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Efficient functionalizations of a pyranosido-pyrimidine scaffold

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ABSTRACT

Efficient reaction conditions have been developed to prepare highly functionalized chiral pyranosido-pyrimidine by regioselective alkylation of the pyranoside ring and palladium-catalyzed cross-coupling reaction on the pyrimidine ring under microwave activation. Such scaffold contains three different functions suitable for selective derivatization and could find applications in the design of peptidomimetics.

1. Introduction

In the last ten years, the drug discovery process has been profoundly modified by the introduction of combinatorial chemistry. The 'scaffold' concept[1] is now extensively used in the construction combinatorial libraries of compounds with high chemical and stereochemical diversity. In relation with the latter concept, the use of carbohydrates as scaffolds emerged.[2,3] Sugars have been used as templates to construct new active compounds by mimicking bioactive peptides. The first examples of the use of a monosaccharide as template for the design of peptidomimetics were reported by Hirschmann et al. and by Papageorgiou et al. to create mimetics of somatostatin.[4] Since these pioneering reports, the use of carbohydrates as scaffold for construction of bioactive compounds has been widely reported.[5]

Our previous investigation on the design of (Arg-Gly-Asp) RGD mimetics based on single pyranose sugar scaffolds led us to search for a platform that would be larger and more rigid than a single pyranose ring.[6,7] Thus, we focused our attention towards easily accessible polycyclic structures. Previous investigations of our group towards such structures led us to consider carbohydrate enones successfully used to form fused pyrano-pyranoside structures by hetero Diels–Alder reactions or by radical addition.[8] However, these homologated pyranosides are not prone to subsequent extensive functionalization. Using the same type of keto-sugars as intermediates, Peseke et al. elegantly developed a series of annelated pyranoside derivatives including pyrazolo and pyrimidino-pyranosides as nucleoside analogues.[9] We recently reported a rapid and efficient synthesis and functionalization of enantiomerically pure pyrano-pyrazoles.[10] Subsequently, we turned our attention to pyrimidino-pyranosides, which are much prone to functionalization. This paper presents our results in the synthesis of this scaffold and efficient methods for its functionalization en route to peptidomimetics.

2. Results and discussion

Starting from the methyl α-D-mannopyranoside, the 2-dimethylaminomethylene-3-ulose derivative **1** was prepared in three steps in good yields according to the literature procedure.[8,10] The pyrimidine-annelated pyranoside **2** was then prepared by an improvement of the reported procedure.[9d] Thus, treatment of the branched-chain ulose **1** with *S*-methylisothiouronium sulfate in the presence of triethylamine in refluxing ethanol gave **2** in 85% yield (Scheme 1). Functionalization of the latter was explored along two lines: first by benzylidene cleavage and subsequent regioselective alkylation of OH-6 and OH-4 hydroxyls and second by palladium-catalyzed cross-coupling reactions on the pyrimidine ring.

2.1. Regioselective alkylation of the 4,6-diol

The functionalization of the bicyclic scaffold **2** has been subjected to manipulation of the sugar moiety by benzylidene cleavage using a catalytic amount of PTSA in refluxing methanol for 12 h giving the 4,6-diol **3** in 72% yield (Scheme 1). Selective functionalization of this diol was not an obvious problem given the similar reactivity of the primary hydroxyl group and the secondary allylic one.[11] Thus, regioselective alkylation of **3** with various alkyl halides was developed using three different methods referred to as A, B and C (Table 1). Three different alkyl halides, suitable for further modifications and suitable to mimic amino acid side chains, were used.

In method A, NaH was used as the base and dry DMF as the solvent. In method B, Phase Transfer Catalysis (PCT) was used, alkylation reactions being performed by stirring equimolar amounts of the diol and the appropriate alkyl halide in the

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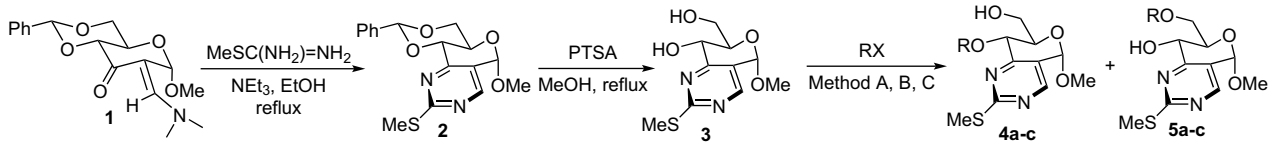


Scheme 1. Preparation of pyrimidino-pyranoside **2** and regioselective alkylation.

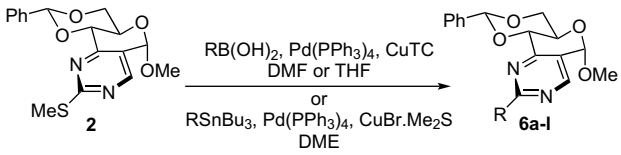
presence of 30% aqueous sodium hydroxide and tetrabutylammonium hydrogenosulfate in toluene. Under these basic conditions, methods A and B both allow an easy access to 4-alkylated compound **4** as the major product, in line with a higher acidity of the allylic OH-4 proton. If no traces of the 6-alkylated compounds **5b** and **5c** were observed using method A or B (entries 3 and 5), **5a** was formed using methyl iodide in 9% and 11% yield, respectively (entry 1). It is noteworthy that 10–15% of dialkylated products were obtained for all alkyl halides using either method A or B.

Alternatively, alkylation via formation of 4,6-*O*-stannylidene acetal intermediates was investigated (method C). As previously noted, dibutylstannylidene acetal, which included a primary hydroxyl group are alkylated on the primary alcohol.[12,13] Preparation of the stannylidene intermediate by refluxing dibutyltin oxide with diol **3** followed by treatment with an alkylating agent furnished the 6-alkylated product **5** as the only compound in good yield using methyl iodide and allylbromide as electrophile (entries 2 and 4). No traces of 4-alkylated or 4,6-dialkylated products were observed but 15% of the starting material was recovered. However, when using *tert*-butyl bromoacetate as the electrophile, a modest regioselectivity was observed and a mixture of alkylated compounds was obtained (entry 6). It is known that the selectivity of stannylidene acetal alkylation strongly depends on the alkylating reagent.[13]

Having developed efficient methods of alkylation of the bicyclic scaffold either at *O*-6 or *O*-4, for the introduction of two points of molecular diversity, we turned to the functionalization at position 2 of the pyrimidine ring for the introduction of a third point of diversity.

2.2. Functionalization by palladium cross-coupling reaction

Palladium-catalyzed cross-coupling reaction is a widely used technique for C–C bond formation on aromatic rings. We took advantage of the presence of an SMe leaving group on the pyrimidine moiety to introduce a substituent at this position (Scheme 2). Liebeskind et al. first reported the use of thioether or thioester leaving groups for the palladium-catalyzed coupling of boronic acids for the synthesis of ketones, alkynes, amidines and thioethers using nonbasic, copper(I) thiophene-2-carboxylate (CuTC) as the promoter.[14] Recently, the use of this new and excellent electrophile has been developed for either Stille or Suzuki reaction. The method has been applied to aromatics, heteroaromatics[15a–e] and sugar-derivatives[15f] bearing a thioether leaving group.



Scheme 2. Functionalization of the pyrimidine ring by Suzuki and Stille palladium-catalyzed cross-coupling reaction.

To explore the scope and limitations of Suzuki cross-coupling reactions on scaffold **2**, seven different boronic acids were selected (Scheme 2) and a series of experiments were performed to find the best conditions. The results, summarized in Table 2, demonstrate the generality and efficiency of this reaction on **2**. Almost all reactions were completed within 3–24 h at 80 °C. The substituted compounds **6a**–**f** were obtained in moderate to good yields. The reaction tolerated a variety of alkenyl, aryl and heteroaromatic boronic acids. Using $Pd(Ph_3)_4$ in catalytic amount (5 mol %), CuTC (1.5 equiv) and boronic acid (1.5 equiv) lead to recovery of the starting material **2** (50–70%) for almost all boronic acids, except for (*Z*)-propenylboronic acid and 2-furane boronic acid (entries 4 and 6) (Table 2, method A). Lower temperature (50 °C) was necessary for coupling (*Z*)-propenylboronic acid (entry 4). With several boronic acids, the use of 2.5 equiv of CuTC and 2 equiv of boronic acids gave much improved results (method B).

The formation of **6a**–**g** in THF under microwave irradiation in an open reaction vessel was next explored. All reactions were completed within 15 min (Table 2, method C). The use of 1.5 equiv of CuTC and 1.5 equiv of boronic acid is sufficient to transform all the starting material in the expected compounds in good yields. With methyl 4-carboxylate phenyl boronic acid, only degradation products were obtained using thermal conditions. The coupling product was obtained in 63% yield under microwave irradiation (entry 7). In this case, THF was the most appropriate solvent. These results show that microwave activation is of major interest in this area, leading to significant reduction of the reaction times and the amounts of reactants, i.e., CuTC and boronic acid.

A second series of experiments were performed to evaluate the feasibility of the carbon–carbon bond formation under Stille

Table 1
Alkylation of diol **3**

Entry	R	**4**/**5**	Method	Yield %		
				4	**5**	Dialkyl
1	Me	a	A/B	71/67	9/11	10/6
2	Me	a	C	—	57	—
3	CH_2–CH=CH_2	b	A/B	62/66	—	14/10
4	CH_2–CH=CH_2	b	C	—	61	—
5	CH_2–COO^{t}Bu	c	A/B	58/61	—	15/15
6	CH_2–COO^{t}Bu	c	C	24	45	6

Method A: NaH, RX, DMF, 0 °C. Method B: NaOH 30%, Bu_4NHSO_4, RX, toluene, 0 °C to rt. Method C: (a) Bu_2SnO, toluene, 110 °C; (b) RX, CsF, DMF, 90 °C.

Table 2
Suzuki palladium-catalyzed reactions on **2**

Entry	R	Method	Time (h)	Product	Yield %
1	Ph	B/C	24/0.2	**6a**	69/72
2	4-$MeOC_6H_4$	B/C	24/0.2	**6b**	71/68
3	4-$NO_2C_6H_4$	B/C	24/0.2	**6c**	72/79
4	(*Z*)-CH_3–CH=CH	A[a]/C	18/0.2	**6d**	75/79
5	4-Pyridyl	B	4	**6e**	71
6	2-Furyl	A/C	3/0.25	**6f**	76/66
7	4-C_6H_4COOMe	A/C	24/0.2	**6g**	0/63

Method A: $Pd(PPh_3)_4$ (5 mol %), CuTC (1.5 equiv), $RB(OH)_2$ (1.5 equiv), DMF, 80 °C. Method B: $Pd(PPh_3)_4$ (5 mol %), CuTC (2.5 equiv), $RB(OH)_2$ (2 equiv), DMF, 80 °C. Method C: $Pd(PPh_3)_4$ (5 mol %), CuTC (1.5 equiv), $RB(OH)_2$ (1.5 equiv), THF, 80 °C, microwave.

[a] 50 °C instead of 80 °C.

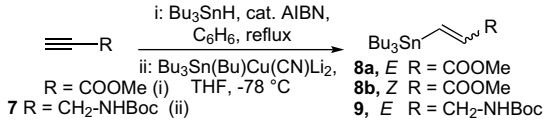
Table 3
Stille palladium-catalyzed reactions on **2**

Entry	R	Method	Time (h)	Product	Yield (%)
1	Ph	A	12	**6a**	69
2	$CH=CH_2$	A/B	12/0.15	**6h**	45/traces
3	2-Thienyl	A/B	12/0.15	**6i**	55/85
4	(*E*)-CH=CH–C_6H_5	A/B	6/0.15	**6j**	65/71
5	(*E*)-CH=CH–COOMe **8a**	A	4	**6k**	*E*-27/*Z*-9
		B	0.15		*E*-46/*Z*-35
6	(*Z*)-CH=CH–COOMe **8b**	A	4	**6k**	*E*-46
		B	0.15		*E*-78
7	(*E*)-CH=CH–CH_2–NHBoc **9**	A	4	**6l**	*E*-45
		B	0.15		*E*-58

Method A: $Pd(PPh_3)_4$ (5 mol %), CuBr·Me_2S (2.2 equiv), $RSnBu_3$ (2.2 equiv). Method B: $Pd(PPh_3)_4$ (5 mol %), CuBr·Me_2S (2.2 equiv), $RSnBu_3$ (2.2 equiv), DME, 80 °C, microwave.

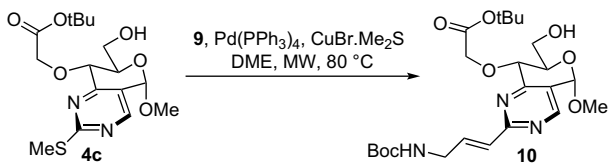
reaction conditions. Four readily available aryl, heteroaryl and vinylstannanes were reacted with the pyrimidino-pyranoside **2** (Scheme 2). The CuBr·Me_2S complex was used as a source of copper(I) and $Pd(PPh_3)_4$ as the catalyst, all reactions being completed at 80 °C in DME (Table 3, method A). Coupling products with aromatic, heteroaromatic and alkenyl-stannanes were obtained in moderate to good yields (entries 1–4). Prolonged reaction times did not improve the yield. As described above for Suzuki reactions, we explored the formation of **6h–j** in DME under microwave irradiation in an open vessel at 80 °C controlled by a standard external IR-sensor (Table 3, method B). All microwave-assisted coupling reactions proceeded with considerably reduced reaction times and gave better yields except for vinyl stannane for which only traces of the expected product were observed (entry 2).

To mimic amino acid side chains, two functionalized vinylstannanes **8** and **9** were used. The carboxylate function of **8** and the amino group of **9** could mimic acid aspartic side chain and lysine or arginine side chains, respectively. Methyl propiolate was hydrostannylated according to the literature procedures to give a mixture of separable (*E*)- and (*Z*)-tributylstannylacrylate **8a** and **8b** (35% and 30% yields, respectively) (Scheme 3).[16] Modest yields of coupled product **6k** were obtained with either (*Z*)- and (*E*)-vinylstannane (Table 3, entries 5 and 6). Condensation of (*Z*)-tributylstannylacrylate **8b** with **2** gave a mixture of separable *E*/*Z* isomers (3:1), the thermodynamically more stable (*E*)-isomer being obtained as the major product (entry 5), as already observed for Stille reaction with several vinylstannanes.[17] Here again, compound **6k** was formed in better yield under microwave irradiation (entry 6).



Scheme 3. Synthesis of functionalized vinylstannanes.[16,18]

The (*E*)-tributylstannylallylamine **9** was prepared regio- and stereospecifically from *N*-(*tert*-butoxycarbonyl)propargylamine by reaction with Lipshutz reagent $Bu_3Sn(Bu)Cu(CN)Li_2$ according to the literature procedure.[18] Tributylstannylallylamine **9** was coupled to *S*Me-pyrimidino derivative **2** in fair yield under thermal



Scheme 4. Multiple functionalization of **2**.

conditions. Improved yield of compound **6l** was obtained under microwave irradiation (entry 7).

2.3. Multiple functionalization of the template

Having in hands the above successful methods of derivatization, multiple functionalization of scaffold **2** was investigated. We examined the palladium-catalyzed coupling of an alkylated scaffold bearing a functionalized chain and a free hydroxyl group (Scheme 4). For example, compound **4c** was coupled with tributylstannylallylamine **9** under microwave irradiation in DME to give **10** in 53% yield. This demonstrates the mildness and the efficacy of the coupling reaction, which tolerates the presence of alcohol and ester function and the high potential of functionalization of template **2**.

3. Conclusion

We have developed efficient methods for the functionalization of a readily accessible chiral pyrimidino-pyranoside scaffold. Regioselective alkylation of the sugar moiety and palladium-catalyzed cross-coupling on the pyrimidine ring using a thiomethyl leaving group has been carried out. Such a molecular template was shown to be versatile to various transformations and could find applications in drug design as a rigid template carrier of three functional groups suitable for selective derivatization and molecular diversity introduction. This methodology could find applications for the construction of peptidomimetic libraries.

4. Experimental

4.1. General

Solvents and liquid reagents were purified and dried according to recommended procedures. TLC analyses were performed using standard procedures on Kieselgel 60 F_{254} plates or RP-18 F_{254} plates (Merck). Compounds were visualized using UV light (254 nm) and a solution of cerium sulfate tetrahydrate and phosphomolybdic acid in 10% aqueous sulfuric acid. Column chromatography was performed on silica gel SI 60 (63–200 μm) (Merck). Melting points were determined with a Tottoli apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 141 polarimeter. ^1H and ^{13}C NMR spectra were recorded on a Bruker spectrometer AC250 (250 MHz and 62.9 MHz, respectively) and DRX400 (400 MHz and 100.6 MHz, respectively). For complete assignment of ^1H and ^{13}C signals, two-dimensional $^1H,^1H$ COSY and $^1H,^{13}C$ correlation spectra were recorded. Chemical shifts (δ) are given in parts per million relative to the solvent residual peak. The following abbreviations are used for multiplicity of NMR signals: s=singlet, d=doublet, t=triplet, q=quadruplet, m=multiplet, br=broad signal and app=apparent multiplicity. The *J* values given refer to apparent multiplicities and do not represent the true coupling constants. Mass spectra were obtained with a VG-Platform Micromass-Waters (ESI^+/quad) and a Shimadzu GC–MS-QP2010 apparatus (CI). HRMS spectra were recorded on a Bruker MicroTOF apparatus. The ratio of the solvent systems is v/v everywhere. Microwave syntheses were performed on a CEM Discover mono-mode oven. The temperature was controlled by a standard external IR-sensor.

4.2. Methyl (2*E*)-2-deoxy-2-[(dimethylamino)methylene]-4,6-*O*-[(*R*)-phenylmethylene]-α-D-*erythro*-hexopyranosid-3-ulose (1)

To a solution of 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose (5.7 g, 21 mmol) in dichloromethane (150 mL) was added *N*,*N*-dimethylformamide dimethylacetal (13 mL, 0.1

mol). The resulting mixture was heated until evaporation of the solvent. After completion of the reaction (TLC monitoring), compound **1** precipitated during cooling. The product was recrystallized from dichloromethane/hexane. Yield: 81% as yellow needles; mp 168–169 °C; R_f=0.54 (CH_2Cl_2/MeOH, 95:5); $[\alpha]_D$ +174.0 (*c* 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.15 (s, 6H), 3.40 (s, 3H), 3.80 (app t, 1H, *J*=10 Hz), 4.05 (d, 1H, *J*=10.0 Hz), 4.20–4.40 (m, 2H), 5.58 (s, 1H), 5.62 (s, 1H), 7.30–7.60 (m, 5H), 7.64 (s, 1H).

4.3. (2*R*,4a*R*,6*S*,10b*S*)-4,4a,6,10b-Tetrahydro-6-methoxy-9-methylsulfanyl-2-phenyl-[1,3]-dioxino[4′,5′:5,6]-pyrano[4,3-*d*]-pyrimidine (2)

In a dry round-bottomed flask equipped with a reflux condenser, a mixture of *S*-methylthiouronium sulfate (6.5 g, 23.5 mmol) and triethylamine (6.5 mL, 47 mmol) in 100 mL of ethanol was refluxed for 30 min. Enaminoketone **1** (5.0 g, 15.6 mmol) was added and the mixture was stirred at reflux. After the reaction had completed (TLC monitoring), the mixture was cooled down. The precipitate was filtered off and recrystallized from ethanol. Yield: 85% as white needles; mp 230–231 °C; R_f=0.60 (CH_2Cl_2/MeOH, 99:1); $[\alpha]_D$ −4.5 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 2918, 1586 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57 (s, 3H), 3.57 (s, 3H), 3.94 (app t, 1H, *J*=9.9 Hz), 4.15 (app td, 1H, *J*=9.9, 4.8 Hz), 4.43 (dd, 1H, *J*=9.9, 4.8 Hz), 4.62 (d, 1H, *J*=9.9 Hz), 5.52 (s, 1H), 5.75 (s, 1H), 7.35–7.40 (m, 3H), 7.55–7.60 (m, 2H), 8.41 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.4, 56.3, 63.0, 69.7, 75.9, 96.6, 102.6, 122.3, 126.6, 128.4, 129.3, 137.1, 156.5, 161.1, 173.7; MS (CI) *m*/*z* 347 (54, $[M+H]^+$), 315 (48), 269 (23), 197 (30), 149 (100), 121 (50).

4.4. (5*S*,7*R*,8*S*)-2-Methylsulfanyl-5,8-dihydro-7-hydroxymethyl-5-methoxy-pyrano[3,4-*e*]pyrimidin-8-ol (3)

Compound **2** (130 mg, 0.5 mmol) was treated with PTSA (20 mol %) in MeOH (15 mL) at reflux during 12 h. The mixture was then diluted with saturated $NaHCO_3$ aqueous solution (20 mL) and extracted with dichloromethane (3×30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel. Yield: 72% as a white powder; mp 171–172 °C; R_f=0.48 (CH_2Cl_2/MeOH, 90:10); $[\alpha]_D$ +48.7 (*c* 1.02, $CHCl_3$); IR (KBr) ν_{max} 3369, 1639 cm^{-1}; ^{1}H NMR (250 MHz, MeOH-d_4) δ 2.59 (s, 3H), 3.56 (s, 3H), 3.80–4.00 (m, 3H), 4.48 (d, 1H, *J*=9.6 Hz), 5.59 (s, 1H), 8.40 (s, 1H); ^{13}C NMR (62.9 MHz, MeOH-d_4) δ 14.2, 56.1, 62.6, 66.3, 73.2, 97.2, 124.0, 157.2, 167.0, 174.3; MS (ES) *m*/*z* 281 (100, $[M+Na]^+$); HRMS (ESI^+) calculated for $C_{10}H_{15}N_2O_4$ $[M+H]^+$: 259.0747, found: 259.0754 calculated for $C_{10}H_{14}N_2O_4Na$ $[M+Na^+]$: 281.0566, found: 281.0577.

4.5. General alkylation procedures for 4a–c and 5a–c

4.5.1. Method A

To a solution of **3** (200 mg, 0.77 mmol) in dry THF (10 mL) at 0 °C was added 60% NaH in oil (40 mg, 1.0 mmol) and the suspension was stirred for 30 min. The alkyl halide (0.85 mmol) was added dropwise and the mixture was stirred at 0 °C until the reaction had completed (TLC monitoring). The reaction was quenched with water (1 mL) and evaporated under reduced pressure. The residue was partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL), and the isolated aqueous phase extracted with CH_2Cl_2 (2×20 mL). The organic phases were combined, washed with satd aqueous NH_4Cl (10 mL) and water (10 mL). The isolated organic phase was dried over $MgSO_4$, concentrated under reduced pressure and the residue purified by column chromatography on silica gel.

4.5.2. Method B

To a solution of **3** (200 mg, 0.77 mmol) in toluene (3 mL) at 0 °C were successively added 50% aqueous NaOH (3 mL), NBu_4HSO_4 (680 mg, 1.9 mmol). The mixture was stirred for 30 min at 0 °C. Alkyl halide (0.85 mmol) was added dropwise and the mixture was stirred at 0 °C until the reaction had completed (TLC monitoring). The reaction was quenched with water (10 mL) and the aqueous phase extracted with CH_2Cl_2 (3×10 mL). The organic phases were combined, washed with satd aqueous NH_4Cl (2×10 mL) and water (10 mL). The isolated organic phase was dried over $MgSO_4$, concentrated under reduced pressure and the residue purified by column chromatography on silica gel.

4.5.3. Method C

A mixture of **3** (200 mg, 0.77 mmol) and dibutyltin oxide (290 mg, 1.15 mmol) in toluene (5 mL) was refluxed in a flask equipped with a Dean Stark separator until obtaining a clear solution. The solution was then concentrated to dryness and dissolved in dry dimethylformamide (5 mL). Alkyl halides (1.7 mmol) and cesium fluoride (175 mg, 1.15 mmol) were added and the mixture was heated at 90 °C for 12 h. Evaporation to dryness gave a residue purified by column chromatography on silica gel.

*4.5.3.1. (5S,7R,8S)-2-Methylsulfanyl-5,8-dihydro-7-hydroxymethyl-5,8-dimethoxy-pyrano[3,4-e]pyrimidine (**4a**).* Yield: 71% (method A), 67% (method B) as colourless crystals; mp 141–142 °C; R_f=0.45 (hexane/EtOAc, 35:65); $[\alpha]_D$ +91.1 (*c* 1.01, $CHCl_3$); IR (KBr) ν_{max} 3202, 1580 cm^{-1}; ^{1}H NMR (250 MHz, MeOH-d_4) δ 2.58 (s, 3H), 3.53 (s, 3H), 3.87 (s, 3H), 3.93–4.08 (m, 3H), 4.31 (d, 1H, *J*=9.5 Hz), 5.48 (s, 1H), 8.34 (s, 1H); ^{13}C NMR (62.9 MHz, MeOH-d_4) δ 14.5, 56.1, 61.5, 62.3, 70.0, 73.9, 96.4, 122.4, 156.0, 165.2, 175.6; HRMS (ESI^+) calculated for $C_{11}H_{16}N_2NaO_4S$ $[M+Na]^+$: 295.0728, found: 295.0719.

*4.5.3.2. (5S,7R,8S)-2-Methylsulfanyl-5,8-dihydro-7-methoxymethyl-5-methoxy-pyrano[3,4-e]-pyrimidin-8-ol (**5a**).* Yield: 71 % (method C) as colourless crystals; mp 105–106 °C; R_f=0.58 (hexane/EtOAc, 35:65); $[\alpha]_D$ +40.6 (*c* 1.05, $CHCl_3$); IR (KBr) ν_{max} 3229, 2916, 1580, 1545 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.57 (s, 3H), 3.49 (s, 3H), 3.56 (s, 3H), 3.81 (d, 2H, *J*=3.3 Hz), 4.04 (app dt, 1H, *J*=9.8, 3.3 Hz), 4.62 (d, 1H, *J*=9.8 Hz), 5.59 (s, 1H), 8.39 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.4, 56.1, 59.7, 65.1, 70.1, 71.4, 96.3, 121.6, 156.1, 164.8, 173.1; HRMS (ESI^+) calculated for $C_{11}H_{16}N_2NaO_4S$ $[M+Na]^+$: 295.0723, found: 295.0721.

*4.5.3.3. (5S,7R,8S)-2-Methylsulfanyl-5,8-dihydro-7-hydroxymethyl-5-methoxy-8-allyloxy-pyrano[3,4-e]pyrimidine (**4b**).* Yield: 62% (method A), 66% (method B) as colourless crystals; mp 140–141 °C; R_f=0.55 (hexane/EtOAc, 35:65); $[\alpha]_D$ +159.1 (*c* 1.01, $CHCl_3$); IR (KBr) ν_{max} 3283, 1580, 1540 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.58 (s, 3H), 3.54 (s, 3H), 3.86–4.00 (m, 2H), 4.09 (app dt, 1H, *J*=9.8, 3.7 Hz), 4.44 (app ddt, 1H, *J*=12.0, 5.5, 1.5 Hz), 4.49 (d, 1H, *J*=9.8 Hz), 4.82 (app ddt, 1H, *J*=12.0, 5.5, 1.5 Hz), 5.25 (br d, 1H, *J*=10.5 Hz), 5.35 (app dq, 1H, *J*=19.0, 1.5 Hz), 5.50 (s, 1H), 6.03 (ddt, 1H, *J*=19.0, 10.5, 5.5 Hz), 8.34 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.5, 56.0, 62.1, 70.0, 71.4, 74.4, 96.3, 118.1, 122.3, 134.5, 155.9, 165.3, 173.3; HRMS (ESI^+) calculated for $C_{13}H_{18}N_2NaO_4S$ $[M+Na]^+$: 321.0879, found: 321.0890.

*4.5.3.4. (5S,7R,8S)-2-Methylsulfanyl-5,8-dihydro-7-allyloxymethyl-5-methoxy-pyrano[3,4-e]pyrimidin-8-ol (**5b**).* Yield: 61% (method C) as colourless crystals; mp 184–185 °C; R_f=0.63 (hexane/EtOAc, 35:65); $[\alpha]_D$ +19.7 (*c* 1.02, $CHCl_3$); IR (KBr) ν_{max} 3229, 2927 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.58 (s, 3H), 3.57 (s, 3H), 3.85 (br d, 1H, *J*=4.8 Hz), 3.88 (br d, 1H, *J*=2.5 Hz), 4.06 (ddd, 1H, *J*=9.9, 4.8, 2.5 Hz), 4.15 (ddd, 2H, *J*=5.5, 2.1, 1.2 Hz), 4.63 (d, 1H, *J*=9.9 Hz), 5.22 (ddt, 1H,

J=10.6, 3.2, 1.2 Hz), 5.34 (ddt, 1H, J=19.0, 3.2, 2.1 Hz), 5.58 (s, 1H), 5.97 (ddt, 1H, J=19.0, 10.6, 5.5 Hz), 8.39 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.4, 56.1, 65.3, 69.1, 70.3, 72.8, 96.2, 117.4, 121.7, 134.7, 156.1, 164.9, 173.2; HRMS (ESI$^+$) calculated for $C_{13}H_{18}N_2NaO_4S$ [M+Na]$^+$: 321.0879, found: 321.0847.

*4.5.3.5. (5S,7R,8S)-2-Methylsulfanyl-5,8-dihydro-8-[(tert-butoxycarbonylmethyl)oxy]-7-hydroxymethyl-5-methoxy-pyrano[3,4-e]pyrimidine (**4c**).* Yield: 58% (method A), 61% (method B) as a colourless oil; R_f=0.48 (hexane/EtOAc, 35:65); [α]$_D$ +196.6 (c 1.02, $CHCl_3$); IR (NaCl) ν_{max} 3460, 2927, 1747, 1723 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.50 (s, 9H), 2.58 (s, 3H), 3.54 (s, 3H), 3.87–3.99 (m, 2H), 4.02–4.20 (m, 1H), 4.20–4.35 (m, 1H), 4.50 (d, 1H, J=17.9 Hz), 4.64 (d, 1H, J=9.8 Hz), 5.09 (d, 1H, J=17.9 Hz), 5.50 (s, 1H), 8.35 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.5, 28.2, 56.1, 61.7, 69.4, 70.3, 71.6, 83.1, 96.4, 122.3, 156.1, 165.5, 172.0, 172.9; HRMS (ESI$^+$) calculated for $C_{16}H_{24}N_2NaO_6S$ [M+Na]$^+$: 395.1247, found: 395.1221.

*4.5.3.6. (5S,7R,8S)-2-Methylsulfanyl-5,8-dihydro-7-[(tert-butoxycarbonylmethyl)oxy]-5-methoxy-pyrano[3,4-e]pyrimidine-8-ol (**5c**).* Yield: 45% (method C) as a white powder; mp 144–145 °C; R_f=0.33 (hexane/EtOAc, 50:50); [α]$_D$ +37.3 (c 1.01, $CHCl_3$); IR (KBr) ν_{max} 3428, 2928, 1757, 1582 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.48 (s, 9H), 2.57 (s, 3H), 3.55 (s, 3H), 3.90–4.09 (m, 3H), 4.06 (d, 1H, J=16.5 Hz), 4.15 (d, 1H, J=16.5 Hz), 4.75 (d, 1H, J=9.7 Hz), 5.56 (s, 1H), 8.37 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.2, 28.1, 55.9, 65.0, 69.0, 70.0, 70.3, 82.0, 96.2, 121.6, 155.8, 164.7, 169.8, 173.1; HRMS (ESI$^+$) calculated for $C_{16}H_{24}N_2NaO_6S$ [M+Na]$^+$: 395.1247, found: 395.1246.

4.6. General procedure for Suzuki cross-coupling (6a–g)

4.6.1. Conventional heating

In a dry round-bottomed flask equipped with a condenser flushed with argon, 5 mL of dry DMF, compound **4** (300 mg, 0.87 mmol), Pd(PPh$_3$)$_4$ (5 mol %), CuTC (400 mg, 2.1 mmol) and boronic acid (1.74 mmol) were stirred and heated at 80 °C until reaction completion. The reaction was then allowed to cool to room temperature and was evaporated to dryness under reduced pressure. The residue was diluted with satd aqueous NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3×20 mL). The dried organic layer was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel.

4.6.2. Microwave irradiation

In a dry round-bottomed flask equipped with a condenser flushed with argon, 5 mL of dry DMF, compound **4** (300 mg, 0.87 mmol), Pd(PPh$_3$)$_4$ (5 mol %), CuTC (249 mg, 1.3 mmol) and boronic acid (1.3 mmol) were stirred and heated by microwave irradiation at constant temperature (80 °C controlled by a standard external IR-sensor). All reactions were completed within 15 min. The reaction was then allowed to cool to room temperature and was evaporated to dryness under reduced pressure. The residue was diluted with satd aqueous solution of NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3×20 mL). The dried organic layer was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel.

*4.6.2.1. (2R,4aR,6S,10bS)-4,4a,6,10b-Tetrahydro-6-methoxy-2,9-diphenyl-1,3-dioxino[4′,5′:5,6]pyrano[4,3-d]pyrimidine (**6a**).* Yield: 69% (method B), 72% (method C) as white crystals; mp 241–242 °C; R_f=0.6 (CH_2Cl_2/MeOH, 99:1); [α]$_D$ −12.0 (c 1.0, $CHCl_3$); IR (KBr) ν_{max} 2924, 1590, 1583 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (s, 3H), 3.99 (app t, 1H, J=10.2 Hz), 4.24 (app td, 1H, J=10.2, 4.7 Hz), 4.48 (dd, 1H, J=10.2, 4.7 Hz), 4.74 (d, 1H, J=10.2 Hz), 5.61 (s, 1H), 5.83 (s, 1H), 7.41–7.48 (m, 6H), 7.63 (d, 2H, J=7.9 Hz), 8.45–8.48 (m, 2H), 8.70 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 56.4, 63.2, 69.5, 76.2, 96.7, 102.6, 124.9, 126.6, 128.4, 128.7, 128.8, 129.3, 131.2, 137.2, 156.8, 161.2, 165.0; MS (CI) m/z 377 (39, [M+H]$^+$), 345 (20), 227 (29), 149 (100).

*4.6.2.2. (2R,4aR,6S,10bS)-4,4a,6,10b-Tetrahydro-6-methoxy-2-phenyl-9-(4-methoxyphenyl)-1,3-dioxino[4′,5′:5,6]pyrano[4,3-d]pyrimidine (**6b**).* Yield: 71% (method B), 68% (method C) as white crystals; mp 204–205 °C; R_f=0.63 (CH_2Cl_2/MeOH, 99:1); [α]$_D$ −32.7 (c 1.08, $CHCl_3$); IR (KBr) ν_{max} 2901, 1572 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.61 (s, 3H), 3.86 (s, 3H), 3.98 (app t, 1H, J=9.8 Hz), 4.23 (app td, 1H, J=9.8, 4.7 Hz), 4.47 (dd, 1H, J=9.8, 4.7 Hz), 4.72 (d, 1H, J=9.8 Hz), 5.59 (s, 1H), 5.81 (s, 1H), 6.97 (d, 2H, J=8.8 Hz), 7.35–7.45 (m, 3H), 7.60–7.70 (m, 2H), 8.42 (d, 2H, J=8.8 Hz), 8.64 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 55.5, 56.3, 63.2, 69.5, 76.2, 96.8, 102.6, 114.0, 124.1, 126.6, 128.4, 129.3, 129.9, 130.5, 137.2, 156.7, 161.0, 162.3; MS (CI) m/z 406 (100, [M]$^+$), 375 (36), 329 (18), 257 (38), 149 (70); HRMS (ESI$^+$) calculated for $C_{23}H_{23}N_2O_5$ [M+H]$^+$: 407.1601, found: 407.1601.

*4.6.2.3. (2R,4aR,6S,10bS)-4,4a,6,10b-Tetrahydro-6-methoxy-2-phenyl-9-(4-nitrophenyl)-1,3-dioxino[4′,5′:5,6]pyrano[4,3-d]pyrimidine (**6c**).* Yield: 72% (method B), 79% (method C) as white crystals; mp 242–243 °C; R_f=0.65 (CH_2Cl_2/MeOH, 99:1); [α]$_D$ −0.3 (c 1.01, $CHCl_3$); IR (KBr) ν_{max} 1524, 1345 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (s, 3H), 4.01 (app t, 1H, J=9.8 Hz), 4.24 (app td, 1H, J=9.8, 4.9 Hz), 4.50 (dd, 1H, J=9.8, 4.9 Hz), 4.76 (d, 1H, J=9.8 Hz), 5.64 (s, 1H), 5.84 (s, 1H), 7.40–7.45 (m, 3H), 7.60–7.65 (m, 3H), 8.31 (br d, 1H, J=7.7 Hz), 8.75 (s, 1H), 8.82 (d, 1H, J=7.7 Hz), 9.33 (d, 1H, J=1.8 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 56.5, 63.2, 69.4, 76.1, 96.5, 102.7, 123.8, 125.6, 126.1, 126.6, 128.5, 129.4, 129.7, 134.5, 137.1, 139.0, 148.9, 157.1, 161.7, 162.7; MS (CI) m/z 422 (18, [M+H]$^+$), 390 (18), 344 (42), 272 (35), 149 (100); HRMS (ESI$^+$) calculated for $C_{23}H_{19}KN_3O_6$ [M$^+$]: 460.0905, found: 460.0906.

*4.6.2.4. Z-(2R,4aR,6S,10bS)-4,4a,6,10b-Tetrahydro-6-methoxy-2-phenyl-9-(1-propenyl)-1,3-dioxino[4′,5′:5,6]pyrano[4,3-d]pyrimidine (**6d**).* Yield: 75% (method A), 79% (method C) as white crystals; mp 114–115 °C; R_f=0.56 (CH_2Cl_2/MeOH, 99:1); [α]$_D$ +10.2 (c 1.04, $CHCl_3$); IR (KBr) ν_{max} 2927, 1583 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.29 (dd, 3H, J=7.3, 1.8 Hz), 3.61 (s, 3H), 3.97 (app t, 1H, J=9.9 Hz), 4.19 (app td, 1H, J=9.9, 4.7 Hz), 4.46 (dd, 1H, J=9.9, 4.7 Hz), 4.70 (d, 1H, J=9.9 Hz), 5.58 (s, 1H), 5.80 (s, 1H), 6.32 (dq, 1H, J=12.0, 7.3 Hz), 6.60 (dq, 1H, J=12.0, 1.8 Hz), 7.35–7.40 (m, 3H), 7.55–7.65 (m, 2H), 8.64 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 15.8, 56.4, 63.3, 69.5, 76.1, 96.7, 102.5, 123.6, 126.6, 128.4, 128.5, 129.3, 137.2, 139.2, 156.1, 160.6, 166.0; MS (CI) m/z 341 (60, [M+H]$^+$), 309 (38), 263 (27), 149 (100); HRMS (ESI$^+$) calculated for $C_{19}H_{21}N_2O_4$ [M+H$^+$]: 341.1496, found: 341.1529.

*4.6.2.5. (2R,4aR,6S,10bS)-4,4a,6,10b-Tetrahydro-6-methoxy-2-phenyl-9-(4-pyridyl)-1,3-dioxino[4′,5′:5,6]pyrano[4,3-d]pyrimidine (**6e**).* Yield: 71% (method B) as white crystals; mp 249–250 °C; R_f=0.33 (CH_2Cl_2/MeOH, 98:2); [α]$_D$ +14.9 (c 1.01, $CHCl_3$); IR (KBr) ν_{max} 2983, 1586 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.63 (s, 3H), 4.00 (app t, 1H, J=9.8 Hz), 4.22 (app td, 1H, J=9.8, 4.7 Hz), 4.50 (dd, 1H, J=4.7, 9.8 Hz), 4.76 (d, 1H, J=9.8 Hz), 5.64 (s, 1H), 5.84 (s, 1H), 7.40–7.50 (m, 5H), 7.55–7.65 (m, 2H), 8.30–8.40 (m, 2H), 8.76 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 56.5, 63.2, 69.4, 76.0, 96.5, 102.6, 122.5, 126.5, 128.5, 129.4, 137.1, 144.4, 150.5, 157.1, 161.7, 162.9; MS (CI) m/z 378 (100, [M+H]$^+$), 377 (31), 346 (16), 228 (46), 149 (51); HRMS (ESI$^+$) calculated for $C_{21}H_{21}N_3O_4$ [M+H]$^+$: 378.1448, found: 378.1443.

*4.6.2.6. (2R,4aR,6S,10bS)-4,4a,6,10b-Tetrahydro-6-methoxy-2-phenyl-9-(2-furyl)-1,3-dioxino[4′,5′:5,6]pyrano[4,3-d]pyrimidine (**6f**).* Yield: 76% (method A), 66% (method C) as white crystals; mp 255–256 °C; R_f=0.35 (CH_2Cl_2/MeOH, 99:1); [α]$_D$ −17.0 (c 1.0, $CHCl_3$); IR

(KBr) ν_{max} 2921, 1693 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.62 (s, 3H), 3.98 (app t, 1H, J=9.8 Hz), 4.22 (app td, 1H, J=9.8, 4.7 Hz), 4.48 (dd, 1H, J=9.8, 4.7 Hz), 4.72 (d, 1H, J=9.8 Hz), 5.59 (s, 1H), 5.80 (s, 1H), 6.56 (dd, 1H, J=3.6, 1.8 Hz), 7.35–7.45 (m, 4H), 7.55–7.65 (m, 3H), 8.65 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 56.4, 63.2, 69.4, 76.0, 96.6, 102.8, 112.5, 114.8, 124.5, 126.7, 128.4, 129.4, 137.1, 145.6, 151.8, 156.9, 157.8, 161.5; MS (CI) m/z 367 (50, $[M+H]^+$), 367 (54), 355 (25), 289 (15), 217 (34), 149 (100); HRMS (ESI^+) calculated for $C_{20}H_{18}N_2NaO_5$ $[M+Na]^+$: 389.1108, found: 389.1126.

*4.6.2.7. (2R,4aR,6S,10bS)-4,4a,6,10b-Tetrahydro-6-methoxy-2-phenyl-9-(4-(methoxycarbonyl)phenyl)-1,3-dioxino[4′,5′:5,6]pyrano[4,3-d]-pyrimidine (**6g**).* Yield: 63% (method C) as white crystals; mp 224–225 °C; R_f=0.40 (CH_2Cl_2/MeOH, 98:2); $[\alpha]_D$ −13.6 (c 1.0, $CHCl_3$); IR (KBr) ν_{max} 2921, 1720 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.63 (s, 3H), 3.94 (s, 3H), 4.01 (app t, 1H, J=9.8 Hz), 4.25 (app td, 1H, J=9.8, 4.7 Hz), 4.49 (dd, 1H, J=9.8, 4.7 Hz), 4.76 (d, 1H, J=9.8 Hz), 5.63 (s, 1H), 5.83 (s, 1H), 7.40–7.50 (m, 2H), 7.60–7.65 (m, 2H), 8.13 (d, 2H, J=8.4 Hz), 8.54 (d, 2H, J=8.5 Hz), 8.73 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 52.4, 56.5, 63.2, 69.4, 76.1, 96.6, 102.6, 125.6, 126.6, 128.5, 128.7, 129.4, 129.9, 132.3, 137.1, 141.2, 156.9, 161.4, 164.0, 167.0; HRMS (ESI^+) calculated for $C_{24}H_{22}N_2O_6Na$ $[M+Na]^+$: 457.1370, found: 457.1382.

4.7. General procedure for Stille cross-coupling (6h–l)

4.7.1. Conventional heating

In a dry round-bottomed flask equipped with a condenser flushed with argon, 5 mL of dry DME, compound **4** (300 mg, 0.87 mmol), $Pd(PPh_3)_4$ (5 mol %), $CuBr\cdot Me_2S$ (392 mg, 1.9 mmol), n-tributylstannane (1.9 mmol) were stirred and heated at 80 °C until reaction completion. The mixture was diluted with an aqueous solution of KF (20%) (20 mL) and extracted with CH_2Cl_2 (3×20 mL). The dried organic layer was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel.

4.7.2. Microwave irradiation

In a dry round-bottomed flask equipped with a condenser flushed with argon, 5 mL of dry DMF, compound **4** (300 mg, 0.87 mmol), $Pd(PPh_3)_4$ (5 mol %), $CuBr\cdot Me_2S$ (392 mg, 1.9 mmol), n-tributylstannane (1.9 mmol) were stirred and heated by microwave irradiation at constant temperature (80 °C controlled by a standard external IR-sensor). All reactions were completed within 5–8 min. The reaction was then allowed to cool to room temperature and was evaporated to dryness under reduced pressure. The residue was diluted with aqueous solution of KF (20%) (20 mL) and extracted with CH_2Cl_2 (3×20 mL). The dried organic layer was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel.

*4.7.2.1. (2R,4aR,6S,10bS)-4,4a,6,10b-Tetrahydro-6-methoxy-2-phenyl-9-vinyl-1,3-dioxino[4′,5′:5,6]pyrano[4,3-d]pyrimidine (**6h**).* Yield: 45% (method A) as white crystals; mp 284–285 °C; R_f=0.55 (CH_2Cl_2/MeOH, 99:1); $[\alpha]_D$ +7.3 (c 1.05, $CHCl_3$); IR (KBr) ν_{max} 2916, 1583, 1543 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.61 (s, 3H), 3.97 (app t, 1H, J=9.8 Hz), 4.20 (app td, 1H, J=9.8, 4.7 Hz), 4.46 (dd, 1H, J=4.7, 9.8 Hz), 4.70 (d, 1H, J=9.8 Hz), 5.58 (s, 1H), 5.75 (dd, 1H, J=10.6, 1.8 Hz), 5.79 (s, 1H), 6.67 (dd, 1H, J=1.8, 17.5 Hz), 6.93 (dd, 2H, J=10.6, 17.5 Hz), 7.35–7.45 (m, 3H), 7.55–7.65 (m, 2H), 8.61 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 56.5, 63.2, 69.5, 76.1, 96.7, 102.9, 125.2, 126.8, 128.4, 129.5, 136.4, 137.1, 156.7, 161.0, 164.7; HRMS (ESI^+) calculated for $C_{18}H_{19}N_2O_4$ $[M+H]^+$: 327.1339, found: 327.1337.

*4.7.2.2. (2R,4aR,6S,10bS)-4,4a,6,10b-Tetrahydro-6-methoxy-2-phenyl-9-(2-thienyl)-1,3-dioxino[4′,5′:5,6]pyrano[4,3-d]pyrimidine (**6i**).* Yield: 55% (method A), 85% (method B) as white crystals; mp 260–271 °C; R_f=0.66 (CH_2Cl_2/MeOH, 99:1); $[\alpha]_D$ −40.7 (c 1.0, $CHCl_3$); IR (KBr) ν_{max} 2916, 1580 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.60 (s, 3H), 3.98 (app t, 1H, J=9.8 Hz), 4.19 (app td, 1H, J=9.8, 4.7 Hz), 4.47 (dd, 1H, J=9.8, 4.7 Hz), 4.70 (d, 1H, J=9.8 Hz), 5.58 (s, 1H), 5.81 (s,1H), 7.13 (dd, 1H, J=5.1, 3.6 Hz), 7.38–7.45 (m, 3H), 7.49 (dd, 1H, J=5.1, 1.1 Hz), 7.60–7.65 (m, 2H), 8.06 (dd, 1H, J=3.6, 1.1 Hz), 8.59 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 56.3, 63.1, 69.4, 76.0, 96.7, 102.5, 124.3, 126.6, 128.4, 129.3, 130.2, 130.6, 137.2, 142.8, 156.8, 161.3, 161.7; MS (CI) m/z 382 (46, $[M]^+$), 351 (22), 233 (25), 149 (100); HRMS (ESI^+) calculated for $C_{20}H_{19}N_2O_4S$ $[M+H]^+$: 383.1060, found: 383.1075.

*4.7.2.3. E-(2R,4aR,6S,10bS)-4,4a,6,10b-Tetrahydro-6-methoxy-2-phenyl-9-(styryl)-1,3-dioxino[4′,5′:5,6]pyrano[4,3-d]pyrimidine (**6j**).* Yield: 65% (method A), 71% (method B) as white crystals; mp 209–210 °C; R_f=0.45 (hexane/EtOAc, 50:50); $[\alpha]_D$ −13.0 (c 1.0, $CHCl_3$); IR (KBr) ν_{max} 2916, 1580 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.62 (s, 3H), 3.99 (app t, 1H, J=9.8 Hz), 4.23 (app td, 1H, J=9.8, 4.7 Hz), 4.47 (dd, 1H, J=9.8, 4.7 Hz), 4.72 (d, 1H, J=9.8 Hz), 5.59 (s, 1H), 5.81 (s, 1H), 7.27–7.45 (m, 7H), 7.55–7.65 (m, 4H), 8.02 (d, 1H, J=15.7 Hz), 8.63 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 56.4, 63.1, 69.4, 76.1, 96.6, 103.0, 124.3, 126.8, 127.2, 127.9, 128.4, 128.9, 129.4, 129.5, 136.0, 137.1, 139.3, 156.5, 161.0, 165.1; MS (ES) m/z 425 (30, $[M+Na]^+$), 403 (68), 280 (100); HRMS (ESI^+) calculated for $C_{24}H_{23}N_2O_4$ $[M+H^+]$: 403.1652, found: 403.1647.

*4.7.2.4. (2R,4aR,6S,10bS)-4,4a,6,10b-Tetrahydro-6-methoxy-2-phenyl-9-(2-E-(methoxycarbonyl)ethenyl)-1,3-dioxino[4′,5′:5,6]pyrano[4,3-d]-pyrimidine (**6k**).* Yield: 46% (method A), 78% (method B) as white crystals; mp 225–226 °C; R_f=0.35 (hexane/EtOAc, 50:50); $[\alpha]_D$ −7.3 (c 1.0, $CHCl_3$); IR (KBr) ν_{max} 2916, 1723 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.62 (s, 3H), 3.82 (s, 3H), 3.98 (app t, 1H, J=9.9 Hz), 4.21 (app td, 1H, J=9.9, 4.7 Hz), 4.48 (dd, 1H, J=9.9, 4.7 Hz), 4.72 (d, 1H, J=9.9 Hz), 5.60 (s, 1H), 5.80 (s, 1H), 7.22 (d, 1H, J=15.7 Hz), 7.38–7.45 (m, 3H), 7.54–7.65 (m, 2H), 7.75 (d, 1H, J=15.7 Hz), 8.68 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 52.1, 56.5, 63.1, 69.3, 75.9, 96.4, 102.8, 126.2, 126.6, 128.0, 128.5, 129.5, 136.9, 142.6, 156.8, 161.3, 163.0, 166.7; MS (ES) m/z 407 (100, $[M+Na]^+$), 385 (45); HRMS (ESI^+) calculated for $C_{20}H_{20}N_2NaO_6$ $[M+Na]^+$: 407.1214, found: 407.1244.

*4.7.2.5. (2R,4aR,6S,10bS)-4,4a,6,10b-Tetrahydro-6-methoxy-2-phenyl-9-(2-Z-(methoxycarbonyl)ethenyl)-1,3-dioxino[4′,5′:5,6]pyrano[4,3-d]-pyrimidine (**6k**).* Yield: 9% (method A), 35% (method B) as white crystals; mp 141–142 °C; R_f=0.25 (hexane/EtOAc, 50:50); $[\alpha]_D$ −1.2 (c 1.0, $CHCl_3$); IR (KBr) ν_{max} 2932, 1728 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.47 (s, 3H), 3.60 (s, 3H), 3.95 (app t, 1H, J=9.8 Hz), 4.19 (app td, 1H, J=9.8, 4.8 Hz), 4.45 (dd, 1H, J=9.8, 4.8 Hz), 4.68 (d, 1H, J=9.8 Hz), 5.56 (s, 1H), 5.75 (s, 1H), 6.34 (d, 1H, J=12.0 Hz), 6.87 (d, 1H, J=12.0 Hz), 7.35–7.45 (m, 3H), 7.55–7.62 (m, 2H), 8.61 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 52.0, 56.5, 63.1, 69.5, 76.0, 96.5, 103.1, 125.5, 126.9, 128.4, 128.9, 129.6, 133.9, 137.0, 156.5, 161.0, 162.9, 168.0; MS (CI) m/z 423 (18, $[M+K]^+$), 407 (100), 193 (30); HRMS (ESI^+) calculated for $C_{20}H_{20}N_2NaO_6$ $[M+Na]^+$: 407.1214, found: 407.1245.

*4.7.2.6. (2R,4aR,6S,10bS)-4,4a,6,10b-Tetrahydro-6-methoxy-2-phenyl-9-(1-(3-E-(tert-butoxycarbonylamino)propenyl))-1,3-dioxino[4′,5′:5,6]-pyrano[4,3-d]pyrimidine (**6l**).* Yield: 45% (method A), 58% (method B) as white crystals; mp 295–296 °C; R_f=0.48 (hexane/EtOAc, 50:50); $[\alpha]_D$ +4.7 (c 1.0, $CHCl_3$); IR (KBr) ν_{max} 3320, 2921, 1677 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.45 (s, 9H), 3.60 (s, 3H), 3.96 (app t, 1H, J=9.8 Hz), 3.98–4.05 (m, 2H), 4.20 (app td, 1H, J=9.8, 4.7 Hz), 4.46 (dd, 1H, J=9.8, 4.7 Hz), 4.68 (d, 1H, J=9.8 Hz), 5.57 (s, 1H), 5.78 (s, 1H), 6.74 (d, 1H, J=15.7 Hz), 7.18 (dt, 1H, J=15.7, 4.7 Hz), 7.35–7.45 (m, 3H), 7.55–7.65 (m, 2H), 8.58 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 28.5, 42.0, 56.4, 63.1, 69.4, 76.0, 79.7, 96.6, 102.9, 124.7, 126.7, 128.4, 129.4, 129.5, 137.0, 138.8, 155.7, 156.6,

160.9, 164.4; MS (CI^+) *m*/*z* 478 (100, $[M+Na]^+$); HRMS (ESI^+) calculated for $C_{24}H_{29}N_3O_6Na$ $[M+Na]^+$: 478.1949, found: 478.1963.

*4.7.2.7. (5S,7R,8S)-2-[1-(3-(tert-butoxycarbonylamino))propenyl]-5,8-dihydro-8-[(tert-butoxycarbonylmethyl)oxy]-7-hydroxymethyl-5-methoxy-pyrano[3,4-d]-pyrimidine (**10**).* Prepared from **4c** according to general procedure for Stille cross-coupling. Yield: 53% as a colourless oil; R_f=0.2 (hexane/EtOAc, 3:1); $[\alpha]_D$ +85.1 (*c* 1.03, $CHCl_3$); IR (NaCl) ν_{max} 3358, 2927, 1709 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.47 (s, 9H), 1.50 (s, 9H), 3.55 (s, 3H), 3.85–4.10 (m, 4H), 4.28 (br d, 1H, *J*=9.9 Hz), 4.52 (d, 1H, *J*=17.6 Hz), 4.68 (d, 1H, *J*=9.9 Hz), 4.75–4.85 (m, 1H), 5.18 (d, 1H, *J*=17.6 Hz), 5.53 (s, 1H), 6.67 (br d, 1H, *J*=15.7 Hz), 7.12 (dt, 1H, *J*=15.7, 5.5 Hz), 8.49 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 28.2, 28.5, 42.1, 56.1, 61.7, 69.4, 70.5, 71.6, 79.8, 83.1, 96.4, 124.6, 129.8, 137.9, 155.9, 156.0, 163.8, 165.2, 172.1; HRMS (ESI^+) calculated for $C_{23}H_{35}N_3O_8Na$ $[M+Na]^+$: 504.2322, found: 504.2293.

4.8. Synthesis of functionalized stannanes

*4.8.1. E and Z-Methyl-3-tributylstannylacrylate (**8a** and **8b**)*

A mixture of tributyltin hydride (1.45 g, 5 mmol), methyl propiolate (0.52 g, 6.25 mmol) and α,α′-azobis(isobutyronitrile) (catalytic amount) in benzene (30 mL) was refluxed overnight. After concentration of the reaction mixture, the product was purified by column chromatography on silica gel. Compound **8a** *E*-isomer: yield: 35% as a colourless liquid. Compound **8b** *Z*-isomer: yield: 30% as a colourless liquid. Spectroscopic data are in agreement with the literature data.[16]

*4.8.2. E-N-(tert-Butoxycarbonyl)-3-tributylstannyl-2-propen-1-amine (**9**)*

CuCN (158 mg, 1.8 mmol) is suspended in THF (5 mL), cooled at −78 °C and then treated with 1.6 M BuLi in hexane (2.4 mL, 3.8 mmol). The mixture is allowed to react for 15 min and then Bu_3SnH (1.0 mL, 3.8 mmol) is added dropwise. After stirring for 10 min at this temperature *N*-(*tert*-butoxycarbonyl)propargylamine (280 mg, 1.8 mmol) is added and allowed to react for 10 min. After workup with NH_4Cl/NH_4OH buffer solution at low temperature and evaporation of the solvent, the crude mixture was purified by column chromatography on silica gel. Yield: 75% as a colourless liquid. Spectroscopic data are in agreement with the literature data.[18]

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