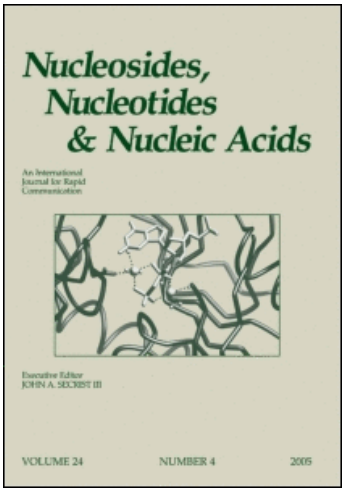

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A SYNTHETIC APPROACH TO CARBOCYCLIC SINEFUNGIN

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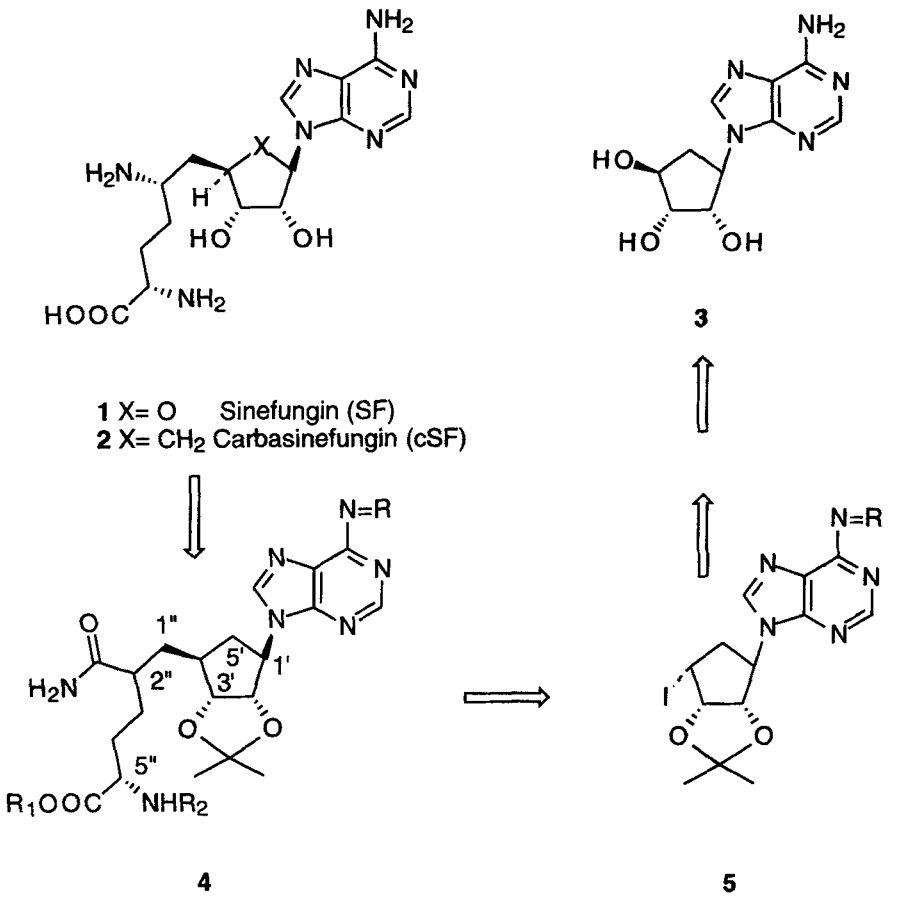
Abstract An approach to an asymmetric synthesis of carbocyclic sinefungin (cSF) **2** is proposed. The sequence, which uses an original radical based chemistry for C-C bond formation, led to the immediate precursor **18** of the protected desired compound. While the overall yield is modest, it is noticeable that only a limited number of steps are needed to obtain the target compound.

Sinefungin (SF) **1** belongs to a class of natural complex nucleosides[1] usually isolated from *Streptomyces* fermentation broth, namely *S.griseolus*[2] and *S. incarnatus*[3]. The structure of this nucleoside presents a remarkable close analogy with that of *S*-adenosylmethionine (SAM) and *S*-adenosylhomocysteine (SAH) which, respectively, are substrate and reaction product of biological trans-methylase catalysed methylation reactions. This could explain why SF **1** exhibits a vast array of biological activities. Unfortunately, while SF **1** shows noticeable antiviral[4] and antiparasite properties[5], its applications in a therapeutical context have been precluded because it was found toxic in some *in vivo* testing[5]. For this reason, in the past few years, many efforts have been accomplished to design efficient syntheses of SF **1** which, eventually, can be applied to elaborate new derivatives of this nucleoside, hopefully devoid of detrimental side effects[6].

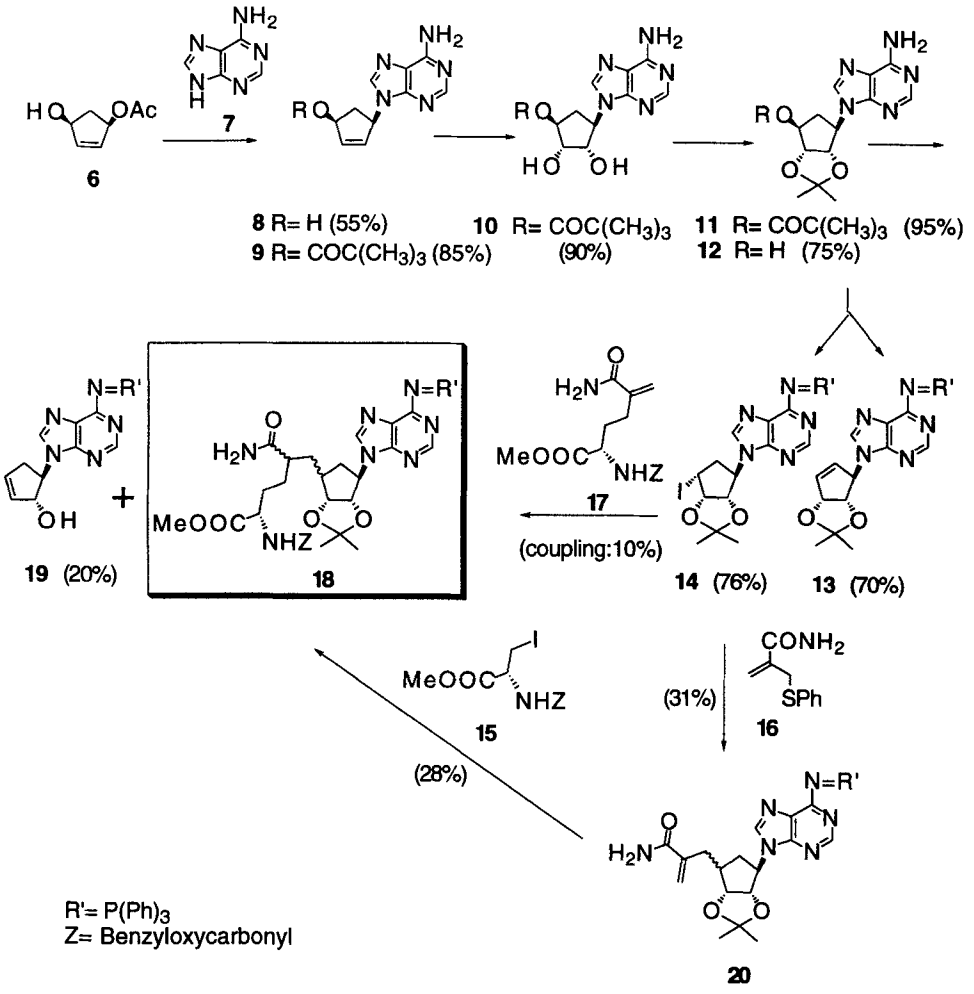
Curiously, to the best of our knowledge, among the variety of compounds which have been synthesized in the sinefungin series, there is no report which proposed the synthesis of carbocyclic sinefungin (cSF) **2**. Indeed, such a synthesis can be fully justified if one observes that there is a great number of naturally occurring and synthetic



Scheme 1

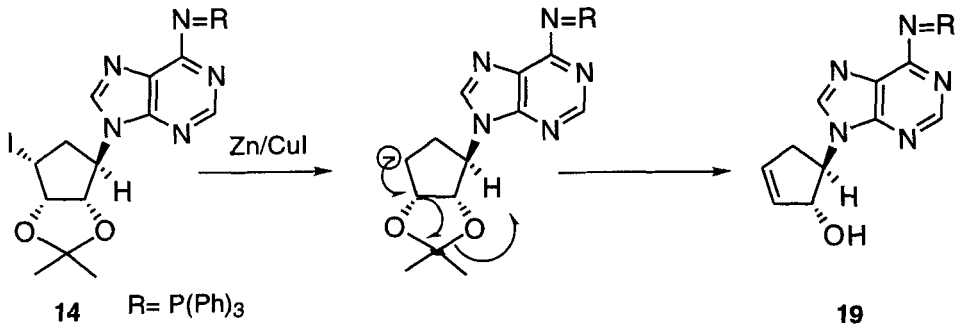
carbocyclic nucleoside analogues which are endowed of useful biological properties[7]. Moreover, we were prompted to undertake a synthetic work with cSF **2** as a target, since we found that 5'-noraristeromycin **3**[8] exhibited promising anti-leishmanial activity[8c].

Toward this goal, we proposed to prepare cSF **2** by following the retrosynthetic route outlined in Scheme 1 . We anticipated that the latter compound could be derived from carboxamide **4** after an Hofmann degradation reaction which has been successively used by us[6b] and others[6e] in previous syntheses of SF **1**. To obtain compound **4** we wished to take advantage of a newly developed radical methodology for C-C bond formation[9], which has already been used to prepare a series of analogues of sinefungin[6n]. In this methodology nucleophilic radicals, produced by the simple treatment of an iodide with a zinc-metal couple, are trapped by activated olefins.



Scheme 2: For experimental conditions see text.

Herein we describe the reaction sequence which was devised to provide the carboxamide derivative **18** in modest overall yield en route to cSF **2**. A key intermediate in this synthesis was compound **12** which can be readily obtained, starting from the conveniently available 1-(*R*)-acetoxy-4(*S*)-hydroxy-2-cyclopentene **6**, by application of straightforward reaction conditions. Thus, using palladium chemistry[10], **6** was adenylated to yield derivative **8** which was further acylated after a treatment with pivaloyl chloride. The resulting compound **9** was submitted to catalytic osmium tetroxide dihydroxylation to give stereoselectively and in excellent yield the dihydroxy derivative



14 R= P(Ph)3 19

Scheme 3

10. Isopropylidene protection of the diol of **10** provided **11** which was subsequently deacylated to afford the required **12** in quantitative yield. The transformation of **12** into iodide **14** proved to be troublesome. Thus, treatment of **12** by the triphenylphosphine/imidazole/iodine system[11] in refluxing toluene gave a 70% yield of olefin **13**. The adenine amino group was concomitantly protected by formation of the corresponding N^6-triphenylphosphoranylidene derivative[8c]. Consequently, a less basic reagent was needed to avoid hydrogen iodide elimination. Finally, triiodoimidazole in the presence of triphenyl phosphine[11] proved to be the reagent of choice to accomplish this transformation in refluxing toluene. The desired compound **14** was obtained in 76% yield and under these conditions the formation of **13** was avoided.

The next stage of the synthesis proposed to generate from iodide **14**, the corresponding C-4' centered radical to be trapped by olefin **17**. The required olefin **17** was easily prepared in two steps from the known compounds **15**[12] and **16** using our radical procedure. Thus, a test tube containing a powdered mixture of Zn and CuI to which was added succesively water, ethanol and an ethanol solution of olefin **16** and then stepwisely a solution of iodoserine **15**, was strongly agitated using a vortex. Under these conditions olefin **17** could be obtained in 50% yield after usual work up .

Unfortunately, when similar reaction conditions were applied to iodide **14** and olefin **17**, to generate compound **18**, the latter was obtained in low yield (10%). Moreover the reaction product consisted of a mixture of the four possible stereoisomers, which could be separated by HPLC and characterized. The structures of these isomers, designed **18a-d** according their increasing polarity in TLC, were tentatively assigned on the basis of the interpretation of the NMR data. Because in the 2D-NOESY spectra of **18b** and **18d** an interaction between H-1' and H-4' was observed, it was concluded that the substituents

at these positions were in a cis-relation for both compounds. In constrat, no such an observation could be made in the cases of **18a** and **18c**. However a strong interaction between H-3' and H-4' could be considered as indicative of their cis-relationship. Consequently, for both **18a** and **18c**, we suggest an α stereochemistry for the substituent in C-4' position. Finally, the configuration of the carbon bearing the $CONH_2$ group was tentatively assigned on the basis of the 2D-NOESY data which revealed (or excluded) interactions between H-3' and H-2". Accordingly, we attributed the C-2" (*S*) configuration to **18a** and **18d** and the C-2" (*R*) configuration to **18b** and **18c**, respectively.

These disappointing results, in terms of reactivity and stereoselectivity, compared to those observed in the ribose series, could be ascribed to the behavioural differences between the two types of radical involved to obtain either SF **1** (furanosyl radical)[13] or its carbocyclic analogue cSF **2** (cyclopentyl radical). In fact, under the reaction conditions the radical derived from **14** was further reduced as indicated by the elimination reaction to give olefin **19** as the main reaction product, which is likely formed according to the proposed mechanism outlined in Scheme 3. Structure **19** is fully supported by the spectral data. In particular, the ^1H nmr spectrum of **19** is characterized by the presence of a signal at 5.9 ppm (2H) attributed to the olefinic protons H-3' and H-4'. Moreover, the COSY spectrum of **19** revealed the coupling between H-1' and H-2'.

To avoid this side reaction yielding **19**, we had to use a more reactive olefin than **17**. Accordingly, we modified our strategy and combined iodide **14** with olefin **16**, being aware, as a consequence of the above results, that the isopropylidene group might not be very effective at directing the stereochemical course of the reaction. Indeed, treatment of compounds **14** and **16** under the usual conditions led to the formation of a 1/1 mixture of two compounds, corresponding to structure **20**, which were isolated in a modest 31% yield after purification by silica preparative HPLC. The relative orientation of the adenine residue and the newly introduced side chain on the cyclopentane ring was established on the basis of the nOe data. In particular, the 2D-NOESY spectrum of isomer **20a** (less polar isomer) showed significative interactions between H-4' and H-8 of the adenine part and between H-3' and H-4', suggesting a trans relation between the residues at C-1' and C-4'. No such interactions were detected in the case of the other isomer **20b** (more polar isomer). Finally, compound **20b** served as an acceptor for the radical derived from iodoserine **15** to give a mixture of two compounds in 28% yield which expectedly differed by the stereochemistry at C-2". Both compounds (1/1 mixture) could be separated by preparative HPLC and found identical to **18b** and **18d** confirming the stereochemical attribution at C-4'.

In conclusion, we have synthesized a protected precursor of carbocyclic sinefungin (cSF) **2**. Although one might be disappointed by the low overall yield of the proposed sequence to give **18** several precedents in this series demonstrate that the latter could be a reasonable precursor of **2**. Indeed, **18** should readily undergo an Hofmann degradation to give the required amine at C-6'[6b,6e]. Unfortunately, the major drawback of the proposed approach remains the low stereoselectivity encountered as in most radical reactions together with the modest yields when these reactions are applied to highly functionalized molecules. More efforts will be needed to circumvent these problems.

EXPERIMENTAL SECTION

Most ^{1}H and ^{13}C NMR spectra were recorded on Brucker WP 200 SY and AC 300 spectrometers. Chemical shifts are reported in ppm. Electron impact (EI) mass spectra were measured with an AEI MS 50 mass spectrometer. Fast atom bombardment (FAB) mass spectra, using glycerol (or thioglycerol) matrices, were obtained with a Kratos MS 80 instrument. Microanalyses were performed by the Service de Microanalyse du CNRS. Column chromatography was carried out on Silica gel Kieselgel 60. Silicagel TLC was performed on Schleicher and Schuell plates with UV light for visualisation. Analytical and preparative HPLC were accomplished on Intersil 5µ columns using CH_2Cl_2/MeOH solvent system.

(+)-[(1'*R*,4'*S*)-4'-hydroxy-2'-cyclopenten-1'-yl]-9-*H*-adenine (**8**): To a stirred solution of adenine (900 mg, 6.6 mmoles) in 12.8 mL anhydrous dimethylformamide (DMF) was added sodium hydride (60% oil dispersion, 276 mg, 6.9 mmoles). The solution was maintained at 60°C under an argon atmosphere during 30 min. Then a solution of 1-(*R*)-acetoxy-4(*S*)-hydroxy-2-cyclopentene **6**[13] (920 mg, 6.5 mmol) and $Pd(PPh_3)_4$ (300 mg, 0.22 mmol) in 0.9 mL anhydrous DMF was slowly added. The reaction mixture was kept at 60°C for 18 h. The solvent was removed under vacuum and the reaction products purified by column chromatography (eluent: ethyl acetate:MeOH 9/1) to give **8** (600 mg, amorphous solid) in 55% yield. $[\alpha]_D^{20}$ +82.5° (c = 1.60 ; H_2O). MS *m/z*: 217 $(M)^+$; 135 (Base + H)$^+$. Calc. for $C_{10}H_{11}N_5O$: C, 53.09; H, 5.31; N, 30.97: found C, 53.17; H, 5.25; N, 31.30. ^{1}H NMR (200 MHz, D_2O) δ ppm: 7.89 (2s, 2H, H-2, H-8); 6.24 (m, 1H, H-2'); 5.99 (dd, $J_{2';3'}$= 6 Hz; $J_{3';4'}$= 1 Hz, 1H, H-3'); 5.23 (m, 1H, H-4'); 4.86 (m, 1H, H-1'); 4.78 (d, $J_{4';OH}$= 5 Hz, 1H, OH); 2.97 (m, 1H, H-5'a); 1.66 (m, $J_{5'a;5'b}$= 14.4 Hz, 1H, H-5'b). ^{13}C NMR (50.32 MHz, D_2O): δ ppm: 157.3 (C-9); 154.1 (C-8); 150.1 (C-5); 142.6 (C-2); 141.1 (C-2'); 133.4 (C-3'); 120.8 (C-6); 77.0 (C-4'); 60.6 (C-1); 42.8 (C-5').

(+)-[(1'*R*,4'*S*)-4'-trimethylacetoxy-2'-cyclopenten-1'-yl]-9-*H*-adenine (9): To a solution of **8** (35 mg, 0.16 mmole) in 6 mL anydrous pyridine was added under argon at 0°C pivaloyl chloride (0.04 ml, 0.32 mmol). The mixture was heated at 65°C during 3 h. Then methanol (0.5 ml) was added and the solvent removed under reduced pressure. The residue was purified by silica gel column chromatography (eluent: CH_2Cl_2:MeOH 9/1) to give **9** in 85% yield. m. p. 190-191°C (CH_2Cl_2-ether). $[\alpha]_D^{20}$ +22.4° (c = 1.43 ; CH_2Cl_2). MS *m/z*: 301 $(M)^+$; 200 $(M\text{-}OPv)^+$. Calc. for $C_{15}H_{19}N_5O_2$: C, 59.78; H, 6.35; N, 23.24: found C, 59.35; H, 6.37; N, 22.60. ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 8.28 (s, 1H, H-2); 8.03 (s, 1H, H-8); 7.32 (s, 2H, NH_2); 6.43 (dd, $J_{2',3'}$= 5.5 Hz; $J_{1',2'}$= 2 Hz, 1H, H-2'); 6.39 (m, 1H, H-3'); 5.72 (m, 1H, H-4'); 5.64 (m, 1H, H-1'); 3.08 (qd, $J_{5'a;5'b}$= 15 Hz, $J_{1;5'a}$= 7.5 Hz, $J_{4;5'a}$= 7.5 Hz, 1H, H-5'a); 1.94 (dt, $J_{1;5'b}$= 3 Hz, $J_{4;5'a}$= 3 Hz, 1H, H-5'b); 1.20 (s, 9H, $3xCH_3$). ^{13}C NMR (62.89 MHz, $CDCl_3$) δ ppm: 155.7 (C-2); 153.0 (C-8); 135.7-134.2 (C-2', C-3'); 77.0 (C-4'); 56.9 (C-1'); 38.8 (C-5'); 27.2 ($3xCH_3$).

(-)-β-(2'α, 3'α-dihydroxy-4'β-trimethylacetoxycyclopent-1'-yl)-9-*H*-adenine (10): To a solution of **9** (360 mg, 1.07 mmol) and osmium tetroxide (5 mg, 0.02 mmol) in 4 ml DMF was added under stirring at 0 °C, 1 mL acetone and 0.3 mL of a solution of trimethylamine N-oxide (200 mg, 1.8 mmol) in water. The reaction mixture was stirred at rt during 15 h. The solvents were removed under vacuum and the residue dissolved in water. After addition of a saturated $NaHSO_3$ aqueous solution (1 mL) the aqueous phase was extracted with ethyl acetate. Evaporation of the solvent gave compound **10** in 90% yield. m. p. 173-174°C (ethyl acetate). $[\alpha]_D^{20}$ -3.2° (c = 1 ; CH_3OH). MS *m/z*: 335 $(M)^+$; 234 $(M\text{-}OPv)^+$. Calc. for $C_{15}H_{21}N_5O_4$, 1/2 H_2O: C, 52.31; H, 6.43; N, 20.34: found C, 52.69; H, 6.28; N, 20.72. ^1H NMR (300 MHz, DMSO) δ ppm: 8.24 (s, 1H, H-2); 8.20 (s, 1H, H-8); 7.31 (s, 2H, NH_2); 5.44 (d, 1H, $J_{OH;2'}$= 4 Hz; OH); 5.31 (d, 1H, $J_{OH;3'}$= 6.7 Hz; OH); 4.91 (m, 1H, H-1'); 4.87 (m, 1H, $J_{3';4'}$= 8 Hz, $J_{4';5'a}$= 7 Hz, H-4'); 4.72 (m, 1H, H-3'); 3.98 (m, 1H, H-2'); 2.85 (m, 1H, H-5'a); 2.16 (m, 1H, H-5'b); 1.31 (s, 9H, $3xCH_3$). ^{13}C NMR (62.89 MHz, $CDCl_3$) δ ppm: 179.0 (CO); 155.0 (C-6); 153.3 (C-2); 150.2 (C-4); 142.0 (C-8); 118.0 (C-5); 77.5; 75.8; 75.6; (C-2', C-3', C-4'); 60.7 (C-1'); 34.1 (C-5'); 27.4 ($3xCH_3$).

(-)-β-(2'α,3'α-*O*-isopropylidenedioxy-4'β-trimethylacetoxycyclopent-1'-yl)-9-*H*-adenine (11): A solution of **10** (200 mg, 0.6 mmol) and p-toluenesulfonic acid (TsOH.H_2O, 3 mg) in 10 mL dimethoxypropane was stirred at rt during 60 h. The reaction product was extracted with ether to give **11** as crystals in 95% yield. m. p. 82°C (ether). $[\alpha]_D^{20}$ -0.5° (c = 0.2 ; $CHCl_3$). MS *m/z*: 375 $(M)^+$. ^1H NMR (300 MHz,

$CDCl_3$) δ ppm: 8.38 (s, 1H, H-2); 7.92 (s, 1H, H-8); 6.08 (s, 2H, NH_2); 5.25 (m, 1H, H-4'); 5.16 (dd, 1H, $J_{1',2'}$= 2 Hz, $J_{2',3'}$= 6 Hz, H-2'); 4.92 (m, 1H, H-1'); 4.62 (m, 1H, H-3'); 2.89 (m, 1H, $J_{5'a;5'b}$= 15 Hz, $J_{1';5'a}$= 7.2 Hz, $J_{4';5'a}$= 7.2 Hz, H-5'a); 2.46 (dt, $J_{1';5'b}$= 5 Hz, $J_{4';5'b}$= 5 Hz, 1H, H-5'b); 1.56 (s, 3H, 3xCH_3); 1.32 (s, 3H, CH_3); 1.16 (s, 9H, 3xCH_3). ^{13}C NMR (62.89 MHz, $CDCl_3$) δ ppm: 177.5 (CO_2); 155.7 (C-6); 153.1 (C-2); 150.2 (C-4); 139.0 (C-8); 118.0 (C-5); 112.7 (Cq isop.); 84.7 (C-2'); 83.9 (C-3'); 78.3 (C-4'); 60.7 (C-1'); 35.3 (C-5'); 27.2; 27.1; 27.0; 26.9; 24.6 (3 CH_3 Piv, 2 CH_3 isop.).

(-)-β-(4'β-hydroxy-2'α,3'α-*O*-isopropylidenedioxycyclopent-1'-yl)-9-*H*-adenine (12): A solution of **11** (120 mg, 0.32 mmol) in 10 mL methanol containing 0.2 ml 5N NaOH was stirred 12 h at rt. The solvent was evaporated under reduced pressure and the residue chromatographed (eluent: CH_2Cl_2:MeOH 98/2) to give **12** in 75% yield. m. p. 104°C (ether). $[\alpha]_D^{20}$ -64.4° (c = 0.27; $CHCl_3$). MS *m/z*: 291 $(M)^+$. Calc. for $C_{13}H_{17}N_5O_3$: C, 53.59; H, 5.88; N, 24.04: found C, 53.39; H, 5.82; N, 23.90. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.30 (s, 1H, H-2); 8.28 (s, 1H, H-8); 6.78 (s, 2H, NH_2); 4.94 (d, 1H, $J_{4';OH}$= 10 Hz, H-4'); 4.90 (d, 1H, $J_{2',3'}$= 5.2 Hz, H-2'); 4.76 (m, 1H, H-3'); 4.48 (m, 1H, H-1'); 2.90 (m, 1H, H-5'a); 2.20 (m, 1H, H-5'a); 1.46 (s, 3H, CH_3); 1.26 (s, 3H, CH_3). ^{13}C NMR (62.89 MHz, $CDCl_3$) δ ppm: 156.1 (C-6); 152.4 (C-2); 150.2 (C-4, C-5); 141.0 (C-8); 118.0 (C-5); 111.6 (Cq isop.); 87.8 (C-2'); 86.5 (C-3'); 75.9 (C-4'); 63.4 (C-1'); 38.2 (C-5'); 27.0; 24.5 (2CH_3 isop.).

N^6-triphenylphosphinimino-(2'α,3'α-*O*-isopropylidendioxy-4'-cyclopenten-1'β-yl)-9-*H*-adenine (13): To a stirred solution of alcohol **12** (720 mg, 1.92 mmol) in 140 mL toluene maintained at 80°C was added triphenylphosphine (1.51 g, 5.76 mmol), imidazole (0.39 g, 5.76 mmol) and iodine (0.97 g, 3.84 mmol). After the mixture has been kept at 120°C for 12 h it was diluted with toluene and the organic phase was washed with water. The residue obtained after solvent removal was taken in ether to precipitate triphenylphosphine oxide. Complete purification was achieved by silica gel column chromatography (eluent: CH_2Cl_2:MeOH 97/3) to give a 70% yield of compound **13** (amorphous). Fab MS *m/z*: 534 $(MH)^+$ ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.11 (s, 1H, H-2); 7.93-7.40 (m, 16H, PPh_3, H-8); 6.29 (d, $J_{4';5'}$= 6 Hz, 1H, H-4'); 5.95 (dd, 1H, H-5'); 5.60 (d, $J_{1';5'}$= 3 Hz, 1H, H-1'); 5.46 (dd, $J_{2';3'}$= 4 Hz, $J_{3';4'}$= 1 Hz, 1H, H-3'); 4.65 (d, 1H, H-2'); 1.47 (s, 3H, CH_3); 1.32 (s, 3H, CH_3).

(+)N^6-triphenylphosphinimino-(4'α-iodo-2'α,3'α-*O*-isopropylidendioxycyclopent-1'β-yl)-9-*H*-adenine (14): To a mixture of **13**

(550 mg, 1.92 mmol) and triphenylphosphine (760 mg, 2.88 mmol) in 40 mL toluene maintained at 120°C was added over 3 h triodoimidazole (640 mg, 1.44 mmol). Then a new amount of triphenylphosphine (500 mg, 1.92 mmol) and triodoimidazole (430 mg, 0.96 mmol) was added. The mixture was stirred an additional 18 h at the same temperature. Then a saturated solution of sodium hydrogencarbonate was added and the mixture stirred for 5 min. Finally, iodine was added in portions until the toluene phase remained coloured. After an additional 10 min stirring, excess iodine was removed by treatment with aqueous sodium thiosulfate. The organic phase was washed with water, dried over sodium sulfate, filtered and concentrated. Most of triphenylphosphine oxide was precipitated from ether and the product purified by silica gel column chromatography (eluent: CH_2Cl_2:MeOH, 97/3) to give a 76% yield (560 mg) of iodide **14**. m. p. 126-128°C (ethyl acetate). $[\alpha]_D^{20}$ +38,5° (c = 1 ; $CHCl_3$). MS *m/z*: 534 $(M-127)^+$; 274 $[M-127(I)-260\ (PPh_3)]^+$. Calc. for $C_{31}H_{29}N_5O_2IP$, H_2O: C, 54.79; H, 4.59; N, 10.30: found C, 54.73; H, 4.91; N, 9.91. ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 8.01 (s, 1H, H-2); 7.95-7.85 and 7.57-7.40 (m, 15H, PPh3); 7.68 (s, 1H, H-8); 5.07 (d, $J_{2';3'}$= 4.8 Hz; 1H, H-2'); 4.88 (dd, 1H, H-3'); 4.78 (m, 1H, H-4'); 4.65 (d, $J_{1';5'a}$= 6.8 Hz,1H, H-1'); 2.77 (m, 1H, H-5'a); 2.40 (dd, $J_{5'a;5'b}$= 14 Hz; $J_{4';5'b}$= 6 Hz, 1H, H-5'b); 1.57 (s, 3H, CH_3); 1.37 (s, 3H, CH_3). ^{13}C NMR (62.89 MHz, $CDCl_3$) δ ppm: 152.0 (C-2); 138.7 (C-8); 133.5; 133.3; 132.0; 128.5; 128.3 (PPh_3); 111.2 (Cq isop); 83.5; 82.5 (C-2', C-3'); 62.5 (C-4'); 42.5 (C-5'); 26.3; 24.4 ($2CH_3$ isop.); 22.1 (C-1').

General procedures for the coupling reaction between an electron deficient olefin and an alkyl iodide in the presence of the Zn/Cu couple: *Method A*. A solid mixture was prepared by combining zinc powder (500 mg, 8 mmol, 325 mesh) with CuI (356 mg, 2.4 mmol) in 2 mL water in a test tube which was stirred vigorously during 5 min under a nitrogen atmosphere using a vibromixer. Then a 2 mL ethanol solution of iodide (1 mmol) and olefin (5 mmol) was added over a 30 min period. After maintaining the stirring during 6 h at rt, the reaction mixture was diluted with a saturated aqueous NaCl solution. The aqueous phase which was obtained after filtration over celite, was extracted with chloroform. The solid was also rinsed with chloroform. The organic phases were combined and evaporated to give the reaction mixture which was purified by silica gel column chromatography. *Method B*. To a suspension of the Zn/Cu couple prepared as above was added a 2 mL solution of olefin (2 mmol) in ethanol. Subsequently, the solution of iodide (1 mmol) in 1 mL of ethanol was added over a period of 60 min. After 6 h of stirring at rt, the mixture was treated as in *method A*.

(+) **Methyl 2-*N*-benzyloxycarbonylamino-5-carboxamidohex-5-enate (17)**: This compound was prepared starting from reagents **15** and **16** in 35 % (*Method A*) and 50% (*Method B*) yields after purification by column chromatography (eluent: ethyl acetate). $[\alpha]_D^{20}$ + 12° (c = 1.4 ; $CHCl_3$). MS *m/z*: 320 $(M)^+$. Calc. for $C_{16}H_{20}N_2O_5$ + 1/2 H_2O: C, 58.30; H, 6.38; N, 8.50: found C, 57.98; H, 6.05; N, 8.11. ^1H NMR (200 MHz, $CDCl_3$) δ ppm: 7.34 (s, 5H, Ph); 5.92 (m, 2H, 2xCONH); 5.38 (s, 1H, =CH); 5.10 (s, 2H, CH_2Ph); 4.38 (m, 1H, =CH); 3.73 (s, 3H, OCH_3); 2.37 (m, 2H, CH_2C=); 2.15-1.75 (m, 2H, CH_2). ^{13}C NMR (50.32 MHz, $CDCl_3$) δ ppm: 173.0; 170.5; 144.3; 128.6; 128.2; 128.1; 119.7; 67.1; 53.6; 52.4; 31.2; 28.4.

***N*^{6}-triphenyphosphinimino-[2'α,3'α-*O*-isopropylidendioxy-4'-(5''*S*-benzyloxycarbonylamino)-2''-carboxamido-5''-*S*-(methoxycarbonylpent-1''-yl)-cyclopent-1'β-yl]-9-*H*-adenine (18):** For the preparation of **18** *Method B* was used. The reaction between olefin **17** (638 mg, 2 mmol) and iodide **14** (661 mg, 1 mmol) gave four isomers **18a-d** in 10% overall yield together with compound **19** (20%) which were separated by preparative HPLC (silica, isocratic elution with CH_2Cl_2:MeOH 95/5). Compounds **18a-d** which exhibited the same FAB mass spectrum are described in their decreasing elution order (TLC: CH_2Cl_2:MeOH 96/4). Fab MS *m/z*: 857 MH^+; 536 $(856\text{-}PPh_3\text{-}C_2H_5CO_2)^+$; 478 $(856\text{-}PPh_3\text{-}C_2H_5CO_2\text{-}(CH_3)_2CO)^+$. *Isomer* **18a** (Rf= 0.49) $[\alpha]_D^{20}$ +16° (c = 0.23; $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 8.10 (s, 1H, H-2); 7.70 (m, 1H, H-8); 7.90-7.80 and 7.50-7.40 (m, 15H, PPh_3); 7.35 (s, 5H, $CH_2\underline{Ph}$); 5.90 (s, 1H, NH); 5.48 (bs, 1H, NH); 5.16 (s, 1H, NH); 5.08 (s, 2H, $\underline{CH_2}Ph$); 4.87 (d, $J_{2';3'}$= 5 Hz, 1H, H-2'); 4.74 (m, 1H, H-1'); 4.70 (t, $J_{3';4'}$= 5 Hz, 1H, H-3'); 4.38 (m, 1H, H-5"); 3.70 (s, 3H, CH_3); 2.60 (m, 1H, H-4'); 2.35 (m, 1H, H-2"); 2.12 (m, 2H, 2xH-5'); 1.98 (m, 1H, H-1"a); 1.90 (m, 1H, H-4"a); 1.60 (m, 4H, H-1"b, 2xH-3", H-4"b); 1.49; 1.30 (2s, 6H, $2xCH_3$). *Isomer* **18b** (Rf= 0.44) $[\alpha]_D^{20}$ -2° (c = 0.2; $CHCl_3$) ^1H NMR (600 MHz, $CDCl_3$) δ ppm: 8.45 (s, 1H, H-2); 7.80; 7.52; 7.48 (3m, 16H, PPh_3, H-8); 7.28 (s, 5H, $CH_2\underline{Ph}$); 6.23 (s, 1H, NH); 5.37 (s, 1H, NH); 5.27 (bs, 1H, NH); 5.05 (s, 2H, $\underline{CH_2}Ph$); 4.99 (dd, $J_{2';3'}$ = 7 Hz, 1H, H-2'); 4.52 (ddd, $J_{1';5'a}$= 11 Hz, $J_{1';2'}$= 5.4 Hz, $J_{1';5'b}$ = 5 Hz, 1H, H-1'); 4.46 (t, $J_{3';4'}$= 6.7 Hz, 1H, H-3'); 4.33 (dd, $J_{4";5"}$= 13 Hz, 1H, H-5"); 3.73 (s, 3H, CH_3); 2.45 (m, 1H, H-7'); 2.25 (m, 2H, $J_{5'a;5'b}$= 12 Hz, 2xH-5'); 2.10 (m, 1H, H-4'); 1.90 (m, 3H, 2xH-3", H-1"a); 1.70 (m, 3H, 2xH-4", H-1"b); 1.50 (s, 3H, CH_3); 1.28 (s, 3H, CH_3). *Isomer* **18c** (Rf 0.41) $[\alpha]_D^{20}$ -6° (c = 0.12; $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ ppm: 8.50 (s, 1H, H-2); 7.80; 7.50; 7.40 (3m, 16H, PPh_3, H-8); 7.30 (s, 5H, $CH_2\underline{Ph}$); 6.05 (s, 1H, NH); 5.53 (s, 1H,

NH); 5.40 (bs, 1H, NH); 5.05 (s, 2H, $\underline{CH_2}Ph$); 4.85 (d, $J_{2';3'}$= 6 Hz, 1H, H-2'); 4.80 (t, $J_{3';4'}$= 5.5 Hz, 1H, H-3'); 4.63 (d, $J_{1';5'}$= 7 Hz, H-1'); 4.35 (m, 1H, H-5"); 3.70 (s, 3H, OCH_3); 2.40 (m, 1H, H-4'); 2.30 (m, 1H, H-2"); 2.10 (m, 1H, H-5'a); 1.85 (m, 2H, H-5'b, H-4"a); 1.68 (m, 5H, 2xH-1", 2xH-3", H-4"b); 1.40 (s, 3H, CH_3); 1.26 (s, 3H, CH_3). *Isomer* **18d** (Rf 0.38) $[\alpha]_D^{20}$ +6° (c = 0.10; CHCl3). ^{1}H NMR (400 MHz, CDCl3) δ ppm: 8.30 (s, 1H, H-2); 7.70; 7.52; 7.50 (3m, 16H, PPh3, H-8); 7.30 (s, 2H, $CH_2\underline{Ph}$); 6.30 (s, 1H, NH); 5.40 (bs, 1H, NH); 5.35 (s, 1H, NH); 5.00 (s, 2H, $\underline{CH_2}Ph$); 4.96 (dd, J2';3'= 7Hz, 1H, H-2'); 4.60 (ddd, J1';5'a= 10Hz, J1', 2'= 5.4Hz, J1';5'b= 5Hz, 1H, H-1'); 4.40 (t, J3';4'= 6.4Hz, 1H, H-3'); 4.30 (dd, J4";5"= 13Hz, 1H, H-5"); 3.70 (s, 3H, CH3); 2.35 (m, 2H, H-5'a, H-2"); 2.25 (m, 1H, H-5'b); 2.20 (m, 1H, H-4'); 1.80 (m, 5H, 2xH-3", 2xH-4", H-1"); 1.68 (m, 1H, H-1"); 1.50 (s, 3H, CH3); 1.30 (s, 3H, CH3).

***N*^{6}-triphenylphosphinimino-(2'α-hydroxy-3'-cyclopenten-1'-yl)-9-*H*-adenine (19):** Fab MS *m/z*: 478 MH^+, 396 $(AdPPh_3)^+$. Calc. for $C_{28}H_{24}N_5OP$: C, 70.43; H, 5.07; N, 14.66: found C, 70.18; H, 4.98; N, 14.50. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.10 (s, 1H, H-2); 7.90-7.10 and 7.60-7.40 (3m, 15H, PPh_3); 7.80 (s, 1H, H-8); 5.90 (s, 2H, H-3', H-4'); 5.12 (d, J1';2'= 2.5Hz, 1H, H-2'); 4.55 (q, J1';2'= 2.5Hz, J1';5'b = 2.5Hz, J1';5'a= 5Hz, 1H, H-1'); 3.14 (dd, J5'a;5'b= 13Hz, 1H, H-5'a); 2.93 (dd, 1H, H-5'b); 2.20-1.60 (broad, 1H, OH).

***N*^{6}-triphenylphosphinimino-[(2'α,3'α)-*O*-isopropylidendioxy-4'-(2''-carboxamidoprop-3''-en-1''-yl)-cyclopent-1'β-yl]-9 *H*-adenine (20a)** and **(20b)**: *Method B* was used, with some minor modifications, thus to a mixture of Zn/CuI (Zn: 100 mg, 1.6 mmol; CuI: 71 mg, 0.48 mmol) in 0.4 mL H_2O was added a solution of olefin **16** (220 mg, 1.17 mmol) in 0.5 mL acetonitrile. Then, under strong stirring, was added over a 1 h period a solution of iodide **14** in ethyl acetate. After 9 h of stirring, the reaction products were isolated as indicated and purified by preparative HPLC (silica, isocratic elution with CH_2Cl_2:MeOH 95/5) to give an equimolecular amount of **(20a)** and **(20b)** in 31% combined yield. *Isomer* **20a** (Rf 0.40). $[\alpha]_D^{20}$ -6.9° (c= 0.9; CHCl3). Fab MS *m/z*: 618 (M^+); 394 [M - 224(AdPPh3)]$^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.08(s, 1H, H-2); 7.85-7.76 and 7.48-7.37(2 m, 20H, Ph, PPh3); 7.70 (s, 1H, H-8); 5.90 (br s, 1H, NH); 5.60 (s, 1H, =CH); 5.40 (s, 2H, =CH, NH); 4.48 (m, 1H, H-2'); 4.63 (m, 1H, H-1'); 4.43 (m, 1H, H-3'); 2.53 (m, 2H, H-1", H-4'); 2.32-2.10 (m, 3H, H-1", 2xH-5'); 1.48 and 1.20 (2s, 6H, 2xCH3). *Isomer* **20b** (Rf 0.39) $[\alpha]_D^{20}$ -6.4° (c= 0.8; $CHCl_3$). Calc. for $C_{35}H_{35}N_6O_3P$: C, 67.95; H, 5.70; N, 13.58: found C, 67.60; H, 5.85; N, 13.55. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.14

(s, 1H, H-2); 7.90-7.30 (m, 20H, Ph, PPh_3); 7.70 (s, 1H, H-8); 6.10 (br s, 1H, NH); 5.80 (s, 1H, =CH); 5.60 (br s, 1H, NH); 5.50 (s, 1H, =CH); 4.95 (m, 1H, H-2'); 4.75 (m, 2H, H-1', H-3'); 2.50 (m, 2H, H-1"a, H-4'); 2.47 (m, 1H, H-1"b); 2.15 (m, 2H, 2xH-5'); 1.50 (s, 3H, CH_3); 1.30 (s, 3H, CH_3).

(N^6-triphenyphosphinimino)-[2'α,3'α-*O*-isopropylidendioxy-4'β-(5"-*S*-benzyloxycarbonylamino-2"-carboxamido-5"-*S*-methoxycarbonylpent-1"-yl)-cyclopent-1'β-yl]-9-*H*-adenine (18b and **18d):** The Zn/Cu couple was prepared as in the case of compounds **20**. After addition of olefin **20b** (60 mg, 0.08 mmol) in 0.3 mL acetonitrile, was added slowly over a period of 40 min a solution of iodide **15** (230 mg; 0.63 mmol) in 0.3 mL acetonitrile. After stirring the reaction mixture during 5 h at rt the reaction products were isolated and purified by preparative HPLC (silica, isocratic elution with CH_2Cl_2:MeOH 95/5) to provide the C-7' epimers **18b** and **18d** (TLC CH_2Cl_2:MeOH 94/6) having Rf 0.44 and 0.38, respectively.

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