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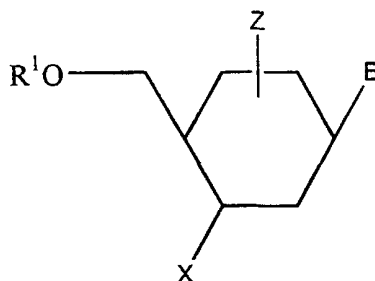
(I)

(57) Abstract: A six membered, at least partially unsaturated, carbocyclic nucleoside compound, including the (-) enantiomer, the (+) enantiomer, and pharmaceutically acceptable salts and esters thereof, the compounds represented by general formula (I) wherein: Z represents the presence of 1 or more double bonds in the six membered carbocyclic ring, B is a heterocyclic ring selected from the group consisting of pyrimidine and purine bases, X is a hydrogen, azido, F, or OR^2, R^1 and R^2 are the same or different and represent the same or different protecting groups, hydrogen, alkyl, alkenyl, acyl or phosphate moieties wherein; the alkyl moiety is a saturated, substituted or unsubsituted straight or branched chains hydrocarbon radical having from 1 to 20, for example 1-16, 1-14, 1-12, 1-10, 1-8, 1-4, carbon atoms, the alkenyl moiety is an unsaturated congener of the alkyl group and, the acyl moiety is an alkanoyl or aroyl moiety, wherein alkanoyl is an alkyl carbonyl radical, wherein alkyl is as described above and aroyl represents benzoyl substituted benzoyl or naphtoyl.

CARBOCYCLIC NUCLEOSIDES AND PROCESS FOR OBTAINING SUCH

The invention relates to carbocyclic nucleoside
analogues and their pharmaceutically acceptable salts,
and to a method for the production of such, and to their
use as anti-viral agents, amongst others.

5   Most antiviral compounds belong to the
nucleoside field and the development of new modified
nucleosides as antiviral agents is an active field of
research. An object of the present invention is to
provide an agent exhibiting pharmaceutical activity.

10   According to a first aspect of the present
invention there is provided a carbocyclic nucleoside
analogue as described in claims 1-14.

These carbocyclic nucleotides exhibit good
pharmaceutical activity.

15   According to a second aspect of the present
invention there is provided a process for providing these
carbocyclic compounds and intermediates thereof according
to claims 15-24.

According to a further aspect of the present
20 invention there is provided a carbocyclic compound
according to any of the claims 24-35.

According to a further aspect of the present
invention there is provided a pharmaceutical composition
and the use of such, according to the claims 36-39.

25   Further aspects of the invention are detailed
in claims 40-43.

The inventors have developed an
enantioselective approach toward the synthesis of (D)-
cyclohexene nucleoside 4 (Figure 3) using R-(-)-carvone
30 (1) as inexpensive starting material. A sequence of
chemical transformations led to intermediate 2,
possessing four chiral centers and, disregarding the
protecting groups R₁-R₄, a plane of symmetry. Intermediate

2 allows for the synthesis of both the (D)- and the (L)-
cyclohexene nucleosides 4 and 5, and 7 and 8,
respectively.

The synthesis of (D)-adenine cyclohexene
5 nucleoside 4 was accomplished by using a Mitsunobu type
reaction on enol 3 to introduce the adenine base moiety
on the cyclohexenyl ring. The corresponding guanine
derivative 5 was synthesized in a similar way. Enol 3 was
reacted with 2-amino-6-chloropurine in the presence of
10 DEAD and triphenyl phosphine in dioxane to give 9 (Figure
4), which was converted to 5 by treatment with TFA-H_2O
3:1. Under these reaction conditions the two TBDMS
protecting groups were simultaneously removed. The
overall yield starting from 3 was 46%. Analytically pure
15 5 was obtained by reversed-phase HPLC purification.

The synthesis of the (L)-cyclohexene
nucleosides 7 and 8 was carried out by protection of the
C4-CH_2OH and C5-OH groups (2b), followed by conversion of
the OR_2 and OR_4 groups into enol 6. This compound was then
20 used for the introduction of the base moiety according to
the same strategy as used for the (D)-series.
Intermediate 2b ($R_1 = R_3 = H$; $R_2 = R_4 = TBDMS$) was
converted to dibenzoate 10 (Figure 5) using standard
reaction conditions (Bz_2O, DMAP, CH_2Cl_2, 98%). The
25 equatorial C3-OTBDMS protecting group was selectively
removed in the presence of the axial C1-OTBDMS to give 11
by using one equivalent of TBAF in THF at room
temperature (74%). The selectivity of the desilylation
reaction has been observed before[13c]. The C3 alcohol 11
30 was converted to the corresponding mesylate 12, the C1-
OTBDMS group was removed using TBAF to give the alcohol
13 (96%), which was oxidized using PDC in CH_2Cl_2. This
oxidation was accompanied by simultaneous elimination of
the C3-OMs group to afford directly the desired enone 15
35 (68%). Stereoselective reduction of enone 15 using $NaBH_4$
in the presence of $CeCl_3.7H_2O$ in MeOH gave enol 6 (75%).

A Mitsunobu reaction was then applied for
introduction of the base moiety (Figure 6). Upon reaction

of **6** with adenine in the presence of DEAD and PPh₃ in
dioxane, the desired adenine derivative **16a** was isolated
in 40% yield, together with 15% of N7-isomer **16b** (Figure
6). Finally, removal of the benzoyl protecting groups

5using K₂CO₃ in MeOH gave the (L)-adenine cyclohexene
nucleoside **7** in 72% yield. The corresponding (L)-guanine
nucleoside **8** was synthesized in an analogous way. The
enol **6** was treated with 2-amino-6-chloropurine under the
same reaction condition as described above for **9**, and the

10obtained 6-chloropurine **17** was converted to the guanine
derivative **18** using TFA-H₂O 3:1 (58% yield from **6**). Final
deprotection was carried out by heating **18** in a saturated
solution of NH₃ in MeOH in a sealed vessel for 2 days and
reversed-phase HPLC purification gave pure (L)-guanine

15cyclohexene nucleoside **8** in 73% yield.

Antiviral activity

The anti-herpesvirus activity of D-cyclohexene
G and L-cyclohexene G and the respective adenine

20analogues was determined in human embryonic skin muscle
fibroblast (E₆SM: HSV-1, HSV-2) and in human embryonic
lung (HEL) cells [varicella-zoster virus (VZV),
cytomegalovirus (CMV)] (Table I). The source of the
viruses and the methodology used to monitor antiviral

25activity have been previously described (De Clercq, E.,
Descamps, J., Verhelst, G., Walker, R.T., Jones, A.S.,
Torrence, P.F., Shugar, D. Comparative efficacy of
antiherpes drugs against different strains of herpes
simplex virus. J.Infect. Dis. 1980, **141**, 563-574; De

30Clercq, E., Hóly, A., Rosenberg, I., Sakuma, T.,
Balzarini, J., Maudgal, P.C. A novel selective broad-
spectrum anti-DNA virus agent. Nature, 1986, **323**, 464-
467). The antiviral activity was compared with the
activity of known and approved antiviral drugs from which

35two with a purine base moiety (acyclovir, ganciclovir)
and two with a pyrimidine base moiety (brivudine,
cidofovir).

D-cyclohexene G as well as L-cyclohexene G did

4

not show toxicity in four different cell lines (HeLa,
Vero, E_6SM, HEL) (Table II), pointing to their selective
antiviral mode of action, as reflected by the high
selectivity index of the compounds (Table I). A salient
5 feature is that the activity spectrum of both enantiomers
is remarkably similar. Both compounds display the same
activity against HSV-1 and HSV-2. Against VZV and CMV the
potency of L-cyclohexene G is about 2-fold lower than
that of D-cyclohexene G. Against HSV-1, the cyclohexene G
10 nucleosides are as active as acyclovir and brivudin.
Against HSV-2, their activity is very similar to that of
acyclovir. The cyclohexene G nucleosides retain activity
against the TK^- strains of HSV-1 and VZV, although the
activity is reduced as compared to the activity against
15 the wild type. The activity of D-cyclohexene G against TK^+
and TK^- VZV strains is higher than the respective
activities of acyclovir and brivudin against these
viruses. D-cyclohexene G has the same activity against
CMV as ganciclovir. In conclusion the activity spectrum
20 of the cyclohexene nucleosides of the present invention
is very similar to that of the known antiviral compounds
possesing a guanine base moiety (acyclovir, ganciclovir).
Both the D- and the L-enantiomers of cyclohexene G are
antivirally active. The high selectivity indexes observed
25 for D- and L-cyclohexene G indicates the utility of these
compounds against herpesvirus infections.

D-cyclohexene G as well as L-cyclohexene G
exhibited potent and selective anti-herpes virus (HSV1,
HSV2, VZV, CMV) activity. Their activity spectrum is
30 comparable to that of the known antiviral drugs acyclovir
and ganciclovir. D- and L-cyclohexene G represent a very
potent antiviral nucleosides containing a six-membered
carbohydrate mimic. In contrast to the nucleosides with a
cyclohexane, pyranose or hexitol ring, the cyclohexene
35 nucleosides have a very flexible conformation. The
inventors theorize that this flexibility may be an
important structural determinant for their potent
antiviral activity.

Experimental (1)

General Methods

5   Melting points were determined in capillary
tubes with a Büchi-Tottoli apparatus and are uncorrected.
Ultraviolet spectra were recorded with a Philips PU 8740
UV/vis spectrophotometer. ^{1}H NMR and ^{13}C NMR were
determined with a 200 MHz Varian Gemini apparatus with
10 tetramethylsilane as internal standard for the ^{1}H NMR
spectra and DMSO-d_{6} (39.6 ppm) or CDCl$_{3}$ (76.9 ppm) for the
^{13}C NMR spectra (s = singlet, d = doublet, dd = double
doublet, t = triplet, br s = broad singlet, br d = broad
doublet, m = multiplet). Liquid secondary ion mass
15 spectra (LSIMS) with Cs^{+} as primary ion beam were recorded
on a Kratos Concept IH (Kratos, Manchester, U.K.) mass
spectrometer equipped with a MASPEC2 data system (Mass
Spectrometry Services Ltd., Manchester, U.K.). Samples
were directly dissolved in glycerol (gly)/thioglycerol
20 (thgly)/m-nitrobenzyl alcohol (nba) and the secondary
ions accelerated at 7kV. Scans were performed at 10
s/decade from m/z 1000 down to m/z 50. Precoated Machery-
Nagel Alugram SIL G/UV$_{254}$ plates were used for TLC (in
solvent systems: A CH$_{2}$Cl$_{2}$-MeOH 98:2, B CH$_{2}$Cl$_{2}$-MeOH 9:1, C
25 CH$_{2}$Cl$_{2}$-EtOAc 4:1); the spots were examined with UV light
and sulfuric acid/anisaldehyde spray. Elemental analyses
were done at the University of Konstanz, Germany.

9-[(1S,4R,5S)-5-(tert-butyldimethylsilyloxy)-4-(tert-
30 butyldimethylsilyloxymethyl)-2-cyclohexenyl]-2-amino-6-
chloropurine (9)

To a mixture of 3 (130 mg, 0.35 mmol), 2-amino-
6-chloropurine (119 mg, 0.70 mmol) and PPh$_{3}$ (184 mg, 0.70
mmol) in dry dioxane (7 mL) under N$_{2}$ at room temperature
35 was added a solution of DEAD (110 µL, 0.70 mmol) in dry
dioxane (3 mL) over a period of 1.5 hr. The reaction
mixture was stirred at room temperature for two days and
concentrated. The residue was chromatographed on silica

gel (CH₂Cl₂-MeOH 50:1, then 20:1) to yield crude **9** (170 mg) as a yellow foam: ^{1}H NMR (CDCl₃) δ -0.10 (s, 3H), -0.04 (s, 3H), 0.07 (s, 6H), 0.82 (s, 9H), 0.90 (s, 9H), 2.04 (t, 2H, J = 5.6 Hz), 2.27 (m, 1H), 3.66 (dd, 1H, J = 9.9, 55.1 Hz), 3.77 (dd, 1H, J = 9.9, 4.4 Hz), 3.98 (m, 1H), 5.21 (m, 1H), 5.43 (s, 2H, NH₂), 5.79 (dm, 1H, J = 9.9 Hz), 6.00 (dm, 1H, J = 9.9 Hz), 7.79 (s, 1H); ^{13}C NMR (CDCl₃) δ -5.6 (q), -5.5 (q), -5.1 (q), -4.8 (q), 17.8 (s), 18.2 (s), 25.6 (q), 25.8 (q), 36.0 (t), 46.9 (d), 1049.2 (d), 62.9 (t), 64.6 (d), 124.4 (d), 125.4 (s), 134.4 (d), 141.3 (d), 151.1 (s), 153.3 (s), 159.1 (s);

9-[(1*S*,4*R*,5*S*)-5-hydroxy-4-hydroxymethyl-2-cyclohexenyl]guanine (5)

Crude **9** (170 mg) was treated with TFA-H₂O (3:1, 10 mL) at room temperature for two days. The reaction mixture was concentrated and co-evaporated with toluene (2x). The residue was chromatographed on silica gel (CH₂Cl₂-MeOH 10:1, then 1:1) to afford **5** (45 mg, 46% overall yield starting from **3**): Mp >230 °C; UV λ$_{max}$ (MeOH) = 253 nm, ^{1}H NMR (CD₃OD) δ 1.94-2.27 (m, 3H), 3.77 (d, 2H, J = 4.7 Hz), 3.85 (m, 1H), 5.17 (m, 1H), 5.88 (dm, 1H, J = 10.2 Hz), 6.09 (dm, 1H, J = 10.2 Hz), 7.73 (s, 1H); ^{13}C NMR (CD₃OD) δ 37.1 (t), 47.7 (d), 50.6 (d), 63.1 (t), 64.8 (d), 125.8 (d), 135.4 (d), 138.5 (d); LISMS (THGLY/NBA) 278 (M+H)$^+$; HRMS calcd for C₁₂H₁₆N₅O₃ (M+H)$^+$ 278.1253, found 278.1270; Anal. Calcd for C₁₂H₁₅N₅O₃.0.77H₂O: C 49.49, H 5.73, N 24.05; Found: C 49.45, H 5.55, N 24.22.

(1*S*,2*S*,3*R*,5*R*)-3-Benzoyl-2-benzoylmethyl-1,5-di(*tert*-butyldimethylsilyloxy)-cyclohexane (10)

To a solution of **2b** (2.2 g, 5.64 mmol) in dry dichloromethane (20 mL) at 0 °C under N₂ was added DMAP (3.44 g, 28.2 mmol, 5 eq) and Bz₂O (3.83 g, 16.92 mmol, 3 eq) sequentially and in portions. After stirring at 0 °C for 2 hr, the reaction was quenched with ice. The

reaction mixture was poured into CH_2Cl_2 (250 ml) and washed with water and brine, dried over Na_2SO_4 and concentrated. The crude product was chromatographed on silica gel (n-hexane-EtOAc 10:1) to yield **10** (3.3 g, 98%) as a light yellow oil.

^1H NMR ($CDCl_3$) δ 0.03 (s, 3H), 0.06 (s, 3H), 0.13 (s, 3H), 0.17 (s, 3H), 0.89 (s, 9H), 1.01 (s, 9H), 1.58 (m, 2H), 2.09 (m, 2H), 2.37 (m, 1H), 4.29 (br-s, 1H), 4.40 (td, 1H, J = 10.3, 4.0 Hz), 4.49 (dd, 1H, J = 11.4, 2.0 Hz), 4.61 (dd, 1H, J = 11.4, 2.2 Hz), 5.66 (td, 1H, J = 11.0, 4.6 Hz), 7.37 - 7.44 (m, 4H), 7.49 - 7.59 (m, 2H), 8.02 (m, 4H);

^{13}C NMR ($CDCl_3$) δ -5.3 (q), -5.2 (q), -5.1 (q), -4.5 (q), 17.8 (s), 25.6 (q), 25.7 (q), 38.2 (t), 42.4 (t), 49.5 (d), 60.0 (t), 65.2 (d), 66.4 (d), 68.5 (d), 128.3 (d), 129.6 (d), 130.3 (s), 130.4 (s), 132.8 (d), 165.6 (s), 166.5 (s);

(1S,2S,3R,5S)-3-Benzoyl-2-benzoylmethyl-5-(*tert*-butyldimethylsilyloxy)-cyclohexanol (11)

A solution of TBAF 1M in THF (5.38 ml, 5.38 mmol) was added slowly to a solution of **10** (3.23 g, 5.38 mmol) in THF (50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 hr and further at room temperature for 3 hr. Ice was added and the reaction mixture was poured into EtOAc (300 ml) which was washed with NH_4Cl solution, water and brine, dried over Na_2SO_4 and concentrated. The crude product was purified on silica gel (n-hexane-EtOAc 5:1 then 1:1) to yield **11** (1.93 g, 74%) as a white foam.

^1H NMR ($CDCl_3$) δ 0.02 (s, 3H), 0.09 (s, 3H), 0.81 (s, 9H), 1.50 - 1.63 (m, 2H), 1.96 (m, 1H), 2.13 (m, 1H), 2.32 (m, 1H), 3.24 (d, 1H, J = 4.8 Hz, -OH), 4.04 (m, 1H), 4.25 (m, 1H), 4.33 (dd, 1H, J = 11.4, 2.2 Hz), 5.04 (dd, 1H, J = 11.4, 2.2 Hz), 5.60 (td, 1H, J = 11.0, 4.5 Hz), 7.36 - 7.60 (m, 6H), 8.06 (m, 4H);

^{13}C NMR ($CDCl_3$) δ -5.2 (q), 17.6 (s), 25.4 (q), 38.2 (t),

40.8 (t), 50.4 (d), 59.8 (t), 64.1 (d), 66.1 (d), 68.4
(d), 128.4 (d), 129.6 (d), 129.8 (d), 130.4 (s), 133.0
(d), 133.2 (d), 165.6 (s), 167.6 (s);

LISMS (THGLY/TFA): 485 (M+H)$^+$; HRMS calcd for $C_{27}H_{37}O_6Si$
5 (M+H)$^+$ 485.2359, found 485.2376.

(1S,2S,3R,5S)-3-Benzoyl-2-benzoylmethyl-5-(*tert*-butyldimethylsilyloxy)-1-methanesulfonyloxy-cyclohexane (12)

10   To a solution of **11** (1.90 g, 3.92 mmol) in dry
dichloromethane (20 mL) at 0 °C under N_2 was added slowly
triethylamine (2.71 ml, 19.6 mmol, 5 eq) and MsCl (456
µl, 5.89 mmol, 1.5 eq) sequentially. After stirring at 0
°C for 1 hr, the reaction was quenched with ice. The
15 reaction mixture was poured into CH_2Cl_2 (250 ml) and
washed with a saturated NH_4Cl solution, water and brine,
dried over Na_2SO_4 and concentrated. The residue was
chromatographed on silica gel (*n*-hexane-EtOAc 1:1) to
afford **12** (2.17 g, 98%) as a white foam.

20 ^1H NMR (CDCl$_3$) δ 0.13 (s, 3H), 0.15 (s, 3H), 0.96 (s, 9H),
1.62 (td, 1H, J = 12.0, 2.0 Hz), 1.85 (td, 1H, J = 12.0,
2.0 Hz), 2.26 - 2.58 (m, 3H), 2.98 (s, 3H), 4.34 (m, 1H),
4.50 (dd, 1H, J = 11.4, 2.0 Hz), 4.60 (dd, 1H, J = 11.4,
2.0 Hz), 5.28 (td, 1H, J = 11.1, 4.8 Hz), 5.69 (td, 1H, J
25 = 11.0, 4.8 Hz), 7.42 (m, 4H), 7.57 (m, 2H), 8.03 (m,
4H);

^{13}C NMR (CDCl$_3$) δ -5.3 (q), -5.2 (q), 17.8 (s), 25.5 (q),
37.8 (t), 38.1 (q), 39.9 (t), 46.7 (d), 58.9 (t), 65.9
(d), 67.8 (d), 75.9 (d), 128.5 (d), 129.6 (d), 129.9 (s),
30 133.1 (d), 165.4 (s), 166.3 (s);

LISMS (THGLY/GLY): 563 (M+H)$^+$; HRMS calcd for $C_{28}H_{39}O_8SSi$
(M+H)$^+$ 563.2135, found 563.2188.

(1R,3S,4S,5R)-5-Benzoyl-4-benzoylmethyl-3-
35 **methanesulfonyloxy-cyclohexanol (13)**

        To a solution of **12** (2.15 g, 3.82 mmol) in THF
(50 mL) at room temperature was added slowly a 1 M

solution of TBAF (7.64 ml, 7.64 mmol, 2 eq) in THF. The reaction was stirred at room temperature for 2.5 hr and quenched with ice. After standard work-up and purification on silica gel (n-hexane-EtOAc 1:1), **13** (1.55 5g, 86%) was obtained as a white foam.

^{1}H NMR (CDCl$_3$) δ 1.71 (td, 1H, J = 12.1, 2.2 Hz), 1.90 (td, 1H, J = 12.2, 2.3 Hz), 2.29 - 2.65 (m, 4H), 3.00 (s, 3H), 4.41 (m, 1H), 4.52 (dd, 1H, J = 11.7, 2.8 Hz), 4.61 (dd, 1H, J = 11.7, 2.8 Hz), 5.27 (td, 1H, J = 10.6, 4.8 10Hz), 5.65 (td, 1H, J = 10.6, 4.7 Hz), 7.42 (m, 4H), 7.55 (m, 4H), 8.02 (m, 4H);

^{13}C NMR (CDCl$_3$) δ 37.3 (t), 38.2 (q), 39.0 (t), 46.8 (d), 59.3 (t), 65.1 (d), 67.9 (d), 75.8 (d), 128.5 (d), 129.7 (d), 133.2 (d), 133.3 (d), 165.6 (s), 166.4 (s);

15 LISMS (THGLY/TFA): 449 (M+H)$^{+}$; HRMS calcd for C$_{22}$H$_{25}$O$_8$S (M+H)$^{+}$ 449.1270, found 449.1244.

(4S,5R)-5-Benzoyl-4-benzoylmethyl-cyclohex-2-en-1-one (15)

20   A mixture of **13** (500 mg, 1.12 mmol) and PDC (2.1 g, 5.60 mmol, 5 eq) in dry CH$_2$Cl$_2$ (30 mL) was stirred vigorously at room temperature for 24 h. The reaction mixture was filtered through Celite® and washed with CH$_2$Cl$_2$. The filtrate was concentrated and the residue was 25chromatoghraphed on silica gel (n-hexane-EtOAc 2:1, then 1:2) to yield starting material **13** (100 mg, 20 %) and enone **15** (267 mg, 68%) as a light yellow oil.

^{1}H NMR (CDCl$_3$) δ 2.73 (dd, 1H, J = 16.5, 8.8 Hz), 3.10 (dd, 1H, J = 16.5, 4.4 Hz), 3.27 (m, 1H), 4.50 (dd, 1H, J 30= 11.3, 4.7 Hz), 4.66 (dd, 1H, J = 11.3, 5.5 Hz), 5.66 (ddd, 1H, J = 8.8, 7.3, 4.4 Hz), 6.26 (dd, 1H, J = 10.2, 2.2 Hz), 6.96 (dd, 1H, J = 10.2, 3.3 Hz), 7.40 - 7.63 (m, 6H), 8.01 (m, 4H);

^{13}C NMR (CDCl$_3$) δ 41.3 (d), 42.1 (t), 63.2 (t), 70.0 (d), 35128.6 (d), 129.5 (2s), 129.7 (d), 129.8 (d), 131.4 (d), 133.5 (d), 146.5 (d), 165.5 (s), 166.4 (s), 195.8 (s);

(1S,4S,5R)-5-Benzoyl-4-benzoylmethyl-cyclohex-2-en-1-ol (6)

To a solution of 15 (267 mg, 0.76 mmol) in MeOH (10 mL) at room temperature under N_2 was added $CeCl_3 \cdot 7H_2O$ (426 mg, 1.14 mmol, 1.5 eq). The mixture was stirred for 0.5 h and a clear solution was obtained. $NaBH_4$ (35 mg, 0.91 mmol, 1.2 eq) was added in portions and H_2 evolved. The reaction mixture was stirred for 1 h and quenched with ice. The mixture was stirred for 15 min and concentrated. The residue was distributed into EtOAc, washed with H_2O and brine, dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (n-hexane-EtOAc 10:1) to give 6 (200 mg, 75%) as a light yellow oil.

^{1}H NMR (CDCl$_3$) δ 1.77 (d, 1H, J = 7.2 Hz), 1.93 (ddd, 1H, J = 12.1, 10.2, 8.0 Hz), 2.54 (ddd, 1H, J = 12.1, 5.8, 3.3 Hz), 3.00 (m, 1H), 4.32 (dd, 1H, J = 11.4, 5.5 Hz), 4.44 (dd, 1H, J = 11.4, 5.5 Hz), 4.50 (m, 1H), 5.35 (ddd, 1H, J = 10.2, 7.3, 2.9 Hz), 5.78 (dt, 1H, J = 10.2, 1.8 Hz), 5.97 (dt, 1H, J = 10.2, 2.5 Hz), 7.34 - 7.60 (m, 6H), 8.00 (m, 4H);

^{13}C NMR (CDCl$_3$) δ 36.6 (t), 40.9 (d), 46.6 (t), 65.8 (d), 69.9 (d), 126.6 (d), 128.4 (d), 128.5 (d), 129.7 (d), 129.8 (s), 130.9 (s), 132.7 (d), 133.1 (d), 133.2 (d), 166.0 (s), 166.5 (s);

LISMS (THGLY/TFA): 353 (M+H)$^+$; HRMS calcd for $C_{21}H_{21}O_5$ (M+H)$^+$ 353.1389, found 353.1440.

9-[(1R,4S,5R)-5-Benzoyl-4-benzoylmethyl-2-cyclohexenyl]adenine (16a)

To a mixture of 6 (65 mg, 0.18 mmol), adenine (48 mg, 0.36 mmol, 2 eq) and PPh$_3$ (94 mg, 0.36 mmol, 2 eq) in dry dioxane (4 mL) under N_2 at room temperature was added a solution of DEAD (56 µL, 0.36 mmol, 2 eq) in dry dioxane (3 mL) over a period of 1 hr. The reaction mixture was stirred at room temperature overnight and concentrated. The residue was chromatographed on silica

gel (CH_2Cl_2-MeOH 50:1, 20:1, 10:1) to yield **16a** (33 mg, 40%) as a white solid.

UV λ_{max} (MeOH): 231 and 263 nm.

^{1}H NMR ($CDCl_3$) δ 2.48 (ddd, 1H, J = 13.6, 8.3, 5.8 Hz), 52.57 (ddd, 1H, J = 13.6, 6.0, 3.2 Hz), 4.50 (dd, 1H, J = 10.4, 5.0 Hz), 4.63 (dd, 1H, J = 10.4, 6.1 Hz), 5.53 (m, 2H), 5.92 (s, 2H), 6.09 (dm, 1H, J = 10.0 Hz), 6.17 (dm, 1H, J = 10.0 Hz), 7.41 (m, 4H), 7.57 (m, 2H), 7.86 (s, 1H), 8.04 (m, 4H), 8.35 (s, 1H);

10 ^{13}C NMR ($CDCl_3$) δ 32.4 (t), 40.6 (d), 48.7 (d), 64.3 (t), 68.2 (d), 120.1 (s), 126.8 (d), 128.5 (d), 128.6 (d), 129.6 (d), 129.7 (d), 131.0 (d), 133.4 (d), 138.8 (d), 149.8 (s), 153.1 (d), 155.8 (s), 165.8 (s), 166.5 (s);

LISMS (THGLY/NBA): 470 (M+H)$^+$; HRMS calcd for $C_{26}H_{24}N_5O_4$
15(M+H)$^+$ 470.1828, found 470.1845.

9-[(1R,4S,5R)-5-hydroxy-4-hydroxymethyl-2-cyclohexenyl]adenine (7)

Compound **16a** (33 mg, 0.07 mmol) was treated
20with anhydrous K_2CO_3 (100 mg) in MeOH (3 mL) at room temperature for 3 hr. Small portion of silica gel was added to the reaction mixture and the solvent was evaporated. The residue was chromatographed on silica gel (CH_2Cl_2-MeOH 10:1, 1:1) to give **7** (14 mg, 77%).

25^{1}H NMR (CD_3OD) δ 2.02 - 2.32 (m, 3H), 3.79 - 3.90 (m, 3H), 5.35 (m, 1H), 5.93 (dm, 1H, J = 9.9 Hz), 6.15 (dm, 1H, J = 9.9 Hz), 8.09 (s, 1H), 8.21 (s, 1H);

^{13}C NMR (CD_3OD) δ 37.2 (t), 47.7 (d), 51.1 (d), 63.0 (t), 64.7 (d), 120.6 (s), 125.4 (d), 136.0 (d), 141.6 (d), 30150.3 (s), 153.8 (d), 157.5 (s);

LISMS (THGLY/TFA): 262 (M+H)$^+$; HRMS calcd for $C_{12}H_{16}N_5O_2$ (M+H)$^+$ 262.1304, found 262.1323.

9-[(1R,4S,5R)-5-Benzoyl-4-benzoylmethyl-2-35cyclohexenyl]guanine (18)

Compound **6** (160 mg, 0.45 mmol) was treated with 2-amino-6-chloropurine (153 mg, 0.90 mmol, 2 eq) in the

presence of PPh₃ (235 mg, 0.90 mmol, 2 eq) and DEAD (140 μl, 0.90 mmol, 2 eq) in dry dioxane (12 mL) at room temperature overnight. After concentration and purification on silica gel (CH₂Cl₂-EtOAc 1:1), crude **17** (500 mg) was obtained, which was treated with CF₃COOH/H₂O (3:1, 12 mL) at room temperature for 2 days. The reaction mixture was concentrated and coevaporated with toluene. The residue was purified on silica gel (CH₂Cl₂-MeOH 20:1) to yield **18** (126 mg, 58% over two steps) as a white solid.

UV λ_{max} (MeOH): 251 and 256 nm.

^{1}H NMR (500 MHz, DMSO-d_6) δ 2.30 (ddd, 1H, J = 13.6, 8.3, 5.9 Hz), 2.42 (ddd, 1H, J = 13.6, 6.4, 3.2 Hz), 3.00 (m, 1H), 4.52 (m, 2H), 5.17 (m, 1H), 5.37 (m, 1H), 6.03 (dm, 1H, J = 10.2 Hz), 6.11 (dm, 1H, J = 10.2 Hz), 6.45 (s, 2H), 7.51 (m, 4H), 7.66 (m, 2H), 7.69 (s, 1H), 7.95 (m, 4H), 10.61 (s, 1H);

^{13}C NMR (DMSO-d_6) δ 31.4 (t), 40.0 (d, overlapped with DMSO-d_6 peak), 47.9 (d), 64.4 (t), 68.5 (d), 116.9 (s), 127.0 (d), 128.9 (d), 129.3 (d), 129.4 (d), 130.2 (d), 133.6 (d), 135.7 (d), 150.9 (s), 153.8 (s), 156.9 (s), 165.3 (s), 165.8 (s);

LISMS (THGLY/GLY): 486 (M+H)$^+$; HRMS calcd for $C_{26}H_{24}N_5O_5$ (M+H)$^+$ 486.1777, found 486.1816;

UV (MeOH): 231, 256.

9-[(1R,4S,5R)-5-Hydroxy-4-hydroxymethyl-2-cyclohexenyl]guanine (8)

A mixture of **18** (85 mg) in an ammonium MeOH solution (75 mL) was sealed and heated at 80 °C for 2 days. After cooling to room temperature, the mixture was concentrated and the residue was purified by reverse HPLC (4% CH₃CN in water) to afford **8** (36 mg, 75%) as a white powder.

Mp: 255 °C (decomp.)

UV λ_{max} (MeOH) = 254 nm.

^{1}H NMR (500 HMz, DMSO-d_6) δ 1.85 (m, 1H), 1.98 (m, 1H),

2.11 (m, 1H), 3.54 (dd, 1H, J = 10.3, 5.5 Hz), 3.60 (dd, 1H, J = 10.3, 4.8 Hz), 3.70 (m, 1H), 4.68 (br-s, 1H, -OH), 4.75 (br-s, 1H, -OH), 4.99 (m, 1H), 5.77 (dm, 1H, J = 9.8 Hz), 5.97 (dm, 1H, J = 9.8 Hz), 6.57 (s, 2H, -NH$_2$), 57.50 (s, 1H), 10.8 (br-s, 1H, -NH);

^{13}C NMR (125 MHz, DMSO-d_6) δ 35.9 (t), 46.4 (d), 48.2 (d), 61.5 (t), 62.7 (d), 116.9 (s), 124.8 (d), 133.7 (d), 135.6 (d), 150.8 (s), 154.1 (s), 157.6 (s);

LISMS (THGLY/NBA) 278 (M+H)$^+$; HRMS calcd for C$_{12}$H$_{16}$N$_5$O$_3$ 10 (M+H)$^+$ 278.1253, found 278.1247; Anal. Calcd for C$_{12}$H$_{15}$N$_5$O$_3$.1.5H$_2$O: C 47.35, H 5.96, N 23.03; Found: C 47.46, H 5.64, N 22.87.

As detailed above, the inventors have developed an enantioselective approach to the synthesis of six-
15 membered carbocyclic nucleosides of type **2b** (R = OH) starting from (R)-(-)-carvone (**4**, Figure 7, corresponding substantially with Figure 1). A key step involving hydroboration of the exo double bond of cyclohexene **6b** to afford hydroxymethyl substituted **7b** with the correct
20 stereochemistry at C4. Precursor **6a** provided an ideal starting material for the synthesis of **3** as it had (1) a protected hydroxyl group at C3, (2) a protected hydroxyl substituent at C1, which at a final stage can be used to introduce a base moiety with retention of the
25 configuration using Pd-chemistry, and (3) a free hydroxyl group at C5, which could be used to introduce the double bond.

The most straightforward approach seemed to introduce the C5-C6 double bond via conversion of the OH
30 at C5 into a suitable leaving group, followed by a regioselective elimination. The latter might be achieved via a E$_2$-type elimination reaction by treatment with base, which requires a neighbouring hydrogen trans to the leaving group, only available on C6. In order to explore
35 this strategy, alcohol **6a** was converted into diol **7a** via hydroboration using 9-BBN in THF. The reaction gave **7a** as the major isomer, together with a small amount of epimer

8a. The β-stereochemistry at C4 was easily established by
NMR spectrometry. Selective protection of the primary
hydroxyl group of **7a** (TBDMSCl, imidazole, DMF) gave **9**
(Figure 8) and the leaving group was introduced (MsCl,
5Et₃N, dichloromethane) to give **10**. However, upon treatment
of mesylate **10** with DBU in toluene, cyclohexene **11** was
not formed. More vigorous reaction conditions (KOH, H₂O-
THF),[5] likewise, failed to yield the unsaturated compound
11. Direct elimination of the 5-OH of **9** under Mitsunobu
10conditions (DEAD, PPh₃, THF)[6] was also unsuccessful. **9** was
converted into the β-iodide **12** (I₂, PPh₃, imidazole,
toluene), with inversion of the stereochemistry at C5,
followed by treatment with DBU in refluxing toluene. This
reaction resulted in an inseparable mixture (yield 68%)
15of cyclohexenes **11** and **13** in a 1:2.3 ratio, respectively,
in favour of the undesired regioisomer.

   The inventors also investigated a different
synthetic strategy, i.e. the construction of an allylic
acetate of type **A** or **B** (Figure 1) as intermediate for the
20Pd coupling reaction to introduce the base moiety.

   Diol **14** (Figure 9) was protected as cyclic
acetal **15** (2,2-dimethoxypropane, PPTS, acetone-THF), the
Bn group was removed (10% Pd on carbon, HCOONH₄, MeOH,
reflux) to give alcohol **16**, and oxidation of the C5-OH
25(PDC, dichloromethane) provided ketone **17**. Cleavage of
the TBDMS ether using tetrabutylammonium fluoride (TBAF)
in THF led mainly to diol **18**. However, under neutral
reaction conditions (KF, 18-crown-6, THF) the desired
enone **19** was isolated in 62% yield; the β-hydroxy ketone
30intermediate **20** could not be detected. The critical
reduction of enone **19** to the corresponding allylic
alcohol **22** with β-oriented OH at C5 proved to be
problematic, leading almost exclusively to the α-isomer
21 under the applied reaction conditions (NaBH₄,
35CeCl₃.7H₂O, MeOH and 9-BBN, THF). In an attempt to invert
the stereochemistry at C5 of α-alcohol **21**, the latter was

subjected to a Mitsunobu type reaction (DEAD, PPh$_3$, AcOH),
but the desired β-acetate **23** was not formed. However,
compound **21** might be used to synthesize the α-analogue of
the aforementioned cyclohexene nucleoside, interesting
5 for as well conformational analysis as for determination
of antiviral activity.

The intended Pd coupling reaction was
investigated on the α-acetate **24**, easily prepared from **21**
(Ac$_2$O, DMAP, dichloromethane). When **24** was treated with
10 the anion (NaH) of adenine in the presence of
tetrakis(triphenylphosphine)palladium(0) in DMF-THF, only
24 was recovered and no trace of the 1α-adenine **25** could
be detected. Reasoning that this failure might be due to
the rigidity of the cyclic acetal present, **24** was treated
15 with PPTS in MeOH to give diol **26**, which was then
converted into the corresponding dibenzoate **27** (Bz$_2$O,
DMAP, dichloromethane). However, upon subjection of **27** to
the same reaction conditions for coupling as applied
above to **24**, the expected 1α-adenine product **28** could not
20 be isolated.

The above failure having exhausted the
possibilities of the Pd coupling strategy, the most
reliable alternative (for the introduction of the base
moiety seemed) a Mitsunobu reaction was utilized, i.e. by
25 substitution with inversion of the configuration of an α-
oriented hydroxyl group at C1. Therefore the inventors
had to synthesize an appropriately protected precursor
7c. Epoxide **5b** (Figure 7, R$_1$ = Bn) was converted into **6c**
under the reported conditions (LiTMP and Et$_2$AlCl in
30 benzene-toluene 1:1) in 79% yield. Hydroboration of **6c**
with 9-BBN in THF afforded **7c** as major isomer (74%),
together with its epimer **8c** (20%). Similar to
configurational assignment of **7a** and **7b**, the β-
stereochemistry at C4 of **7c** was established by ^{1}H-NMR. The
35 primary hydroxyl group of **7c** was selectively protected
using 1.2 equivalents of TBDMSCl and imidazole in DMF t_e

2ve **29** (70%, Figure 10), followed by conversion of the
free alcohol at C5 into the corresponding mesylate **30** by
treatment with MsCl and Et$_3$N in dichloromethane.
Hydrogenolytic cleavage of the benzyl ether at C1 using
5 20% Pd(OH)$_2$ on carbon in the presence of cyclohexene in
MeOH gave **31** in low yield (21%), which could be improved
to 76% by the use of 10% Pd on carbon and HCOONH$_4$ in
refluxing MeOH. Oxidation of alcohol **31** using PDC in
dichloromethane gave a mixture of ketone **32** and enone **33**
10 in a combined yield of 39%. However, using MnO$_2$ in
dichloromethane, an incomplete but clean reaction took
place. The ketone **32** was not isolated and enone **33** was
obtained in 48% yield and recovered **31** (47%) could be
recycled. Finally, enone **33** was reduced using NaBH$_4$ in the
15 presence of CeCl$_3$.7H$_2$O in MeOH and gave the desired α-
alcohol **34** as a single isomer in almost quantitative
yield. The stereochemistry of **34** was confirmed by ^{1}H NMR
spectral data. In CDCl$_3$ conformation **A** (Figure 2), with
the three substituents in a pseudoaxial position,
20 predominates due to intramolecular hydrogen bonding
between the C1-OH and C3-OTBDMS groups, while in DMSO-d_6
it adopts conformation **B**. This reflects the much lower
axial-equatorial energy differences in cyclohexenes as
compared to the corresponding cyclohexanes.
25   With intermediate **34** in hand, the base moiety
(adenine) was introduced under Mitsunobu reaction
conditions. Upon treatment of **34** with adenine in the
presence of DEAD and PPh$_3$ in dioxane at room temperature
for 1 day, **35a** was isolated in 66% yield, together with
30 17% of its N_7-isomer **35b** (Figure 11). Complete
deprotection of **35a** using TBAF in THF at room temperature
afforded the desired cyclohexene carbocyclic nucleoside
36 in almost quantitative yield. However, the compound
was contaminated with tetrabutylammonium salts which
35 could not be removed by standard chromatographic
techniques. Recently Parlow et al. described a work-up
procedure to remove tetrabutylammonium salts by the

direct addition to the reaction mixture of mixed ion-
exchange resins Amberlite® 15 and Amberlite® 15 in the Ca^{2+}
form. Applied to the above TBAF reaction a complex
mixture was obtained, giving **36** in low yield. In order to
avoid the use of TBAF, Megron's method (Megron, G.;
Vasquezy, F.; Galderon, G.; Cruz, R.; Gavino, R.; Islas,
G. Synth. Commun. 1998, 26(16), 3021-3027) was used:
compound **35a** was treated with potassium *tert*-butoxide in
DMF at room temperature. However, only a complex,
reaction mixture was obtained, due to the strong basic
character of the reaction conditions. Finally **35a** was
treated with a 3:1 mixture of TFA and H_2O at room
temperature, which smoothly gave **36** in 54% overall yield
starting from **34**. According to our experience, this is
the best procedure to cleave TBDMS ethers of this type of
compound. Finally, **36** was purified by reversed-phase HPLC
for analysis and determination of biological activity.

The above intermediate 36 (Figure 11) gave the
inventors the opportunity to obtain as yet 2a (B =
adenine) in enantiopure form via reduction of the double
bond. Thus, 36 was hydrogenated using H2 under
atmospheric pressure in the presence 10% Pd on carbon in
MeOH at room temperature to afford D-2a in 75% yield. The
spectral data of D-2a were superimposable with those of a
DL mixture of 2a. The enantiomeric purity of D-2a was
examined by HPLC on a chiral column. The separation of a
DL mixture of 2a together with the HPLC profile of D-2a
synthesized by the above approach is depicted in
reference 3c. Its enantiomeric purity proved 99%, at the
same time establishing the high enantiomeric purity of
36.

The inventors have developed an
enantioselective approach towards the synthesis of
cyclohexene carbocyclic nucleosides starting from (R)-
carvone **4**. The synthetic methodology makes use of a
Mitsunobu reaction as the key step to introduce the
heterocyclic base moiety. The reaction proved to be
efficient as well as chemo- and stereoselective, while

the commonly applied palladium-mediated coupling strategy
was unsuccessful. ^{1}H NMR and computation results show that
in solution the synthesized adenine derivative **36** exists
predominantly in a ^{3}H$_2$ half-chair conformation with the
5 adenine base orienting in a pseudoaxial position. The
energy difference between ^{3}H$_2$ and ^{2}H$_3$ is, however, low.
This compound may therefore be considered as a good mimic
of a furanose nucleoside, showing two low energy
conformations with a preference for the "3'-endo
10 conformation". This is also the preferred conformation of
a hexitol nucleoside, in the ^{1}C$_4$ conformation. Moreover,
the inventors theorize that the easy interconversion
among both conformers might be a factor for antiviral
activity.
15

Experimental (2)

**(1R,3S,5R)-5-Benzyloxy-3-(*tert*-butyldimethylsilyloxy)-2-
methylenecyclohexanol (6c)**
20   A solution of 2,2,6,6-tetramethylpiperidine
(TMP, 27.3 mL, 162 mmol) in dry benzene (80 mL) and dry
toluene (80 mL) was cooled to 0 °C under N$_2$ and a solution
of *n*-BuLi in hexane (1.6 M, 64.8 mL, 162 mmol) was added
dropwise. The resulting mixture was stirred at 0 °C for 10
25 min and a solution of Et$_2$AlCl (1.8 M, 90 mL, 162 mmol) in
toluene was slowly added over a period of 1 hr. The
reaction was stirred for an additional 30 min. A solution
of **5b** (14.1 g, 40.5 mmol) in benzene (30 mL) was added
slowly. The reaction mixture was stirred at 0 °C for 3 h,
30 then poured into an ice-cold NH$_4$Cl solution (300 mL). A 3
N HCl solution was added until a clear emulsion was
obtained. The layers were separated and the aqueous layer
was extracted with EtOAc (3x). The combined organic
layers were washed with H$_2$O and brine, dried over Na$_2$SO$_4$
35 and concentrated. The residue was chromatographed on
silica gel (*n*-hexane-EtOAc 10:1) to give **6c** (10.2 g, 71%)
as a light-yellow oil: ^{1}H NMR (CDCl$_3$) δ 0.09 (s, 6H), 0.92

(s, 9H), 1.90 (m, 4H), 2.69 (d, 1H, J = 7.3 Hz, OH), 4.05
(m, 1H), 4.45 (m, 2H), 4.58 (s, 2H), 5.05 (s, 1H), 5.07
(s, 1H), 7.33 (m, 5H); ^{13}C NMR (CDCl$_3$) δ -5.1 (q), 18.0
(s), 25.7 (q), 40.7 (t), 40.9 (t), 70.4 (d and t,
5 overlapped), 70.8 (d), 71.3 (d), 107.1 (t), 127.5 (d),
128.4 (d), 138.7 (s), 150.7 (s).

(1R,2S,3S,5R)-5-Benzyloxy-3-(tert-butyldimethylsilyloxy)-
2-hydroxymethyl-cyclohexanol (7c) and its epimer 8c

10   To a solution of _0 (10.8 g, 31.03 mmol) in dry
THF (80 mL) at 0 °C under N$_2$ was added slowly a solution
of 9-BBN in THF (0.5 M, 155 mL, 77.58 mmol). The reaction
mixture was slowly warmed up to rt overnight. The
reaction was cooled to 0 °C and treated sequentially with
15 EtOH (30 mL), a 2 N NaOH solution (60 mL) and a 35% H$_2$O$_2$
solution (60 mL) under stirring. The resulting mixture
was stirred at rt for 24 h, then poured into a mixture of
EtOAc (300 mL) and H$_2$O (300 mL). The layers were separated
and the aqueous layer was extracted with EtOAc (3x). The
20 combined organic layers were washed with H$_2$O and brine,
dried over Na$_2$SO$_4$ and concentrated. The crude product was
separated on silica gel (n-hexane-EtOAc 5:1, then 1:1) to
yield **7c** (8.4 g, 74%) and epimer **8c** (2.28 g, 20%) as a
light-yellow oils.

25 **7c**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.09 (2s, 6H), 0.91 (s, 9H),
1.52 (ddd, 1H, J = 13.1, 10.1, 2.8 Hz), 1.54 (ddd, 1H, J
= 13.1, 10.1, 3.1 Hz), 1.69 (tdd, 1H, J = 10.0, 7.5, 4.1
Hz), 2.10 (dt, 1H, J = 13.1, 4.1 Hz), 2.16 (dt, 1H, J =
13.1, 4.1 Hz), 2.71 (s, 1H), 3.11 (s, 1H), 3.78 (dd, 1H,
30 J = 10.1, 7.5 Hz), 3.85 (td, 1H, J = 10.0, 4.2 Hz), 3.86
(m, 1H), 3.97 (br-td, 1H, J = 10.1, 4.1 Hz), 4.04 (br-dd,
1H, J = 10.1, 4.1 Hz), 4.51 (s, 2H), 7.26-7.37 (m, 5H);
^{13}C NMR (CDCl$_3$) δ -5.0 (q), -4.3 (q), 17.8 (s), 25.7 (q),
38.1 (t), 38.4 (t), 53.2 (d), 63.4 (t), 68.0 (d), 69.4
35 (d), 70.3 (t), 72.4 (d), 127.4 (d), 127.6 (d), 128.4 (d),
138.7 (s); LISMS (THGLY): 367 (M+H)$^+$; HRMS calcd for
C$_{20}$H$_{35}$O$_4$Si (M+H)$^+$ 367.2305, found 367.2341.

8c: ^{1}H NMR (CDCl$_3$) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.85 (s, 9H), 1.40-1.87 (m, 3H), 2.25 (dm, 1H, J = 13.2 Hz), 2.48 (dm, 1H, J = 13.2 Hz), 3.69 - 4.20 (m, 6H), 4.33 (m, 1H), 4.53 (d, 1H, J = 11.7 Hz), 4.62 (d, 1H, J = 11.7 Hz), 57.33 (m, 5H), 8.79 (s, 1H); ^{13}C NMR (CDCl$_3$) δ -5.6 (q), -5.0 (q), 21.9 (s), 25.5 (q), 39.2 (2t, overlapped), 45.9 (d), 61.3 (t), 69.0 (d), 69.4 (d), 70.4 (t), 70.8 (d), 127.6 (d), 127.7 (d), 128.4 (d), 138.6 (s); LISMS (THYLY): 367 (M+H)$^+$; HRMS calcd for C$_{20}$H$_{35}$O$_4$Si (M+H)$^+$ 10367.2305, found 367.2335.

(1R,2R,3S,5S)-5-Benzyloxy-3-(*tert*-butyldimethylsilyloxy)-2-(*tert*-butyldimethylsilyloxy methyl)cyclohexanol (29).

To a solution of **7c** (2.5 g, 6.83 mmol) in DMF (50 mL) at rt were added imidazole (930 mg, 13.66 mmol) and TBDMSCl (1.23 g, 8.2 mmol) in portions. The reaction was stirred at rt overnight and quenched with ice. The resulting mixture was evaporated to remove DMF and the residue was partitioned between EtOAc and H$_2$O. The layers were separated and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were washed with H$_2$O and brine, dried over Na$_2$SO$_4$ and concentrated. The residue was chromatographed on silica gel (*n*-hexane-EtOAc 5:1) to yield **29** (2.28 g, 70%) as a light-yellow oil: ^{1}H NMR (CDCl$_3$) δ 0.05, 0.06, 0.09 (3s, 12H), 0.89, 0.91 (2s, 18H), 1.53 (m, 2H), 1.72 (qd, 1H, J = 9.5, 4.4 Hz), 2.11 (m, 2H), 3.67 (t, 1H, J = 9.5 Hz), 3.78 (td, 1H, J = 9.5, 4.4 Hz), 3.87 (m, 1H), 4.01 (m, 1H), 4.16 (dd, 1H, J = 9.5, 4.4 Hz), 4.46 (d, 1H, J = 15.2 Hz), 4.48 (d, 1H, J = 15.2 Hz), 7.33 (m, 5H); ^{13}C NMR (CDCl$_3$) δ -5.7 (q), -5.1 (q), -4.3 (q), 17.8, 18.0 (2s), 25.7 (2q), 37.0 (t), 38.4 (t), 52.2 (d), 66.2 (t), 67.2 (d), 70.1 (t and d overlapped), 72.4 (d), 127.3 (d), 127.4 (d), 128.4 (d), 138.9 (s); LISMS (GLY): 481 (M+H)$^+$; HRMS cald for 35C$_{26}$H$_{49}$O$_4$Si$_2$ (M+H)$^+$ 481.3169, found 481.3199.

(1R,2R,3S,5S)-5-Benzyloxy-2-(*tert*-

butyldimethylsilyloxymethyl)-3-(tert-butyldimethyl-
silyoxy)-1-methanesulfonyloxy-cyclohexane (30)

To a solution of **29** (5.4 g, 11.25 mmol) in
CH_2Cl_2 (120 mL) at 0 °C was added triethylamine (7.8 mL,
556.25 mmol), followed by dropwise addition of MsCl (1.3
mL, 16.87 mmol). The reaction was stirred at 0 °C for 1h
and treated with ice. The resulting mixture was separated
and the aqueous layer was extracted with CH_2Cl_2 (2x). The
combined organic layers were washed with a diluted HCl
solution, H_2O and brine, dried over Na_2SO_4 and
concentrated. The residue was chromatographed on silica
gel (n-hexane-EtOAc 5:1) to afford **30** (5.81 g, 92%) as a
white solid: mp 100-101 °C; ^1H NMR ($CDCl_3$) δ 0.08 (2s,
12H), 0.89 (s, 9H), 0.90 (s, 9H), 1.43 (ddd, 1H, J =
13.9, 10.0, 2.8 Hz), 1.62 (tt, 1H, J = 10.2, 2.0 Hz),
1.71 (ddd, 1H, J = 12.8, 10.6, 2.2 Hz), 2.24 (br-d, 1H, J
= 13.9 Hz), 2.69 (br-d, 1H, J = 12.8 Hz), 3.01 (s, 3H),
3.74 (dd, 1H, J = 9.9, 2.2 Hz), 3.89 (m, 1H), 3.91 (dd,
1H, J = 9.9, 1.8 Hz), 4.19 (td, 1H, J = 10.0, 4.7 Hz),
4.45 (d, 1H, J = 12.0 Hz), 4.57 (d, 1H, J = 12.0 Hz),
5.13 (td, 1H, J = 10.6, 4.8 Hz), 7.33 (m, 5H); ^{13}C NMR
($CDCl_3$) δ -5.6 (q), -5.3 (q), -4.6 (q), -3.7 (q), 17.9
(s), 25.8 (q), 35.5 (t), 38.5 (t), 38.8 (q), 51.8 (d),
56.9 (t), 65.1 (d), 70.1 (t), 72.0 (d), 77.5 (d), 127.4
(d), 128.4 (d), 138.5 (s); LISMS(GLY/NBA) 559 (M+H)$^+$; HRMS
calcd for $C_{27}H_{51}O_6SSi_2$ (M+H)$^+$ 559.2945, found 559.2979;
Anal. Calcd for $C_{27}H_{51}O_6SSi_2$: C 58.02, H 9.02; Found: C
57.96, H 8.82.

30 (1*S*,3*R*,4*R*,5*S*)-4-*tert*-Butyldimethylsilyloxymethyl-5-*tert*-
butyldimethylsilyloxy-3-methanesulfonyloxy-cyclohexanol
(**31**)

A mixture of **30** (3.5 g, 6.27 mmol), Pd/C (10 %,
4.4 g) and $HCOONH_4$ (2.2 g) in MeOH (100 mL) was refluxed
and 2 x 1.1 g of $HCOONH_4$ were added every 3 h interval.
The reaction was refluxed until all the starting material
was consumed (total 14 h). After cooling to rt, the

reaction mixture was filtered through Celite® and the
residue was washed with CH$_2$Cl$_2$ (3x). The filtrate was
concentrated to afford crude **31** (2,83 g, 97%) as a white
solid, which was used as such for the next step: mp 135-
5137 °C; ^{1}H NMR (CDCl$_3$) δ 0.08, 0.09 (2s, 12H), 0.89 (s,
9H), 0.92 (s, 9H), 1.43 - 1.68 (m, 3H), 1.83 (ddd, 1H, J
= 13.2, 10.6, 2.8 Hz), 2.07 (br-d, 1H, J = 13.2 Hz), 2.44
(br-d, 1H, J = 13.2 Hz), 3.02 (s, 3H), 3.72 (dd, 1H, J =
10.0, 2.4 Hz), 3.90 (dd, 1H, J = 10.0, 2.4 Hz), 4.19 (td,
101H, J = 10.6, 4.1 Hz), 4.26 (m, 1H), 5.14 (td, 1H, J =
10.6, 4.7 Hz); ^{13}C NMR (CDCl$_3$) δ -5.6 (q), -5.3 (q), -4.7
- (q), -3.8 (q), 17.9 (s), 25.8 (q), 38.8 (q), 38.9 (t),
40.8 (t), 51.7 (d), 57.1 (t), 64.9 (d), 65.5 (d), 77.3
(d); LISMS (GLY/NBA) 469 (M+H)$^+$; HRMS calcd for C$_{20}$H$_{45}$O$_6$SSi$_2$
15(M+H)$^+$ 469.2475, found 469.2453; Anal. Calcd for
C$_{20}$H$_{45}$O$_6$SSi$_2$: C 51.24, H 9.46; Found: C 51.24, H 9.36.

(4R,5S)-4-*tert*-Butyldimethylsilyloxymethyl-5-tert-
butyldimethylsilyloxy-cyclohex-2-en-1-one (**33**)
20   A mixture of crude **31** (2.83 g, 6.27 mmol) and
MnO$_2$ (13.6 g, 156.8 mmol) in dry CH$_2$Cl$_2$ (100 mL) was
stirred vigorously at rt for 21 h. The reaction mixture
was filtered through Celite® and washed with CH$_2$Cl$_2$. The
filtrate was concentrated and the residue was
25chromatoghraphed on silica gel (*n*-hexane-EtOAc 5:1, then
1:2) to yield starting material **30** (1.56 g, 53 %) and
enone **33** (920 mg, 40% over two steps) as a light-yellow
oil (solid upon storing in the refrigerator): ^{1}H NMR
(CDCl$_3$) δ 0.07 (s, 12H), 0.89 (s, 18H), 2.50 (m, 1H), 2.46
30(dd, 1H, J = 16.1, 10.6 Hz), 2.72 (dd, 1H, J = 16.1, 4.8
Hz), 3.73 (dd, 1H, J = 9.9, 5.6 Hz), 3.85 (dd, 1H, J =
9.9, 4.4 Hz), 4.09 (ddd, 1H, J = 10.6, 8.1, 4.8 Hz), 6.06
(dd, 1H, J = 10.2, 2.6 Hz), 6.88 (dd, 1H, J = 10.2, 2.6
Hz); ^{13}C NMR (CDCl$_3$) δ -5.6 (q), -5.5 (q), -5.1 (q), -4.4
35(q), 17.8 (s), 18.2 (s), 25.6 (q), 25.8 (q), 47.1 (t),
48.0 (d), 61.8 (t), 68.0 (d), 130.2 (d), 150.6 (d), 199.0
(s); LISMS (THGLY/NBA) 371 (M+H)$^+$; HRMS calcd for

$C_{19}H_{39}O_3Si_2$ $(M+H)^+$ 371.2438, found 371.2432.

(1R,4R,5S)-5-(tert-Butyldimethylsilyloxy)-4-(tert-
butyldimethylsilyloxymethyl)-cyclohex-2-en-1-ol (34)

5   To a solution of **33** (920 mg, 2.49 mmol) in MeOH
(35 mL) at rt under N_2 was added $CeCl_3.7H_2O$ (1.39 g, 3.73
mmol). The mixture was stirred for 0.5 h and a clear
solution was obtained. $NaBH_4$ (113 mg, 2.99 mmol) was added
in portions and H_2 evolved. The reaction mixture was
10 stirred for 1 h and quenched with H_2O. The mixture was
stirred for 15 min and concentrated. The residue was
diluted with EtOAc, washed with H_2O and brine, dried over
Na_2SO_4 and concentrated. The residue was chromatographed
on silica gel (n-hexane-EtOAc 10:1) to give **34** (844 mg,
1591%) as a colourless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 0.04
(s, 3H), 0.05 (s, 3H), 0.10 (s, 3H), 0.11 (s, 3H), 0.89
(s, 9H), 0.90 (s, 9H), 1.94 (ddd, 1H, J = 13.7, 5.3, 3.9
Hz), 1.99 (ddd, 1H, J = 13.7, 4.5, 2.6 Hz), 2.36 (m, 1H),
2.94 (d, 1H, J = 9.8 Hz), 3.38 (dd, 1H, J = 10.1, 7.8
20 Hz), 3.56 (dd, 1H, J = 10.1, 5.0 Hz), 4.09 (pseudo sext,
1H, J = 9.8, 4.5, 4.0, 3.9 Hz), 4.20 (pseudo pent, 1H, J
= 5.3, 3.4, 2.6 Hz), 5.61 (dd, 1H, J = 10.0, 3.9 Hz),
5.95 (ddd, 1H, J = 10.0, 4.0, 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ -
5.5 (q), -5.4 (q), -4.9 (q), -4.8 (q), 18.0 (s), 18.3
25 (s), 25.8 (q), 25.9 (q), 35.6 (t), 46.5 (d), 63.5 (t),
64.8 (d), 67.7 (d), 127.0 (d), 131.1 (d); LISMS
(THGLY/NBA) 373 $(M+H)^+$; HRMS calcd for $C_{19}H_{40}O_3Si_2$ $(M+H)^+$
373.2594, found 373.2626; Anal. Calcd for $C_{19}H_{40}O_3Si_2$: C
61.23, H 10.82; Found: C 61.34, H 10.83.
30
9-[(1S,4R,5S)-5-(tert-Butyldimethylsilyloxy)-4-(tert-
butyldimethylsilyloxymethyl)-2-cyclohexenyl]adenine (35a)
         To a mixture of **34** (660 mg, 1.774 mmol),
adenine (480 mg, 3.55 mmol) and PPh_3 (931 mg, 3.55 mmol)
35 in dry dioxane (20 mL) under N_2 at rt was added a solution
of DEAD (565 μL, 3.55 mmol) in dry dioxane (10 mL) over a
period of 45 min. The reaction mixture was stirred at rt

overnight, concentrated and the residue was chromatographed on silica gel (CH$_2$Cl$_2$-MeOH 50:1, then 20:1) to yield crude **35a** (960 mg) as a yellow foam: ^{1}H NMR (CDCl$_3$) δ -0.12 (s, 3H), -0.06 (s, 3H), 0.10 (s, 3H), 0.11 (s, 3H), 0.83 (s, 9H), 0.94 (s, 9H), 2.01 - 2.25 (m, 2H), 2.32 (m, 1H), 3.73 (dd, 1H, J = 9.9, 4.8 Hz), 3.82 (dd, 1H, J = 9.9, 4.4 Hz), 3.97 (ddd, 1H, J = 10.2, 7.0, 4.0 Hz), 5.37 (m, 1H), 5.73 (s, 2H), 5.88 (ddd, 1H, J = 9.9, 3.7, 2.5 Hz), 6.06 (ddd, 1H, J = 9.9, 2.2, 1.1 Hz), 7.86 (s, 1H), 8.39 (s, 1H); ^{13}C NMR (CDCl$_3$) δ -5.5 (q), -5.4 (q), -5.0 (q), -4.6 (q), 17.8 (s), 18.3 (s), 25.6 (q), 25.9 (q), 36.5 (t), 47.2 (d), 49.6 (d), 62.9 (t), 64.5 (d), 120.2 (s), 124.4 (d), 134.9 (d), 139.9 (d), 149.8 (s), 153.0 (d), 155.5 (s); LISMS (THGLY/NBA) 490 (M+H)$^+$; HRMS calcd for C$_{24}$H$_{44}$N$_5$O$_2$Si$_2$ (M+H)$^+$ 490.3034, found 490.3058.

9-[(1S,4R,5S)-5-Hydroxy-4-hydroxymethyl-2-cyclohexenyl]adenine (36)

Crude **35a** was treated with TFA-H$_2$O (3:1, 40 mL) at rt overnight. The reaction mixture was concentrated and co-evaporated with toluene (2x). The residue was chromatographed on silica gel (CH$_2$Cl$_2$-MeOH 20:1, then 5:1) to afford **36** (149 mg, 54% over two steps):

Mp 90 - 92 °C; ^{1}H NMR (CD$_3$OD) δ 2.01-2.33 (m, 3H), 3.80 (d, 2H, J = 4.8 Hz), 3.84 (m, 1H), 5.33 (m, 1H), 5.94 (ddd, 1H, J = 9.9, 3.7, 2.6 Hz), 6.13 (ddd, 1H, J = 9.9, 2.5, 1.4 Hz), 8.09 (s, 1H), 8.21 (s, 1H); ^{13}C NMR (CD$_3$OD) δ 37.3 (t), 47.9 (d), 51.1 (d), 63.1 (t), 64.7 (d), 120.6 (s), 125.3 (d), 136.1 (d), 141.6 (d), 150.4 (s), 153.7 (d), 157.5 (s); UV λ$_{max}$ (MeOH) = 260 nm; LISMS (THGLY/NBA) 262 (M+H)$^+$; HRMS calcd for C$_{12}$H$_{16}$N$_5$O$_2$ (M+H)$^+$ 262.1304, found 262.1359; Anal. Calcd for C$_{12}$H$_{16}$N$_5$O$_2$.0.7H$_2$O: C 52.62, H 6.04, N 25.57; Found: C 52.62, H 5.95, N 25.77.

9-[(1R,3S,4R)-3-Hydroxy-4-hydroxymethyl-cyclohexanyl]adenine (2a)

A mixture of **36** (45 mg, 0.17 mmol) and Pd/C
(10%, 40 mg) in MeOH (5 mL) was stirred under H_2 at rt for
24 h. The reaction mixture was cooled to rt and filtered
through Celite® and washed with MeOH. The filtrate was
5concentrated and theireÿidue was purified by reversed-
phase HPLC (5% CH_3CN in H_2O) to yield **2a** (35 mg, 78%) as a
white foam: ^1H NMR (CD_3OD) δ 1.71 (m, 1H), 1.87-2.18 (m,
5H), 2.39 (m, 1H), 3.69 (dd, 1H, J = 14.0, 7.3 Hz), 3.74
(dd, 1H, J = 14.0, 6.9 Hz), 4.12 (m, 1H), 4.87 (m, 1H,
10overlapped with HOD), 8.18 (s, 1H), 8.21 (s, 1H); ^{13}C NMR
(CD_3OD) δ 22.6 (t), 28.7 (t), 36.1 (t), 53.6 (d), 51.9
(d), 63.3 (t), 68.4 (d), 120.4 (s), 141.1 (d), 150.6 (s),
153.5 (d), 157.4 (s); LISMS (THGLY/NBA) 264 $(M+H)^+$; HRMS
calcd for $C_{12}H_{18}N_5O_2$ $(M+H)^+$ 264.1460, found 264.1449.

15   Figure 1. Mechanism of Pd (0) coupling reaction
which may yield the desired compound C.

          Figure 2. ^1H NMR experiment demonstrates the
solvent-dependent conformational equilibrium of compound
34.

20

          Figure 8 (a) TBDMSCl (1.2 eq), imidazole (2
eq), DMF, r.t., 48% starting from **6a**; (b) MsCl, Et_3N,
25CH_2Cl_2, 0 °C, 93 %; (c) DBU, toluene, or KOH, H_2O / THF;
(d) DEAD, PPh_3, THF; (e) I_2, PPh_3, imidazole, toluene,
reflux, 34%; (f) DBU, toluene, reflux, 68%.

          Figure 9 (a) $(CH_3)_2C(OCH_3)_2$, PPTS, acetone/THF
(1:2), r.t., 94%; (b) Pd-C (10%), $HCOONH_4$, MeOH, reflux,
30100%; (c) PDC, CH_2Cl_2, r.t., 94%; (d) TBAF, THF, r.t.; (e)
KF, 18-Crown-6, THF, r.t., 62% **19**; (f) $CeCl_3.7H_2O$, $NaBH_4$,
MeOH, 90%; (g) PPh_3, DEAD, AcOH, THF; (h) Ac_2O, DMAP,
CH_2Cl_2, 0 °C, 95%; (i) Adenine, NaH, $Pd(PPh_3)_4$, DMF/THF;
(j) PPTS, MeOH, r.t., 59%; (k) Bz_2O, DMAP, CH_2Cl_2, 0 °C,
3595%.

          Figure 10 (a) TBDMSCl (1.2 eq), imidazole (1.5
eq), DMF, r.t., 70%; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 100%;

(c) Pd-C(10%), HCOONH₄, MeOH, reflux, 76%; (d) MnO₂,
CH₂Cl₂, r.t., 48% and 47% recovery of **31**; (e) NaBH₄,
CeCl₃.7H₂O, MeOH, 0 °C → r.t., 100%.

5

Sodium salt of Ethyl-β-hydroxyacrylate sodium salt   (1)

10
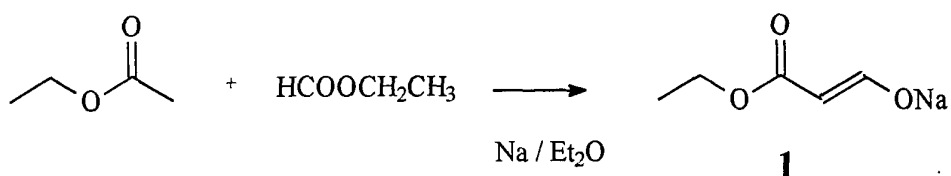
15   In a 1 L three necked flask, under inert
atmosphere and equipped with an addition funnel, a well
stirred suspension of fresh sodium pieces (23.0 g, 1.0
mol) in dry diethyl ether (400 mL) was prepared. A
mixture of ethyl acetate (88.0 g, 1.0 mol) and ethyl
20 formate (74.0 g, 1.0 mol) was added dropwise over a
period of 45 minutes. Stirring was continued for an
additional 14 hours using an ice bath, avoiding the
reaction to become too vigorous. The resulting suspension
was kept in the refrigerator for 8 hours, after which it
25 was filtered, washed with dry diethyl ether (100 mL) and
dried *in vacuo* to obtain **1** as a pale yellow solid (85.0
g, 61% yield).

Ethyl β-acetoxyacrylate   [cis (2') + trans (2)]

EPO - DG 1

0 7. 12. 2000

5   (54)

$C_7H_{10}O_4$
Exact Mass: 158.1
Mol.Wt.: 158.2
C, 53.1; H, 6.37; O, 40.47
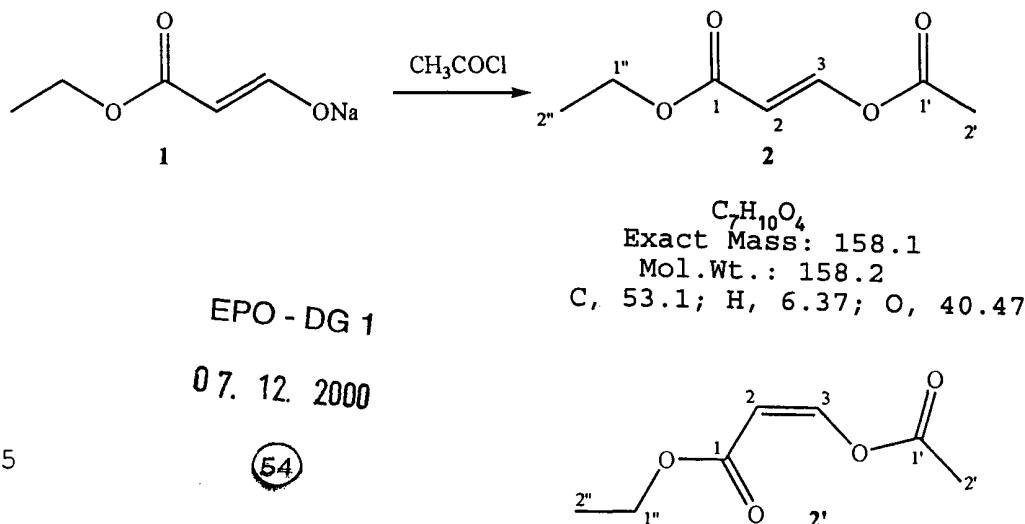
In a 2 L flask on an ice-bath, under an inert
10 atmosphere, a well stirred suspension of the sodium salt
1 (85.0 g, 616 mmol) was prepared in dry diethyl ether
(850 mL), to which acetyl chloride (52.9 mL, 58.2 g, 739
mmol) was added dropwise over 15 minutes. The mixture was
stirred for an additional 6 hours, after which it was
15 neutralized with a saturated aqueous solution of NaHCO₃
(250 mL). Both phases were separated and the aqueous
phase was extracted with diethyl ether (5 x 200 mL). The
combined organic phases were dried over Na₂SO₄, filtered
and evaporated in vacuo to obtain a residual red oil
20 (59.1 g). Distillation in vacuo (70 °C, 1 Torr aprox.)
afforded a mixture of 2 and 2', as a pure colorless oil
(36.5 g, 23 % yield in two steps) with a cis / trans
proportion of 4:10 (¹H-NMR).

25 analytical data of 2 (trans isomer)

¹H-NMR (200 MHz, CDCl₃) δ: 1.30 (t, J = 7.2 Hz, 3H, 2"-H),
2.22 (s, 3H, 2'-H), 4.21 (q, J = 7.2 Hz, 2H, 1"-H), 5.72
(d, J = 12.6 Hz, 1H, 2-H), 8.30 (d, J = 12.6 Hz, 1 H, 3-

H).

<u>analytical data of 2' (*cis* isomer)</u>

^{1}H-NMR (200 MHz, CDCl$_3$) δ: 1.30 (t, *J* = 7.2 Hz, 3H, 2"-H),
2.28 (s, 3H, 2'-H), 4.20 (q, *J* = 7.4 Hz, 2H, 1"-H), 5.30
5 (d, *J* = 7.3 Hz, 1H, 2-H), 7.54 (d, *J* = 7.3 Hz, 1H, 3-H).

<u>Isomerization of the *cis/trans* mixture (2/2') to ethyl
trans-β-acetoxyacrylate (2)</u>

10

2   2'
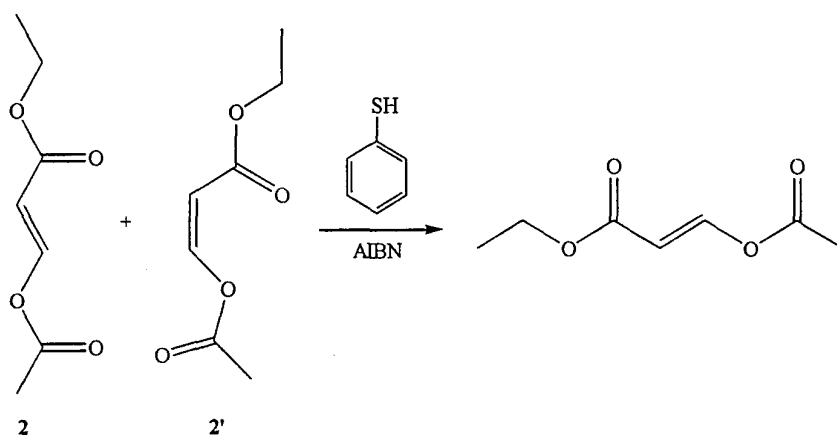
15

In a well-closed flask, under magnetic
stirring, the 2/2' mixture obtained from several
operations (52.5 g, 39:100 *cis / trans* proportion, 332
mmol) was treated with thiophenol (16.3 ml, 17.5 g, 159
20 mmol) and 2,2'-azobis(2-methylpropionitrile) (AIBN, 8.31
g, 50.6 mmol) and the mixture was heated to 80 ºC for 2.5
hours. The flask was cooled for 2 hours and the crude was
diluted with ethyl acetate (400 mL) and washed with an
aqueous solution of NaOH 0.01 N (400 mL). The organics
25 were dried over Na$_2$SO$_4$, filtered and evaporated *in vacuo*
to leave a pale yellow oil. Distillation *in vacuo* (53 ºC,
0.5-1.0 Torr) afforded 2 (55.8 g, quantitative yield)
with a *cis / trans* proportion of 3:97 (^{1}H-NMR), slightly

contaminated with aromatic sulphurated products.

Preparation of (E)-1-methoxy-3-trimethylsilyloxy-1,3-
butadiene (4)

5

3   4
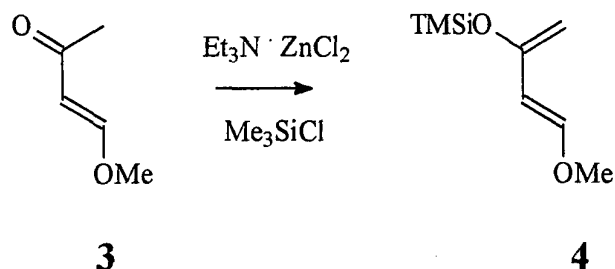
10

Under an inert atmosphere anhydrous ZnCl₂ (2.52
g, 18.5 mmol) was slowly added under magnetic stirring to
triethylamine (distilled over KOH) (145 g, 200 mL, 1.43
mol). The mixture was stirred for 1 hour at room
15 temperature until a fine suspension was obtained. A
solution of compound 3 (63.1 g, 630 mmol) in toluene (190
mL) was then added over 5 min, followed by gradual
addition of chlorotrimethylsilane (137.0 g, 160 mL, 1.26
mol) over a period of 10 min. An exothermic reaction was
20 noted. After 30 minutes, the temperature was raised to 40

°C and stirring was continued overnight. Following
cooling, the reaction mixture was diluted with diethyl
ether (1 L), filtered and washed with diethyl ether (4 x
100 mL). The combined filtrate and ether washings were
25 concentrated *in vacuo* to leave a brown oil. Distillation
trough a Vigreux column (52 °C, 1.0 Torr) afforded
compound 4 in a middle cut, slightly contaminated with
compound 3 [80.1 g, 91% purity (¹H-NMR), 67% yield of 4].

NOTE: compound 4 is commercially available (e.g.
30 Aldrich®).

analytical data of **4**.

^{1}H-NMR (200 MHz, CDCl$_3$) δ: 0.23 [s, 9H, OSi(CH$_3$)$_3$], 3.59 (s, 3H, OCH$_3$), 4.09 (d, J = 8.2 Hz, 2H, 4-H), 5.35 (d, J = 512.2 Hz, 1H, 2-H), 6.83 (d, J = 12.2 Hz, 1H, 3-H).

Diels-Alder adduct of 2 and 4:

5-O-acetyl-4-ethoxycarbonyl-3-O-methyl-1-O-trimethylsilyl-cyclohexen-1,3,5-triol

10 [(±) 5a + 5b]
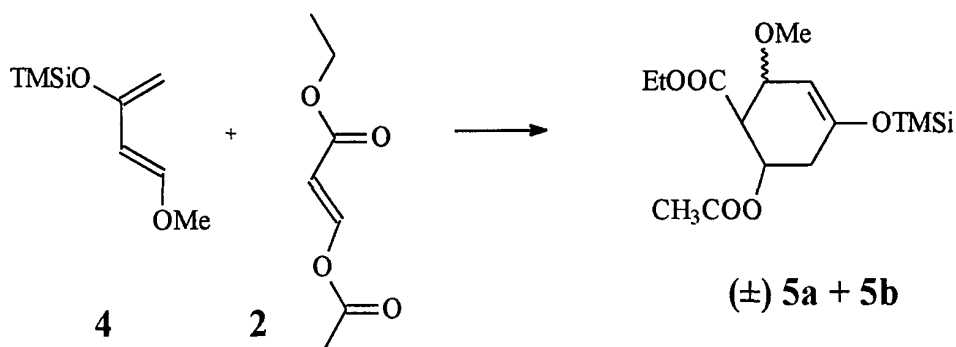
In a 250 mL round bottom flask a small amount of hydroquinone (372 mg) was added under magnetic stirring to a mixture of the Danishefky diene [**4**, 72.9 g, 91% purity (^{1}H-NMR), 385 mmol] and 2 (55.8 g, cis/trans 3:97, 353 mmol) and the mixture was heated at 180 °C for 1.5 hours. An additional amount of 372 mg of hydroquinone was added and the reaction mixture was distilled in vacuo (94 °C, 3.0 x 10^{-} mm Hg) to afford a slightly contaminated mixture of (±) **5a** + **5b** (72.0 g, 62% yield), with the substituents at the 4- and 5-position oriented

in *trans*.

NOTE: Upon increasing the temperature of the
distillation bath to 170 °C or higher, different
5 quantities of the phenolic derivative **6** are obtained. The
phenol derivative **6** likewise is obtained as the main
isolated product when purification on silica gel is
undertaken. The addition of fresh hydroquinone right
before the distillation seems to avoid the formation of
10 **6**. Compound **6** could not detected by NMR when using this
improved procedure.

representative analytical data for the major derivative

(±) **5a**   (substituents at 3 and 4 in trans)

15 ^{1}H NMR (CDCl$_3$) δ 0.21 (s, 9H), 1.27 (t, 3H, J = 7.3 Hz),
2.01 (s, 3H), 2.19 (m, 1H), 2.55 (dd, 1H, J = 16.7, 5.5
Hz), 2.77 (dd, 1H, J = 11.4, 8.4 Hz), 3.31 (s, 3H), 4.20
(m, 2H), 4.35 (dm, 1H, J = 8.4 Hz), 4.94 (t, 1H, J = 2.2
Hz), 5.13 (ddd, 1H, J = 11.0, 9.2, 5.9 Hz).

20 ^{13}C NMR (CDCl$_3$) δ 0.06 (q), 14.2(q), 20.8 (q), 35.4 (t),
51.1 (t), 55.4 (q), 60.9 (t), 68.8 (d), 76.5 (d), 103.3
(d), 149.3 (s), 170.0 (s), 172.2 (s).

Ethyl p-hydroxybenzoate (**6**) : analytical data

25

6
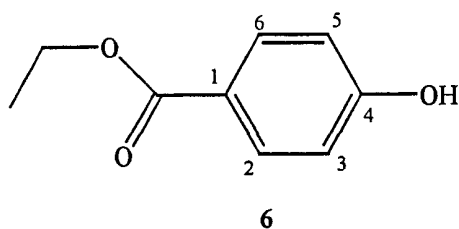
^{1}H-NMR (200 MHz, CDCl$_3$) δ: 1.39 (t, J = 7.2 Hz, 3H, -
5CH$_2$CH$_3$), 4.37 (q, 2H, -CH$_2$CH$_3$), 6.91 [d, J = 8.9 Hz, 2H,
3(5)-H], 7.36 (broad s, 1H, 4-OH), 7.96 [d, J = 8.9 Hz,
2H, 2(6)-H].

^{13}C-NMR (50.3 MHz, CDCl$_3$) δ: 14.1 (-CH$_2$CH$_3$), 61.1 (-CH$_2$CH$_3$),
115.3 [C3(5)], 122.2 (C1), 132.0 [C2(6)], 160.7 (C4),
10167.6 (C=O).

(±) 4-hydroxymethyl-cyclohex-2-en-1,5-diol (7a)

15
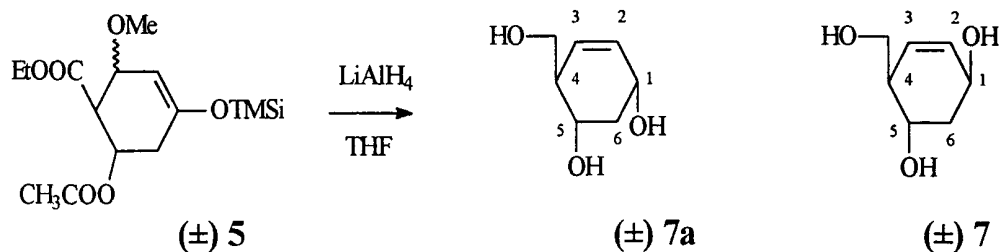
In a 1L three necked bottom flask on a ice-NaCl
bath, a suspension of LiAlH$_4$ (25.0 g, 658 mmol) in dry THF
(220 mL) was prepared under magnetic stirring in an inert
atmosphere. To this cooled suspension, a solution of the
20impure mixture of **5a** + **5b** (27.2 g) in dry THF (85 mL) was
added dropwise during 30 minutes. After stirring at 0 °C

for 2 hours, the reaction was continued at room
temperature for an additional 19 hours. The mixture
became very viscous and was diluted with dry THF (110
mL). After cooling on an ice-NaCl bath, the mixture was
5 treated consecutively and very carefully (equipping the
system with a good gas-exit) with water (25 mL), stirring
for 15 minutes, with 15% aqueous NaOH (25 ml), stirring
for 15 minutes more, and finally with more water (75 ml).
A dry granular precipitate was produced, which was easy
10 to filter and wash. The suspension was stirred for 30
minutes and the precipitate was filtered over a layer of
Celite®, and washed with water (5 x 100 mL) and ethyl
acetate (3 x 100 mL). Both phases were separated and the
aqueous phase was washed with ethyl acetate (3 x 100 mL).
15 The aqueous phase was evaporated to dryness to give a
brown gummy residue (21.1 g) which was filtered through a
silica gel column (210 g) packed with ethyl acetate,
eluting with mixtures of EtOAc/MeOH of increasing
polarity. The title product **7a** was isolated as a pale
20 yellow oil (3.55g, 24.7 mmol, 30%), preceded by its
epimer **7b** (6.44g) as an impure mixture.

<u>analytical data of **7a**</u>

^{1}H NMR (CDCl$_3$ + DMSO-d_6) δ 1.48 (td, 1H, J = 11.3, 9.2
Hz), 2.02 - 2.23 (m, 2H), 3.35 (m, 1H), 3.61 (m, 2H),
25 3.75 (d, 1H, J = 5.8 Hz, OH), 4.01 (t, 1H, J = 4.6 Hz,
OH), 4.11 (m, 1H), 4.20 (d, 1H, J = 3.3 Hz, OH), 5.25
(dt, 1H, J = 9.9, 2.0 Hz), 5.58 (dm, 1H, J = 9.9 Hz).

^{13}C NMR (CDCl$_3$ + DMSO-d_6) δ 39.7 (t), 45.8 (d), 65.2 (t),
65.9 (d), 69.4 (d), 126.1 (d),
30 132.4 (d).

LISMS (THGLY/NaOAc) 167 (M+Na)$^+$ (C$_7$H$_{12}$O$_3$)

Data of **7b**:

^{1}H NMR (DMSO-d_6) δ 1.37 (td, 1H, J = 11.7, 9.9 Hz), 1.92 -
2.10 (m, 2H), 3.24 - 3.45 (m, 2H), 3.63 (dt, 1H, J =

10.2, 4.4 Hz), 4.07 (m, 1H), 4.49 (t, 1H, J = 5.3 Hz, OH), 4.63 (d, 1H, J = 5.1 Hz, OH), 4.70 (d, 1H, J = 5.9 Hz, OH), 5.52 (d, 1H, J = 11.0 Hz), 5.57 (d, 1H, J = 11.0 Hz).

5 ^{13}C NMR (DMSO-d_6) δ 42.0 (t), 47.2 (d), 62.2 (t), 65.9 (d), 66.3 (d), 127.7 (d), 132.8 (d).

LISMS (THGLY/TFA) 145 (M+H)[+] ($C_7H_{12}O_3$)

Formation of the ketal of 7a:

10 **(±) 5,7-O-benzylidene-4-hydroxymethyl-cyclohex-2-en-1,5-diol (8)**
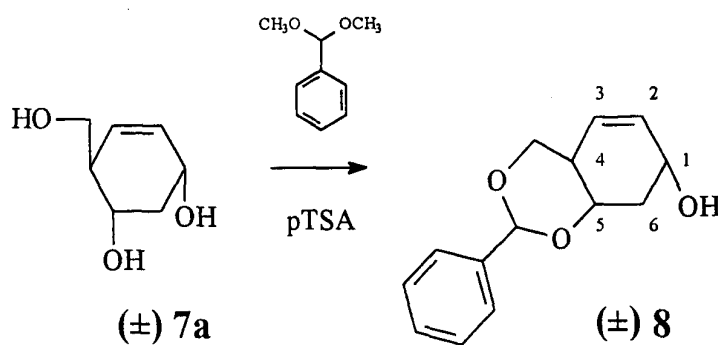
15   Under an inert atmosphere benzaldehyde dimethyl acetal (6.2 mL, 41.2 mmol) and p-toluenesulfonic acid monohydrate (300 mg, 1.58 mmol) were added to a solution of (±)7a (4.49 g, 31.1 mmol) in dry dioxane (140 mL). The mixture was stirred at room temperature for 24 hours and 20 subsequently poured into ethyl acetate (100 mL), washed with water (250 mL), dried over Na_2SO_4 and concentrated to give a white residue (8.91 g). Chromatographic purification on silica gel (270 g) eluting with mixtures of hexane/EtOAc of increasing polarity afforded the 25 desired product 8 as a white crystalline solid (5.06 g,

70% yield, 80% yield based on recovered **7a**).

The aqueous phase was evaporated to dryness, to recover the starting material **7a** (600 mg, 13 % recovery).

analytical data of **8a**

^{1}H-NMR (500 MHz, CDCl$_3$) δ: 1.60 (d, J = 7.3 Hz, 1H, OH), 1.80 (ddd, 1H, 6-H$_a$), 2.53 (ddd, 1H, 6-H$_e$), 2.60 (m, 1H, 4-H), 3.61 (t, J = 11.2 Hz, 1H, 7-H$_a$), 3.68 (ddd, 1H, 5-H), 4.26 (dd, J = 10.7 and 4.4 Hz, 1H, 7-H$_e$), 4.53 (m, 1H, H-1), 5.42 (ddd, J = 9.7 Hz, 1H, 2-H), 5.59 (s, 1H, PhC$\underline{H}$), 5.74 (ddd, J = 9.8 Hz, 1H, 3-H), 7.31-7.40 and 7.48-7.53 (m, 5H, arom-H).

^{13}C-NMR (500 MHz, CDCl$_3$) δ: 38.6 (C-6), 40.1 (C-4), 68.0 (C-1), 70.7 (C-7), 77.7 (C-5), 102.2 (PhCH), 125.0 (C-2), 126.2 (ar-C$_o$), 128.3 (ar-C$_m$), 129.0 (ar-C$_i$), 132.7 (C-3), 138.1 (ar-C$_p$).

LISMS (GLY/TFA) 233 (M+H)$^+$ (C$_{14}$H$_{16}$O$_3$)

Additional amounts of the desired **8a** can be obtained using the other epimer **7b**, using an oxidation – reduction cycle as outlined below.

Therefore, the crude **7b** (2.3 g, 14.58 mmol) was treated with benzaldehyde dimethyl acetal (3.28 mL, 21.87 mmol) in the presence of p-toluenesulfonic acid monohydrate (PTSA, 138 mg, 0.73 mmol) in 1,4-dioxane (30 mL) at r.t. for two days. Ice was added and the mixture was stirred at r.t. for 0.5 hr and extracted with EtOAc (3x). The combined organic solvents were washed with water and brine, dried over sodium sulfate and concentrated. The residue was purified on silica gel (hexane /EtOAc 1:1) to afford a mixture of **8b** and **8a** (3:1, 1.2 g) as a light yellow solid.

The mixture of **8a/8b** (3:1, 415 mg, 1.79 mmol) and MnO$_2$ (1.56 g, 17.9 mmol, 10 eq) in dry CH$_2$Cl$_2$ (15 mL)

was stirred at rt for 21 hrs. The reaction mixture was
diluted with CH$_2$Cl$_2$ and filtered through Celite. The
filtrate was concentrated and the residue was
chromatographed on silica gel (hexane – EtOAc 2:1) to
5 afford **9** (340 mg, 83%) as a colourless oil.

^{1}H NMR (CDCl$_3$) δ 2.65 (dd, 1H, J = 16.4, 13.1 Hz), 2.83
(m, 1H), 2.95 (dd, 1H, J = 16.4, 4.8 Hz), 3.79 (t, 1H, J
= 11.1 Hz), 4.04 (ddd, 1H, J = 13.1, 9.2, 4.8 Hz), 4.45
(dd, 1H, J = 11.1, 4.8 Hz), 5.63 (s, 1H), 6.13 (dd, 1H, J
10 = 9.9, 2.9 Hz), 6.58 (dd, 1H, J = 9.9, 1.8 Hz), 7.39 (m,
3H), 7.51 (m, 2H).

^{13}C NMR (CDCl$_3$) δ 39.9 (d), 44.3 (t), 69.2 (t), 77.4 (d),
101.7 (d), 126.1 (d), 128.4 (d), 129.2 (d), 132.1 (d),
137.5 (s), 144.9 (d), 196.8 (s).

15 LISMS (NBA) 231 (M+H)$^+$. (C$_{14}$H$_{14}$O$_3$)

Conversion of **9** to **8a**:

To a solution of **9** (340 mg, 1.5 mmol) in MeOH (15 mL) at
rt was addded CeCl$_3$.7H$_2$O (838 mg, 2.25 mmol, 1.5 eq).
20 After stirring at rt for 1 hr, NaBH$_4$ (68 mg, 1.8 mmol, 1.2
eq) was added in portions. The reaction was stirred at rt
for 2 hrs and quenched with crushed ice. The resulting
mixture was stirred at rt for 0.5 hr and concentrated.
The residue was taken into ethyl acetate and washed with
25 water and brine, dried over sodium phosphate and
concentrated. The residue was chromatographed on silica
gel (hexane – EtOAc 5:1 and 1:1) to give **8a** as a white
solid which proved identical to the previous material.

30   The product **8a**, or its analogues, either under
their racemic form, or under the form of their separated
isomers, as represented by the general structure **III**, can
be used for synthesis of cyclohexenyl nucleoside

analogues of general structure **IV**, according to standard
procedures for alkylation of heterocyclic bases. Hereto,
in the general structure **III**, R^1 and R^2 are representing
protecting groups (e.g. R_1, R_2 = $C_6H_5-CH=$), and R^3
5 represents a leaving functionality (e.g. R^3 = SO_2CH_3,
SO_2CF_3, $SO_2C_6H_4CH_3$, $SO_2C_6H_4CH_3$, $SO_2C_6H_4Br$) enabling
nucleophilic substitution reactions, or R^3 represents
hydrogen, to be used in Mitsunobu reactions.

(**III**)   (**IV**)
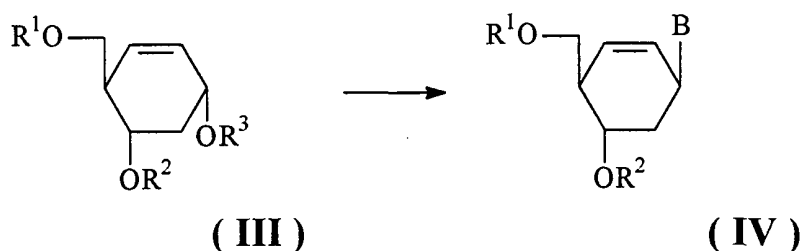
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example:

15 N^2-Benzoyl-9-(5-hydroxy-4-hydroxymethyl-2-
cyclohexenyl)guanine ((±) 11)

To a mixture of (±) **8a** (696 mg, 3 mmol), 2-
amino-6-chloropurine (1.02 g, 6 mmol) and triphenyl
phosphine (PPh$_3$, 1.57 g, 6 mmol) in dry 1,4-dioxane (30
20 mL) was added slowly a solution of DEAD (945 mL, 6 mmol)
in dry 1,4-dioxane (10 mL). The reaction was stirred at
r.t. overnight and concentrated. The residue was taken on
silica gel and chromatographed on silica gel (CH$_2$Cl$_2$ /
MeOH 100:1 and 50:1) to afford the crude **10** (2 g) and the
25 N$_7$-epimer (140 mg) as a white solid.

The crude **10** (2 g) was treated with TFA/H$_2$O
(3:1, 20 mL) at r.t. for 2 days. The reaction mixture was

concentrated and coevaporated with toluene. The residue was chromatographed on silica gel (CH_2Cl_2 / MeOH 50:1 and 10:1) to produce (±) **11** (220 mg, 27 % overall yield starting from **8a**).

5   The spectrum of **11** is identical to that previously reported.

Table I

Antiviral activity of D-cyclohexenyl G and L-cyclohexenyl G in comparison with approved antiviral drugs: 50% inhibitory concentration (IC$_{50}$) values are given in μg/ml.

Virus	D-cyclohexenyl G		L-cyclohexenyl G		Brivudin	Acyclovir	Ganciclovir	Cidofovir
	Activity	Selectivity index	Activity	Selectivity index				
HSV-1 (KOS)[a]	0.002[b]	$>2.10^5$	0.003[b]	$>5.10^3$	0.001[b]	0.01[b]	0.001[b]	ND
HSV-1 (F)[a]	0.002[b]	$>2.10^5$	0.003[b]	$>5.10^3$	0.001[b]	0.003[b]	0.001[b]	ND
HSV-1 (McIntyre)[a]	0.004[b]	$>1.10^5$	0.004[b]	$>4.10^3$	0.001[b]	0.005[b]	0.001[b]	ND
HSV-2 (G)[a]	0.05[b]	$>8.10^3$	0.07[b]	$>2.2\,10^2$	>80[b]	0.02[b]	0.002[b]	ND
HSV-2 (196)[a]	0.07[b]	$>5.10^3$	0.1[b]	$>1.6\,10^2$	>80[b]	0.02[b]	0.001[b]	ND
HSV-2 (Lyons)[a]	0.07[b]	$>5.10^3$	0.07[b]	$>2.2\,10^2$	>80[b]	0.02[b]	0.001[b]	ND
HSV-1 (TK⁻ KOS ACV')[a]	0.38[b]	$>1.10^3$	1.28[b]	>12	>80[b]	9.6[b]	0.48[b]	ND
HSV-1 (TK⁻/TK⁺ VMW1837)[a]	0.01[b]	$>4.10^4$	0.01[b]	$>1.6\,10^3$	>80[b]	0.07[b]	0.01[b]	ND
VZV (YS)[c]	0.49[d]	>40	1.2[d]	>16	0.03[d]	1.1[d]	ND	ND
VZV (OKA)[c]	0.64[d]	>30	1.9[d]	>10	0.003[d]	0.8[d]	ND	ND
VZV (TK⁻ 07/1)[c]	2.1[d]	>10	5.8[d]	>3	>20[d]	13[d]	ND	ND
VZV (TK⁻ YS/R)[c]	2.0[d]	>7	6.0[d]	>3	>50[d]	28[d]	ND	ND
CMV (AD 169)[c]	0.6[d]	>30	1.5[d]	>13	ND	ND	0.6[d]	0.08[d]
CMV (Davis)[c]	0.8[d]	>25	1.7[d]	>12	ND	ND	0.8[d]	0.2[d]

(a)   Activity determined in E$_6$SM cell cultures
(b)   Minimum inhibitory concentration (μg/ml) required to reduce virus-induced cytopathogenicity by 50%
(c)   Activity determined in HEL cells
(d)   Inhibitory concentration (μg/ml) required to reduce virus plaque formation by 50%. Virus input was 20 plaque forming units (PFU)
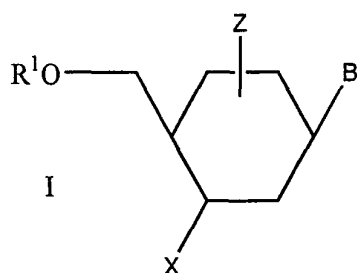ND : not determined

Table II

Cytotoxicity of D-cyclohexenyl G and L-cyclohexenyl G in four different cell lines (concentrations in µg/ml)

Cell line	D-cyclohexenyl G	L-cyclohexenyl G	Brivudin	Acyclovir	Ganciclovir	Cidofovir
HeLa[a]	400	400	≥ 400	ND	ND	ND
Vero[a]	400	400	≥ 400	ND	ND	ND
E₆SM[a]	> 400	> 16	≥ 400	≥ 400	> 100	ND
HEL[b]	> 20	> 20	> 50	> 50	> 50	> 50
HEL[c]	11	> 20	> 200	> 200	> 50	> 50

(a)   Minimum cytotoxic concentration causing a microscopically detectable alteration of cell morphology
(b)   Cytotoxic concentration required to reduce cell growth by 50%

CLAIMS

1. A six membered, at least partially
unsaturated, carbocyclic nucleoside compound, including
the (-) enantiomer, the (+) enantiomer, and pharma-
ceutically acceptable salts and esters thereof, the
5 compounds represented by the general formula I:

I

10

wherein:

   - Z represents the presence of 1 or more double
bonds in the six membered carbocyclic ring,

   - B is a heterocyclic ring selected from the
15 group consisting of pyrimidine and purine bases,

   - X is a hydrogen, azido, F, or OR^2,

   - R^1 and R^2 are the same or different and
represent the same or different protecting groups,

hydrogen, alkyl, alkenyl, acyl or phosphate moieties
wherein;

   - the alkyl moiety is a saturated, substituted
or unsubstituted straight or branched chains hydrocarbon
5radical having from 1 to 20, for example 1-16, 1-14,

1-12, 1-10, 1-8, 1-4, carbon atoms,

   - the alkenyl moiety is an unsaturated congener
of the alkyl group and,

   - the acyl moiety is an alkanoyl or aroyl moie-
10ty, wherein alkanoyl is an alkyl carbonyl radical, whe-
rein alkyl is as described above and aroyl represents
benzoyl substituted benzoyl or naphtoyl.

   2. A six membered, at least partially
unsaturated, carbocyclic nucleoside compound, according
15to claim 1, being a cyclhexenyl nucleoside compound
having the general formula II or III, preferably II:

$$R^1O \overbrace{}^{} B$$

II

X

20

R¹O—CH₂— ... **III** ... with substituents B, X
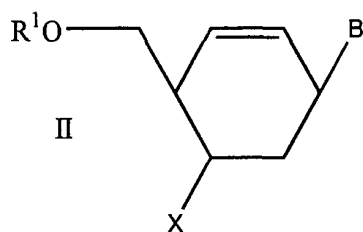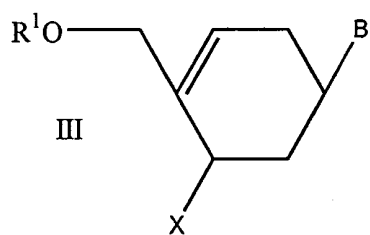
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3. Compound according to claims 1 or 2,
selected from the following group of compounds
10represented by the formulas IV-X':

15

V

VI

5

VII

10

VIII

IX

5

X

10

$$R^1O \underset{X'}{\overset{}{\diagdown}} \quad \text{(ring structure)} \quad B$$
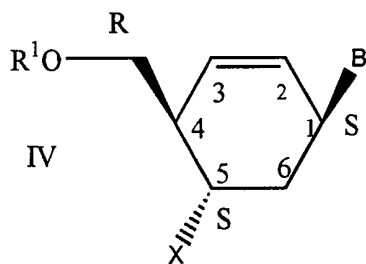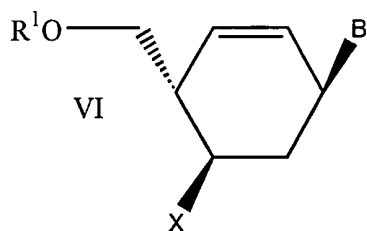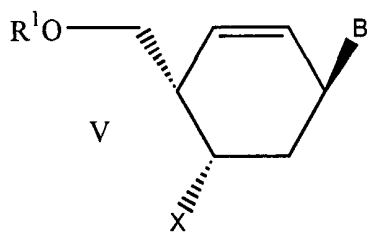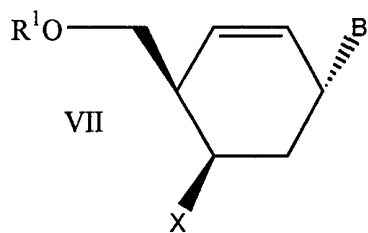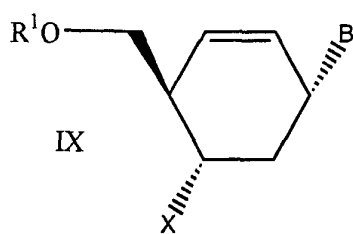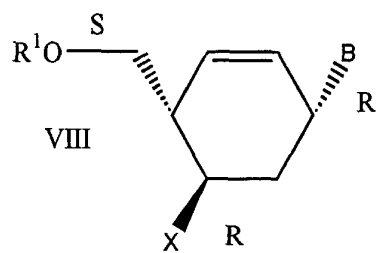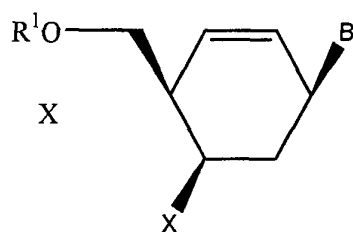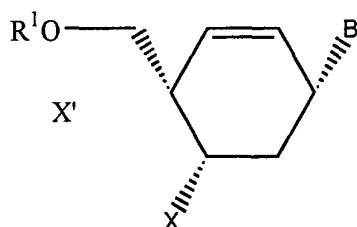
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4. Compound according to any of the preceding claims, wherein the C_1 bearing B substituent and the C_5 bearing X substituent both have the (S)-configuration, and the C_4 bearing $-OR^1$ substituent has the (R)-
10configuration, as depicted by formula IV in claim 3.

5. Compound according to claims 1,2 or 3, wherein the C_1 bearing B substituent and the C_5 bearing X substituent both have the (R)-configuration, and the C_4 bearing $-OR^1$ substituent has the (S)-configuration, as
15depicted by formula VIII in claim 3.

6. Compound according to any of the claims 1-4, wherein X is represented by a hydroxyl group in the (S)-configuration.

7. Compound according to any of the claims 1,
202,3 and 5, wherein X is hydroxyl in the (R)-configuration.

8. Compound according to any of the preceding claims wherein B is derived from the group consisting of pyrimidine bases.

25   9. Compound according to claim 7 wherein the

pyrimidine base has the general formula XI:

XI
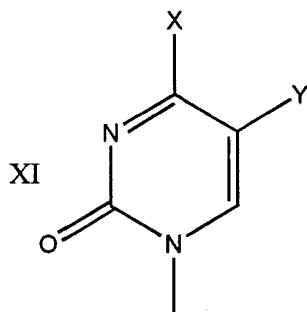
5

wherein X is chosen from the following;

- OH, NH$_2$, NHQ,

wherein;

10   - Q is selected from the following;

OH or C$_{1-5}$ alkyl,

-Y is selected from the following;

H, F, Cl, Br, I, C$_{1-5}$ alkyl, haloethyl or
CH=CH-R, wherein R represents hydrogen, halogen or C$_{1-5}$
15alkyl, and wherein haloethyl contains from 1 to 4 F, CI
or Br atoms.

10. Compound according to any of the preceding
claims wherein B is selected form the group consisting of
substituted and unsubstituted adenine, guanine, 2,6-
20diaminopurine, hypoxanthine and xanthine.

11. Compound according to any of the preceding
claims wherein the B is selected from the group of aza,
deaza deoxy or deamino analogues of the heterocyclic

48

rings, as defined in any of the claims 8-10.

12. Compound according to any of the preceding claims wherein the protecting group comprises a silyl protecting group, preferably TBDMS, and/or a benzoyl 5protecting group and or a C6H5-CH= group.

13. Compound according to any of the preceding claims 1-11 selected from:

- 9-[1S,4R,5S)-5-hydroxy-4-hydroxymethyl-2-cyclohexenyl] guanine

10- 9-[1R,4S,5R)-5-hydroxy-4-hydroxymethyl-2-cyclohexenyl].

14. Compound according to any of the claims 1-11 selected from the following group:

- 9-[(1S,4R,5S)-5-(tert-Butyldimethylsilyloxy)-4-
15   (tert-butyldimethylsilyloxymethyl)-2-cyclohexenyl]adenine

- 9-[(1S,4R,5S)-5-Hydroxy-4-hydroxymethyl-2-cyclohexenyl]adenine

- 9-[(1S,4R,5S)-5-(tert-butyldimethylsilyloxy)-4-
20   (tert-butyldimethylsilyloxymethyl)-2-cyclohexenyl]-
      2-amino-6-chloropurine

- 9-[(1S,4R,5S)-5-hydroxy-4-hydroxymethyl-2-cyclohexenyl]guanine

- 9-[(1R,4S,5R)-5-Benzoyloxy-4-benzoyloxymethyl-2-
25   cyclohexenyl]adenine

- 9-[(1R,4S,5R)-5-hydroxy-4-hydroxymethyl-2-cyclohexenyl]adenine

- 9-[(1R,4S,5R)-5-Benzoyloxy-4-benzoyloxymethyl-2-cyclohexenyl]guanine

30- 9-[(1R,4S,5R)-5-Hydroxy-4-hydroxymethyl-2-cyclohexenyl]guanine

15. Process for providing a compound, the (-)
enantiomer, the (+) enantiomer, and pharmaceutically
acceptable salts and esters thereof according to any of
5 the preceding claims, said process comprising the steps
of:

- providing cyclohexenyl compound of the gene-
ral formula XII;

10

$$R^1O \overset{XII}{\longrightarrow} \quad \begin{array}{c} OR^3 \\ OR^2 \end{array}$$

15
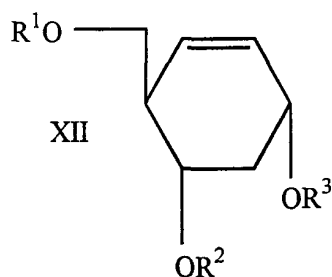
- wherein R^1 and R^2 are protecting groups and R^3
is a leaving group or an Hydrogen atom, followed by the
step of substituting the OR^{-3} group by a pyrimidine or
purine base.

20   16. Process according to claim 15 wherein R^3 is
hydrogen and wherein a Mitsunobo type reaction is

utilised.

17. Process according to claim 15 wherein R^3

is a leaving group enabling nucleophilic substitution.

18. Process according to any of the preceding
claims 15-17 wherein the compound of general formula XII
has the chemical formula XIII;

5
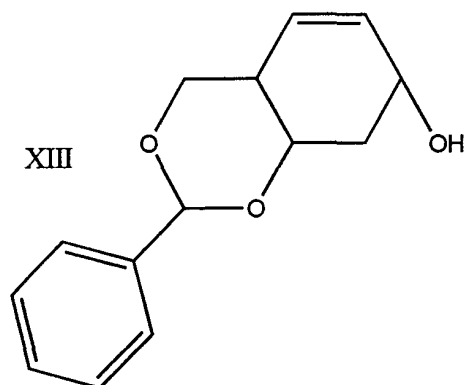
XIII

or analogues thereof either in a racemate form or sepa-
10 rated isomers thereof.

19. Process according to any of the preceding
claims 15-18 wherein compound XIII is provided by
reacting (±) 4-hydroxymethyl- cyclohex-2-en-1,5 Diol of
formula XIV;

15
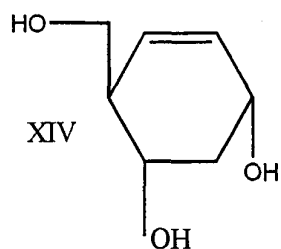
with a benzaldehyde analogue and a lewis acid, preferably
being benzaldehyde dialkyl acetal, most preferably
5dimethyl acetal, and p-toluenesulfonic acid.

20. Process according to any of the preceding
claims 15-19 wherein compound XIV is provided by the
reduction of compound XVA or XVB, preferably utilising
lithium aluminium hydride or an equivalent thereof as
10reducing agent;

15
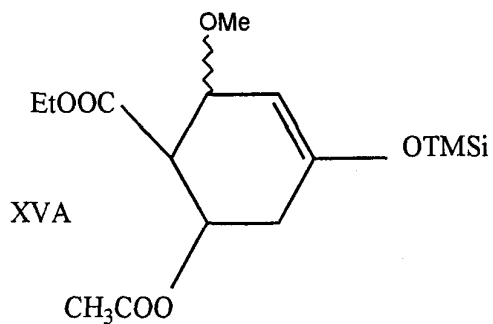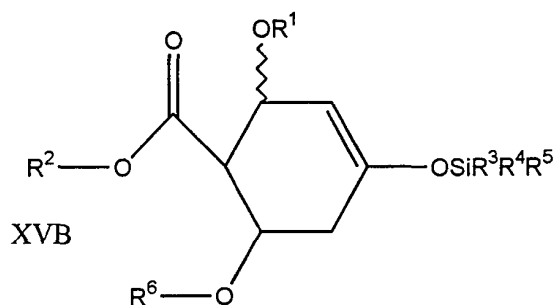
5 wherein for XVB:

R^1 and R^2 are alkyl or alkenyl moieties,

wherein:

- R^1 and R^2 are the same or different, and

- alkyl is a saturated, substituted or
10 unsubstituted hydrocarbon radical having from 1 to 20 for
example 1-16, 1-14, 1-12, 1-10, 1-8, 1-4, carbon atoms
and being straight or branched chain, and

- alkenyl is the unsaturated congener of the
alkyl group, and

15   R^3, R^4 and R^5 are alkyl, alkenyl or aryl
moieties, wherein:

- R^3, R^4 and R^5 are the same or different, and

- alkyl is a saturated, substituted or
unsubstituted straight or branched chain hydrocarbon
20 radical having from 1 to 20 for example 1-16, 1-14, 1-12,
1-10, 1-8, 1-4, carbon atoms and

- alkenyl is the unsaturated congener of the
alkyl group, and

    - aryl represents phenyl or substituted phenyl,
and

R⁶ is a alkyl, alkenyl or acyl moiety, wherein:

    - alkyl is a saturated, substituted or
5unsubstituted hydrocarbon straight or branched chain
radical having from having from 1 to 20 for example 1-16,
1-14, 1-12, 1-10, 1-8, 1-4, carbon atoms,

   - alkenyl is the unsaturated congener of the
alkyl group, and

10   - acyl is an alkanoyl or aroyl moiety, wherein
alkanoyl is an alkyl carbonyl radical, wherein alkyl is
as described above and aroyl represents benzoyl,
substituted benzoyl or naphtoyl.

    21. Process according to claim 20 wherein

15compound XVA or XVB is provided by a diels-alder
reaction, by the cyclo addition of a suitable diene and
dienophile wherein preferably the diene and dienophile
are heated together in the presence of hydroquinone.

    22. Process according to claim 21 wherein the
20diene has the following chemical structure XVI, and the
dienophile has the following chemical structure XVII,
wherein R¹, R², R³, R⁴, R⁵ and R⁶ are as defined in claim
20;

$$R^3R^4R^5SiO$$

XVI

$$OR^1$$
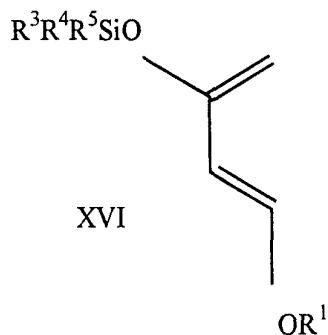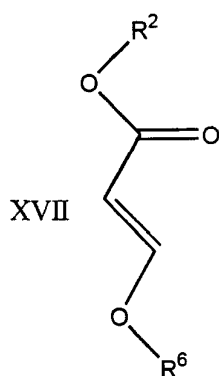
XVII
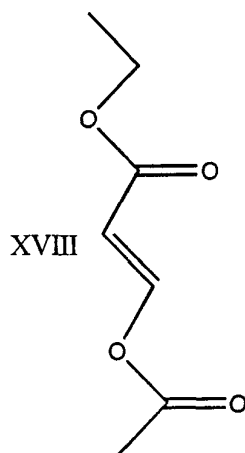
5   23. Process according to claim 22 wherein the
diene has the chemical structure XVI' and the dienophile
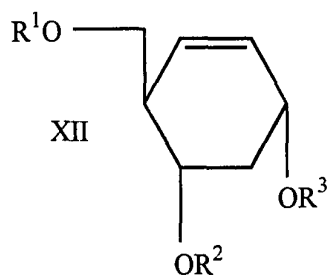has the chemical structure XVIII;
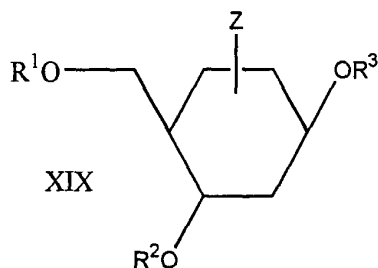

TMSiO

XVI'

OMe

10

15

XVIII
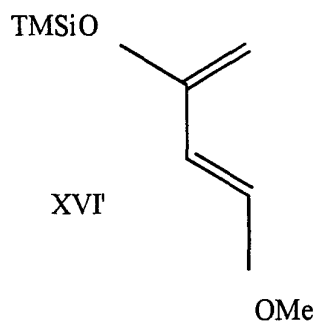
5   24. A six membered, at least partially
unsaturated, carbocyclic nucleoside compound, including
the (-) enantiomer, the (+) enantiomer, and pharma-
ceutically acceptable salts and esters thereof, the
compounds represented by the general formula XII or XIX;

10

XII

15

XIX

wherein:

- Z represents the presence of 1 or more double bonds in the carbocyclic ring,

- R^1 and R^2 are protecting groups and R^3 is a leaving group or an Hydrogen atom.

25. Compound according to claim 24 wherein;

R^1 and R^2 are the same or different and hydrogen, alkyl, alkenyl, acyl or phosphate moieties are represented, or R^1 and R^2 represent a cyclic protecting group; wherein:

- alkyl is a saturated, substituted or unsubstituted straight or branched chain hydrocarbon radical having from 1 to 20 for example 1-16, 1-14, 1-12, 1-10, 1-8, 1-4, carbon atoms, and

- alkenyl is the unsaturated congener of the alkyl group, and

- acyl is an alkanoyl or aroyl moiety, wherein alkanoyl is an alkyl carbonyl radical, wherein alkyl is as described above and aroyl represents benzoyl, substituted benzoyl or naphtoyl; and

R^3 represents a hydrogen, an alkylsulfonyl or an arylsulfonyl moiety, wherein:

- alkyl is a saturated, substituted or
unsubstituted hydrocarbon radical having from 1 to 6
carbon atoms and straight or branched chain, and

- aryl represents phenyl or substituted phenyl,
5 and

26. A cyclohexenyl compound, including the (-)
enantiomer, the (+) enantiomer, and pharmaceutically
acceptable salts and esters thereof, the compound
represented by the general formula XVB;

10
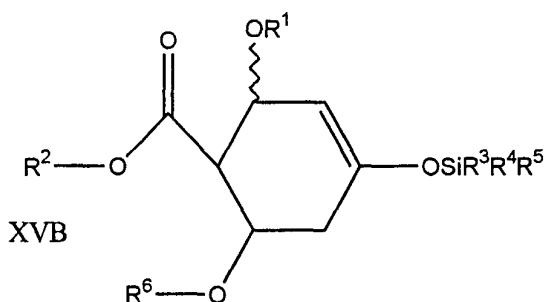
15   wherein R^1 and R^2 are alkyl or alkenyl moieties,
   wherein:

- R^1 and R^2 are the same or different, and

- alkyl is a saturated, substituted or
unsubstituted straight or branched chain hydrocarbon
20 radical having from 1 to 20 for example 1-16, 1-14, 1-12,
1-10, 1-8, 1-4 carbon atoms,

- alkenyl is the unsaturated congener of the
alkyl group, and

R^3, R^4 and R^5 are alkyl, alkenyl or aryl

moieties, wherein:

- R^3, R^4 and R^5 are the same or different, and

- alkyl is a saturated, substituted or unsubstituted straight or branched chain hydrocarbon radical having from 1 to 20 for example 1-16, 1-14, 1-12, 1-10, 1-8, 1-4 carbon atoms and,

- alkenyl is the unsaturated congener of the alkyl group, and

- aryl represents phenyl or substituted phenyl, and

R^6 is a alkyl, alkenyl or acyl moiety, wherein:

- alkyl is a saturated, substituted or unsubstituted straight or branched chain hydrocarbon radical having from 1 to 20 for example 1-16, 1-14, 1-12, 1-10, 1-8, 1-4 carbon atoms, and

- alkenyl is the unsaturated congener of the alkyl group, and

- acyl is an alkanoyl or aroyl moiety, wherein alkanoyl is an alkyl carbonyl radical, wherein alkyl is as described above and aroyl represents benzoyl, substituted benzoyl or naphtoyl.

27. Compound according to claim 26 having the formula XVA being; 5-O-acetyl-4-ethoxycarbonyl-3-O-methyl-1-O-trimethylsilyl-cyclohexen-1,3,5-triol and its isomers;

OMe

EtOOC

OTMSi

XVA

CH₃COO
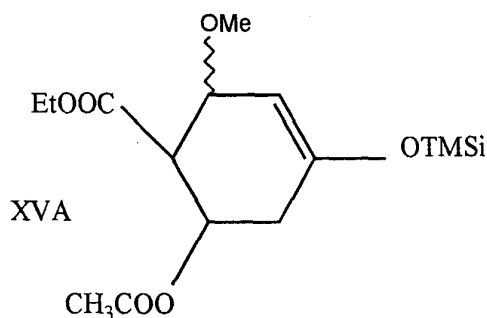
5   28. (±) 4-hydroxymethyl-cyclohex-2-en-1,5-diol.

        29. (1*R*, 4*R*, 5*S*)-4-hydroxymethyl-cyclohex-2-en-
1,5-diol.

        30. (1*S*, 4*S*, 5*R*)-4-hydroxymethyl-cyclohex-2-en-
1,5-diol.

10   31. (±) 5,7-*O*-benzylidene-4-hydroxymethyl-
cyclohex-2-en-1,5-diol.

        32. (1*R*, 4*R*, 5*S*)-5,7-*O*-benzylidene-4-
hydroxymethyl-cyclohex-2-en-1,5-diol.

        33. (1*S*, 4*S*, 5*R*)-5,7-*O*-benzylidene-4-
15hydroxymethyl-cyclohex-2-en-1,5-diol.

        34. Compound according to any of the preceding
claims 24-26 selected from the following group:

-        (4*S*,5*R*)-5-Benzoyloxy-4-benzoyloxymethyl-cyclohex-2-
        en-1-one,

20-   (1S,4*S*,5*R*)-5-Benzoyloxy-4-benzoyloxymethyl-cyclohex-
        2-en-1-ol,

-        (4*R*,5*S*)-4-*tert*-Butyldimethylsilyloxymethyl-5-tert-
        butyldimethylsilyloxy-cyclohex-2-en-1-one,

- (1R,4R,5S)-5-(tert-Butyldimethylsilyloxy)-4-(tert-butyldimethylsilyloxymethyl)-cyclohex-2-en-1-ol.

35. Compound according to any of the claims 1-14, 24-34 obtainable according to the process according 5 to any of the claims 15-23.

36. Pharmaceutical composition comprising a compound according to any of the claims 1-14, 24-34.

37. A pharmaceutical composition as claimed in any of the claims 1-14, 24-34, having antiviral activity 10 towards herpetic viruses selected but not limited from the group consisting of herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), Varicella zoster virus (VZV), and cytomegalovirus (CMV), as well as towards pox viruses, e.g. vaccinia virus (VV).

15   38. A pharmaceutical composition as claimed in claim 37 comprising said active ingredient in a concentration ranging from about 0.1-100 % by weight.

39. A pharmaceutical composition as claimed in claim 38, having the form which is selected from the 20 group consisting of powders, suspensions, solutions, sprays, emulsions, unguents and creams.

40. The use of a compound according to any of the claims 1-14, 24-34 as a pharmaceutical preferably anti-viral agent.

25   41. The use of a compound according to any of the claims 1-14, 24-34 as an agent having biological activity.

42. The use of a compound according to any of the claims 1-14, 24-34 as an agent having antiviral 30 activity towards herpes viruses, pox viruses and related viruses.

43. The use of a compound according to any of the claims 1-14, 24-34 for the preparation of a pharmaceutical composition having antiviral activity towards herpes viruses, pox viruses and related viruses.
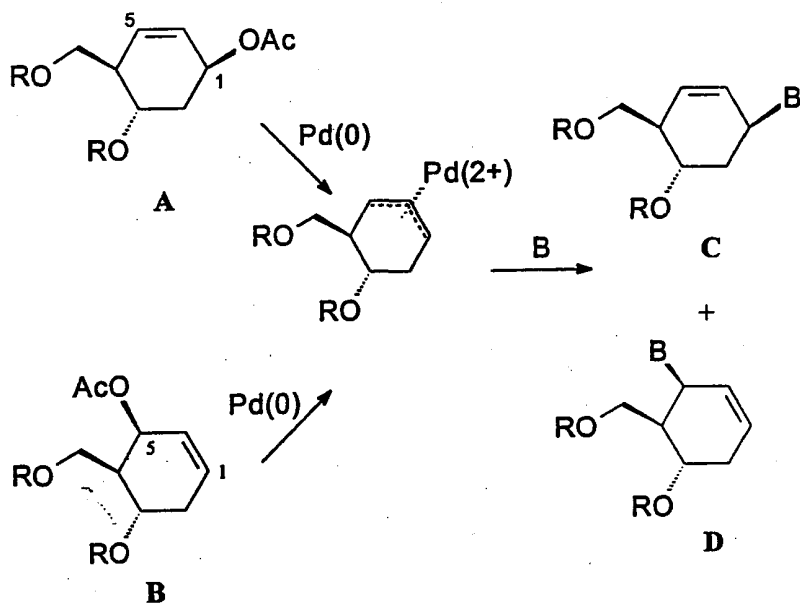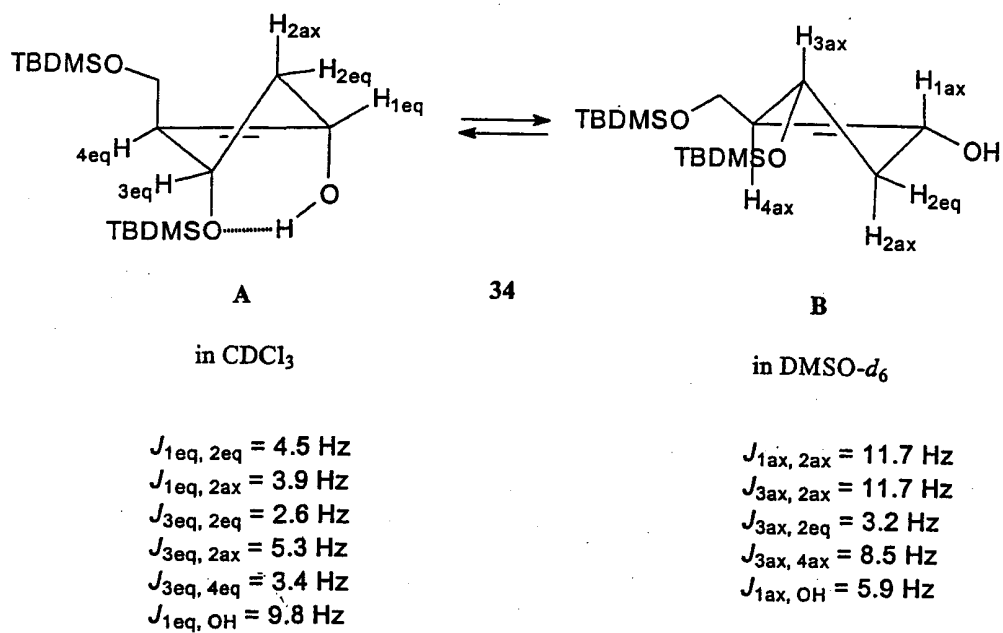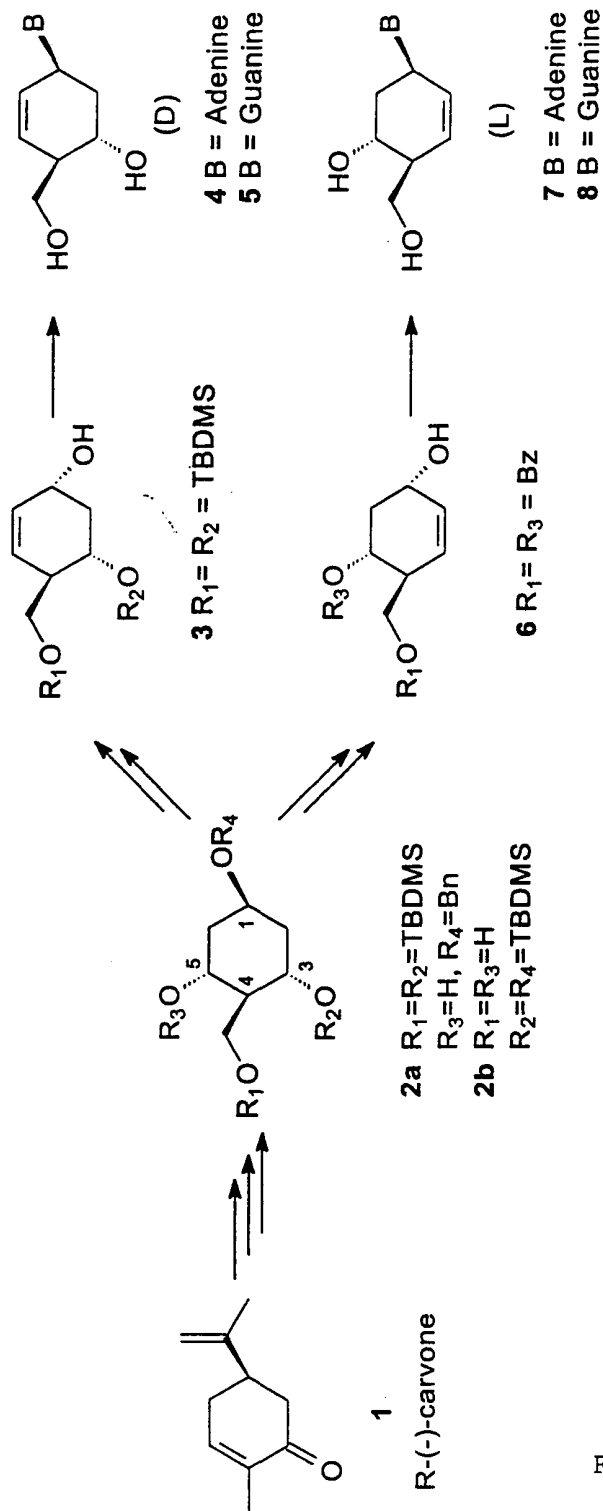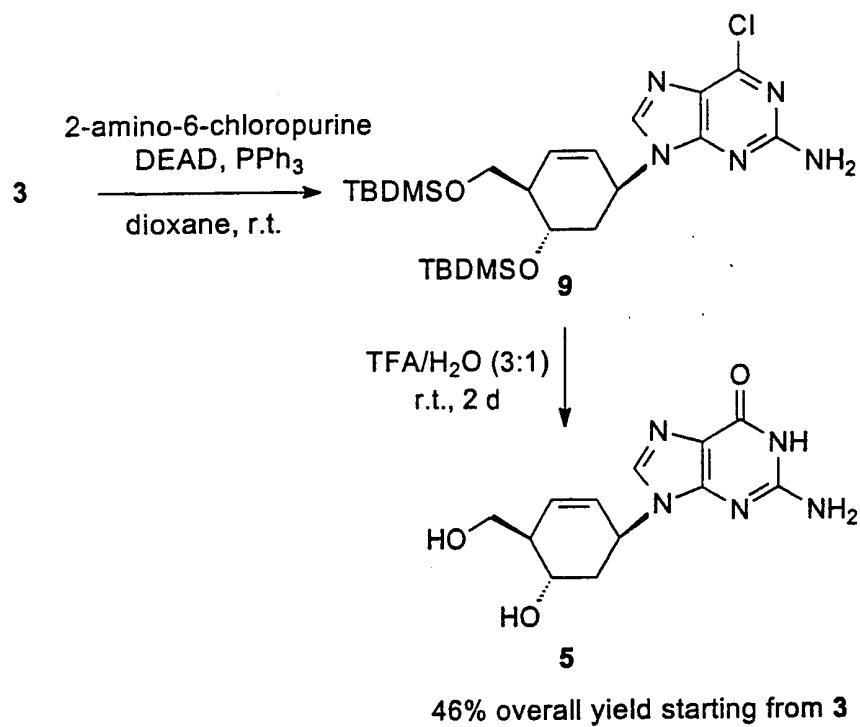
FIG. 1

FIG. 2

FIG. 3

46% overall yield starting from **3**

FIG. 4
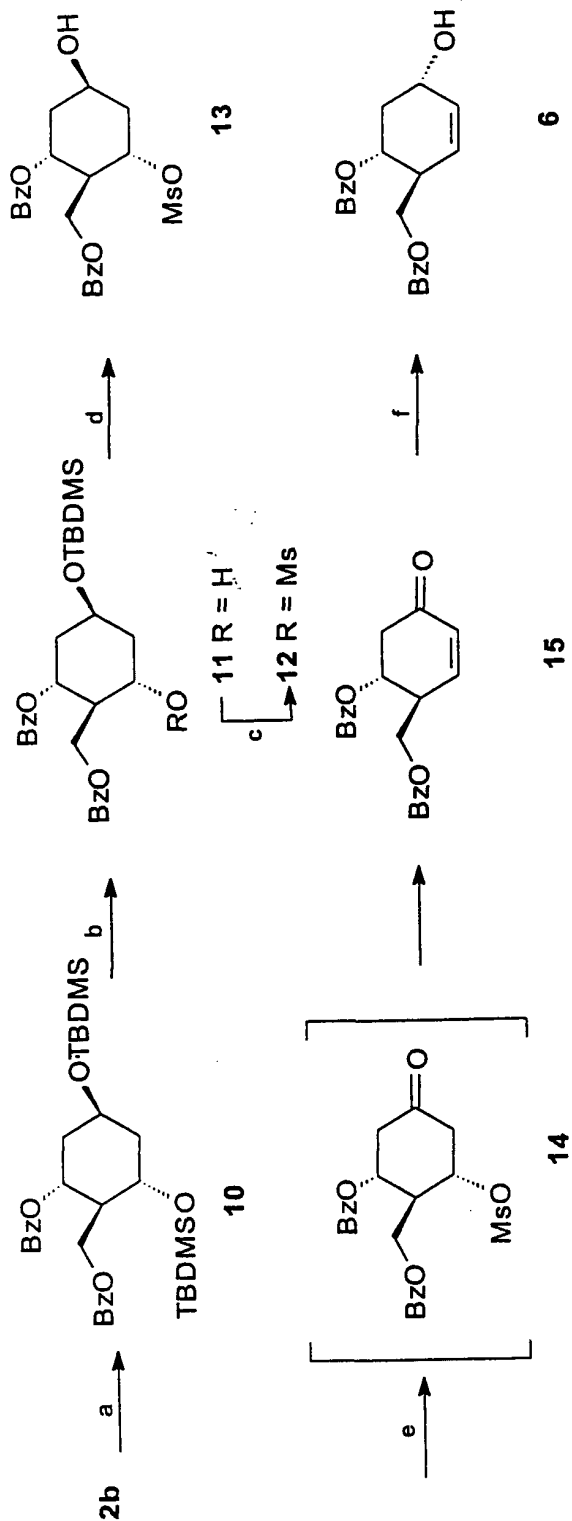
a. Bz$_2$O, DMAP, CH$_2$Cl$_2$, 0 °C, 98%; b. TBAF (1eq), THF, r.t., 74%; c. MsCl, Et$_3$N, CH$_2$Cl$_2$, 0°C, 98%; d. TBAF, THF, r.t., 86%; e. PDC, CH$_2$Cl$_2$, r.t., 68%; f. NaBH$_4$, CeCl$_3$.7H$_2$O, MeOH, r.t., 75%.

FIG. 5
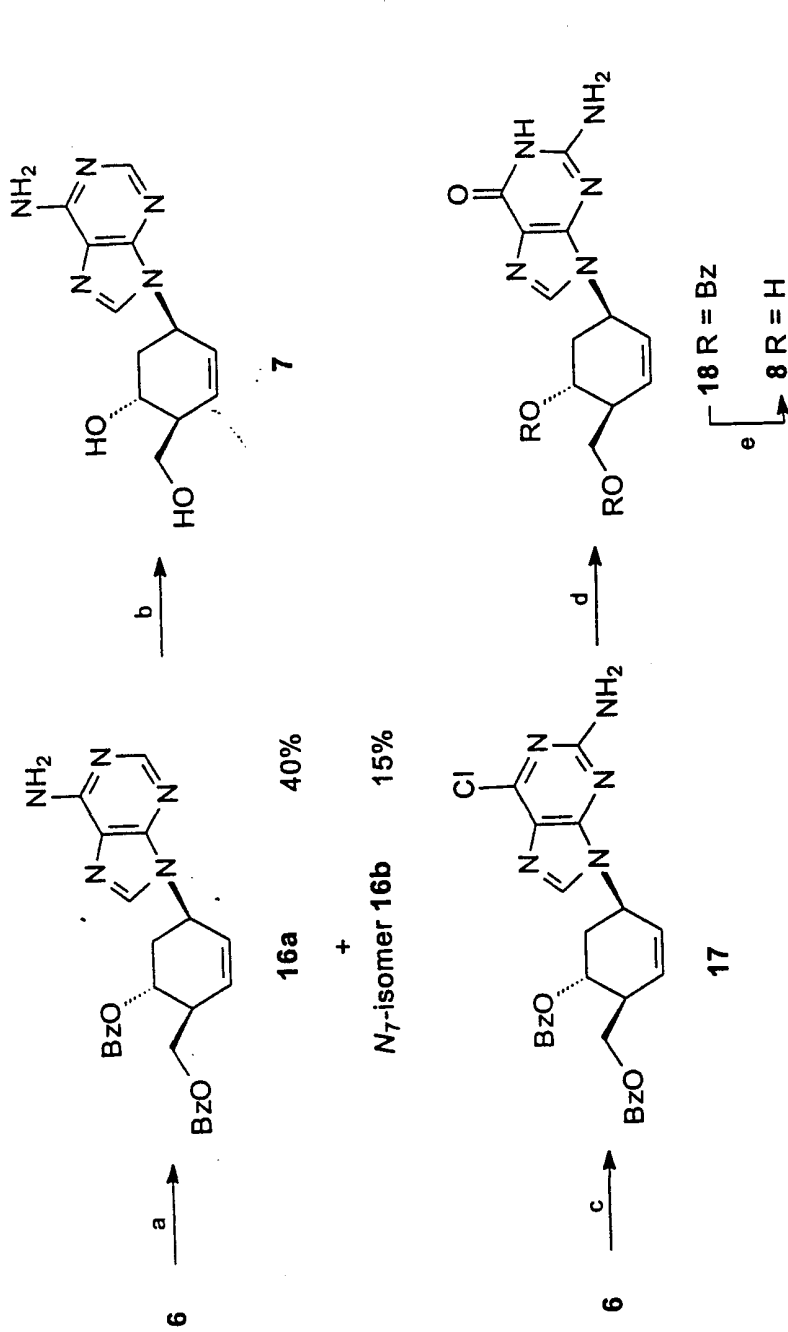
FIG. 6

a. Adenine, DEAD, PPh₃, dioxane, r.t.; b. K₂CO₃, MeOH, r.t., 77%; c. 2-amino-6-chloro purine,
DEAD, PPh₃, dioxane, r.t.; d. TFA/H₂O (3:1), r.t., 2 d, 58% from 6; e. NH₃/MeOH, 80 °C, 2 d, 73%.

FIG. 7

R = TBDMS

FIG. 8

FIG. 9
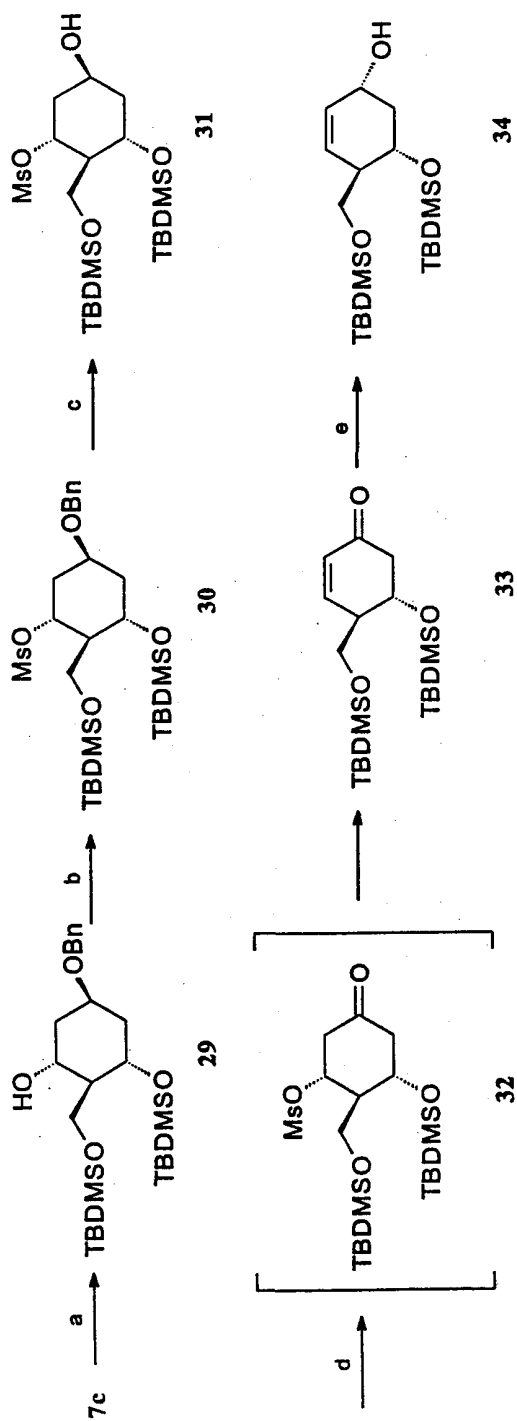
FIG. 10

FIG. 11

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D473/32 C07D473/18 C07D473/34 C07D239/46 C07C43/188
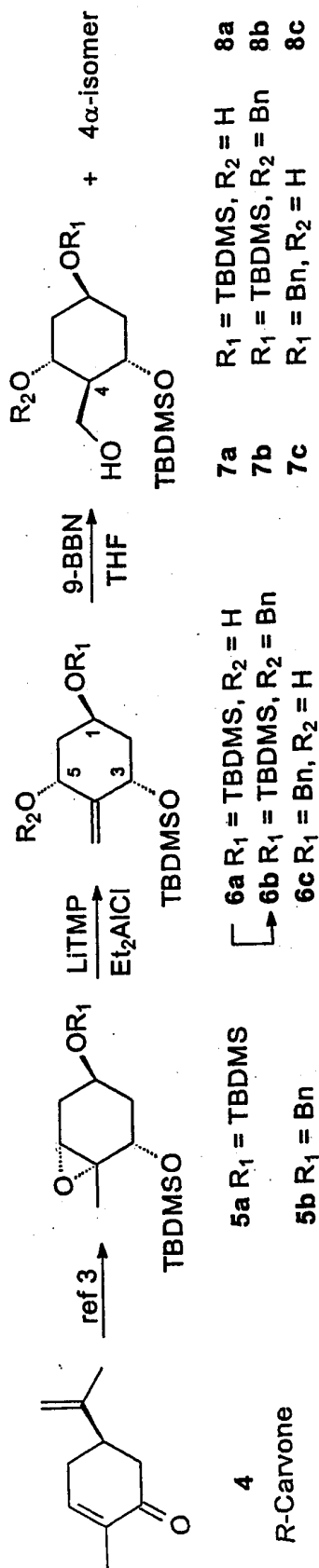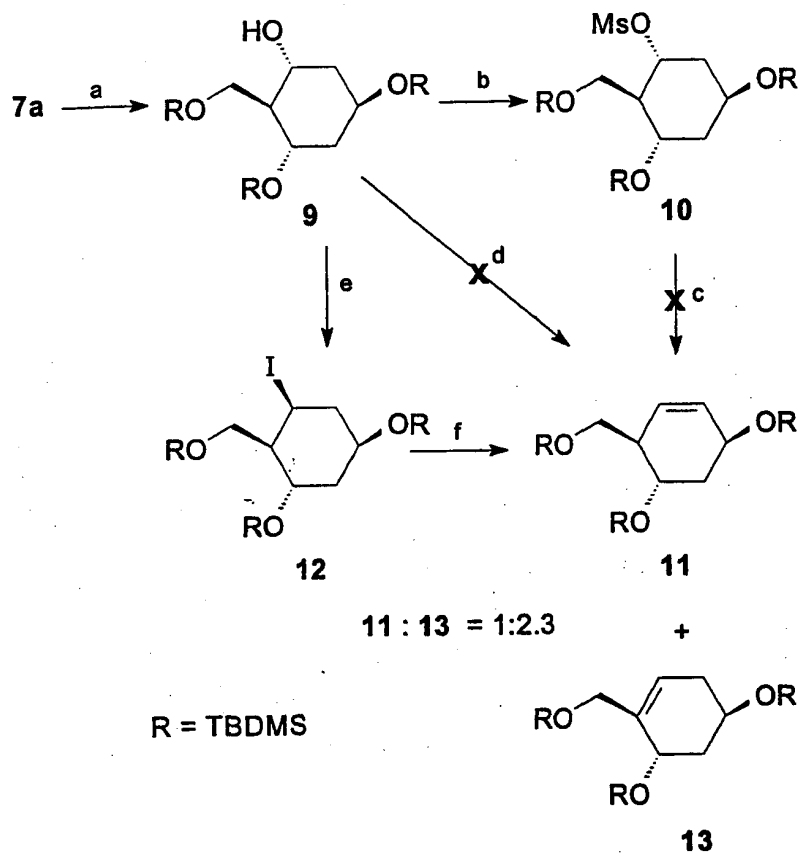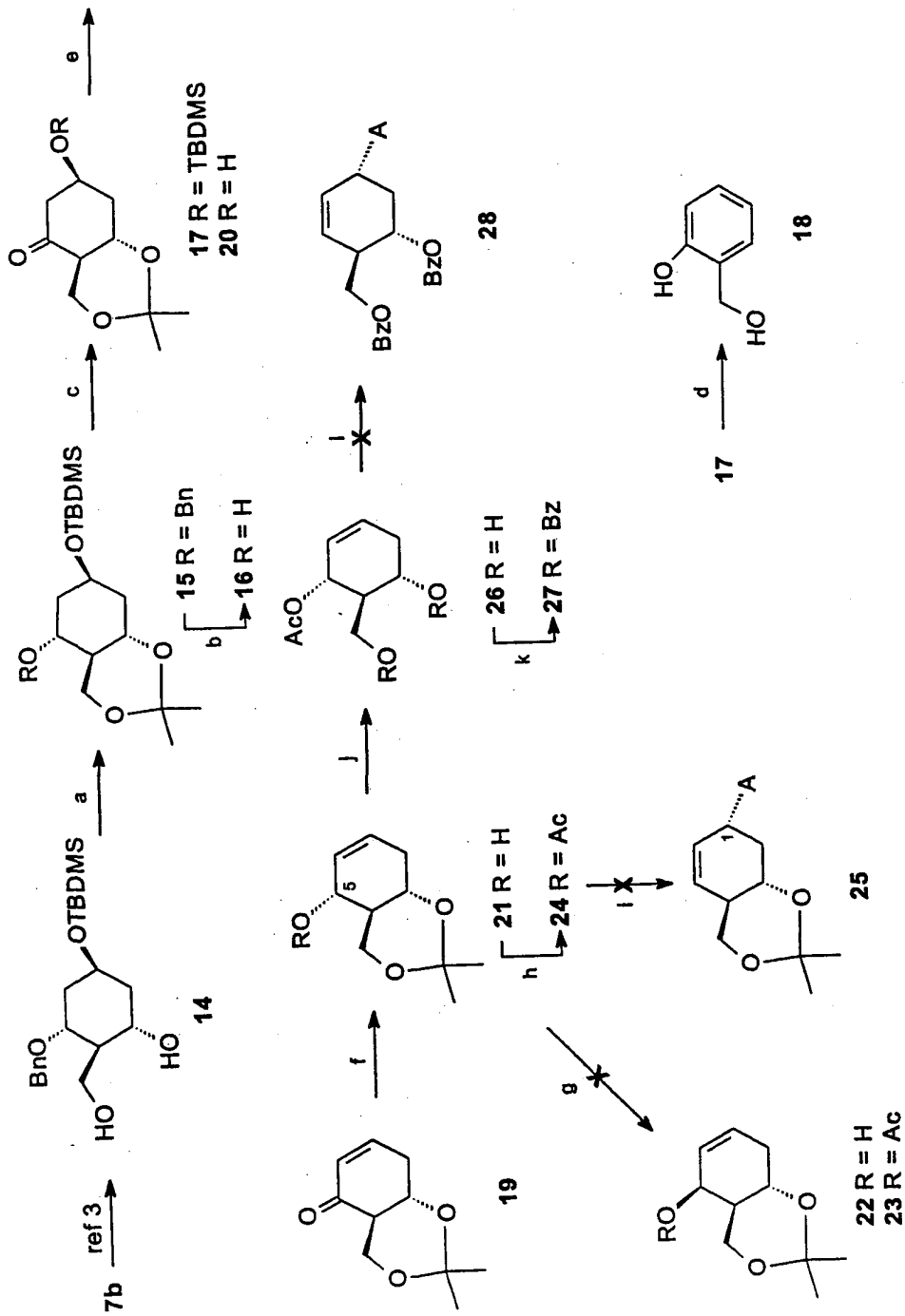   C07C35/18   C07F7/18   A61K31/52   A61K31/522 A61P31/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07C C07F A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

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A	GB 2 097 785 A (BRISTOL MYERS CO) 10 November 1982 (1982-11-10) claims	1-43

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[X] Further documents are listed in the continuation of box C.   [X] Patent family members are listed in annex.

° Special categories of cited documents:

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 January 2001	05/02/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340-2040, Tx. 31 651 epo nl, Fax: (+31–70) 340-3016	Chouly, J

Form PCT/ISA/210 (second sheet) (July 1992)

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page 1 of 2

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
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P,X	J. WANG ET AL: "The cyclohexene ring system as a furanose mimic: synthesis and antiviral activity of both enantiomers of cyclohexenylguanine" JOURNAL OF MEDICINAL CHEMISTRY, vol. 43, no. 4, 24 February 2000 (2000-02-24), pages 736-745, XP002157747 WASHINGTON US the whole document	1-43

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