Synthesis of a Carbohydrate-Derived 1-Oxaspiro[4.4]nonane Skeleton and Its Conversion into Spironucleosides

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Abstract: An easy entry to the 1-oxaspiro[4.4]nonane skeleton has been developed starting from a D-glucose-derived substrate. The key steps involve (a) installation of olefin moieties at the appropriate places through simple transformations and (b) construction of spiro rings by utilizing ring-closing metathesis reactions between these olefin functionalities. Subsequent deprotection of the acetonide functionality, peracetylation, nucleosidaton under Vorbrüggen reaction conditions, and final deprotections result in the formation of the spironucleosides. The involvement of an interesting intra/intermolecular acetyl migration has been used to rationalize the product distribution during desilylation. Various 1D and 2D NMR techniques and X-ray analyses of some important intermediates were used for assigning the structures and stereochemistry of the products.

Key words: alkenes, spiro compounds, ring-closing metathesis, nucleosides, carbohydrates

The observations that the first natural herbicidal spironucleoside (+)-hydantocidin[1] shows potent plant-growth-regulatory activities and low toxicity to microorganisms and mammals and that the synthetic spironucleoside TSAO-T[2] exhibits anti-HIV activity inspired Miyasaka[3] and others[4] to synthesize C-1′-spironucleosides as conformationally restricted molecules. Although conformations of the ribose ring in natural nucleosides equilibrate in solution between C-3′-*endo* (N-type) and C-2′-*endo* (S-type) due to low energy barriers,[5,6] restriction of this conformational flipping could provide nucleoside analogues with greater selectivity and less toxicity[7] for the treatment of viral diseases. Paquette[8] subsequently introduced the concept of spirocyclic restriction in nucleosides through insertion of a carbocyclic ring at C-4′ of furanose/thiofuranose rings. The free-radical-induced degradation of the ribose ring of nucleosides by C-4′ hydrogen abstraction can thus be precluded, resulting in enhanced metabolic stability as well as conformational rigidity in the furanose ring. These nucleosides carrying a ring residue between C-4′ and C-5′ could occupy more space, affecting the conformation of the furanose ring, and the product would be expected to play a different role in the biochemical reactions, improving the binding properties and the base pairing preference when inserted in oligonucleotides. Considerable attention has thereafter been paid to structural modifications of nucleosides,[9–12] and syntheses of a number of spiro derivatives including C-1′-spiro,[13] C-2′-spiro,[14] C-3′-spiro,[15] and C-4′-spironucleosides,[8,16,17] as conformationally restricted/biased analogues, have appeared in the literature. The structures of some of these nucleosides (**1**,[13] **2**,[14] **3**,[15] **4**,[8] **5**,[16c] and **6**[9]) are shown in Figure 1.

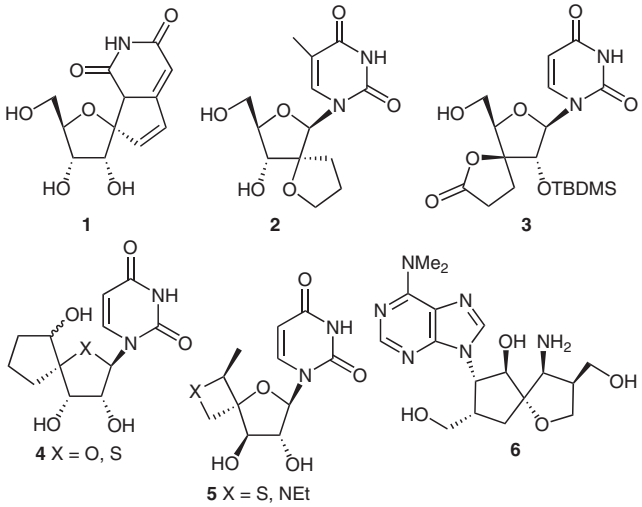
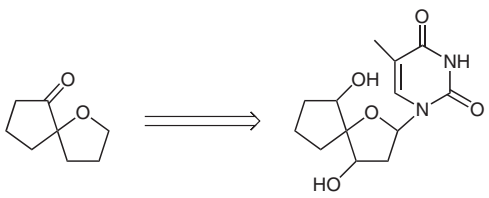


Figure 1 Some structurally unique spironucleosides

Several years ago Paquette's group[18] reported pinacolic ring expansion initiated by oxonium ions to generate a spiroketone that could serve as a sugar mimic after a series of transformations including chiral resolution at an appropriate stage (Scheme 1). But the synthesis of such nucleosides or similar analogues starting from carbohydrates has received scant attention. We decided to utilize easily derived intermediates from natural carbohydrates to synthesize spirocyclic nucleosides in enantiomerically pure form. The present article deals with the results on the generation of spiro[5.5] rings at C-4 of the furanose moiety



Scheme 1 Spiro sugar mimic

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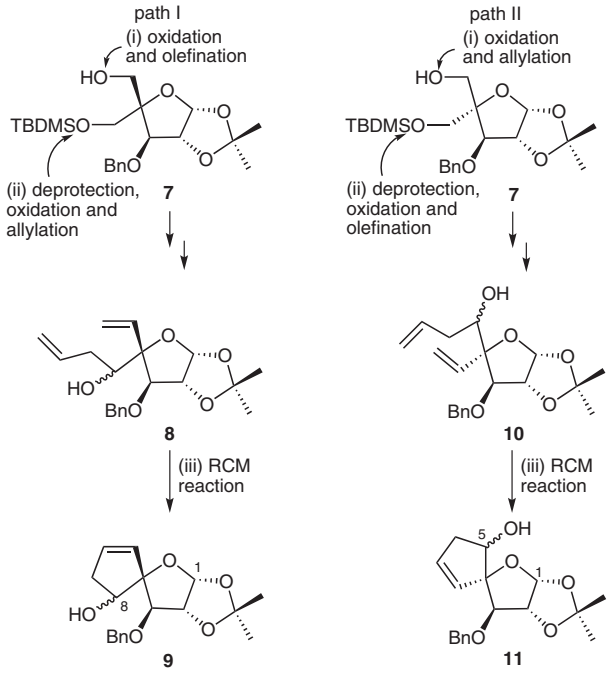
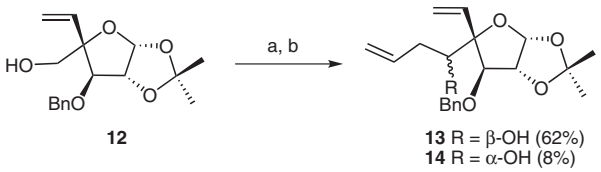
followed by insertion of a nucleoside base at the anomeric center from D-glucose-derived substrates.

Our intended synthetic scheme was based on the utilization of the known starting material **7**[16c] (Scheme 2) containing a 4,4-disubstituted furanose ring. The free CH_2OH group was to be elaborated through oxidation followed by methylenation (path I) or Barbier allylation (path II). The silyl-protected primary alcohol group could then be deprotected and subjected to oxidation followed by allylation (path I) or methylenation (path II). Subsequent ring-closing metathesis (RCM) reaction of the two olefin-bearing substituents at C-4 of the furanose ring was expected to provide spiro rings for further elaboration, culminating in the introduction of the nucleoside base. The results of these studies are discussed below.



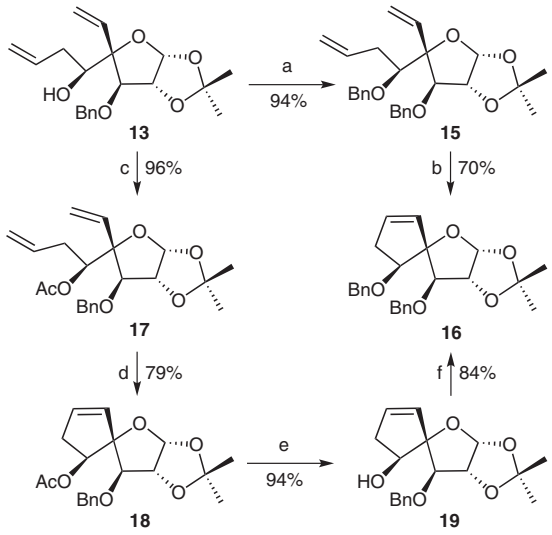
Scheme 2 Pathways to generate spiro rings

The dienes **13** and/or **14**, the key intermediates required for the preparation of the spiro[5.5] rings, with a hydroxy group at C-8 (via path I) could be synthesized from easily accessible 4-vinylfuranose derivative **12**[19] (Scheme 3). Oxidation of **12** with Dess–Martin periodinane and subsequent Barbier allylation of the resulting aldehyde by using allyl bromide and zinc dust provided diene **13** (62%) as the major product in addition to **14** (8%) as the minor product, via the preferential attack of the allyl anion on the aldehyde group (in forming **13**) from the less hindered side, opposite to the vinyl group. The presence of two vinyl groups in each of these products was inferred from NMR spectral analyses. The orientation of the hydroxy group in **13** as indicated was confirmed by subsequent X-ray diffraction analysis of **18**, derived from the RCM reaction of the acetate derivative of **13**. This automatically settled the structure of **14** as well.



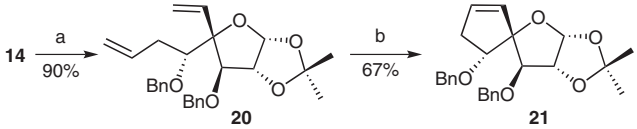
Scheme 3 *Reagents and conditions*: (a) DMP, CH_2Cl_2, 0 °C, 1 h; (b) aq NH_4Cl–THF (5:1), AllBr, 0 °C, 5 min, Zn dust, 0 °C to r.t., 12 h.

The diene **13** was then treated with the Grubbs catalyst in dichloromethane–benzene, but without success. However, benzylation of its hydroxy group afforded the hydroxy-protected diene **15** (Scheme 4), which upon RCM reaction in benzene in the presence of the first-generation Grubbs catalyst under prolonged reflux furnished **16** (70%). Similarly, RCM reaction of **17** (where the hydroxy group was protected by an acetyl group) generated **18** (79%). The structure of **18** was confirmed by X-ray diffraction analysis (Figure 2). Deacetylation of **18** afforded **19** (94%), which could be converted into **16** through benzylation of the hydroxy group, thus completing the correlation.



Scheme 4 *Reagents and conditions*: (a) 1. NaH, THF, 0 °C, 5 min; 2. BnBr, TBAI, r.t., 2 h; (b) Grubbs I cat., benzene, reflux, 45 h; (c) Ac_2O, py, r.t., 12 h; (d) Grubbs I cat., CH_2Cl_2, r.t., 5 h; (e) K_2CO_3, MeOH, r.t., 30 min; (f) 1. NaH, THF, r.t., 10 min; 2. BnBr, TBAI, reflux, 10 h.

The diene **14** was also elaborated to the spirocycle **21** via benzylation of the hydroxy group and RCM reaction using the first-generation Grubbs catalyst (Scheme 5). The success of the RCM reaction of **20** in obtaining **21** was evident from the absence of two olefinic carbon signals and



Scheme 5 *Reagents and conditions*: (a) 1. NaH, THF, 0 °C, 5 min; 2. BnBr, TBAI, r.t., 2 h; (b) Grubbs I cat., benzene, reflux, 45 h.

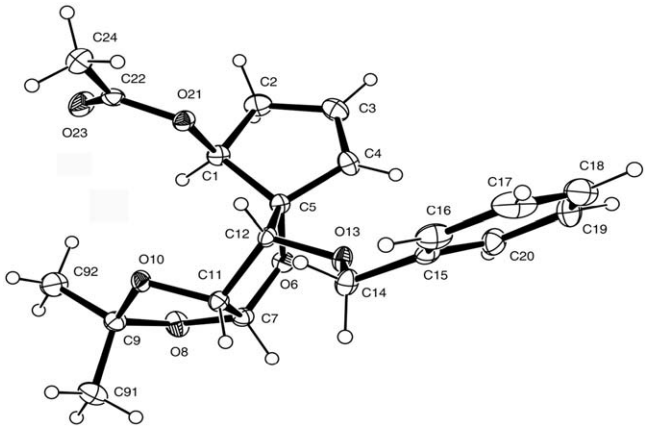
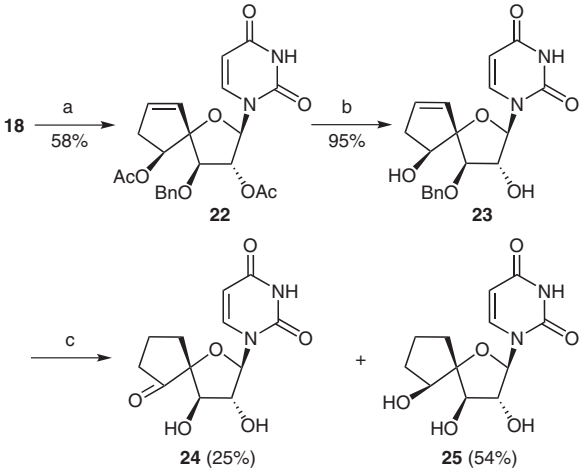


Figure 2 ORTEP diagram of **18** with ellipsoids at 30% probability

the presence of only two olefinic proton signals in the ^{13}C and ^{1}H NMR spectra of the product.

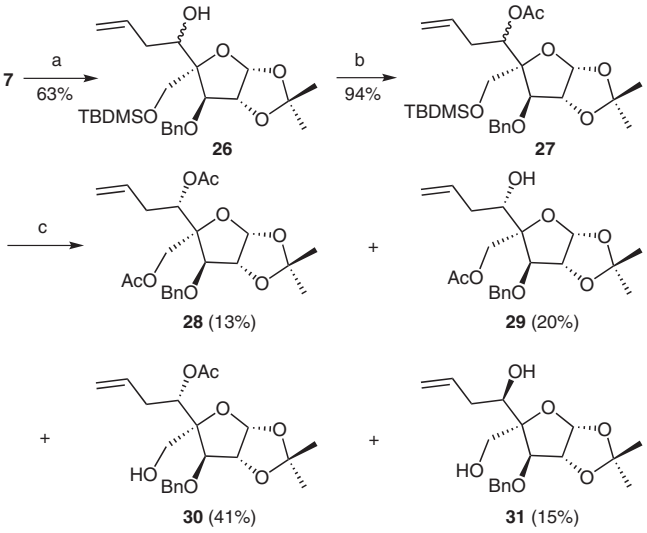
To realize our goals to synthesize spiro[5.5] nucleosides with a C-8′ hydroxy group we set about as follows. Removal of 1,2-acetonide protection from **18** by acid treatment and subsequent peracetylation generated an anomeric mixture of diacetates, which, without purification, was subjected to nucleosidation under Vorbrüggen reaction conditions[20] (Scheme 6) by use of 2,4-bis(trimethylsiloxy)pyrimidine in the presence of a Lewis acid, to provide the β-nucleoside **22** (58%) as the sole product. Removal of the acetyl groups of **22** generated **23** (95%), which produced the keto product **24** (25%) along with the normal trihydroxy product **25** (54%) upon transfer hydrogenolysis. The unexpected formation of the keto functionality in the nucleosides could be explained by invoking migration of the double bond under catalytic conditions to give the enol form and subsequent tautomerization.

On the other hand, due to the poor yield of **14**, the spirocycle **21** (derived from **14**) was not subjected to the nucleosidation reaction.



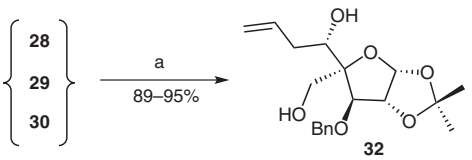
Scheme 6 *Reagents and conditions*: (a) 1. H_2SO_4 (4%), MeCN–H_2O (3:1), r.t., 12 h; 2. Ac_2O, py, r.t., 12 h; 3. 2,4-bis(trimethylsiloxy)pyrimidine, MeCN, TMSOTf, reflux, 6 h; (b) K_2CO_3, MeOH, r.t., 30 min; (c) Pd/C (10%), cyclohexene, EtOH, reflux, 6 h.

Next, with the objective to generate a [5.5]-spirocycle with a C-8 hydroxy group (via path II), the carbohydrate derivative **7** was subjected to Dess–Martin periodinane oxidation (Scheme 7) followed by allylation of the resulting aldehyde with allyl bromide and zinc to produce an epimeric mixture of inseparable alcohols **26**, which on acetylation afforded an acetate mixture **27** (inseparable as well). Treatment of **27** with tetrabutylammonium fluoride for removal of the *tert*-butyldimethylsilyl group led to a mixture of four products, which could be formed in the reaction by intra- and intermolecular acyl migration. These were separated and identified as **28** (13%), **29** (20%), **30** (41%), and **31** (15%).



Scheme 7 *Reagents and conditions*: (a) 1. DMP, CH_2Cl_2, 0 °C, 1 h; 2. aq NH_4Cl–THF (5:1), AllBr, 0 °C, 5 min, Zn dust, 0 °C to r.t, 12 h; (b) Ac_2O, py, r.t., 12 h; (c) TBAF, THF, r.t., 3 h.

Deacetylation of **28**–**30** (Scheme 8) furnished in each case the dihydroxy product **32** (89–95% yield). This was distinct from **31**. As the stereochemistry of the hydroxy group of the solid product **29** was deduced by X-ray diffraction analysis (Figure 3), the stereochemistry of the hydroxy/acetoxy groups in **28**, **30**, and **31** was also settled.



Scheme 8 *Reagents and conditions*: (a) K_2CO_3, r.t., 30 min.

Oxidation of the hydroxy group of **30** by Dess–Martin periodinane and subsequent Wittig reaction with methylenetriphenylphosphorane furnished **33** (65%) (Scheme 9). This diene, upon RCM reaction in the presence of the first-generation Grubbs catalyst in dichloromethane, afforded **34** in 81% yield. The structure of **34** was confirmed by the presence of two olefinic proton signals at δ = 5.77

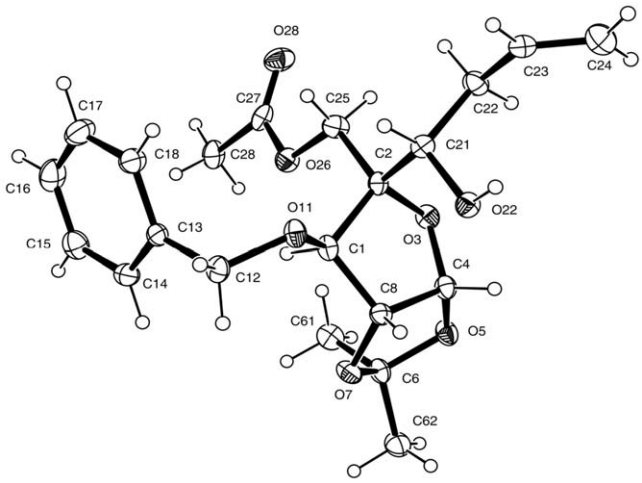
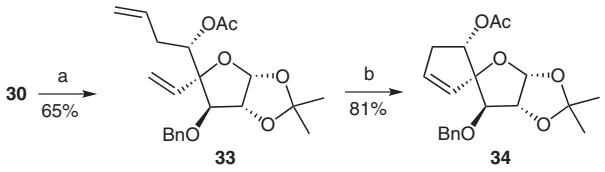


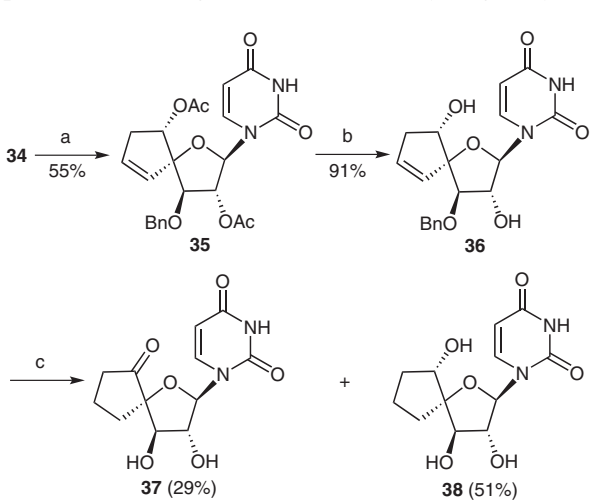
Figure 3 ORTEP diagram of **29** with ellipsoids at 30% probability



Scheme 9 *Reagents and conditions*: (a) 1. DMP, CH_2Cl_2, 0 °C, 1 h; 2. Ph_3PMeBr, *t*-BuOK, THF, 0 °C to r.t., 4 h; (b) Grubbs I cat., CH_2Cl_2, r.t., 5 h.

(d, *J* = 1.8 Hz, 1 H) and 5.94–5.96 (m, 1 H), and carbon signals at δ = 133.1 and 137.3 in the ^1H and ^{13}C NMR spectra, respectively.

Towards the synthesis of the targeted spironucleoside, we applied the known nucleosidation procedure on **34** as well. Opening of the 1,2-acetonide followed by peracetylation and nucleosidation under Vorbrüggen reaction conditions produced the β-spironucleoside **35** (55%) as the sole product (Scheme 10). Deacetylation of this compound (furnishing **36**) and transfer hydrogenolysis with



Scheme 10 *Reagents and conditions*: (a) 1. H_2SO_4 (4%), MeCN–H_2O (3:1), r.t., 12 h; 2. Ac_2O, py, r.t., 12 h; 3. 2,4-bis(trimethylsiloxy)pyrimidine, MeCN, TMSOTf, reflux, 6 h; (b) K_2CO_3, MeOH, 30 min; (c) Pd/C (10%), cyclohexene, EtOH, reflux, 5 h.

cyclohexene and palladium on carbon (10%) yielded the keto nucleoside **37** (29%) along with the normal nucleoside **38** (51%).

In conclusion, the judicious manipulation of inserting a carbocyclic ring into the carbohydrate framework by RCM reactions on D-glucose-derived substrates has permitted entry to spironucleosides with the 1-oxaspiro[4.4]nonane skeleton. The precursor assembly for RCM reactions appears simple, making the strategy an attractive one. The scope of the strategy to synthesize other ring systems could be investigated.

Melting points were determined in open capillaries and are uncorrected. ^1H and ^{13}C NMR spectra of samples in $CDCl_3$, C_5D_5N, or D_2O as solvent and with TMS as internal standard were recorded on a Bruker AM-300 L model spectrometer. Mass spectra were recorded in ESI mode on a Micromass Q-Tof micro TM spectrometer. Specific rotations were measured at 589 nm. Precoated plates (0.25 mm, silica gel 60 F254) were used for TLC. The PE fraction boiling at 60–80 °C was used.

(3a*R*,5*S*,6*R*,6a*R*)-6-(Benzyloxy)-2,2-dimethyl-5-vinyl-5-[(1*S*)-1-hydroxybut-3-enyl]tetrahydrofuro[2,3-*d*][1,3]dioxole (13) and (3a*R*,5*S*,6*R*,6a*R*)-6-(Benzyloxy)-2,2-dimethyl-5-vinyl-5-[(1*R*)-1-hydroxybut-3-enyl]tetrahydrofuro[2,3-*d*][1,3]dioxole (14)

A soln of alcohol **12** (3.00 g, 9.80 mmol) in CH_2Cl_2 (40 mL) was added to a soln of DMP (6.27 g, 14.7 mmol) in CH_2Cl_2 (40 mL) at r.t. under N_2. After 1 h, more CH_2Cl_2 (20 mL) was added to the mixture. The soln was then washed with a 10% aq $Na_2S_2O_3$–sat. aq $NaHCO_3$ mixture (1:1, 40 mL) and subsequently with brine (2 × 40 mL). The organic solvent was dried (Na_2SO_4) and evaporated in vacuo to give the corresponding aldehyde, which was dried (P_2O_5) and used without further purification. To a soln of the above aldehyde (2.68 g) in a sat. aq NH_4Cl–THF mixture (5:1, 48 mL) at 0 °C was added allyl bromide (2.30 mL, 26.46 mmol), and the mixture was stirred for 5 min. Zn dust (3.46 g, 52.92 mmol) was added portionwise at 0 °C and the reaction mixture was stirred at r.t. for 12 h. The reaction was quenched with sat. aq $NaHCO_3$ soln (20 mL) and the solvent was removed by distillation to furnish a residue, which was extracted with $CHCl_3$ (3 × 30 mL). The combined extract was washed with brine (2 × 30 mL), dried (Na_2SO_4), and evaporated in vacuo. The crude product was purified by flash column chromatography (silica gel, 230–400 mesh, EtOAc–PE, 2:23); this gave **13** as thick liquid. The same solvents used in the ratio 9:91 subsequently eluted **14** as a viscous liquid.

Compound 13

Yield: 2.10 g (62%); $[\alpha]_D^{25}$ +3.4 (*c* 0.76, $CHCl_3$).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.38 (s, 3 H), 1.58 (s, 3 H), 2.00–2.05 (m, 1 H), 2.32–2.42 (m, 2 H), 3.64 (d, *J* = 10.1 Hz, 1 H), 4.32 (d, *J* = 1.5 Hz, 1 H), 4.60 (d, *J* = 11.7 Hz, 1 H), partially merged with 4.63 (m, 1 H), 4.75 (d, *J* = 11.7 Hz, 1 H), 5.05–5.09 (m, 2 H), 5.29 (d, *J* = 10.9 Hz, 1 H), 5.49 (d, *J* = 17.3 Hz, 1 H), 5.75–5.89 (m, 1 H), partially merged with 5.85 (d, *J* = 4.5 Hz, 1 H), 6.14 (dd, *J* = 10.9, 17.3 Hz, 1 H), 7.30–7.36 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.4 (CH_3), 27.9 (CH_3), 35.2 (CH_2), 72.1 (CH_2), 74.7 (CH), 83.7 (CH), 86.7 (CH), 90.0 (C), 103.3 (CH), 113.9 (C), 116.1 (CH_2), 117.2 (CH_2), 127.7–127.8 (3 × CH), 128.3 (2 × CH), 134.2 (CH), 135.4 (CH), 137.4 (C).

ESI-MS: *m*/*z* = 369 $[M + Na]^+$.

Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.56. Found: C, 69.08; H, 7.39.

Compound 14

Yield: 275 mg (8%); $[\alpha]_D^{25}$ +7.5 (*c* 0.80, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (s, 3 H), 1.48 (s, 1 H), 1.57 (s, 3 H), 2.04–2.14 (m, 1 H), 2.25 (m, 1 H), 3.65 (d, *J* = 7.2 Hz, 1 H), 4.25 (d, *J* = 2.8 Hz, 1 H), 4.56 (d, *J* = 11.8 Hz, 1 H), 4.64 (apparent t, *J* = 3.5 Hz, 1 H), 4.77 (d, *J* = 11.8 Hz, 1 H), 5.04–5.08 (m, 2 H), 5.31 (d, *J* = 11.0 Hz, 1 H with finer splitting), 5.43 (d, *J* = 17.3 Hz, 1 H with finer splitting), 5.79–5.96 (m, 3 H), 7.35 (br s, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.4 (CH_3), 27.7 (CH_3), 36.0 (CH_2), 72.1 (CH_2), 73.1 (CH), 85.4 (CH), 86.2 (CH), 90.4 (C), 103.4 (CH), 113.8 (C), 116.1 (CH_2), 117.1 (CH_2), 127.6–128.4 (5 × CH), 133.8 (CH), 135.2 (CH), 137.3 (C).

ESI-MS: *m*/*z* = 369 $[M + Na]^+$.

Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.56. Found: C, 69.31; H, 7.53.

(3a*R*,5*S*,6*R*,6a*R*)-6-(Benzyloxy)-2,2-dimethyl-5-vinyl-5-[(1*S*)-1-(benzyloxy)but-3-enyl]tetrahydrofuro[2,3-*d*][1,3]dioxole (15)

Oil-free NaH (157 mg, 6.54 mmol) was added portionwise to a soln of **13** (567 mg, 1.64 mmol) in anhyd THF (30 mL) at 0 °C and the mixture was stirred for 5 min. BnBr (0.23 mL, 1.97 mmol), and TBAI (61 mg, 0.164 mmol) were added to the reaction mixture, which was stirred at r.t. for 2 h. Excess NaH was destroyed by the addition of aq NH_4Cl (6 mL). The solvent was evaporated in vacuo and the residue was extracted with $CHCl_3$ (3 × 25 mL). The $CHCl_3$ soln was washed with H_2O (2 × 30 mL), dried (Na_2SO_4), and concentrated to afford a liquid, which was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 7:93); this gave **15** as a colorless liquid.

Yield: 672 mg (94%); $[\alpha]_D^{25}$ – 6.3 (*c* 0.16, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (s, 3 H), 1.52 (s, 3 H), 2.21–2.28 (m, 1 H), 2.42–2.49 (m, 1 H), 3.65 (dd, *J* = 2.9, 9.3 Hz, 1 H), 4.27 (d, *J* = 1.7 Hz, 1 H), 4.54 (d, *J* = 11.9 Hz, 1 H), 4.61–4.67 (m, 4 H), 4.99 (br d, *J* = 10.0 Hz, 1 H), 5.08 (br d, *J* = 17.1 Hz, 1 H), 5.27 (dd, *J* = 2.0, 10.9 Hz, 1 H), 5.49 (dd, *J* = 2.0, 17.4 Hz, 1 H), 5.79–5.94 (m, 2 H), 6.13 (dd, *J* = 10.9, 17.4 Hz, 1 H), 7.26–7.29 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.2 (CH_3), 27.6 (CH_3), 35.9 (CH_2), 72.5 (CH_2), 74.7 (CH_2), 83.1 (CH), 84.9 (CH), 86.6 (CH), 91.7 (C), 104.4 (CH), 113.5 (C), 116.1 (CH_2), 116.9 (CH_2), 127.2–128.8 (10 × CH), 134.9 (CH), 136.8 (CH), 138.0 (C), 138.9 (C).

ESI-MS: *m*/*z* = 459 $[M + Na]^+$.

Anal. Calcd for $C_{27}H_{32}O_5$: C, 74.29; H, 7.39. Found: C, 74.09; H, 7.23.

(2*R*,3*R*,4*R*,5*S*,9*S*)-4,9-Bis(benzyloxy)-2,3-*O*-isopropylidene-1-oxaspiro[4.4]non-6-ene (16)

*From **15***: The Grubbs I cat. (123 mg, 0.149 mmol) was added to a soln of **15** (650 mg, 1.49 mmol) in benzene (248 mL), and the soln was heated at reflux for 45 h under N_2. The solvent was evaporated under vacuum and the residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 1:19); this gave **16** as a thick liquid.

Yield: 426 mg (70%).

*From **19***: NaH (45 mg, 1.88 mmol) was added to a soln of **19** (130 mg, 0.41 mmol) in THF (15 mL), and the mixture was stirred at r.t. for 10 min. BnBr (0.67 mL, 0.56 mmol) and TBAI (15 mg, 0.04 mmol) were added to the mixture, which was then heated at reflux for 10 h under N_2. After the mixture had been cooled and the excess of NaH had been destroyed by the addition of aq NH_4Cl (2 mL), the solvent was evaporated under vacuum to provide a crude residue, which was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 1:19); this gave **16** as a viscous liquid.

Yield: 140 mg (84%); $[\alpha]_D^{25}$ –10.8 (*c* 0.11, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (s, 3 H), 1.52 (s, 3 H), 2.42 (d, *J* = 16.8 Hz, 1 H), 2.78 (br d, 1 H), 4.22 (d, *J* = 3.2 Hz, 1 H), 4.57–4.67 (m, 5 H), 4.76 (d, *J* = 3.9 Hz, 1 H), 5.88 (d-like, *J* = 3.9 Hz, 2 H), 6.05 (d, *J* = 5.7 Hz, 1 H), 7.29 (br s, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.2 (CH_3), 26.8 (CH_3), 37.6 (CH_2), 71.7 (CH_2), 72.3 (CH_2), 81.5 (CH), 83.2 (CH), 85.9 (CH), 100.3 (C), 104.1 (CH), 112.2 (C), 127.4–128.3 (10 × CH), 129.8 (CH), 134.3 (CH), 137.8 (C). 138.3 (C).

ESI-MS: *m*/*z* = 431 $[M + Na]^+$.

Anal. Calcd for $C_{25}H_{28}O_5$: C, 73.51; H, 6.91. Found: C, 73.28; H, 6.69.

(3a*R*,5*S*,6*R*,6a*R*)-5-[(1*S*)-1-Acetoxybut-3-enyl]-6-(benzyloxy)-2,2-dimethyl-5-vinyltetrahydrofuro[2,3-*d*][1,3]dioxole (17)

A soln of **13** (1.35 g, 3.90 mmol) in py (20 mL) was treated with Ac_2O (0.44 mL, 4.68 mmol) and the mixture was stirred at r.t. for 12 h. The solvent was evaporated and the crude product was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 1:9); this gave **17** as a viscous liquid.

Yield: 1.45 g (96%); $[\alpha]_D^{25}$ –21.3 (*c* 0.18, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (s, 3 H), 1.62 (s, 3 H), 1.86 (s, 3 H), 2.07–2.19 (m, 1 H), 2.45–2.51 (m, 1 H), 4.05 (d, *J* = 1.9 Hz, 1 H), 4.49 (1 H, *J* = 12.0 Hz), 4.62 (dd, *J* = 2.0, 4.4 Hz, 1 H), 4.73 (d, *J* = 12.0 Hz, 1 H), 4.95–5.02 (m, 2 H), 5.23 (dd, *J* = 2.6, 10.6 Hz, 1 H), 5.34 (dd, *J* = 1.8, 10.9 Hz, 1 H), 5.49 (dd, *J* = 1.8, 17.4 Hz, 1 H), 5.58–5.73 (m, 1 H), 5.91 (d, *J* = 4.4 Hz, 1 H), 6.00 (dd, *J* = 10.9, 17.4 Hz, 1 H), 7.28–7.45 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8 (CH_3), 26.9 (CH_3), 27.2 (CH_3), 34.0 (CH_2), 71.9 (CH_2), 74.6 (CH), 85.3 (CH), 85.7 (CH), 88.6 (C), 103.9 (CH), 113.4 (C), 116.4 (CH_2), 117.3 (CH_2), 127.7 (2 × CH), 127.8 (CH), 128.3 (2 × CH), 133.2 (CH), 134.1 (CH), 137.3 (C), 170.1 (C).

ESI-MS: *m*/*z* = 411 $[M + Na]^+$.

Anal. Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27. Found: C, 67.91; H, 7.00.

(2*R*,3*R*,4*R*,5*S*,9*S*)-9-Acetoxy-4-(benzyloxy)-2,3-*O*-isopropylidene-1-oxaspiro[4.4]non-6-ene (18)

Grubbs I cat. (117 mg, 0.142 mmol) was added to a soln of **17** (1.10 g, 2.84 mmol) in CH_2Cl_2 (473 mL) and the soln was stirred at r.t. for 5 h under N_2. The solvent was evaporated in vacuo and the residue was purified by column chromatography (silica gel, 100–200 mesh, EtOAc–PE, 4:21); this gave **18** as a colorless crystalline solid.

Yield: 806 mg (79%); mp 50–52 °C (EtOAc–PE, 1:8); $[\alpha]_D^{25}$ –36.6 (*c* 0.71, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31 (s, 3 H), 1.50 (s, 3 H), 1.97 (s, 3 H), 2.22–2.28 (m, 1 H), 3.02–3.10 (m, 1 H), 4.39 (s, 1 H), 4.61 (d, *J* = 11.8 Hz, 1 H), 4.71 (d, *J* = 11.8 Hz, 1 H), 4.73 (partially merged d, *J* = 3.7 Hz, 1 H), 5.28 (d, *J* = 5.1 Hz, 1 H), 5.92 (d, *J* = 4.1 Hz, 1 H), 5.95 (m, 1 H), 6.00 (m, 1 H), 7.28–7.36 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8 (CH_3), 25.5 (CH_3), 25.7 (CH_3), 39.8 (CH_2), 72.1 (CH_2), 77.1 (CH), 81.2 (CH), 84.4 (CH), 99.5 (C), 104.5 (CH), 111.6 (C), 127.4 (2 × CH), 127.6 (CH), 128.2 (2 × CH), 128.9 (CH), 135.0 (CH), 137.3 (C), 169.4 (C).

ESI-MS: *m*/*z* = 383 $[M + Na]^+$.

Anal. Calcd for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71. Found: C, 66.41; H, 6.59.

Crystallographic Data of 18[21]

$C_{20}H_{24}O_6$, *M* = 360.39, monoclinic, space group *P*21, *Z* = 2, *a* = 8.2378(11), *b* = 11.1137(11), *c* = 9.9902(11) Å, β = 92.128(11)°,

U = 1860.6(4)°, d_{calc} = 1.310 g·cm^{-3}. 3224 independent data were collected with Mo Kα radiation at 100 K using the Oxford Diffraction X-Calibur CCD System. The crystal was positioned at 50 mm from the CCD. 321 frames were measured with a counting time of 10 s. Data analysis was carried out with the CrysAlis program.[22a] The structure was solved using direct methods with the Shelxs97 program.[22b] The non-hydrogen atoms were refined with anisotropy thermal parameters. The hydrogen atoms bonded to carbon were included in geometric positions and given thermal parameters equivalent to 1.2 times those of the atom to which they were attached. The structure was refined on $F2$ using Shelxl97 to $R1$ 0.0550; $wR2$ 0.1240 for 2726 reflections with $I > 2\sigma(I)$.

(2*R*,3*R*,4*R*,5*S*,9*S*)-4-(Benzyloxy)-9-hydroxy-2,3-*O*-isopropylidene-1-oxaspiro[4.4]non-6-ene (19)

K_2CO_3 (126 mg, 0.91 mmol) was added to a soln of **18** (300 mg, 0.83 mmol) in MeOH (15 mL) and the mixture was stirred at r.t. for 30 min. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 3:17); this gave **19** as a colorless liquid.

Yield: 248 mg (94%); $[\alpha]_D^{25}$ –58.5 (*c* 0.16, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (s, 3 H), 1.60 (s, 3 H), 2.27–2.35 (m, 1 H), 2.91–3.01 (m, 2 H), 4.43 (s, 1 H), 4.50 (dd, *J* = 3.5, 7.4 Hz, 1 H), 4.59 (d, *J* = 11.9 Hz, 1 H), 4.65 (d, *J* = 11.9 Hz, 1 H), 4.70 (d, *J* = 3.7 Hz, 1 H), 5.72–5.76 (m, 1 H), 5.94 (d, *J* = 3.7 Hz, 1 H), 5.99–6.03 (m, 1 H), 7.29–7.37 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.9 (CH_3), 26.3 (CH_3), 41.3 (CH_2), 73.3 (CH_2), 78.8 (CH), 81.9 (CH), 84.3 (CH), 102.4 (C), 105.4 (CH), 112.5 (C), 127.9 (2 × CH), 128.3 (CH), 128.9 (2 × CH), 129.5 (CH), 135.4 (CH), 137.9 (C).

ESI-MS: *m*/*z* = 341 [M + Na]$^+$.

Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 67.75; H, 6.71.

(3a*R*,5*S*,6*R*,6a*R*)-6-(Benzyloxy)-2,2-dimethyl-5-vinyl-5-[(1*R*)-1-hydroxybut-3-enyl]tetrahydrofuro[2,3-*d*][1,3]dioxole (20)

Compound **14** (208 mg, 0.60 mmol) was benzylated by employing the procedure used for the preparation of **15** from **13**: NaH (58 mg, 2.42 mmol), BnBr (0.09 mL, 0.72 mmol), TBAI (22 mg, 0.06 mmol), and THF (20 mL). The crude product was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 7:93); this gave **20** as a viscous liquid.

Yield: 235 mg (90%); $[\alpha]_D^{25}$ +3.8 (*c* 0.15, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (s, 3 H), 1.53 (s, 3 H), 2.28–2.35 (m, 2 H), 3.43 (dd, *J* = 3.3, 8.8 Hz, 1 H), 4.17 (d, *J* = 3.1 Hz, 1 H), 4.47 (d, *J* = 11.8 Hz, 1 H), 4.49 (d, *J* = 11.0 Hz, 1 H), 4.57 (d, *J* = 11.0 Hz, 1 H), 4.60 (partially merged dd, *J* = 3.0, 4.5 Hz, 1 H), 4.74 (d, *J* = 11.8 Hz, 1 H), 4.97–5.04 (m, 2 H), 5.32 (dd, *J* = 1.8, 10.8 Hz, 1 H), 5.49 (dd, *J* = 1.8, 17.4 Hz, 1 H), 5.78–5.91 (m, 2 H), 6.00 (dd, *J* = 10.8, 17.4 Hz, 1 H), 7.27–7.35 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.8 (CH_3), 27.9 (CH_3), 34.7 (CH_2), 71.9 (CH_2), 73.8 (CH_2), 81.8 (CH), 85.7 (CH), 86.6 (CH), 89.8 (C), 103.1 (CH), 114.1 (C), 116.3 (CH_2), 116.5 (CH_2), 127.3–128.3 (10 × CH), 134.5 (CH), 136.1 (CH), 137.3 (C), 138.3 (C).

ESI-MS: *m*/*z* = 459 [M + Na]$^+$.

Anal. Calcd for $C_{27}H_{32}O_5$: C, 74.29; H, 7.39. Found: C, 74.19; H, 7.32.

(2*R*,3*R*,4*R*,5*S*,9*R*)-4,9-Bis(benzyloxy)-2,3-*O*-isopropylidene-1-oxaspiro[4.4]non-6-ene (21)

Grubbs I cat. (39 mg, 0.046 mmol) was added to a soln of **20** (200 mg, 0.46 mmol) in benzene (77 mL) and the soln was heated at reflux for 45 h under N_2. The solvent was evaporated in vacuo and the residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 7:93); this gave **21** as a colorless gum.

Yield: 126 mg (67%); $[\alpha]_D^{25}$ –81.7 (*c* 0.17, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (s, 3 H), 1.58 (s, 3 H), 2.41–2.54 (m, 2 H), 3.90 (d, *J* = 1.6 Hz, 1 H), 3.98 (t, *J* = 5.3 Hz, 1 H), 4.42–4.49 (m, 2 H), 4.60 (d, *J* = 11.9 Hz, 1 H), 4.67 (d, *J* = 11.9 Hz, 1 H), 4.71 (dd, *J* = 2.0, 4.3 Hz, 1 H), 5.86–5.97 (m, 3 H), 7.29–7.31 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.5 (CH_3), 27.8 (CH_3), 36.1 (CH_2), 71.9 (CH_2), 72.6 (CH_2), 80.4 (CH), 85.0 (CH), 85.9 (CH), 94.9 (C), 104.8 (CH), 113.8 (C), 127.9–128.8 (10 × CH), 131.5 (CH), 133.1 (CH), 137.8 (C), 138.9 (C).

ESI-MS: *m*/*z* = 431 [M + Na]$^+$.

Anal. Calcd for $C_{25}H_{28}O_5$: C, 73.51; H, 6.91. Found: C, 73.39; H, 6.68.

(2*R*,3*R*,4*R*,5*S*,9*R*)-3,9-Diacetoxy-4-(benzyloxy)-2-(2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-1-oxaspiro[4.4]non-6-ene (22)

Compound **18** (450 mg, 1.25 mmol) was treated with 4% H_2SO_4 (10 mL) in aq MeCN (75%) and stirred at r.t. for 12 h. The mixture was neutralized by portionwise addition of solid $CaCO_3$. The precipitate was collected by filtration and the filtrate was evaporated in vacuo to give a gummy mass (330 mg). It was then acetylated with py (10 mL) and Ac_2O (0.40 mL) to an anomeric mixture of diacetates (456 mg). A soln of uracil (356 mg, 3.18 mmol) in HMDS (12 mL) and TMSCl (2 drops) was heated at 135–140 °C under N_2 for 12 h. The solvent was removed by distillation under vacuum, and the soln of the residue thus obtained in MeCN (8 mL) was added to a stirred soln of the above diacetate mixture in MeCN (15 mL) containing TMSOTf (0.25 mL, 1.36 mmol). The mixture was heated at reflux for 6 h under N_2. The reaction mixture was neutralized with solid $CaCO_3$; H_2O (2–3 drops) was added to it, and the solvent was evaporated to leave a residue, which was extracted with $CHCl_3$–MeOH (98:2, 3 × 25 mL). The combined extract was washed with brine (2 × 25 mL), dried (Na_2SO_4), and concentrated to a gummy residue. The crude product was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 3:7); this gave **22** as white foamy solid.

Yield: 333 mg (58%); mp 80–83 °C; $[\alpha]_D^{25}$ +18.3 (*c* 0.24, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.98 (s, 3 H), 2.08 (s, 3 H), 2.28 (d, *J* = 18.1 Hz, 1 H), 3.06 (br d, *J* = 18.1 Hz, 1 H), 4.32 (s, 1 H), 4.65 (d, *J* = 11.6 Hz, 1 H), 4.74 (d, *J* = 11.6 Hz, 1 H), 5.20 (d, *J* = 4.7 Hz, 1 H), 5.24 (s, 1 H), 5.62 (d, *J* = 7.5 Hz, 1 H), 6.04 (br s, 1 H), 6.07 (s, 1 H), 6.20 (br s, 1 H), 7.26–7.34 (m, 5 H), 7.56 (d, *J* = 8.1 Hz, 1 H), 8.68 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9 (CH_3), 21.3 (CH_3), 40.1 (CH_2), 72.9 (CH_2), 77.3 (CH), 79.8 (CH), 81.2 (CH), 88.4 (CH), 100.7 (C), 102.7 (CH), 127.9 (CH), 128.4 (2 × CH), 128.7 (CH), 128.9 (2 × CH), 137.1 (C), 137.6 (CH), 140.5 (CH), 150.4 (C), 163.2 (C), 169.7 (C), 170.0 (C).

ESI-MS: *m*/*z* = 479 [M + Na]$^+$.

Anal. Calcd for $C_{23}H_{24}N_2O_8$: C, 60.52; H, 5.30; N, 6.14. Found: C, 60.33; H, 5.07; N, 5.86.

(2*R*,3*R*,4*R*,5*S*,9*R*)-4-(Benzyloxy)-2-(2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-3,9-dihydroxy-1-oxaspiro[4.4]non-6-ene (23)

To a soln of **22** (100 mg, 0.22 mmol) in anhyd MeOH (10 mL) was added K_2CO_3 (33 mg, 0.24 mmol) and the mixture was stirred at r.t. for 30 min. The solvent was evaporated and the crude product was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 3:2) to furnish **23** as a foamy solid.

Yield: 78 mg (95%); mp 89–91 °C; $[\alpha]_D^{25}$ +14.6 (*c* 0.18, MeOH).

^{1}H NMR (300 MHz, C_5D_5N): δ = 2.53 (dd, *J* = 1.7, 16.6 Hz, 1 H), 2.89 (dd, *J* = 6.8, 16.6 Hz, 1 H), 4.71–4.83 (m, 4 H), 5.84 (d, *J* = 8.1 Hz, 1 H), 6.05–6.07 (m, 1 H), 6.24 (apparent d, *J* = 5.8 Hz, 1 H), 6.63 (s, 1 H), 7.12 (br s, 1 H), 7.17–7.41 (m, 6 H), 7.99 (d, *J* = 8.1 Hz, 1 H), 8.21 (br s, 1 H), 13.27 (br s, 1 H).

^{13}C NMR (75 MHz, C_5D_5N): δ = 40.8 (CH_2), 72.5 (CH_2), 78.4 (CH), 79.7 (CH), 83.0 (CH), 90.5 (CH), 100.9 (C), 102.1 (CH), 127.9 (3 × CH), 128.6 (2 × CH), 130.8 (CH), 134.6 (CH), 138.8 (C), 140.8 (CH), 152.1 (C), 164.3 (C).

ESI-MS: *m*/*z* = 395 [M + Na]$^+$.

Anal. Calcd for $C_{19}H_{20}N_2O_6$: C, 61.28; H, 5.41; N, 7.52. Found: C, 61.00; H, 5.18; N, 7.27.

(2*R*,3*R*,4*R*,5*R*)-1-(3,4-Dihydroxy-6-oxo-1-oxaspiro[4.4]nonan-2-yl)-1*H*-pyrimidine-2,4-dione (24) and (2*R*,3*R*,4*R*,5*S*,6*S*)-1-(3,4,6-Trihydroxy-1-oxaspiro[4.4]nonan-2-yl)-1*H*-pyrimidine-2,4-dione (25)

To a soln of **23** (50 mg, 0.13 mmol) in EtOH (10 mL) were added Pd/C (10%, 15 mg) and cyclohexene (0.20 mL), and the mixture was heated at reflux for 6 h. The catalyst was collected by filtration, the solvent was evaporated, and the crude residue was purified by column chromatography (silica gel, 100–200 mesh, EtOAc–PE, 39:11); this gave **24** and **25** as white foamy materials.

Compound 24

Yield: 9 mg (25%); mp 95–98 °C (dec); $[\alpha]_D^{25}$ –19.0 (*c* 0.36, MeOH).

^{1}H NMR (300 MHz, C_5D_5N + D_2O): δ = 1.95–2.09 (m, 3 H), 2.21–2.31 (m, 2 H), 2.89–2.96 (m, 1 H), 4.99 (s, 1 H), 5.01 (s, 1 H), 5.97 (d, *J* = 8.1 Hz, 1 H), 6.93 (d, *J* = 8.1 Hz, 1 H), 8.03 (d, *J* = 8.1 Hz, 1 H).

^{13}C NMR (75 MHz, C_5D_5N): δ = 19.5 (CH_2), 33.0 (CH_2), 37.0 (CH_2), 77.9 (CH), 81.8 (CH), 89.9 (CH), 90.1 (C), 104.6 (CH), 142.1 (CH), 153.4 (C), 165.4 (C), 218.5 (C).

ESI-MS: *m*/*z* = 305 [M + Na]$^+$.

Anal. Calcd for $C_{12}H_{14}N_2O_6$: C, 51.06; H, 5.00; N, 9.93. Found: C, 50.82; H, 4.77; N, 9.66.

Compound 25

Yield: 20 mg (54%); mp 118–120 °C; $[\alpha]_D^{25}$ +4.9 (*c* 0.52, MeOH).

^{1}H NMR (300 MHz, C_5D_5N + D_2O): δ = 1.86 (m, 1 H), 2.06–2.09 (m, 2 H), 2.28 (m, 2 H), 2.86 (m, 1 H), 4.68 (s, 1 H), 4.91 (s, 1 H), 5.28 (s, 1 H), 6.00 (d, *J* = 8.0 Hz, 1 H), 6.59 (s, 1 H), 8.26 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (75 MHz, C_5D_5N): δ = 22.0 (CH_2), 33.1 (CH_2), 35.2 (CH_2), 78.1 (CH), 78.8 (CH), 85.2 (CH), 93.2 (CH), 101.1 (C), 103.9 (CH), 143.5 (CH), 153.9 (C), 166.1 (C).

ESI-MS: *m*/*z* = 307 [M + Na]$^+$.

Anal. Calcd for $C_{12}H_{16}N_2O_6$: C, 50.70; H, 5.67; N, 9.85. Found: C, 50.46; H, 5.43; N, 9.58.

(2*R*,3*R*,4*R*,5*R*)-4-(Benzyloxy)-5-(*tert*-butyldimethylsiloxymethyl)-5-[(1*R*/1*S*)-1-hydroxybut-3-enyl]-2,3-*O*-isopropylidenetetrahydrofuran (26)

According to the procedure described above (for the preparation of **13** and **14** from **12**), compound **7** (5.50 g, 12.97 mmol) in CH_2Cl_2 (120 mL) was treated with DMP (8.28 g, 19.46 mmol) and then allylated by using allyl bromide (1.96 mL, 22.56 mmol), Zn dust (2.95 g, 45.12 mmol), and an aq NH_4Cl–THF mixture (5:1, 96 mL). Usual workup followed by purification of the crude products by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 3:47) furnished **32** as an epimeric mixture.

Yield: 3.77 g (63%).

ESI-MS: *m*/*z* = 487 [M + Na]$^+$.

(2*R*,3*R*,4*R*,5*R*)-5-[(1*R*/1*S*)-1-Acetoxybut-3-enyl]-4-(benzyloxy)-5-(*tert*-butyldimethylsiloxymethyl)-2,3-*O*-isopropylidenetetrahydrofuran (27)

The isomeric mixture of **26** (3.5 g, 7.54 mmol) was acetylated according to the procedure described for the preparation of **17**. Usual workup followed by purification by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 1:24) afforded **27** as an isomeric mixture.

Yield: 3.59 g (94%).

ESI-MS: *m*/*z* = 529 [M + Na]$^+$.

(2*R*,3*R*,4*R*,5*R*)-5-[(1*S*)-1-Acetoxybut-3-enyl]-5-(acetoxymethyl)-4-(benzyloxy)-2,3-*O*-isopropylidenetetrahydrofuran (28), (2*R*,3*R*,4*R*,5*R*)-5-(Acetoxymethyl)-4-(benzyloxy)-5-[(1*S*)-1-hydroxybut-3-enyl]-2,3-*O*-isopropylidenetetrahydrofuran (29), (2*R*,3*R*,4*R*,5*R*)-5-[(1*S*)-1-Acetoxybut-3-enyl]-4-(benzyloxy)-2,3-*O*-isopropylidene-5-(hydroxymethyl)tetrahydrofuran (30), and (2*R*,3*R*,4*R*,5*R*)-4-(Benzyloxy)-5-[(1*R*)-1-hydroxybut-3-enyl]-5-(hydroxymethyl)-2,3-*O*-isopropylidenetetrahydrofuran (31)

TBAF (1.83 g, 6.98 mmol) was added portionwise to a soln of **27** (3.21 g, 6.34 mmol) in THF (70 mL) and the mixture was stirred at r.t. for 3 h. The solvent was evaporated in vacuo and the residue was extracted with $CHCl_3$ (3 × 40 mL). The $CHCl_3$ soln was washed with brine (2 × 30 mL), dried (Na_2SO_4), and concentrated to afford a gummy mass, which was then purified by column chromatography (silica gel, 100–200 mesh, EtOAc–PE, 3:22); this gave **28** as a colorless liquid, **29** as a white crystalline solid, and **30** and **31** as viscous liquids.

Compound 28

Yield: 350 mg (13%); $[\alpha]_D^{25}$ +26.1 (*c* 0.36, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 3 H), 1.56 (s, 3 H), 1.94 (s, 3 H), 1.99 (s, 3 H), 2.34–2.45 (m, 2 H), 4.02 (d, *J* = 11.8 Hz, 1 H), 4.16–4.21 (m, 2 H), 4.52 (d, *J* = 11.9 Hz, 1 H), 4.69–4.78 (m, 2 H), 4.99–5.07 (m, 2 H), 5.22 (dd, *J* = 4.4, 8.4 Hz, 1 H), 5.68–5.82 (m, 1 H), 6.01 (d, *J* = 4.4 Hz, 1 H), 7.31–7.36 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.6 (CH_3), 21.4 (CH_3), 27.8 (2 × CH_3), 34.4 (CH_2), 63.7 (CH_2), 72.1 (CH), 72.6 (CH_2), 85.1 (CH), 87.0 (C), 87.4 (CH), 104.8 (CH), 114.3 (C), 117.7 (CH_2), 127.8–128.3 (5 × CH), 133.8 (CH), 137.1 (C), 169.2 (C), 170.1 (C).

ESI-MS: *m*/*z* = 457 [M + Na]$^+$.

Anal. Calcd for $C_{23}H_{30}O_8$: C, 63.58; H, 6.96. Found: C, 63.77; H, 6.71.

Compound 29

Yield: 500 mg (20%); mp 61–63 °C (EtOAc–PE, 1:4); $[\alpha]_D^{25}$ –19.4 (*c* 0.45, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 3 H), 1.57 (s, 3 H), 1.95 (s, 3 H), 2.19–2.25 (m, 1 H), 2.32–2.42 (m, 2 H), 3.85 (dd, *J* = 3.0, 10.0 Hz, 1 H), 4.03 (d, *J* = 11.8 Hz, 1 H), 4.13 (d, *J* = 11.8 Hz, 1 H), 4.22 (d, *J* = 1.4 Hz, 1 H), 4.57 (d, *J* = 11.6 Hz, 1 H), 4.79–4.87 (m, 2 H), 5.07–5.15 (m, 2 H), 5.82–5.96 (m, 1 H), 6.08 (d, *J* = 4.4 Hz, 1 H), 7.32–7.39 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.6 (CH_3), 27.7 (CH_3), 27.8 (CH_3), 34.6 (CH_2), 63.8 (CH_2), 71.8 (CH), 72.8 (CH_2), 85.6 (CH), 87.4 (CH), 88.3 (C), 104.9 (CH), 114.3 (C), 117.1 (CH_2), 128.2 (2 × CH), 128.3 (CH), 128.5 (2 × CH), 135.3 (CH), 136.6 (C), 170.1 (C).

ESI-MS: *m*/*z* = 415 [M + Na]$^+$.

Anal. Calcd for $C_{21}H_{28}O_7$: C, 64.27; H, 7.19. Found: C, 64.06; H, 7.43.

Crystallographic Data of 29[21]

$C_{21}H_{28}O_7$, M = 392.43, orthorhombic, space group $P212121$, Z = 4, a = 11.1647(15), b = 11.6164(15), c = 15.9757(11) Å, U = 2071.9(4)°, d_{calc} = 1.258 g·cm^{-3}. 5731 independent data were collected with Mo Kα radiation at 100 K using the Oxford Diffraction X-Calibur CCD System. The crystal was positioned at 50 mm from the CCD. 321 frames were measured with a counting time of 10 s. Data analysis was carried out with the CrysAlis program.[22a] The structure was solved using direct methods with the Shelxs97 program.[22b] The non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms bonded to carbon were included in geometric positions and given thermal parameters equivalent to 1.2 times those of the atom to which they were attached. The structure was refined on $F2$ using Shelxl97 to $R1$ 0.0593; $wR2$ 0.1206 for 3604 reflections with $I > 2\sigma(I)$.

Compound 30

Yield: 1.02 g (41%); $[\alpha]_D^{25}$ +24.0 (c 0.34, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (s, 3 H), 1.56 (s, 3 H), 1.91 (br s, 1 H), 1.99 (s, 3 H), 2.29–2.40 (m, 2 H), 3.51 (d-like, J = 11.8 Hz, 1 H), 3.69 (d-like, J = 11.8 Hz, 1 H), 4.26 (d, J = 9.0 Hz, 1 H), 4.55 (d, J = 11.8 Hz, 1 H), 4.72 (partially merged d, J = 11.7 Hz, 1 H), 4.74 (t-like, J = 3.3, 4.2 Hz, 1 H), 4.98–5.05 (m, 2 H), 5.19 (dd, J = 4.0, 8.8 Hz, 1 H), 5.67–5.80 (m, 1 H), 5.98 (d, J = 4.6 Hz, 1 H), 7.27–7.37 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3 (CH_3), 27.6 (CH_3), 27.9 (CH_3), 34.5 (CH_2), 62.2 (CH_2), 72.2 (CH), 72.8 (CH_2), 84.8 (CH), 87.1 (CH), 89.6 (C), 104.6 (CH), 114.0 (C), 117.4 (CH_2), 127.6–128.7 (5 × CH), 134.0 (CH), 137.3 (C), 169.4 (C).

ESI-MS: m/z = 415 [M + Na]$^+$.

Anal. Calcd for $C_{21}H_{28}O_7$: C, 64.27; H, 7.19. Found: C, 64.11; H, 7.01.

Compound 31

Yield: 327 mg (15%); $[\alpha]_D^{25}$ –8.1 (c 0.15, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (s, 3 H), 1.55 (s, 3 H), 2.21–2.47 (m, 4 H), 3.77 (d, J = 11.8 Hz, 1 H), 3.86 (d, J = 11.8 Hz, 1 H), 3.96 (dd, J = 2.4, 10.6 Hz, 1 H), 4.29 (d, J = 1.1 Hz, 1 H), 4.57 (d, J = 11.4 Hz, 1 H), 4.78 (d, J = 11.4 Hz, 1 H), overlapping with 4.75–4.76 (m, 1 H), 5.07–5.14 (m, 2 H), 5.78–5.94 (m, 2 H), 7.31–7.39 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.9 (CH_3), 27.4 (CH_3), 36.1 (CH_2), 62.8 (CH_2), 73.1 (CH_2), 73.3 (CH), 85.6 (CH), 85.7 (CH), 89.8 (C), 105.3 (CH), 113.3 (C), 117.5 (CH_2), 128.2–129.2 (5 × CH), 136.2 (CH), 137.1 (C).

ESI-MS: m/z = 373 [M + Na]$^+$.

Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.13; H, 7.48. Found: C, 65.05; H, 7.31.

(2*R*,3*R*,4*R*,5*R*)-4-(Benzyloxy)-5-[(1*S*)-1-hydroxybut-3-enyl]-5-(hydroxymethyl)-2,3-*O*-isopropylidenetetrahydrofuran (32)

Compounds **28** (70 mg, 0.16 mmol), **29** (35 mg, 0.09 mmol), and **30** (40 mg, 0.10 mmol) were separately deacetylated with K_2CO_3 (2.2 equiv for **28** and 1.1 equiv for **29** and **30** respectively) in anhyd MeOH (20 mL for **28** and 10 mL for **29** and **30** respectively) following the procedure adopted for the deacetylation of **18**. Usual workup and purification of the crude product from each of the reactions by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 3:22) furnished the same product **32** as a thick liquid.

Yield: 53 mg (95% from **28**); 29 mg (92% from **29**); 31 mg (89% from **30**); $[\alpha]_D^{25}$ –15.3 (c 0.28, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (s, 3 H), 1.56 (s, 3 H), 2.21–2.39 (m, 2 H), 2.55 (br s, 2 H), 3.56 (d, J = 11.8 Hz, 1 H), 3.67 (d, J = 11.8 Hz, 1 H), 3.80 (dd, J = 3.0, 9.7 Hz, 1 H), 4.31 (d, J = 2.5 Hz, 1 H), 4.58 (d, J = 11.5 Hz, 1 H), 4.78 (d, J = 11.5 Hz, 1 H), 4.81 (partially merged dd, J = 2.7, 4.2 Hz, 1 H), 5.05–5.12 (m, 2 H), 5.81–5.95 (m, 1 H), 6.04 (d, J = 4.5 Hz, 1 H), 7.31–7.36 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.2 (CH_3), 27.6 (CH_3), 35.3 (CH_2), 62.6 (CH_2), 72.2 (CH), 72.8 (CH_2), 85.4 (CH), 86.7 (CH), 91.1 (C), 104.8 (CH), 113.7 (C), 116.8 (CH_2), 127.7 (2 × CH), 128.1 (CH), 128.5 (2 × CH), 135.5 (CH), 136.7 (C).

ESI-MS: m/z = 373 [M + Na]$^+$.

Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.13; H, 7.48. Found: C, 65.01; H, 7.33.

(3a*R*,5*R*,6*R*,6a*R*)-5-[(1*S*)-1-Acetoxybut-3-enyl]-6-(benzyloxy)-2,2-dimethyl-5-vinyltetrahydrofuro[2,3-*d*][1,3]dioxole (33)

A soln of **30** (640 mg, 1.63 mmol) dissolved in CH_2Cl_2 (25 mL) was oxidized to the aldehyde by using DMP (1.04 g, 2.44 mmol) according to the procedure adopted for the preparation of **13** and **14** from **12**. The crude aldehyde (610 mg) was dried (P_2O_5) and subsequently used without further purification. A soln of this aldehyde in THF (10 mL) was added dropwise for 45 min to a soln of Ph_3PMeBr (1.39 g, 3.89 mmol) and *t*-BuOK (381 mg, 3.12 mmol) in anhyd THF (15 mL) at 0 °C under N_2. The mixture was stirred at 0 °C for 2 h and subsequently at r.t. for 2 h. The reaction was quenched by the addition of sat. aq NH_4Cl soln (15 mL). The solvent was evaporated in vacuo and the residue was extracted with $CHCl_3$ (3 × 30 mL). The $CHCl_3$ soln was washed with H_2O (2 × 30 mL) and dried (Na_2SO_4), and the solvent was evaporated to leave a crude product, which was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 1:19); this gave **33** as a viscous liquid.

Yield: 410 mg (65%); $[\alpha]_D^{25}$ +35.5 (c 0.13, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 3 H), 1.47 (s, 3 H), 1.97 (s, 3 H), 2.29–2.35 (m, 2 H), 3.98 (d, J = 2.9 Hz, 1 H), 4.54 (d, J = 11.9 Hz, 1 H), 4.68 (dd, J = 3.0, 4.6 Hz, 1 H), 4.73 (d, J = 11.9 Hz, 1 H), 4.95–5.02 (m, 2 H), 5.14–5.23 (m, 2 H), 5.42 (d, J = 17.2 Hz, 1 H), 5.68–5.81 (m, 1 H), 5.88 (dd, J = 10.9, 17.3 Hz, 1 H), 6.07 (d, J = 4.6 Hz, 1 H), 7.28–7.35 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4 (CH_3), 27.4 (CH_3), 27.9 (CH_3), 34.1 (CH_2), 72.6 (CH_2), 73.9 (CH), 87.3 (CH), 88.7 (C), 89.9 (CH), 104.7 (CH), 114.0 (C), 115.3 (CH_2), 117.2 (CH_2), 127.6 (2 × CH), 127.8 (CH), 128.3 (2 × CH), 134.4 (CH), 137.1 (CH), 137.1 (C), 169.2 (C);

ESI-MS: m/z = 411 [M + Na]$^+$.

Anal. Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27. Found: C, 67.85; H, 7.09.

(2*R*,3*R*,4*R*,5*R*,9*S*)-9-Acetoxy-4-(benzyloxy)-2,3-*O*-isopropylidene-1-oxaspiro[4.4]non-6-ene (34)

Grubbs I cat. (43 mg, 0.052 mmol) was added to a soln of **33** (400 mg, 1.03 mmol) in CH_2Cl_2 (172 mL) and the soln was stirred at r.t. for 5 h under N_2. The solvent was evaporated in vacuo and the residue was purified by column chromatography (silica gel, 100–200 mesh, EtOAc–PE, 1:19); this gave **34** as a thick liquid.

Yield: 300 mg (81%); $[\alpha]_D^{25}$ +32.9 (c 0.15, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (s, 3 H), 1.53 (s, 3 H), 2.05 (s, 3 H), 2.34–2.41 (m, 1 H), 2.73 (dd, J = 6.4, 16.8 Hz, 1 H), 3.96 (d, J = 1.9 Hz, 1 H), 4.52 (d, J = 11.8 Hz, 1 H), 4.71 (a merged signal, 1 H), 4.73 (d, J = 11.8 Hz, 1 H), 5.53 (dd, J = 4.1, 6.4 Hz, 1 H), 5.77 (br d, J = 5.9 Hz, 1 H), 5.87 (d, J = 4.2 Hz, 1 H), 5.94–5.96 (m, 1 H), 7.26–7.36 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1 (CH_3), 26.9 (CH_3), 27.5 (CH_3), 37.0 (CH_2), 72.2 (CH_2), 72.3 (CH), 84.8 (CH), 87.1 (CH), 93.9 (C), 104.6 (CH), 113.0 (C), 127.5 (2 × CH), 127.7 (CH), 128.3 (2 × CH), 132.2 (CH), 133.1 (CH), 137.2 (C), 170.7 (C).

ESI-MS: m/z = 383 $[M + Na]^+$.

Anal. Calcd for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71. Found: C, 66.49; H, 6.45.

(2*R*,3*R*,4*R*,5*R*,9*S*)-3,9-Diacetoxy-4-(benzyloxy)-2-(2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-1-oxaspiro[4.4]non-6-ene (35)

Compound **34** (328 mg, 0.91 mmol) was subjected to a procedure similar to that described for the conversion of **18** to **22**, by using H_2SO_4–MeCN–H_2O (1:18:6, 10 mL) for acetonide deprotection, py (10 mL) and Ac_2O (0.30 mL) for acetylation, and uracil (261 mg, 2.33 mmol), HMDS (10 mL), TMSCl (2 drops), TMSOTf (0.33 mL, 1.82 mmol), and MeCN (15 mL) for nucleosidation. The reaction yielded **35** as white foamy solid after purification by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 7:13).

Yield: 228 mg (55%); mp 79–80 °C; $[\alpha]_D^{25}$ +12.9 (*c* 0.26, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.96 (s, 3 H), 2.15 (s, 3 H), 2.36–2.44 (m, 1 H), 2.71–2.73 (m, 1 H), 3.85 (d, *J* = 1.6 Hz, 1 H), 4.55 (d, *J* = 11.4 Hz, 1 H), 4.69 (d, *J* = 11.4 Hz, 1 H), 5.28 (br d, *J* = 1.8 Hz, 1 H), 5.56 (d, *J* = 8.2 Hz, 1 H), 5.62 (t-like, *J* = 5.7, 6.9 Hz, 1 H), 5.79–5.82 (m, 1 H), 6.01–6.05 (m, 1 H), 6.16 (d, *J* = 1.9 Hz, 1 H), 7.25–7.38 (m, 5 H), 7.99 (d, *J* = 8.2 Hz, 1 H), 9.32 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8 (2 × CH_3), 36.3 (CH_2), 71.9 (CH), 72.2 (CH_2), 79.4 (CH), 83.3 (CH), 87.7 (CH), 95.4 (C), 101.7 (CH), 128.3–128.5 (5 × CH), 130.4 (CH), 134.4 (CH), 136.3 (C), 140.6 (CH), 150.4 (C), 163.3 (C), 169.5 (C), 169.9 (C).

ESI-MS: m/z = 479 $[M + Na]^+$.

Anal. Calcd for $C_{23}H_{24}N_2O_8$: C, 60.52; H, 5.30; N, 6.14. Found: C, 60.27; H, 5.09; N, 5.89.

(2*R*,3*R*,4*R*,5*R*,9*S*)-4-(Benzyloxy)-3,9-dihydroxy-2-(2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-1-oxaspiro[4.4]non-6-ene (36)

Compound **35** (105 mg, 0.23 mmol) was deacetylated according to the procedure described for the preparation of **23** from **22**. Usual workup and purification by column chromatography (silica gel, 60–120 mesh, EtOAc–PE, 63:37) afforded **36** as foamy solid.

Yield: 78 mg (91%); mp 93–95 °C; $[\alpha]_D^{25}$ +33.8 (*c* 0.13, MeOH).

^{1}H NMR (300 MHz, C_5D_5N + D_2O): δ = 2.76 (d, *J* = 6.4 Hz, 2 H), 4.53 (d, *J* = 5.9 Hz, 1 H), 4.87 (d, *J* = 12.0 Hz, 1 H), 4.98 (d, *J* = 12.0 Hz, 1 H), 5.04 (t-like, *J* = 6.7 Hz, 1 H), 5.12 (t, *J* = 5.6 Hz, 1 H), 5.85 (d, *J* = 8.1 Hz, 1 H), 6.07 (d, *J* = 6.0 Hz, 1 H), 6.10 (d, *J* = 6.0 Hz, 1 H), 6.66 (d, *J* = 5.4 Hz, 1 H), 7.38–7.55 (m, 5 H), 8.99 (d, *J* = 8.1 Hz, 1 H).

^{13}C NMR (75 MHz, C_5D_5N): δ = 39.7 (CH_2), 71.0 (CH), 72.7 (CH_2), 77.5 (CH), 86.1 (CH), 87.9 (CH), 92.9 (C), 102.1 (CH), 127.9–128.7 (5 × CH), 133.9 (CH), 134.9 (CH), 138.8 (C), 142.3 (CH), 152.5 (C), 164.2 (C).

ESI-MS: m/z = 395 $[M + Na]^+$.

Anal. Calcd for $C_{19}H_{20}N_2O_6$: C, 61.28; H, 5.41; N, 7.52. Found: C, 61.01; H, 5.15; N, 7.29.

(2*R*,3*R*,4*R*,5*S*)-1-(3,4-Dihydroxy-6-oxo-1-oxaspiro[4.4]nonan-2-yl)-1*H*-pyrimidine-2,4-dione (37) and (2*R*,3*R*,4*R*,5*R*,6*S*)-1-(3,4,6-Trihydroxy-1-oxaspiro[4.4]nonan-2-yl)-1*H*-pyrimidine-2,4-dione (38)

For the hydrogenolysis of **36** (60 mg, 0.16 mmol) in EtOH (9 mL) by Pd/C (10%, 19 mg) and cyclohexene (0.25 mL), the procedure described for the preparation of **24** and **25** was followed. The catalyst was collected by filtration and the solvent was evaporated in vacuo to give the crude product, which was purified by preparative TLC (silica gel, $60F_{254}$, MeOH–EtOAc, 1:49); this gave **37** and **38** as white solids.

Compound 37

Yield: 13 mg (29%); mp 101–102 °C; $[\alpha]_D^{25}$ –12.5 (*c* 0.60, MeOH).

^{1}H NMR (300 MHz, C_5D_5N + D_2O): δ = 1.91–1.95 (br s, 1 H), 2.11–2.30 (m, 3 H), 2.47–2.58 (m, 2 H), 4.89 (d, *J* = 6.5 Hz, 1 H), 5.03 (t, *J* = 6.2 Hz, 1 H), 5.89 (d, *J* = 8.1 Hz, 1 H), 6.76 (d, *J* = 6.0 Hz, 1 H), 8.95 (d, *J* = 8.1 Hz, 1 H).

^{13}C NMR (75 MHz, C_5D_5N): δ = 18.7 (CH_2), 37.0 (CH_2), 37.8 (CH_2), 80.4 (CH), 83.1 (CH), 88.9 (CH), 90.5 (C), 104.3 (CH), 142.7 (CH), 153.8 (C), 165.4 (C) 219.7 (C).

ESI-MS: m/z = 305 $[M + Na]^+$.

Anal. Calcd for $C_{12}H_{14}N_2O_6$: C, 51.06; H, 5.00; N, 9.93. Found: C, 50.85; H, 5.01; N, 9.68.

Compound 38

Yield: 23 mg (51%); mp 120–122 °C; $[\alpha]_D^{25}$ +8.2 (*c* 0.17, MeOH).

^{1}H NMR (300 MHz, C_5D_5N): δ = 1.43–1.57 (m, 1 H), 1.76–1.89 (m, 1 H), 1.97–2.18 (m, 4 H), 4.72 (d, *J* = 6.9 Hz, 1 H), 4.85 (t-like, *J* = 8.4, 9.3 Hz, 1 H), 5.15 (t, *J* = 6.6 Hz, 1 H), 5.73 (d, *J* = 8.1 Hz, 1 H), 6.78 (d, *J* = 6.3 Hz, 1 H), 9.10 (d, *J* = 8.1 Hz, 1 H), 13.13 (br s, 1 H); the peaks for 3 H groups (3 × OH) are not discernible.

^{13}C NMR (75 MHz, C_5D_5N): δ = 19.3 (CH_2), 31.5 (CH_2), 34.8 (CH_2), 73.3 (CH), 78.7 (CH), 79.7 (CH), 87.3 (CH), 92.4 (C), 102.5 (CH), 142.9 (CH), 152.7 (C), 165.1 (C).

ESI-MS: m/z = 307 $[M + Na]^+$.

Anal. Calcd for $C_{12}H_{16}N_2O_6$: C, 50.70; H, 5.67; N, 9.85. Found: C, 50.43; H, 5.41; N, 9.67.

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