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Supporting Information

Convergent synthesis of 2-thioether-substituted (N)-methanocarba-adenosines as purine receptor agonists

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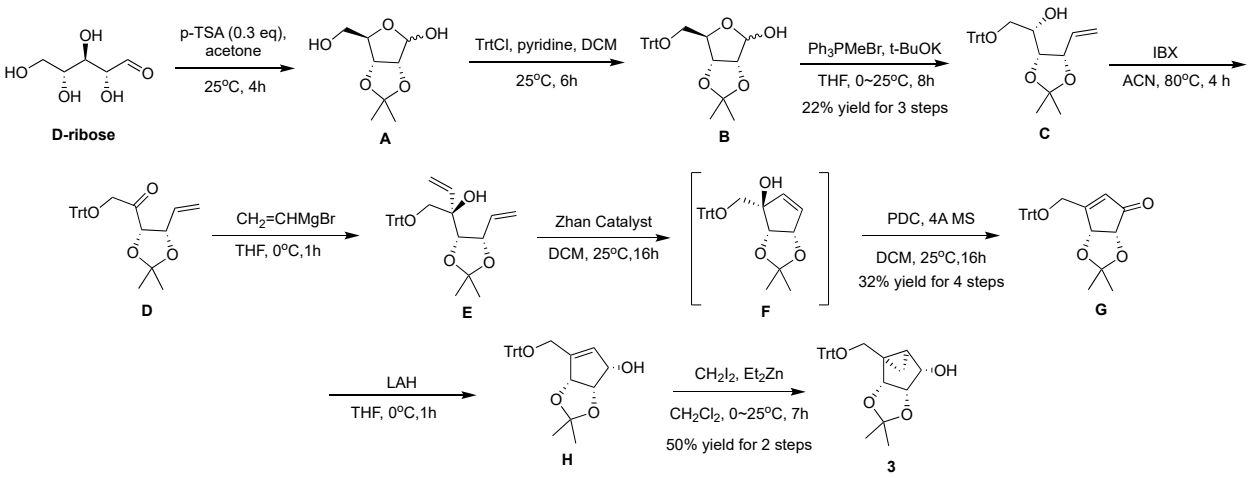
Experimental procedures for large scale synthesis of intermediate 3:



Scheme S1. Synthesis of key bicyclic intermediate **3** containing a 5′-trityl protecting group.[1]

The large-scale synthesis of intermediate **3** was accomplished in 3.52% overall yield from D-ribose **1** (Scheme S1). The choice of the *O*-trityl protecting group was made to enable crystallization of the intermediates.

(3a*R*,6*R*,6a*R*)-6-(Hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol, **A**

A solution of (2*R*,3*R*,4*R*)-2,3,4,5-tetrahydroxypentanal (D-ribose, 6.0 kg, 40.0 mol, 1 eq) in acetone (12 L) in a 50 L round bottom flask was treated with p-toluenesulfonic acid (2.0 g, 10.5 mol, 0.27 eq) at room temperature, and no temperature change was observed. The mixture was stirred at 25°C for 6 h, at which time the solid had dissolved and TLC showed ~70% product. Solid $NaHCO_3$ was added to achieve pH ~8. Solid $MgSO_4$ (3 kg) was added, and the mixture filtered. The filtrate was concentrated under vacuum leaving **A** (7.0 kg, crude, 70% purity by TLC) as a light yellow oil, which was used without further purification.

(3a*R*,6*R*,6a*R*)-2,2-Dimethyl-6-((trityloxy)methyl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol, **B**

Compound **A** (7.0 kg, 25.8 mol, 1 eq) was dissolved in a mixture of pyridine (4.2 L, 28.2 mol, 2.01 eq) and DCM (25 L) in a round bottom flask. Trityl chloride (7.86 kg, 1.1 eq) was added in ten batches slowly over 2 h into the flask at 25°C. Stirring was continued for 14 h, the mixture was cooled to 10°C, and the organic layer was washed with 0.5 M HCl aq. (four times, 10 L each), dried over Na_2SO_4, filter and concentrated under vacuum. The product **B** (7.0 kg, crude, 60% purity by HPLC) was obtained as a light brown oil, which was used without further purification.

(*S*)-1-((4*R*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-(trityloxy)ethan-1-ol, **C**

A solution of Ph_3PMeBr (6.56 kg, 18.4 mol, 2.1 eq) in THF (20 L) in a round bottom flask was cooled to 0°C. *t*-BuOK (2.0 kg, 18.4 mol, 2.1 eq) was added in five batches over 0.5 h while the temperature was maintained below 10°C. Stirring was continued for 1 h at 25°C. The solution was cooled to 0°C and treated with a solution of compound **B** (7.0 kg, 60% purity, 8.93 mol) in THF (5 L) dropwise over 2 h (40 mL/min) while the temperature was kept below 10°C. Stirring was continued overnight at 25°C. The mixture was washed by brine (3 times, 10 L each), dried over Na_2SO_4 and filtered. The organic layers were combined, and the volume reduced under vacuum. The residue was washed four times with two volumes of petroleum ether:ethyl acetate (5:1). The organic layers were combined and concentrated under vacuum. The crude product was purified by silica gel column chromatography (3X volume), eluting with petroleum ether:ethyl acetate (5:1). Compound **C** was obtained as a white solid (3.82 kg, 90% purity by LCMS).

1-((4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-(trityloxy)ethan-1-one, **D**

Compound **C** (3.0 kg, 6.98 mol, 1.0 eq) was dissolved in acetonitrile (15 L) in a round bottom flask. 2-Iodoxybenzoic acid (2.45 kg, 8.75 mol,1.25 eq) was added in five batches over 0.5 h at 25°C. The temperature was raised to 80°C and stirring continued for 4 h. The solution was cooled to 25°C, filtered and washed with ethyl acetate (three times, 3 L each). The combined organic layer was concentrated under vacuum to provide compound **D** as a white powder (2.72 kg, 80% purity by LCMS), which was used without further purification in the next step.

(*R*)-2-((4*S*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)-1-(trityloxy)but-3-en-2-ol, **E**

Vinyl magnesium bromide (5.5 L, 1 M, 1.5 eq) was added to a round bottom flask and cooled to 0°C. Add a solution of **5** (1.5 kg, 3.5 mol, 1.0 eq) in THF (1.5 L) was added dropwise over 1 h while the temperature kept below 10°C. The solution was stirred at 0°C for 1 h and treated with NH_4Cl aq. (1000 mL) slowly over 0.5 h at <20°C. The mixture was filtered and extracted with ethyl acetate (three times, 2 L each). The organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The procedure was performed twice to provide compound **E** as a light yellow solid (3.0 kg, 75% purity by LCMS), which was used without further purification in the next step.

(3a*S*,4*R*,6a*S*)-2,2-Dimethyl-4-((trityloxy)methyl)-3a,6a-dihydro-4*H*-cyclopenta[*d*][1,3]dioxol-4-ol, **F** [not isolated] and

(3a*R*,6a*R*)-2,2-Dimethyl-6-((trityloxy)methyl)-3a,6a-dihydro-4*H*-cyclopenta[*d*][1,3]dioxol-4-one, **G**

Compound **E** (3.0 kg, 6.57 mol, 1.0 eq) was dissolved in dichloromethane (6.0 L) in a round bottom flask, and N_2 gas was dispersed in the solution over 0.5 h. Zhan catalyst (240.0 g, 327.1 mmol, 0.05 eq) was added, and stirring continued at 25°C for 16 h under N_2. Pyridinium dichromate was added (6.0 kg, 16.0 mol, 2.3 eq) in ten batches over 1 h, followed by 4Å molecular sieves (4.5 kg) in ten batches over 2 h. The mixture was stirred at 25°C for 16 h under N_2. Silica gel (5.0 kg) and ethyl acetate (4.0 L) were added and the mixture stirred for 1 h. The mixture was filtered, and the solids additionally washed with ethyl acetate (five times, 1000 mL each). The organic layers were combined and concentrated under vacuum. The crude product was purified by silica gel column

chromatography (4X volume) eluting with petroleum ether:ethyl acetate, from 20:1 to 3:1. Compound **G** (1.4 kg, 80% purity by HPLC) was obtained as a solid.

(3a*S*,4*S*,6a*R*)-2,2-Dimethyl-6-((trityloxy)methyl)-3a,6a-dihydro-4*H*-cyclopenta[*d*][1,3]dioxol-4-ol, **H**

Compound **G** (1.1 kg, 2.58 mol, 1.00 eq) was dissolved in THF (6 L) and treated with $LiAlH_4$ (130.0 g, 3.72 mol, 1.44 eq) slowly over 2 h, while the mixture was maintained at 0~10°C. The mixture was stirred at 0°C for 2 h, at which time TLC and HPLC showed the reaction was complete. The reaction was quenched with water (130 mL) added dropwise at <10°C. The mixture was treated with 15% NaOH (130 mL) dropwise at 0°C followed by water (390 mL) and stirred at 25°C for 30 min. $MgSO_4$ (1.0 kg) was added, and the mixture was stirred at 25 °C for 30 min. The mixture was filtered and the filtrate concentrated under reduced pressure, leaving compound **H** (1.1 kg, 70% purity by LCMS) as light brown oil that was used without further purification and which solidified upon standing.

(3a*R*,3b*R*,4a*S*,5*S*,5a*S*)-2,2-Dimethyl-3b-((trityloxy)methyl)hexahydrocyclopropa[3,4]-cyclopenta[1,2-*d*][1,3]dioxol-5-ol, **3**

Compound **H** (1.1 kg, 2.57 mol, 1.00 eq) was dissolved in dichloromethane (2 L). The solution was treated with diethyl zinc (5.2 L, 1 M in toluene, 2.0 eq) dropwise over 3 h at 0~5°C, and the mixture was stirred at 0°C for an additional 0.5 h. CH_2I_2 (2.5 kg, 9.25 mol, 3.60 eq) was added over 1 h at 0~5°C, and stirring was continued at 25°C for 12 h. TLC and HPLC showed the reaction to be complete. The reaction was quenched with NH_4Cl aq. (3 L) and stirring continued at room temperature for 1 h. The mixture was extracted with ethyl acetate (three times, 2 L each), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (3X volume) eluting with petroleum ether: ethyl acetate, from 15:1 to 5:1. Compound **3** (720 g, 97% purity by LCMS) was obtained as a homogeneous colorless oil, which solidified upon standing.

Table S1. Synthesis yields of N^6-Boc-adenine 2-thioethers **16a–16f** and ether **16g** and their conversion to protected (N)-methanocarba nucleosides by a Mitsunobu reaction with bicyclic intermediate **3**. Footnotes correspond to the reaction conditions shown for Scheme 2 in the main text.

RX =	Adenine precursor **16** (% yield, 1 step)	Protected adenine **20, 21** (% yield, 2 steps)	Protected nucleoside **22, 25** (% yield, 1 step)	Deprotected nucleoside **8** (% yield, 1 step)
CH_3S (large scale)	**16a** (94)[a] (67) [b]	**20a** (60) [e] (45)[g]	**22a** (94)	**8a** (59)[i] (88)[j]
CH_3CH_2S	**16b** (99)[c]	**20b** (58)[e]	**22b** (84)	**8b** (46)[k]
$CH_3(CH_2)_5S$	**16c** (40)[c]	**20c** (60)[e]	**22c** (77)	**8c** (56)[k]
cyclohexyl-S	**16d** (60)[c]	**21d** (94)[f]	**25d** (83)	**8d** (70)[i]
$PhCH_2S$	**16e** (80)[c]	**20e** (69)[e]	**22e** (95)	**8e** (63)[k]
$Ph(CH_2)_2S$	**16f** (87)[c]	**20f** (28)[e], **20f** (36)[g], **21f** (23)[g]	**22f** (78)	**8f** (75)[k]
CH_3O	**16g** (75)[d]	**20g** (41)[g]	**22g** (67)	**8g** (45)[l]

Procedure for a scale of 520 g of 8a (MRS4322):

Step 1:

Compound **9** (500 g, 2.95 mol, 1.00 eq) was added to sodium thiomethoxide solution [NaSMe (3.10 kg, 8.85 mol, 2.82 L, 20% in H_2O, 3.00 eq)] in an autoclave. The solution was purged with the nitrogen for 15 min. The reaction mixture was stirred at 140°C. The reaction was monitored by HPLC, and the starting material (**9**) was consumed completely after 16 h. The solution was cooled to room temperature and neutralized with 6 N HCl until pH becomes 7 to get a precipitate, which was collected by the filtration. The precipitate was washed with water (1 L x3) and dried under vacuum to obtain the compound **16a** as a light brown solid. Yield: 500 g, 2.76 mol, 94%.

Steps 2 and 3:

To a stirred solution of compound **16a** (200 g, 1.10 mol, 1.00 eq) in THF (2 L), Boc_2O (963 g, 4.41 mol, 1.01 L, 4.00 eq) and DMAP (40.5 g, 331 mmol, 0.30 eq) were added at 0°C. The reaction mixture was stirred at 25°C for 16 h. The solution was diluted with EtOAc (2 L) and washed with water (1 L x 2), brine (1 L), dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give compound **19a** as a light red solid. This crude product was carried over to the next step without further purification. Crude yield: 526 g.

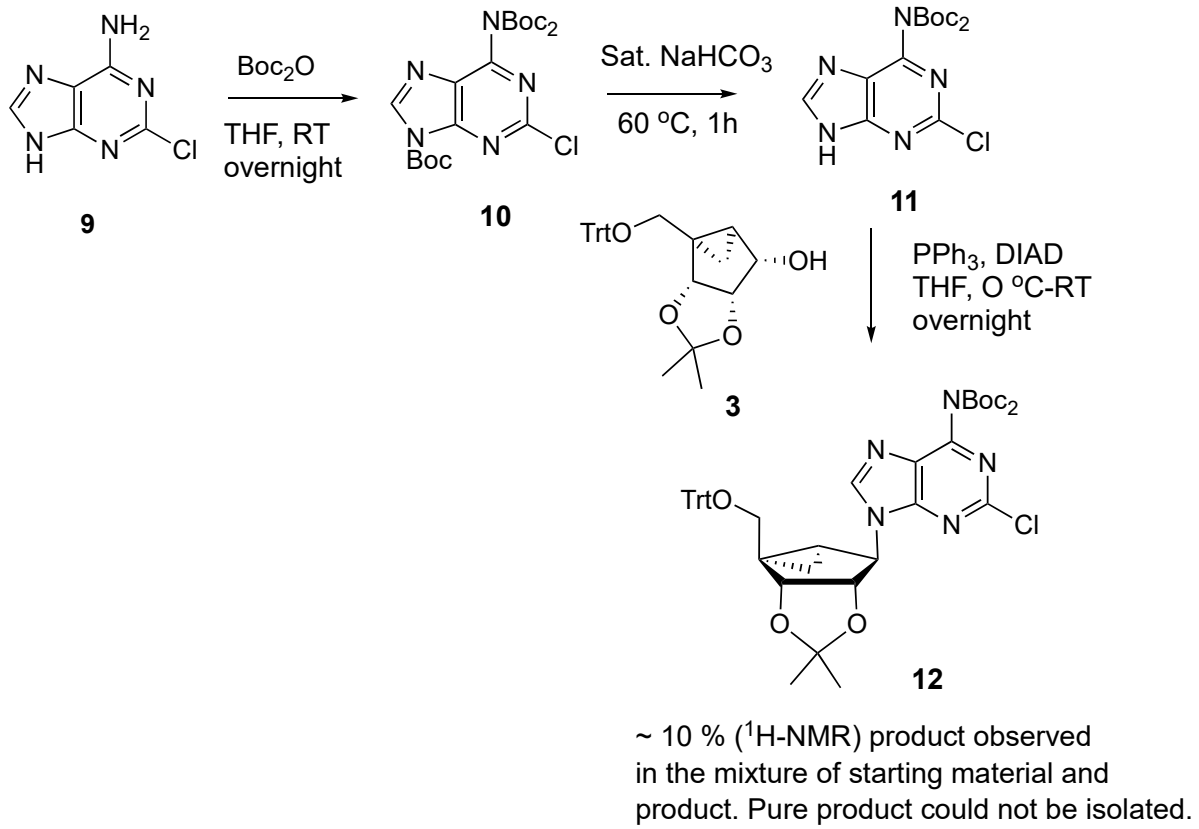
Aq. NaOH (1.04 kg, 26.0 mol, 10 L, 25 eq) was added to a solution of compound **19a** (500 g, 1.04 mol, 1.00 eq) in MeOH (5 L) at 10° – 20°C. The reaction mixture was stirred at 30°C. The reaction was monitored by HPLC, and the starting material (**19a**) was completely consumed after 4 h. The solution was quenched by addition 1 N HCl (25 L) to pH=8 and then added aq. NaH_2PO_4 (5 L) until pH became 6. The reaction mixture was diluted with EtOAc (10 L). The organic phase was separated, washed with brine (10 L), dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give a residue, which was chromatographed on silica using petroleum ether-ethyl acetate (10:1 to 1:1) as eluent to provide compound **20a** as a light red solid. Yield: 180 g, 639.8 mmol, 61.6% ~ 62%.

Step 4:

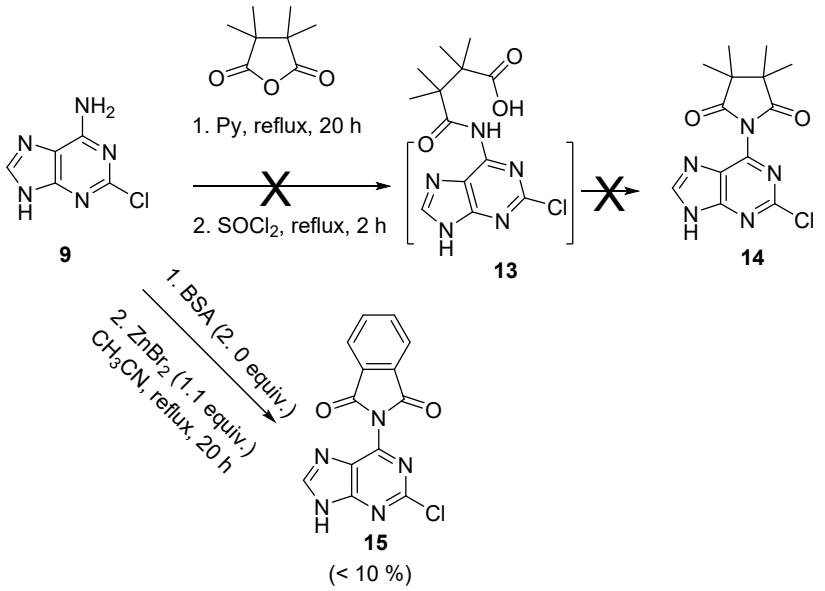
Compound **20a** (769 g, 2.73 mol, 1.10 eq), compound **3** (1.10 kg, 2.49 mol, 1.00 eq), and PPh_3 (782 g, 2.98 mol, 1.20 eq) were dissolved in dry THF (3 L). The solution was concentrated under reduced pressure. This process was repeated two more times with dry THF (2x3 L), and the residue was dried under vacuum for 2 h. The residue was then dissolved in dry THF (30 L) under nitrogen. To this solution, DIAD (603 g, 2.98 mol, 580 mL, 1.20 eq) was added at 0°C under stirring, and the reaction mixture was stirred at 25°C for 1 h. The reaction was monitored by LC-MS and the compound **3** was consumed completely after 1 h. The solution was concentrated under reduced pressure to give a residue, which was chromatographed on silica using petroleum ether-ethyl acetate (20:1 to 3:1) as eluent to provide compound **22a** as a foam white solid. Crude yield: 1.8 kg.

Step 5:

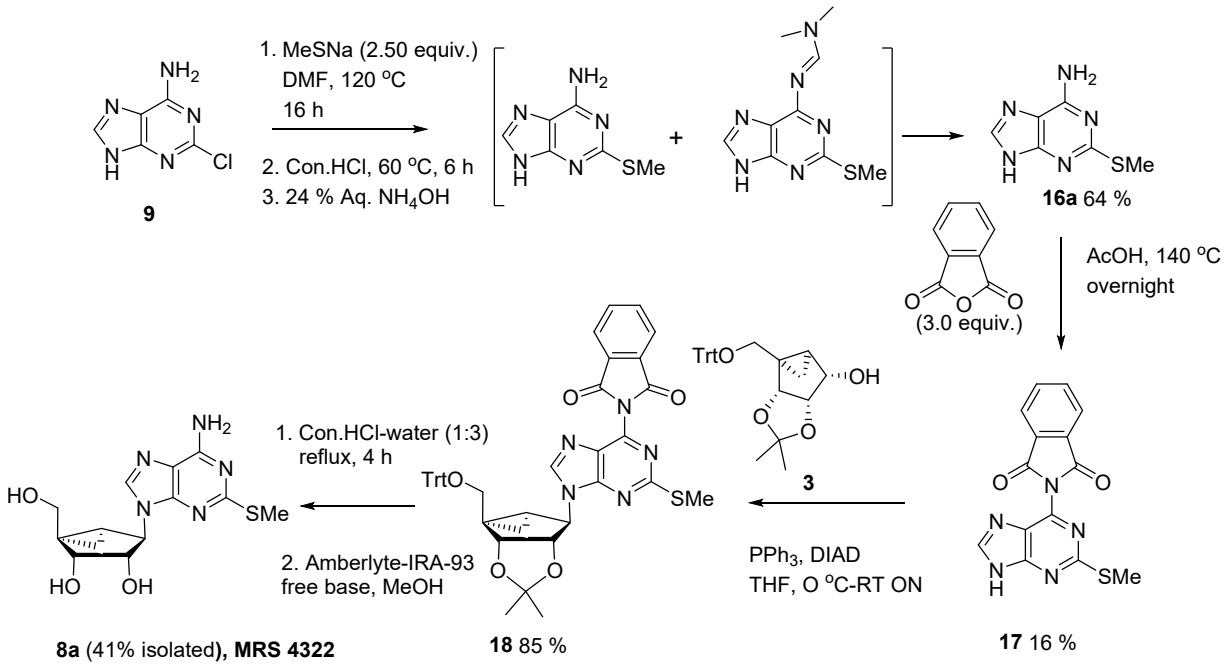
In a 5 L three-neck flask, HCl(g)/MeOH (4 M, 3.15 L, 28.2 eq) was added in one portion to the compound **22a** (315 g, 446 mmol, 1.00 eq). The suspension was stirred at 35°C for 30 min to form clear solution and stirring continued for 16 h. The reaction was monitored by LC-MS and the compound **22a** was consumed completely after 16 h. Five more reactions were carried out under the same conditions in parallel. All the reaction mixture from the six batches were combined at the room temperature and then concentrated under reduced pressure to obtain the residue as off-white solid. To this solid, a mixture of solvent MeOH-TBME (6.0 L, v/v = 1/1) was added and stirred for ~30 min, until the solid well dispersed in the solution. The suspension was filtered to obtain the precipitate as a cake. The filter cake was washed with TBME (3x300 mL) and dried under vacuum for 2 h to get the product as a white solid as HCl salt. The salt was dissolved in a mixture of deionized water/MeOH (6.6 L, v/v = 1/1, 10V) and the suspension was stirred for 15 min to form clear solution. The solution was basified drop wisely with aqueous solution of Na_2CO_3 (~2.2 M) until pH of the solution became ~9. Removal of MeOH using a rotary evaporator at 35°C left the solid, which was filtered and washed. The filter cake was washed with the water until the pH of the filtrate became neutral. The filter cake was dried under vacuum to afford MRS4322 (**8a**) as white solid. Yield: 520 g, 1.61 mol, 60% for 2 steps.



Scheme S2. Attempted synthesis of 2-Cl *bis*-Boc protected nucleoside **12** from bicyclic intermediate **3**.

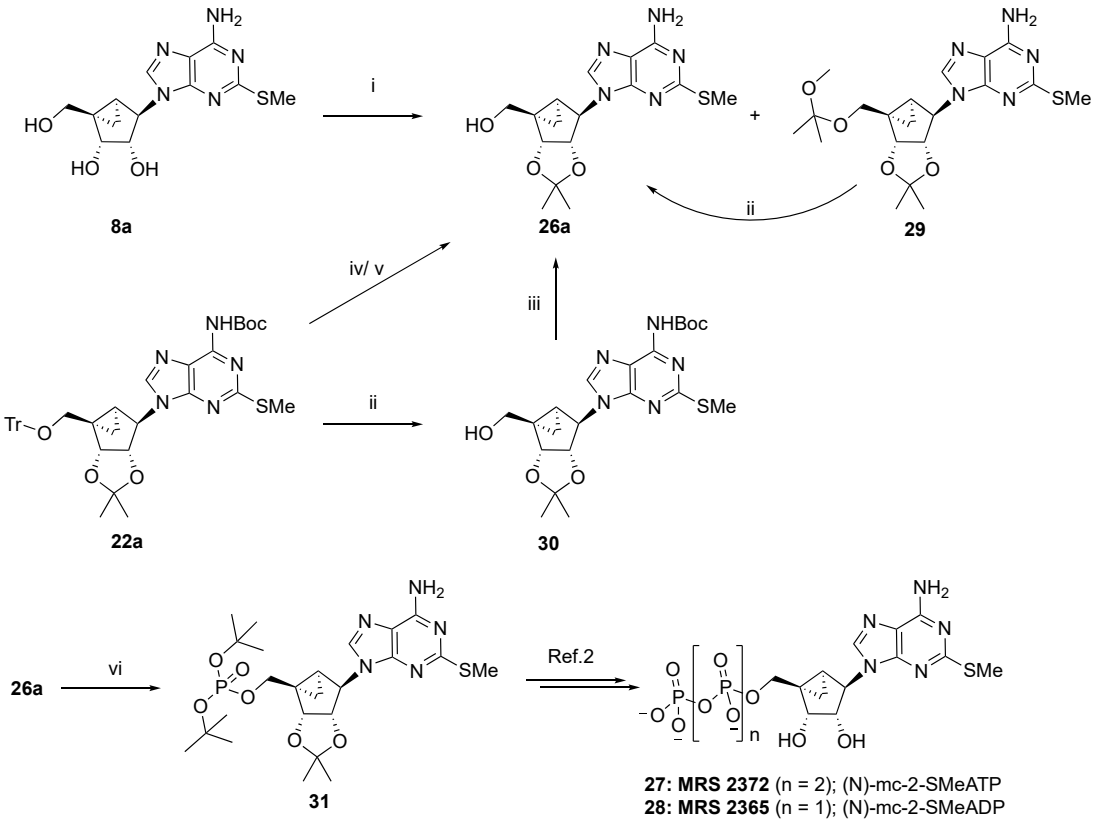


Scheme S3. Alternative N^6-protection approaches for 2-Cl adenine **9**. We attempted to protect the amine of **9** using tetramethylsuccinic anhydride (M_4SA),[1] but the desired tetramethylsuccinoyl-protected product **14** could not be isolated in pure form from the reaction mixture, although a substantial product peak was observed by mass spectrometry. Attempted protection to yield *N*-phthaloyl derivative **15** also had a low yield (<10%).



Scheme S4. Low overall yield synthesis of final nucleoside **8a** via the *N*-phthaloyl-protected nucleobase **17**. We considered the phthaloyl group for the amino-protection of **16a** since it has a good regioselectivity for the β-N^9-nucleoside derivatives,[1] but the yield of the N^6-substituted phthalimide product **17** was low. 2-Methylthioadenine **16a** was treated overnight with phthalic anhydride in AcOH at 140 °C to obtain the 2-MeS-N^6-phthaloyl-adenine **17** in poor yield (16%),

which was coupled to the alcohol (**3**) under Mitsunobu conditions to afford the desired adduct, a β-N^9-nucleoside derivative (**18**) in high yield (85%). However, the attempts to improve the yield of **17** failed. We used phthaloyl chloride, phthalic anhydride with a catalytic amount of p-toluenesulfonic acid (0.1 equivalents), and the conditions ($ZnBr_2$ and bis(trimethylsilyl)acetamide (BSA)) used for the synthesis of *N*-alkyl- and *N*-arylimide derivatives.[2]



Scheme S5. 5′-Phosphorylation of (N)-methanocarba nucleoside **8a** to yield previously characterized $P2Y_1R$ agonists **27** and **28**.[4] Reagents and conditions. (i) anhyd. acetone, 2,2-dimethoxypropane, p-TSA, rt, 18 h; (ii) anhyd. acetone, p-TSA, rt, 18 h, 58% over 2 steps for **29**, 61% for **5**; (iii) anhyd. acetone-TFA (1:1), rt, 3 h, 32%; (iv) anhyd. acetone-TFA (1:2), rt, 3 h, **56%**; (v) anhyd. CH_2Cl_2, anhyd. $ZnBr_2$, 10–20 min, **41%**; (vi) (a) THF, tetrazole, di-*tert*-butyl-*N*,*N*-diethyl-phosphoramidite, rt, 18 h (b) 30% aq. H_2O_2, rt, 3 h, 81%.

Synthesis of nucleotide derivatives 27 and 28

Chemical synthesis

Synthesis of **26a** was realized under various conditions, (N)-methanocarba-2-SMe-adenosine (**8a**; Scheme 1) when reacted with 2,2-dimethoxypropane in acetone in the presence of *p*-TSA gave a mixture of compounds **26a** and **29**. Whereas a reaction without dimethoxypropane removed 5′-methoxypropane group, to furnish **26a**. The same condition on **22a** deprotected trityl but not Boc-group to render **30**, while under strongly acidic conditions of (1:1) acetone-TFA gave **26a**. Similarly, use of analogues protocol directly on **22a** gave **26a** in a comparably moderate yield of 56%. Alternatively, reacting compound **4** with anhydrous $ZnBr_2$ removed both trityl and Boc protecting groups to give **26a** in 41% yield.[3] However, a longer reaction time (ca. 2 h, in this case) removed 2′,3′-O-isopropylidene as well to give **8a** in 22% yields. It is to be noted that since the reaction was performed in dichloromethane, most products separated out as Zn-salt, and the TLC/ HPLC analysis mislead the progress of the reaction, and the reaction seems to be practically completed after 10-20 min (depending on the water content in the reaction mixture).

(N)-Methanocarba-2-SMe-adenosine nucleotides were synthesized as reported earlier.[3] The drawback of this method is the use of *m*-CPBA as an oxidizer in preparing 5′-di-*tert*-butylphosphate ester **31**, which also gave 2-methylsulfoxide by-product in equal or sometimes in major amounts. An effort to improve the method by a direct phosphorylation of **26a** using phosphorous oxychloride was not successful. However, employing hydrogen peroxide to oxidize the 5′-phosphoramidite intermediate (Scheme S5) limited the oxidation to phosphorous, giving the required compound **31** as the sole product [Note: When the next deprotection reaction of **31** was carried out without purification (only workup), sulfoxide product was observed, implying, the increased reactivity of any residual hydrogen peroxide towards thio-alkanes in the presence of acid]. Deprotection of *t*-butyl and isopropylidene groups using aq. TFA[4] or DOWEX-H^+,[5] followed by coupling with phosphate/pyrophosphate gave the desired products, 5′-di- and tri-phosphates **27** and **28**.[4]

Experimental

Chemical synthesis

(N)-methanocarba-2′,3′-O-isopropylidene-2-thiomethyl-adenosine (**26a**[4]):

Method 1: To a suspension of compound **8a** (20 mg, 0.062 mmol) in a mixture (1:1) of anhyd. acetone and 2,2-dimethoxypropane (1.0 mL) were added *p*-toluenesulfonic acid (*p*-TSA.H_2O, 12 mg, 0.062 mmol) and stirred at room temperature for 18 h. The volatile materials were removed by rotary evaporation under reduced pressure. The residue was partitioned between aq. $NaHCO_3$ and 5% i-PrOH in CH_2Cl_2. The organic layer was separated and dried over anhydrous Na_2SO_4. Rotary evaporation under vacuum gave a mixture of compounds **26a** and **29** (TLC eluent, 5% MeOH in CH_2Cl_2; Compound **26a;** R_f = 0.25, ESI-MS $[M+H]^+$ for $C_{16}H_{21}N_5O_3S$ calculated, 364.1438; found, 364.2; Compound **29**, R_f = 0.60, ESI-MS $[M+H]^+$ for $C_{20}H_{29}N_5O_4S$ calculated, 436.2013; found, 436.2). The mixture of compounds **26a** and **29** was dissolved in anhydrous acetone (2.0 mL), to this was added p-TSA.H_2O (12 mg, 0.062 mmol) and stirred overnight (18 h). After a work-up as mentioned above, followed by the purification by silica gel chromatography gave **26a** as a white foam (13 mg, 58%).

Method 2: To a flask containing compound **30** (80 mg, 0.173 mmol) was added a 1:1 mixture of anhyd. acetone-trifluoroacetic acid (2 mL) and stirred at room temperature for 3 h. Volatile materials were evaporated under high vacuum and the residue was co-evaporated with toluene followed by neutralization with 7 N ammonia in methanol. Purification by silica gel column chromatography afforded **26a** as a white solid (20 mg, 32%).

Method 3[1]**:** To a solution of compound **22a** (20 mg, 0.028 mmol) in anhyd. dichloromethane (0.6 mL) was added anhyd. $ZnBr_2$ (64 mg, 0.28 mmol) and stirred vigorously for 2 h (reaction was practically completed in 10-20 min). Water was added, and the product was extracted in ethyl acetate several times, organic phase was separated, dried, evaporated. The residue was purified by silica gel column chromatography to afford the products **8a** (2.0 mg, 22%) and **26a** (4.2 mg, 41%). (N)-methanocarba-2′,3′-O-isopropylidene-N^6-Boc-2-thiomethyl-adenosine (**30**): Compound **22a** (200 mg, 0.283 mmol) was dissolved in anhyd. acetone (3.0 mL) and was added p-TSA.H_2O (108 mg, 0.566 mmol). The reaction was stirred at room temperature for 18 h. The volatile materials were removed by rotary evaporation under reduced pressure. The residue was partitioned between aq. $NaHCO_3$ and 5% i-PrOH in CH_2Cl_2. The organic layer was separated and dried over anhydrous Na_2SO_4. Rotary evaporation under vacuum, followed by purification using silica gel chromatography gave compound **30** as a white foam (80 mg, 61%, TLC eluent, 5% MeOH in CH_2Cl_2; R_f = 0.35). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87 (q, *J* = 3.2, 2.5 Hz, 1H), 7.72 (d, *J* = 4.9 Hz, 1H), 5.55 (dd, *J* = 7.4, 4.6 Hz, 1H), 5.29 (q, *J* = 3.0, 2.2 Hz, 1H), 4.80 (d, *J* = 4.7 Hz, 1H), 4.69 (d, *J* = 6.5 Hz, 1H), 4.24 (dd, *J* = 12.2, 6.7 Hz, 1H), 3.45 (d, *J* = 7.6 Hz, 1H), 3.37 (ddd, *J* = 11.3, 5.0, 2.5 Hz, 1H), 2.69 (q, *J* = 3.1, 2.4 Hz, 3H), 1.69 (q, *J* = 4.7 Hz, 1H), 1.55 (dd, *J* = 6.1, 3.5 Hz, 12H), 1.25 (s, 3H), 1.17 (t, *J* = 5.2 Hz, 1H), 0.97 (dd, *J* = 9.4, 5.0 Hz, 1H). ESI-MS $[M+H]^+$ for $C_{21}H_{29}N_5O_5S$ calculated, 464.1962; found, 464.2.

(N)-methanocarba-2′,3′-O-isopropylidene-2-thiomethyl-adenosine-5′-phosphate di-*tert*-butyl ester (**31**): Vacuum dried mixture of compound **26a** (12 mg, 0.033 mmol) and tetrazole (7.0 mg, 0.10 mmol) was dissolved in anhyd. THF (0.75 mL) under argon atmosphere and to this was added di-*tert*-butyl-*N*,*N*-diethyl-phosphoramidite (14 µL, 0.05 mmol). The reaction mixture was stirred at room temperature for 18 h. 30% aqueous H_2O_2 (3.0 µL, 0.033 mmol) was added and stirred at room temperature for 3 h. The volatile materials were evaporated under high vacuum and the residue was purified by silica gel column chromatography to afford **31** as a white foam (15 mg, 81%, TLC eluent, 5% MeOH in CH_2Cl_2; R_f = 0.40). Spectral data are as reported.[3]
[**Note:** if the next deprotection reaction was carried out without purification (only workup), sulfoxide product was observed, implying, any residual hydrogen peroxide in the presence of acid increases the reactivity of peroxides towards thio-alkanes].

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