m/z*: 548 ($M^+ + 1$). IR (KBr): 3656—2856, 1702, 1532, 1463 cm^{-1}. $[\alpha]_D^{27}$ +16.3° ($c = 0.40$, $CHCl_3$). NMR δ: 1.31 (t, 3H, $J = 7$ Hz), 1.89 (s, 3H), 2.08 (s, 3H), 2.09 (s, 3H), 4.20—4.29 (m, 2H), 4.40 (t, 1H, $J = 4$ Hz), 4.80 (dd, 1H, $J = 3.4$, 8 Hz), 5.12 (d, 1H, $J = 12$ Hz), 5.16 (d, 1H, $J = 12$ Hz), 5.27 (t, 1H, $J = 6$ Hz), 5.54 (t, 1H, $J = 5.9$ Hz), 5.80 (d, 1H, $J = 8$ Hz), 5.97 (d, 1H, $J = 5.9$ Hz), 7.07 (s, 1H), 7.31—7.40 (m, 5H), 8.66 (br, 1H).

1-(5′-Amino-5′-deoxy-β-D-allofuranosyluronic acid)thymine (Thymine Polyoxin C) (1) A mixture of **17** (534 mg, 0.967 mmol) and $LiOH \cdot H_2O$ (204 mg, 4.88 mmol) in a mixed solvent (THF/H_2O (4 : 1), 10 ml) was stirred at 0 °C for 4 h. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The aqueous layer was adjusted with 1 N HCl to pH 2—3 and extracted with EtOAc. The EtOAc layer was dried ($MgSO_4$) and evaporated. A mixture of the residue and 10% Pd–C (50 mg) in MeOH (5 ml) was subjected to catalytic hydrogenation at ordinary temperature and the reaction mixture was filtered with the aid of Celite and activated carbon. The filtrate was evaporated and the residue was crystallized from MeOH and H_2O to give **1** (220 mg, 75% overall yield) as a pale yellow solid. **1**: mp 190—192 °C. $[\alpha]_D^{27}$ +8.5° ($c = 0.53$, H_2O). HRMS (FAB): Calcd for $C_{11}H_{16}N_3O_7$ ($M^+ + 1$) 302.0988. Found 302.0992. IR (KBr): 3600—2921, 1681, 1616, 1469 cm^{-1}. NMR (3% DCl in D_2O) δ: 1.88 (d, 3H, $J = 1.2$ Hz), 4.39 (dd, 1H, $J = 2.9$, 6.9 Hz), 4.45 (dd, 1H, $J = 4$, 6.5 Hz), 4.63 (d, 1H, $J = 2.9$ Hz), 4.69 (t, 1H, $J = 6.6$ Hz), 5.77 (d, 1H, $J = 4$ Hz), 7.33 (d, 1H, $J = 1.2$ Hz).

1-(Ethyl 2′,3′-Di-*O*-acetyl-5′-azido-5′-deoxy-β-D-allofuranosyluronate)-uracil (18) A mixture of uracil (229 mg, 2.05 mmol), 1,1,1,3,3,3-hexamethyldisilazane (6.2 ml, 36.9 mmol) and trimethylsilyl chloride (0.66 ml, 5.12 mmol) was refluxed for 12 h, cooled and evaporated. The residue

was dissolved in 1,2-dichloroethane (10 ml), and the resulting clear solution was used for subsequent reactions. To a solution of **15** (166 mg, 0.445 mmol) in $ClCH_2CH_2Cl$ (8.3 ml) was added the above solution and the reaction mixture was allowed to stir for 5 min. After adding trimethylsilyl trifluoromethanesulfonate (0.48 ml, 2.67 mmol), the reaction mixture was allowed to stir at 100 °C for 2 h and then quenched by adding 7% aqueous $NaHCO_3$. The reaction mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel (10 g) with hexane/EtOAc (1 : 1) to afford **18** (160 mg, 84% yield) as a colorless oil. **18**: *Anal.* Calcd for $C_{16}H_{19}N_5O_9 \cdot H_2O$: C, 43.34; H, 4.77; N, 15.79. Found C, 43.40; H, 4.35; N, 15.29. HRMS (FAB-MS): Calcd for $C_{16}H_{19}N_5O_9$ ($M^+ + 1$) 426.1261. Found 426.1263. IR (KBr): 3067, 2117, 1729, 1458 cm^{-1}. $[\alpha]_D^{25}$ −63.4° ($c = 1.57$, $CHCl_3$). NMR δ: 1.34 (t, 3H, $J = 7$ Hz), 2.08 (s, 3H), 2.13 (s, 3H), 4.33 (q, 2H, $J = 7$ Hz), 4.47 (t, 1H, $J = 3$ Hz), 4.50 (d, 1H, $J = 3.4$ Hz), 5.33 (t, 1H, $J = 6.5$ Hz), 5.40 (dd, 1H, $J = 3$, 6 Hz), 5.86 (dd, 1H, $J = 1.5$, 8.3 Hz), 6.20 (d, 1H, $J = 7.3$ Hz), 7.53 (d, 1H, $J = 8.3$ Hz), 9.44 (br, 1H).

1-(Ethyl 2′,3′-Di-*O*-acetyl-5′-carbobenzyloxyamino-5′-deoxy-β-D-allofuranosyluronate)uracil (19) A mixture of **18** (90 mg, 0.212 mmol) and 5% Pd on $BaSO_4$ (30 mg) in MeOH (3 ml) was subjected to catalytic hydrogenation at ordinary temperature and the reaction mixture was filtered with the aid of Celite. The filtrate was evaporated to give the residue. A mixture of the residue, benzyl chloroformate (0.1 ml, 0.67 mmol), and 7% aqueous $NaHCO_3$ (1 ml) in dioxane (3 ml) was stirred at r.t. for 1 h, and diluted with brine. The reaction mixture was extracted with EtOAc, and the organic layer was dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel (10 g) with hexane/EtOAc (1 : 2) to afford **19** (84 mg, 74% overall yield) as a colorless oil. **19**: *Anal.* Calcd for $C_{24}H_{27}N_3O_{11}$: C, 54.03; H, 5.10; N, 7.88. Found C, 54.03; H, 4.68; N, 8.02. FAB-MS *m/z*: 534 ($M^+ + 1$). IR (KBr): 3300, 3022, 1693, 1529 cm^{-1}. $[\alpha]_D^{25}$ +22.8° ($c = 0.705$, $CHCl_3$). NMR δ: 1.30 (t, 3H, $J = 7$ Hz), 2.04 (s, 3H), 2.08 (s, 3H), 4.19—4.31 (m, 2H), 4.41 (t, 1H, $J = 4.5$ Hz), 4.81 (d, 1H, $J = 4.9$ Hz), 5.11 (d, 1H, $J = 12$ Hz), 5.15 (d, 1H, $J = 12$ Hz), 5.27 (dd, 1H, $J = 5.9$, 6.4 Hz), 5.51 (dd, 1H, $J = 5.4$, 5.9 Hz), 5.66 (dd, 1H, $J = 1.5$, 8 Hz), 5.90 (d, 1H, $J = 8$ Hz), 5.96 (d, 1H, $J = 5.9$ Hz), 7.22 (d, 1H, $J = 8$ Hz), 7.32—7.36 (m, 5H), 9.21 (br, 1H).

1-(5′-Amino-5′-deoxy-β-D-allofuranosyluronic acid)uracil (Uracil Polyoxin C) (2) A mixture of **19** (72 mg, 0.135 mmol) and $LiOH \cdot H_2O$ (28 mg, 0.675 mmol) in a mixed solvent (THF/H_2O (4 : 1), 7.7 ml) was stirred at 0 °C for 2 h. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The aqueous layer was adjusted with 1 N HCl to pH 2—3 and extracted with EtOAc. The EtOAc layer was dried ($MgSO_4$) and evaporated. A mixture of the residue and 10% Pd–C (30 mg) in MeOH (4.5 ml) was subjected to catalytic hydrogenation at ordinary temperature and the reaction mixture was filtered with the aid of Celite and activated carbon. The filtrate was evaporated and the residue was crystallized from H_2O to give **2** (28 mg, 72% overall yield) as a pale yellow solid. **2**: mp 247—250 °C; $[\alpha]_D^{27}$ +15.9° ($c = 0.585$, H_2O). HRMS (FAB): Calcd for $C_{10}H_{14}N_3O_7$ ($M^+ + 1$) 288.0832. Found 288.0855. IR (KBr): 3429—3167, 1687, 1632, 1465 cm^{-1}. NMR (3% DCl in D_2O) δ: 4.23 (dd, 1H, $J = 2.6$, 6.5 Hz), 4.30 (dd, 1H, $J = 4$, 6.5 Hz), 4.45 (d, 1H, $J = 2.6$ Hz), 4.54 (t, 1H, $J = 6.5$ Hz), 5.61 (d, 1H, $J = 4$ Hz), 5.83 (d, 1H, $J = 8$ Hz), 7.37 (d, 1H, $J = 8$ Hz).

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