SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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Abogado
LUIS PATIÑO LEYVA

ASUNTO	Radicación	08-83536
	Trámite	011
	Evento	378
	Actuación	519
	Oficio	
	Folios	6

12520

Patente de Invención ☐ Patente de Modelo de Utilidad ☐
Vía Nacional ☐
Vía PCT (fase nacional) ☐ Cap.I ☐ Cap. II ☐

No. Solicitud Internacional PCT/US2007/002560
Fecha de Presentación Internacional 31 de enero de 2007

Como resultado del Examen de Fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Folios 99-252	12 de agosto de 2008
Reivindicaciones:	Folios 253-277	12 de agosto de 2008
	Folios 307-331	08 de septiembre de 2008
Prioridad:	US 60764487	02 de febrero de 2006

2. Análisis de la Prioridad

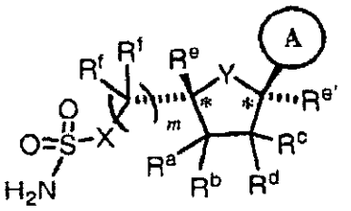
Se acepta la reivindicación de Prioridad porque esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

Título de la solicitud: "inhibidores de enzimas activadoras E1"

El problema planteado en esta solicitud consiste en la necesidad de proporcionar compuestos útiles para inhibir la actividad de enzimas activadoras de tipo E1.

Para resolver este problema técnico la solicitud en estudio proporciona un compuesto de la fórmula (I) y composiciones que lo contienen.



Clasificación Internacional de Patentes (CIP): C07D 471/04; C07H 19/14; A61P 35/00; A61K 31/519.

4. De la Solicitud de Patente

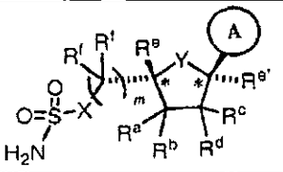
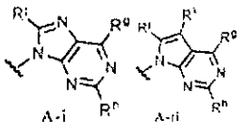
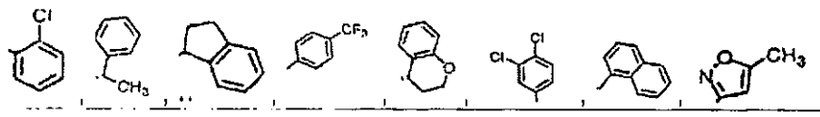
Reivindicaciones (Art 30 D 486, Art 22 PCT)

El capítulo reivindicatorio no es conciso cuando utiliza los términos:

- Alifático: porque no definen el número de carbonos que componen la cadena.
- Arilo: porque no definen el número de carbonos que componen el anillo.
- Heteroarilo o heterocíclico, heterociclilo de 5-6 miembros: porque no definen el número de carbonos que componen el anillo, y además no se define el número y tipo de heteroátomos que componen el anillo.
- Alifático C_{1-4}, Fluorolifático C_{1-4}, Fluorolifático C_{1-6} y similares de común uso en el capítulo reivindicatorio, dan lugar a una innumerable combinación de compuestos que no encuentran soporte en la descripción.
- Anillo espirociclico de 3-6 miembros, anillo carbocíclico de 3-6 miembros, cicloalifàtico de 3-8 miembros: y similares de común uso en el capítulo reivindicatorio, dan lugar a una innumerable combinación de compuestos que no encuentran soporte en la descripción.
- El uso de términos tales como "opcionalmente", "uno o dos sustituyentes", "opcionalmente sustituido", "porción arilo que puede estar opcionalmente sustituida" y otros términos semejantes los cuales no son concisos porque no limitan el alcance la reivindicación, ni la definen de manera adecuada.
- El uso del término "m" que se define como un número entero 0, 1, 2, 3 y 4 no es conciso porque no limita el alcance la reivindicación, ni la define de manera adecuada.

Se sugiere al solicitante, definir cada término de manera apropiado y restringir la solicitud a una generalización razonable de los compuestos ejemplificados.

Para este efecto esta Oficina manifiesta que en la descripción se encuentran soportados los siguientes compuestos a los cuales el solicitante puede tener en cuenta para la respectiva restricción:


A es 
Para X es O
Para Y es O
m es 1
Ra es –OH, H,
Rb es CH_3,
Rd es H, -OH,
V^1 es –NH-, -$N(CH_3)$-, -CH_2-,
T^1 es CH_2
C es 

En la reivindicación 29 no es clara, porque define sus componentes en razón del los sustituyentes de un compuesto de fórmula I-A, lo cual no es manera adecuada de reclamar, se sugiere definir la formulación por sus características esenciales, es decir, debe caracterizar la preparación farmacéutica con los componentes y proporciones.

En las Reivindicaciones 1-19; 21-22 y 24-29 se incluye de manera recurrente la expresión "Grupo protector", se sugiere aclarar para cada vez que se utiliza en el capítulo reivindicatorio definir cual, o cuales fueron los grupos protectores utilizados.

5. Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la fecha de Presentación de la Solicitud de Prioridad: 02 de febrero de 2006

Se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación*
D1	XP002440675 GOSSELIN ET AL	A short and novel synthesis of carbocyclic nucleosides and 4'-epi-carbocyclic nucleosides from 2-cyclopenzen-1-ones	13 octubre 2005
D2	XP009086084 J. -C. MEILLON ET AL	Rapid access to 2'-branched-carbocyclic nucleosides and their 4'-epimers from 2-alkyl-cyclopentene-1-ones	2005

D1 G. GOSSELIN ET AL: "A short and novel synthesis of carbocyclic nucleosides and 4'-epi-carbocyclic nucleosides from 2-cyclopenzen-1-ones" TETRAHEDRON, vol. 62, 2006, pages 906-914, XP002440675.

Divulga análogos de nucleósidos carbocíclicos los cuales son interesantes por su potencial capacidad de combinar la actividad biológica con una mayor estabilidad metabólica que la de sus homólogos de azúcar. Describe la síntesis de ciclopentenonas comerciales (por ejemplo, 1)

D2 J. -C. MEILLON ET AL: "Rapid access to 2'-branched-carbocyclic nucleosides and their 4'-epimers from 2-alkyl-cyclopentene-1-ones" NUCLEOSIDES, NUCLEOTIDES, AND NUCLEIC ACIDS, vol. 24, 2005, pages 695-699, XP009086084

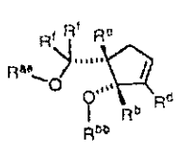
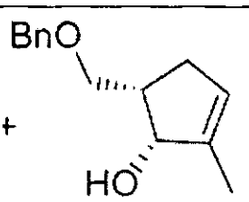
Divulga una nueva ruta de síntesis hacia los nucleósidos carbociclicos-2'-ramificado a partir del 2-metil-2-ciclopenteno-1-ona. Esta metodología fue adaptada de manera eficiente para la preparación de 4'-epi carbociclos. Una serie de esta nueva clase de moléculas se sintetizó como potenciales compuestos antivirales.

Examen de Patentabilidad (Art 14 D486)

Novedad (Art 16 D486)

La reivindicación 19 consiste en un compuesto de fórmula IX

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

Características **esenciales**	**D1**
	
Donde Raa es un grupo protección de hidroxilo	En la posición 5 el oxigeno está protegido con un grupo bencilo.
Rbb y Rb son H,	El carbono 1 tiene como sustituyentes hidrógeno y -OH
Rd es metilo	El carbono 2 se encuentra sustituido por metilo
Re es H	El carbono de la posición 5 el oxigeno está sustituido por un grupo benciloximetil y H

Las características **esenciales** del compuesto de la reivindicación 19 habían sido divulgadas previamente en D1, el cual enseña, un compuesto con fórmula 3b (folio 337, página 907) con la misma estructura divulgada en la presente solicitud.

En consecuencia, la reivindicación 19 no es nueva o carece de novedad, según lo divulgado en el documento D1.

Las reivindicaciones dependientes 20 no menciona alguna característica que haga nueva a la compuesto de la reivindicación 19, por lo cual, no se considera.

En el mismo sentido la reivindicación 21 consiste en un compuesto de fórmula X, el cual es anticipado por el compuesto de fórmula 4 de D1(folio 337, página 907) y compuesto de fórmula 7 de D2 (folio 346, página 696), la reivindicación 24 que consiste en un compuesto de fórmula XI y fórmula XII, los cuales son anticipados por los compuestos de fórmula 5, 6, 8, 9, 19 de D1(folio 337-339, página 907) y compuestos de fórmula 8, 9, 11-13 de D2 (folio 346-347, página 696-697), por lo cual no se consideran nuevos

La reivindicación 28 dependiente de la reivindicación 24 no menciona alguna característica que haga nueva los compuestos de la reivindicación 24 por lo cual tampoco son nuevos.

6. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	XP002440675 GOSSELIN ET AL	19-21, 24 y 28	Novedad
D2	XP009086084 J. -C. MEILLON ET AL	19-21, 24 y 28	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.

JESÚS FERNEL GARCÍA GARCÍA
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha 18 JUL. 2012

Elaborado por: Harvey Alonso Jaramillo
Revisado Por: Jacqueline Alfonso

chosen as the means of introduction of the base[25–27] taking advantage of the presence of the 2′-branching to control the regioselectivity of the reaction. The core of carbocyclic pseudo-nucleosides being a cyclopentane, we were naturally led to cyclopentenones, appropriately substituted in position 2, as our starting point. This class of molecules present several key advantages (a) bearing the targeted 2′-branching, which can be changed by switching to another ketone, (b) having the 3′-oxygen of the future carbocycle, (c) having a double bond ready for epoxidation, (d) having a keto group making possible an α-alkylation for introduction of the 5′-carbon, (e) being achiral and (f) being commercially available at a reasonable price.

2.2. Preparation of key epoxide 4

Introduction of the nucleoside 4′-hydroxymethyl group on ketone **1** (Scheme 1) was not a trivial task: 2-cyclopenten-1-ones are notoriously troublesome substrates for α-alkylation reactions.[28,29] For instance, attempts to react gaseous formaldehyde on the enolate of **1** failed. The successful method came from the use of benzyloxymethyl (BOM) halides as the alkylating agent, which would potentially help introduce an already protected 4′-hydroxymethyl group. Whilst this reaction failed when attempted with BOM chloride at −50 °C and the formation of a complex mixture of products was observed at higher temperatures, freshly prepared BOM bromide[30] gave acceptable yields when it was reacted with the lithium enolate of **1** at −78 °C. When ketone **2** was treated with $LiAlH_4$ at −78 °C, alcohols **3** were obtained in 84% yield as a 2:1 mixture of diastereoisomers favoring the desired trans.

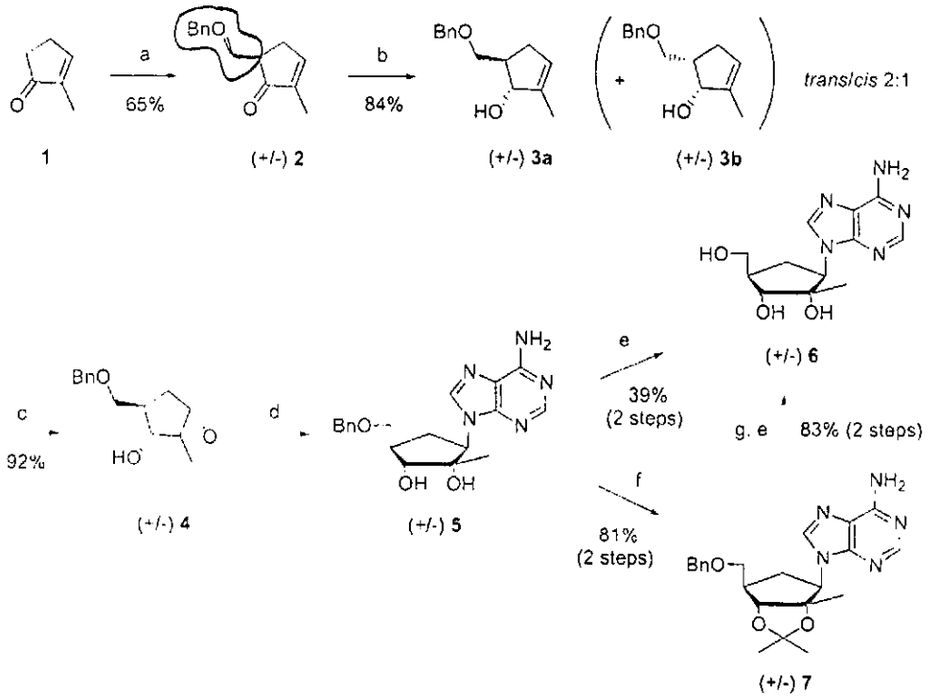
The ratio remained similar at −30 and 0 °C with the concomitant formation of side products. To our delight, alcohols **3a/3b** were very easily separated on silica gel chromatography. The two last nucleoside stereogenic carbons were introduced in one step during the peroxy acid-promoted epoxidation of **3a**. The allylic alcohol allowed perfect control on the stereochemistry of the reaction and epoxide **4** was obtained as the sole product in excellent yield.

2.3. Synthesis of carbocyclic nucleosides

Having everything in place for the introduction of the base, **4** was treated with the sodium salt of adenine in DMF at 100 °C. The 2′-methyl induced a perfect regio- and stereoselectivity, the attack occurring from the β-face on the 1′-carbon exclusively. Due to its poor solubility, purification of nucleoside **5** from the excess of adenine was not satisfactory but could be made much easier when crude **5** was directly protected as its 2′,3′-isopropylidene derivative **7**. Target compound **6** was obtained by either palladium-catalyzed hydrogenolysis of the benzyl protecting group of **5** or double deprotection of **7**. This synthesis resulted in the efficient first synthesis of (+/−)-2′-methyl-aristeromycin **6** in 5–7 steps and 23% overall yield.

A confirmation of the structure of this series of molecules was given by X-ray analysis performed on a single-crystal of **7** grown in DCM/acetone (Fig. 2).

This synthetic method is applicable to other purines, sometimes with minor changes. For instance, guanine reacted very poorly with **4** (ca. 6% yield) but after protection



Scheme 1. Reagents and conditions: (a) LDA, BOM bromide, THF, −78 to −50 °C; (b) $LiAlH_4$, ether, −78 to −60 °C; (c) *m*-CPBA, DCM, 0 °C; (d) NaH, adenine, DMF, 100 °C; (e) palladium hydroxide on charcoal, cyclohexene, MeOH, reflux; (f) *p*-toluenesulfonic acid, 2,2-dimethoxypropane, acetone, RT; (g) trifluoroacetic acid 90%, 0 °C.

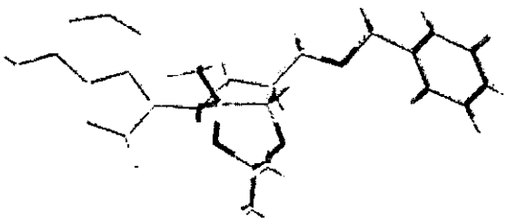
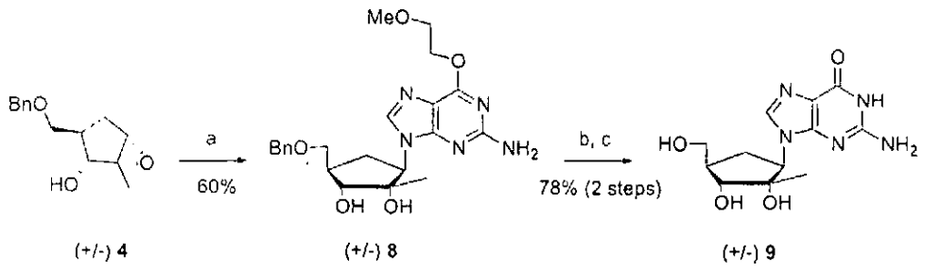


Figure 2. Single-crystal structure of fully protected carbocycle 7 (1*S*,2′*R*,3′*S*,4′*S* enantiomer).

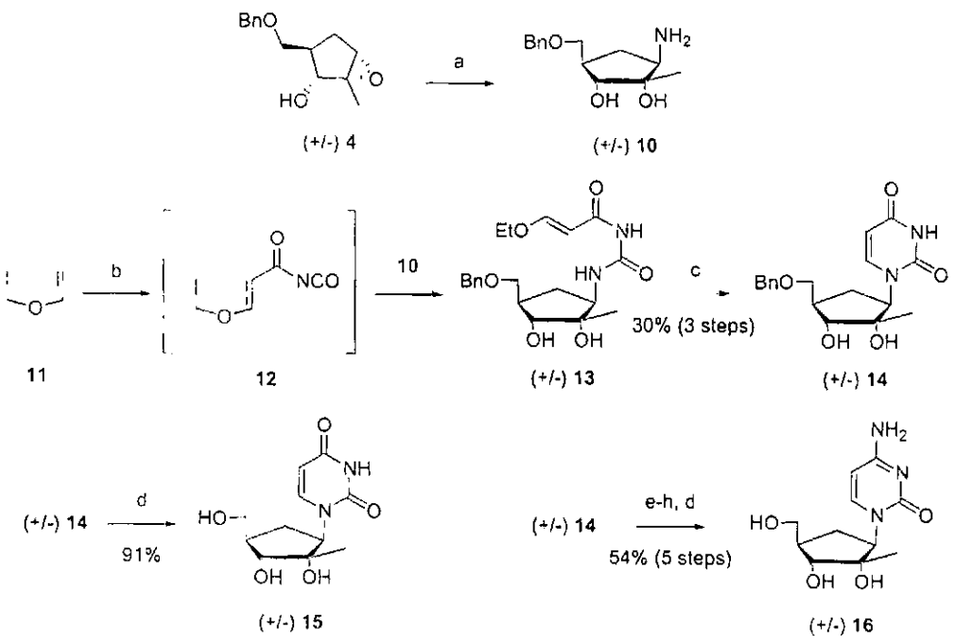
of the base with a methoxyethoxy group,[31,32] the reaction proceeded smoothly and **8** was obtained in reasonable yield (Scheme 2). Carbocycle **8** was then deprotected to afford racemic 2′-methyl-guanosine analogue **9**.

We then turned our attention to the preparation of carbocyclic nucleosides having a pyrimidine base. A slight modification to the general synthesis proved necessary to get acceptable yields. Even though uracil salts were shown to react slowly with epoxides,[32] it was found more advantageous to build the pyrimidine ring by elaboration of the amine group of **10** (Scheme 3). Key epoxide **4** was opened with ammonia with perfect regio- and stereoselective control. Cyclopentylamine **10** was used without purification in a uracil ring-construction process. In order to do that, we adapted previously described procedures:[33–35] ethylvinyl ether **11** was reacted with chlorocarbonyl isocyanate then treated with triethylamine to give isocyanate **12**. The latter compound was directly condensed with **10** in situ. Without prior purification, **13** was cyclized under acidic conditions to afford carbocycle **14**. This 3-step-1-pot synthesis gave access to two pyrimidine derivatives. First, removal of the benzyl-protecting group of **14** afforded uridine analogue **15** in 27% yield from **4**.

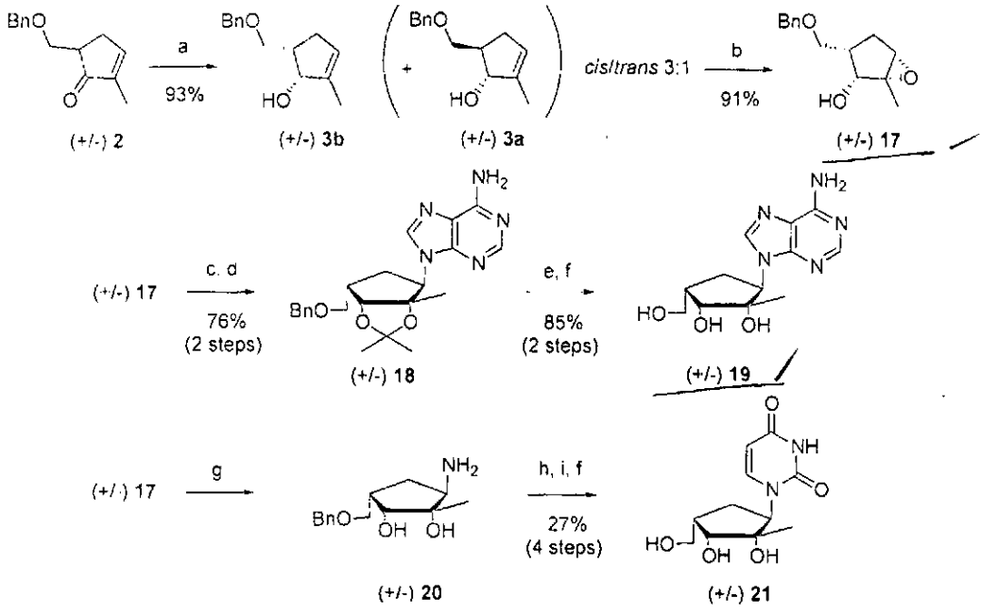
On the other hand, a simple adaptation of the method of Miah et al.[36] provided the cytidine analogue. After protection with an isopropylidene, **14** was activated with *p*-nitrophenol and treated with ammonia. The product was



Scheme 2. Reagents and conditions: (a) NaH, 2-amino-6-(methoxyethoxy)-purine, DMF, 125 °C; (b) 3 N HCl, dioxane, 80 °C; (c) palladium hydroxide on charcoal, cyclohexene, MeOH, reflux.



Scheme 3. Reagents and conditions: (a) NH_3, MeOH, 130 °C; (b) *N*-(chlorocarbonyl)-isocyanate, THF, 0 °C then Et_3N, 0 °C then **10**, −40 °C; (c) 1 N H_2SO_4, dioxane, 100 °C; (d) palladium hydroxide on charcoal, cyclohexene, MeOH, reflux; (e) *p*-toluenesulfonic acid, 2,2-dimethoxypropane, acetone, RT; (f) trifluoroacetic anhydride, *N*-methylpyrrolidine then *p*-nitrophenol, MeCN, 0 °C; (g) NH_3, MeOH, 60 °C; (h) trifluoroacetic acid 90%, 0 °C.



Scheme 4. Reagents and conditions: (a) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, 0 °C; (b) *m*-CPBA, DCM, 0 °C; (c) NaH, adenine, DMF, 100 °C; (d) *p*-toluenesulfonic acid, 2,2-dimethoxypropane, acetone, RT; (e) trifluoroacetic acid 90%, 0 °C; (f) palladium hydroxide on charcoal, cyclohexene, MeOH, reflux; (g) NH_3, MeOH, 130 °C; (h) *N*-chlorocarbonyl-isocyanate, THF, 0 °C then Et_3N, 0 °C then **20**, −40 °C; (i) 1 N H_2SO_4, dioxane, 100 °C.

directly deprotected to give (+/−)-2′-methyl-carbodine **16** in 5 steps and 54% yield from **14**.

2.4. Synthesis of 4′-epi-carbocyclic nucleosides

An interesting feature of our carbocycle synthesis is the possibility of using the minor product of the reduction step of ketone **2** (Scheme 1), cis-alcohol **3b**, for the straightforward preparation of seldom reported 4′-epi-carbocycles.[37] Moreover, after reinvestigation of the reduction of **2**, it proved possible to change dramatically the stereochemical outcome of the reaction. When **2** was subjected to Luche's reduction conditions ($NaBH_4$ in presence of Ce^{3+}),[38,39] **3b** was obtained as the major product of a 3:1 mixture in excellent yield (Scheme 4). Diol **3b** was epoxidized with *m*-chloroperoxybenzoic acid to give **17** as the sole product of the reaction. Then, the chemistry previously described for **4** was applied to **17**. Reaction with adenine sodium salt followed by protection led to carbocycle **18**. In a similar fashion to **7**, the structure of this compound was confirmed by X-ray diffraction of a single crystal grown in DCM/acetone. After two deprotections, racemic 2′-methyl-4′-epi-aristeromycin **19** was obtained in good yield. On the other hand, when submitted to epoxide-opening conditions with ammonia, **17** led to cyclopentylamine **20**. The latter was used in the uracil-ring construction process described for **10** to afford uridine derivative **21** in moderate yield.

3. Conclusion

We have developed a new route for the synthesis of carbocyclic nucleosides. This method was also used for the preparation of 4′-epi-carbocycles. 2-Cyclopenten-1-ones give rapid access to a large number of compounds of potential antiviral interest through key intermediates **4** and **17**. Furthermore, the introduction of any 2′-branching-group can be achieved by using the appropriate ketone as a starting material. This versatile approach gives the shortest access to racemic carbocylic nucleosides reported so far.

Compounds **6**, **9**, **15**, **16**, **19** and **21** were evaluated for antiviral activity in cell culture experiments toward the following viruses: Bovine Viral Diarrhea, Hepatitis B, Human Immunodeficiency, Dengue and West Nile. No activity was found for any of these molecules, nor was there any cytotoxicity to the host cells.

4. Experimental

4.1. General

All ^1H chemical shifts are reported in δ relative to $CHCl_3$ (δ 7.26) or DMSO (δ 2.55). All ^{13}C chemical shifts are reported in δ relative to $CDCl_3$ (centre of triplet, δ 77.2) or DMSO-d_6 (centre of septet, δ 39.5). The spin multiplicities are indicated by the symbols s (singlet), d (doublet), t (triplet), m (multiplet) and, br (broad). Reactions were monitored by thin-layer chromatography (TLC) using Merck silica gel 60-F_{254} precoated plates with visualization by irradiation with a UV lamp or by charring after immersion in a solution of $(NH_4)_2SO_4$ and H_2SO_4 in aqueous EtOH or by charring after immersion in a 5% solution of ninhydrin in EtOH. TLC plates were developed with solvent systems (A) EtOAc/hexanes 1:1, (B) DCM/MeOH 9:1 or (C) DCM/MeOH 8:2. Column chromatographies were performed on either silica gel 60 (normal phase) or C_{18}-branched silica gel 40–63 μm (reverse phase) and eluted with the indicated solvent system. Yields refer to chromatographically and spectroscopically (NMR)

homogeneous materials. The reactions were generally carried out in an argon atmosphere using Fluka dry solvents. BOM bromide was synthesized according to Ref. 30 using either paraformaldehyde or trioxane indifferently. 2-Amino-6 (methoxyethoxy)-purine was synthesized according to Ref. 31. All other chemicals were purchased from Sigma-Aldrich or Acros.

4.1.1. (+/−)-2-Methyl-5-(benzyloxymethyl)-2-cyclopenten-1-one (2). To a solution of 2-methyl-2-cyclopenten-1-one **1** (15.0 g, 156 mmol) in THF (600 mL) was added dropwise a 1.8 M solution of LDA in hexanes (87 mL, 157 mmol) at −78 °C over 10 min. The solution was stirred for 1 h at −78 °C. Then, freshly prepared BOM bromide (purity ca. 70% by NMR) (48.0 g, 167 mmol) was added dropwise over 10 min. The solution was stirred for 3 h at −78 °C then allowed to warm up to −50 °C over 1.5 h. The reaction was quenched with sat. $NaHCO_3$ solution (300 mL) and THF was evaporated. The residue was taken up in EtOAc (400 mL) and the solution was extracted with sat. $NaHCO_3$ solution (2×400 mL) and brine (400 mL). The organic phase was dried over Na_2SO_4 and the solvent was evaporated. The residue was purified by column chromatography (hexanes/EtOAc 9:1) to afford **2** (22.0 g, 65%) as a pale yellow oil: TLC R_f=0.47 (A); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.81 (m, 3H), 2.55–2.80 (m, 3H), 3.64 (dd, 1H, J=6.4, 9.2 Hz), 3.77 (dd, 1H, J=3.8, 9.2 Hz), 4.52 (s, 2H), 7.36 (m, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 9.6, 30.6, 45.1, 69.2, 72.4, 126.9, 127.6, 137.5, 140.7, 157.2, 208.7; HRMS(FAB) Calcd $[M+H]^+$ ($C_{14}H_{17}O_2$): 217.1229, found: 217.1216.

4.1.2. (+/−)-2-Methyl-5-(benzyloxymethyl)-2-cyclopenten-1-ol (3). *Method A.* To a suspension of $LiAlH_4$ (2.2 g, 57.1 mmol) in ether (175 mL) at −78 °C was added dropwise a solution of **2** (12.3 g, 57.0 mmol) in ether (75 mL) over 10 min. The slurry was stirred and slowly warmed up to −60 °C over 2 h. Then, the reaction was quenched with successive careful additions of EtOAc (30 mL), MeOH (30 mL) and H_2O (200 mL). The milky aqueous phase was washed with ether (2×100 mL). The organic phases were pooled and washed with H_2O (2×300 mL), dried over Na_2SO_4 and the solvents were evaporated. The residue was purified by column chromatography (hexanes/EtOAc 9:1). The first eluted product was **3b** (3.5 g, 28%), which was obtained as a colorless oil: TLC R_f=0.47 (A); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.81 (m, 3H), 2.26 (m, 2H), 2.59 (m, 2H), 3.69 (m, 2H), 4.57 (s, 2H), 4.61 (br, 1H), 5.52 (m, 1H), 7.36 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.4, 33.0, 40.8, 69.8, 72.6, 79.1, 126.5, 127.1, 127.8, 137.6, 141.3; HRMS(FAB) Calcd $[M+H]^+$ ($C_{14}H_{19}O_2$): 219.1385, found: 219.1403. This product was followed by **3a** (7.0 g, 56%) as a colorless oil: TLC R_f=0.42 (A); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.78 (m, 3H), 1.96 (m, 1H), 2.12 (br, 1H), 2.37–2.59 (m, 2H), 3.56 (m, 2H), 4.46 (br, 1H), 4.58 (s, 2H), 5.45 (m, 1H), 7.35 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.0, 32.6, 47.6, 72.3, 72.4, 81.7, 125.5, 127.0, 127.1, 127.7, 137.8, 140.5; HRMS(FAB) Calcd $[M+H]^+$ ($C_{14}H_{19}O_2$): 219.1385, found: 219.1404.

Method B. To a solution of **2** (2.0 g, 9.2 mmol) in MeOH (55 mL) was added $CeCl_3 \cdot 7H_2O$ (3.4 g, 14.0 mmol) at 0 °C. The solution was stirred for 30 min at this temperature. Then, $NaBH_4$ (0.7 g, 18.4 mmol) was carefully added portionwise. The milky suspension was allowed to warm up to room temperature and stirred for 3 h. The reaction was quenched by addition of acetic acid (3 mL) and MeOH was evaporated. The remaining solid was taken up in EtOAc (100 mL) and extracted with sat. NH_4Cl solution (2×100 mL), sat. $NaHCO_3$ solution (100 mL) and brine (100 mL). The organic phase was dried over Na_2SO_4 and the solvent was evaporated. The residue was purified by column chromatography (hexanes/EtOAc 9:1) to afford **3b** (1.4 g, 70%) and **3a** (0.5 g, 23%) as colorless oils.

4.1.3. (+/−)-(1α,2β,3α,5α)-1-Methyl-2-hydroxy-3-(benzyloxymethyl)-6-oxabicyclo[3.1.0]hexane (4). To a solution of **3a** (2.0 g, 9.2 mmol) in DCM (45 mL) was added *m*-chloroperoxybenzoic acid 77% (2.8 g, 12.0 mmol) at 0 °C. The solution was stirred at 0 °C for 1 h and then allowed to warm-up to room temperature over 2 h. To the white suspension was added sat. $NaHCO_3$ solution (50 mL). The mixture was extracted with EtOAc/sat. $NaHCO_3$ solution (100 mL each). The organic phase was washed with H_2O (2×100 mL), dried over Na_2SO_4 and evaporated to dryness. The residue was purified by column chromatography (hexanes/EtOAc 8:2) to afford **4** (2.0 g, 92%) as a colorless oil, which solidified in the fridge: TLC R_f=0.25 (A); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (s, 3H), 1.56 (m, 1H), 1.89 (m, 1H), 2.12 (m, 1H), 2.29 (br, 1H), 3.31 (s, 1H), 3.49 (dd, 1H, J=6.3, 9.1 Hz), 3.62 (dd, 1H, J=5.1, 9.1 Hz), 3.90 (d, 1H, J=7.4 Hz), 4.54 (s, 2H), 7.36 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 27.9, 40.9, 60.7, 64.6, 69.9, 72.4, 76.6, 126.9, 127.7; 137.7; HRMS(FAB) Calcd $[M+H]^+$ ($C_{14}H_{19}O_3$): 235.1334, found: 235.1348.

4.1.4. (+/−)-2′-*C*-Methyl-5′-*O*-benzyl-aristeromycin (5). *Method A.* To a suspension of adenine (1.75 g, 12.9 mmol) in DMF (30 mL) was added NaH (60% oil dispersion) (0.43 g, 10.8 mmol) at room temperature. After the evolution of hydrogen had ceased, the creamy suspension was stirred at 80 °C for 20 min. Epoxide **4** (1.04 g, 4.3 mmol) dissolved in DMF (20 mL) was added via a syringe. The resulting suspension was stirred at 100 °C for 18 h then cooled down to room temperature. The solid was filtered over celite and rinsed with DCM. The filtrate was evaporated. The brown residue was purified by column chromatography (DCM/MeOH 94:6) to afford **5** (0.65 g, 41%) as a beige powder: TLC R_f=0.20 (B); mp 180.4–181.5 °C; ^{1}H NMR (200 MHz, DMSO) δ 0.68 (s, 3H), 2.09–2.46 (m, 3H), 3.65–3.74 (m, 3H), 4.56 (s, 2H), 4.65 (s, 1H), 4.73 (m, 1H), 4.90 (d, 1H, J=6.3 Hz), 7.23 (br, 2H), 7.32 (m, 5H), 8.12 (s, 1H), 8.16 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO) δ 20.6, 28.9, 42.0, 60.8, 70.7, 72.0, 76.2, 78.4, 118.5, 127.2, 127.3, 128.1, 138.4, 139.8, 149.7, 152.0, 155.8; HRMS(FAB) Calcd $[M+H]^+$ ($C_{19}H_{24}N_5O_3$): 370.1879, found: 370.1861.

Method B. A solution of **7** (500 mg, 1.22 mmol) in TFA 90% (8 mL) was stirred for 1 h at 0 °C. Then, the solution was basified by the addition of ammonia-saturated methanol and the solvents were evaporated. The residue was taken up in cold H_2O (ca. 10 mL) and filtered. The solid was washed with cold H_2O and dried in the oven at 60 °C under vacuum. Carbocyclic nucleoside **5** was obtained (400 mg, 90%) as a white solid.

4.1.5. (+/−)-2′-*C*-Methyl-aristeromycin (6). A solution of **5** (330 mg, 0.89 mmol) in MeOH (30 mL) was treated with palladium hydroxide (20% on charcoal) (200 mg) at 0 °C. Cyclohexene (10 mL) was added and the mixture was refluxed for 15 h. The suspension was cooled down to room temperature, filtered over celite and the solvents were evaporated. The residue was crystallized from H_2O to afford **6** (228 mg, 92%) as a white powder: TLC R_f=0.21 (C); mp 209.1–210.2 °C; UV (H_2O) λ_{max}=259 nm (ε=13,100); ^{1}H NMR (300 MHz, DMSO) δ 0.68 (s, 3H), 1.95–2.22 (m, 2H), 2.38 (m, 1H), 3.58–3.77 (m, 3H), 4.62 (m, 1H), 4.68–4.89 (m, 3H), 7.23 (br, 2H), 8.14 (s, 1H), 8.26 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO) δ 20.6, 28.4, 44.0, 60.6, 61.1, 75.7, 78.7, 118.4, 139.8, 149.8, 152.0, 155.8; HRMS(FAB) Calcd $[M+H]^+$ ($C_{12}H_{18}N_5O_3$): 280.1410, found: 280.1402.

4.1.6. (+/−)-2′-*C*-Methyl-2′,3′-*O*-isopropylidene-5′-*O*-benzyl-aristeromycin (7). This synthesis began like the preparation of **5** using 500 mg (2.13 mmol) of epoxide **4**. After evaporation of DMF, the brown residue was suspended in acetone (32 mL) and 2,2-dimethoxypropane (8 mL). The suspension was acidified with *p*-toluenesulfonic acid (300 mg, 1.75 mmol) and stirred for 2 h at room temperature. The mixture was filtered, the solid was washed with acetone and the filtrate was neutralized with pyridine (300 μL). The solvents were evaporated. The residue was taken up in DCM (100 mL) and extracted successively with H_2O (100 mL), 1 N HCl (100 mL), sat. $NaHCO_3$ solution (100 mL) and brine (100 mL). The organic phase was dried over Na_2SO_4 and the solvent was evaporated. The remaining solid was purified by column chromatography (DCM/MeOH 96:4) to afford **7** (695 mg, 81%) as a beige powder: TLC R_f=0.38 (B); mp 200.4–201.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 3H), 1.39 (s, 3H), 1.68 (s, 3H), 2.46 (m, 1H), 2.57 (m, 1H), 2.85 (m, 1H), 3.65 (m, 2H), 4.27 (d, 1H, J=2.7 Hz), 4.63 (s, 2H), 5.05 (dd, 1H, J=6.7, 13.5 Hz), 5.97 (br, 2H), 7.35 (m, 5H), 7.87 (s, 1H), 8.36 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.7, 25.9, 27.8, 30.3, 40.2, 63.9, 70.1, 72.6, 86.3, 88.3, 112.4, 119.2, 127.0, 127.1, 127.8, 137.4, 139.8, 150.3, 151.5, 154.4; HRMS(FAB) Calcd $[M+H]^+$ ($C_{22}H_{28}N_5O_3$): 410.2192, found: 410.2203.

4.1.7. (+/−)-2-Amino-6-deamino-6-(methoxyethoxy)-2′-*C*-methyl-5′-*O*-benzyl-aristeromycin (8). A suspension of 2-amino-6-(methoxyethoxy)-purine (950 mg, 4.54 mmol) in DMF (8 mL) was treated with NaH (60% oil dispersion) (160 mg, 4.00 mmol) at room temperature. After the evolution of hydrogen had ceased, the suspension was stirred at 80 °C for 20 min. Epoxide **4** (375 mg, 1.60 mmol) dissolved in DMF (8 mL) was added via a syringe. The resulting brown solution was stirred at 125 °C for 48 h then cooled down to room temperature. The DMF was evaporated. The brown residue was purified by column chromatography (DCM/MeOH 96:4) to afford **8** (425 mg, 60%) as a beige powder: TLC R_f=0.45 (B); mp 175.7–176.6 °C; ^{1}H NMR (200 MHz, DMSO) δ 0.70 (s, 3H), 1.94 (m, 1H), 2.23 (m, 1H), 2.44 (m, 1H), 3.32 (s, 3H), 3.62–3.72 (m, 5H), 4.49–4.66 (s, 6H), 4.91 (d, 1H, J=6.4 Hz), 6.41 (br, 2H), 7.33 (m, 5H), 7.92 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO) δ 20.6, 29.2, 41.9, 57.9, 59.8, 64.4, 69.9, 70.8, 72.0, 76.2, 78.5, 113.3, 127.2, 128.1, 138.3, 138.4, 154.5, 159.3, 160.0; HRMS(FAB) Calcd $[M+H]^+$ ($C_{22}H_{30}N_5O_5$): 444.2247, found: 444.2254.

4.1.8. (+/−)-2′-*C*-Methyl-carbocyclic guanosine (9). A solution of **8** (400 mg, 0.90 mmol) in 3 N HCl (70 mL) was stirred for 3 h at 80 °C. Then, the solution was cooled down, evaporated and the residue was basified with ammonia-saturated MeOH. The solvent was evaporated and the residue was rapidly purified by column chromatography (DCM/MeOH 88:12) to afford 2′-*C*-methyl-5′-*O*-benzyl-carbocyclic guanosine as a beige solid: TLC R_f=0.30 (C); ^{1}H NMR (200 MHz, DMSO) δ 0.71 (s, 3H), 1.88 (m, 1H), 2.23 (m, 1H), 2.40 (m, 1H), 3.59–3.66 (m, 3H), 4.49–4.55 (m, 4H), 4.93 (d, 1H, J=6.2 Hz), 6.52 (br, 2H), 7.34 (m, 5H), 7.75 (s, 1H), 10.64 (br, 1H). A solution of the above 2′-*C*-methyl-5′-*O*-benzyl-carbocyclic guanosine (295 mg, 0.77 mmol) in MeOH (20 mL) was treated with palladium hydroxide (20% on charcoal) (150 mg) at 0 °C. Cyclohexene (5 mL) was added and the mixture was refluxed for 15 h. The suspension was cooled down to room temperature, filtered over celite and the solvents were evaporated. The residue was purified by reverse phase column chromatography (H_2O/MeOH 95:5) to afford **9** (205 mg, 78% from **8**) as a white solid: TLC R_f=0.10 (C); mp >230 °C (dec); UV (H_2O) λ_{max}=252 nm (ε=11,200); ^{1}H NMR (300 MHz, DMSO) δ 0.73 (s, 3H), 1.88 (m, 1H), 2.06 (m, 1H), 2.36 (m, 1H), 3.60–3.66 (m, 3H), 4.42 (s, 1H), 4.52 (m, 1H), 4.73–4.79 (m, 2H), 6.42 (br, 2H), 7.82 (s, 1H), 10.56 (br, 1H); ^{13}C NMR (75.5 MHz, DMSO) δ 15.7, 20.6, 43.9, 59.5, 60.7, 75.6, 78.8, 116.1, 135.8, 151.5, 153.3, 157.1; HRMS(FAB) Calcd $[M+H]^+$ ($C_{12}H_{18}N_5O_4$): 296.1359, found: 296.1339.

4.1.9. (+/−)-(1β,2β,3α,5α)-1,2-Dihydroxy-1-methyl-3-(benzyloxymethyl)-5-amino-cyclopentane (10). A solution of **4** (900 mg, 3.84 mmol) in ammonia-saturated MeOH (20 mL) was heated at 130 °C under pressure for 3 h. The solution was cooled down, degassed and evaporated to dryness to get 960 mg of **10** as an oily brown residue, which was found homogeneous by TLC and used in the next step without purification: TLC R_f=0.14 (C).

4.1.10. (+/−)-2′-*C*-Methyl-5′-*O*-benzyl-carbocyclic uridine (14). To a solution of *N*-(chlorocarbonyl) isocyanate (894 mg, 8.51 mmol) in THF (9 mL) was slowly added a solution of ethylvinyl ether (804 mg, 11.15 mmol) in THF (6 mL) at 0 °C. The resulting solution was stirred for 20 min at 0 °C. Then, triethylamine (852 mg, 8.42 mmol) in THF (9 mL) was slowly added. The resulting suspension was stirred for 5 min at 0 °C and then, cooled down to −40 °C. A solution of amine **10** (1.920 g, 7.64 mmol) in THF (9 mL) was rapidly added to the mixture and the suspension was allowed to slowly warm up to room temperature. Then, THF was evaporated and the residue was dissolved in dioxane (6 mL). To this solution was added 1 N H_2SO_4 (9 mL) and the mixture was heated at 100 °C for 2 h. Then, the solution was cooled down to room temperature and basified with 3 N ammonia (7 mL). The ammonium salts were precipitated with MeOH and the suspension was filtered. The filtrate was evaporated to dryness and the crude material was purified by column chromatography (DCM/MeOH 96:4) to afford **14** (798 mg, 30%) as a white solid: TLC R_f=0.32 (B); mp

183.1–184.2 °C: ^{1}H NMR (300 MHz, DMSO) δ 0.89 (s, 3H), 1.61 (m, 1H), 2.16 (m, 1H), 2.29 (m, 1H), 3.48 (d, 1H, J=9.5 Hz), 3.62 (m, 2H), 4.52 (s, 2H), 4.67 (m, 1H), 5.25 (dd, 1H, J=2.2, 8.1 Hz), 7.34 (m, 5H), 7.66 (d, 1H, J=8.1 Hz), 11.26 (br, 1H): ^{13}C NMR (75.5 MHz, DMSO) δ 20.4, 27.5, 41.8, 61.2, 70.0, 72.2, 76.0, 78.6, 100.7, 127.3, 127.4, 128.1, 138.2, 142.9, 151.2, 162.7; HRMS(FAB) Calcd $[M-H]^-$ ($C_{18}H_{21}N_2O_5$): 347.1607, found: 347.1616.

4.1.11. (+/−)-2′-*C*-Methyl-carbocyclic uridine (15). A solution of **14** (250 mg, 0.72 mmol) in MeOH (20 mL) was cooled down to 0 °C and treated with palladium hydroxide (20% on charcoal) (180 mg). Cyclohexene (7 mL) was added and the mixture was refluxed for 15 h. The suspension was cooled down to room temperature, filtered on celite and the solvents were evaporated. The residue was crystallized from MeOH/*i*-propyl ether to afford **15** (164 mg, 91%) as white crystals: TLC R_f=0.27 (C): mp 181.6–182.5 °C; UV (H_2O) λ_{max}=267 nm (ε=9900): ^{1}H NMR (200 MHz, DMSO) δ 0.92 (s, 3H), 1.61 (m, 1H), 2.00 (m, 1H), 2.17 (m, 1H), 3.44 (m, 1H), 3.56 (m, 2H), 4.39 (s, 1H), 4.67–4.76 (m, 3H), 5.59 (d, 1H, J=8.0 Hz), 7.72 (d, 1H, J=8.0 Hz), 11.29 (br, 1H): ^{13}C NMR (75.5 MHz, DMSO) δ 20.6, 27.0, 43.6, 60.4, 61.1, 75.8, 78.6, 100.9, 142.9, 151.2, 162.8; HRMS(FAB) Calcd $[M-H]^-$ ($C_{11}H_{17}N_2O_5$): 257.1137, found: 257.1139.

4.1.12. (+/−)-2′-*C*-Methyl-carbodine (16). A suspension of **14** (300 mg, 0.87 mmol) in acetone (25 mL) and 2,2-dimethoxypropane (8 mL) was treated with *p*-toluenesulfonic acid (50 mg, 0.3 mmol). After dissolution of the materials, the solution was stirred for 1 h at room temperature. Then, the mixture was neutralized with pyridine (50 μL) and the solvents were evaporated. The residue was rapidly purified by column chromatography (DCM/MeOH 95:5) to afford 2′-*C*-methyl-2′,3′-*O*-isopropylidene-5′-*O*-benzyl-carbocyclic uridine as a white solid: TLC R_f=0.48 (B): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.37 (s, 3H), 1.61 (s, 3H), 2.12–2.22 (m, 2H), 2.47 (m, 1H), 3.51–3.67 (m, 2H), 4.17 (d, 1H, J=2.9 Hz), 4.58 (s, 2H), 5.13 (m, 1H), 5.67 (dd, 1H, J=2.3, 8.1 Hz), 7.22 (d, 1H, J=8.1 Hz), 7.36 (m, 5H), 9.29 (br, 1H). To a solution of the above 2′-*C*-methyl-2′,3′-*O*-isopropylidene-5′-*O*-benzyl-carbocyclic uridine (280 mg, 0.73 mmol) in MeCN (8 mL) was added *N*-methylpyrrolidine (700 μL) and trifluoroacetic anhydride (300 μL, 2.12 mmol) at 0 °C. The mixture was stirred for 30 min then *p*-nitrophenol (300 mg, 2.16 mmol) was added. The yellow solution was stirred for 3 h at 0 °C. The mixture was diluted with DCM (20 mL) and extracted with 1 N HCl (20 mL), sat. $NaHCO_3$ solution (3×20 mL) and brine (20 mL). The organic phase was dried over Na_2SO_4 and the solvents were evaporated. The residue was taken up in ammonia-saturated MeOH (30 mL) and stirred at 60 °C for 15 h. The solvent was evaporated and the residue was purified by column chromatography (DCM/MeOH 94:6) to afford 2′-*C*-methyl 2′,3′-*O*-isopropylidene-5′-*O*-benzyl-carbodine as a yellowish solid: TLC R_f=0.23 (B): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23 (s, 3H), 1.36 (s, 3H), 1.60 (s, 3H), 2.09–2.22 (m, 2H), 2.44 (m, 1H), 3.51–3.64 (m, 2H), 4.15 (d, 1H, J=3.5 Hz), 4.57 (s, 2H), 5.18 (m, 1H), 5.72 (d, 1H, J=7.4 Hz), 7.21 (d, 1H, J=7.4 Hz), 7.35 (m, 5H). A solution of the above 2′-*C*-methyl-2′,3′-*O*-isopropylidene-5′-*O*-benzyl-carbodine (202 mg, 0.52 mmol) in TFA 90% (5 mL) was stirred for 1 h at 0 °C. Then, the solution was basified by the addition of ammonia-saturated methanol and the solvents were evaporated. The residue was taken up in cold H_2O and filtered. The solid was washed with cold H_2O and dried in the oven at 60 °C under vacuum. 2′-*C*-methyl-5′-*O*-benzyl-carbodine was obtained as an off-white solid and used directly in the next step: TLC R_f=0.51 (C). A solution of 2′-*C*-methyl-5′-*O*-benzyl-carbodine (172 mg, 0.50 mmol) in MeOH (20 mL) was cooled down to 0 °C and treated with palladium hydroxide (20% on charcoal) (120 mg). Cyclohexene (7 mL) was added and the mixture was refluxed for 15 h. The suspension was cooled down to room temperature, filtered on celite and the solvents were evaporated. The residue was crystallized from MeOH/*i*-propyl ether to afford **16** (112 mg, 54% from **14**) as a white powder: TLC R_f=0.20 (C): mp >200 °C (dec): UV (H_2O) λ_{max}=274 nm (ε=7400): ^{1}H NMR (200 MHz, DMSO) δ 0.85 (s, 3H), 1.60 (m, 1H), 1.92–2.19 (m, 2H), 3.49–3.63 (m, 3H), 4.54–4.79 (m, 4H), 5.73 (d, 1H, J=7.4 Hz), 7.26 (br, 2H), 7.66 (d, 1H, J=7.4 Hz): ^{13}C NMR (75.5 MHz, DMSO) δ 20.9, 27.4, 44.0, 60.8, 62.3, 76.1, 78.5, 93.4, 143.8, 155.4; 164.0; HRMS(FAB) Calcd $[M+H]^+$ ($C_{11}H_{18}N_3O_4$): 256.1297, found: 256.1302.

4.1.13. (+/−)-(1β,2β,3α,5β)-1-Methyl-2-hydroxy-3-(benzyloxymethyl)-6-oxabicyclo[3.1.0]hexane (17). The preparation was carried out as described for **4**, using **3b** in place of **3a**. Epoxide **17** was obtained in 91% yield as a colorless oil, which solidified in the fridge: TLC R_f=0.25 (A): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.53 (s, 3H), 1.75 (dd, 1H, J=2.1, 14.9 Hz), 1.98 (dd, 1H, J=9.5, 14.9 Hz), 2.51 (m, 1H), 3.29 (s, 1H), 3.38 (dd, 1H, J=5.3, 9.0 Hz), 3.94 (dd, 1H, J=9.0, 9.5 Hz), 4.29 (d, 1H, J=8.2 Hz), 4.46 (d, 1H, J=11.7 Hz), 4.58 (d, 1H, J=11.7 Hz), 7.36 (m, 5H): ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.3, 28.7, 37.0, 61.4, 66.8, 72.4, 72.5, 75.6, 127.1, 127.8; 137.1; HRMS(FAB) Calcd $[M+H]^+$ ($C_{14}H_{19}O_3$): 235.1334, found: 235.1343.

4.1.14. (+/−)-2′-*C*-Methyl-2′,3′-*O*-isopropylidene-4′-epi-5′-*O*-benzyl-aristeromycin (18). The preparation was carried out as described for **7**, using **17** in place of **4**. Carbocyclic nucleoside **18** was obtained in 76% yield (2 steps) as a beige powder: TLC R_f=0.37 (B); mp 104.8–105.7 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.01 (s, 3H), 1.40 (s, 3H), 1.56 (s, 3H), 2.34 (m, 1H), 2.48 (m, 1H), 3.11 (m, 1H), 3.74 (m, 2H), 4.44 (d, 1H, J=4.0 Hz), 4.62 (m, 2H), 5.01 (dd, 1H, J=2.2, 7.1 Hz), 6.38 (br, 2H), 7.35 (m, 5H), 7.88 (s, 1H), 8.40 (s, 1H): ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.0, 25.3, 26.9, 31.9, 42.3, 63.9, 68.9, 72.7, 85.9, 91.6, 110.5, 118.9, 127.0, 127.7, 137.6, 138.7, 149.9, 152.1, 154.7; HRMS(FAB) Calcd $[M+H]^+$ ($C_{22}H_{28}N_5O_3$): 410.2192, found: 410.2173.

4.1.15. (+/−)-2′-*C*-Methyl-4′-epi-aristeromycin (19). The preparation was carried out as described for **6**, using **18** in place of **7**. Carbocyclic nucleoside **19** was obtained in 85% yield (2 steps) as a white powder: TLC R_f=0.23 (C): mp 254.3–255.2 °C; UV (H_2O) λ_{max}=260 nm (ε=13,600): ^{1}H NMR (200 MHz, DMSO) δ 0.88 (s, 3H), 1.95 (m, 1H), 2.56 (m, 2H), 3.44 (m, 1H), 3.61 (m, 1H), 3.71 (m, 1H), 4.50 (t, 1H, J=5.1 Hz), 4.80 (s, 1H), 4.87 (m, 1H), 4.90 (d, 1H,

J=5.1 Hz), 7.21 (br, 2H), 8.12 (s, 1H), 8.17 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO) δ 20.4, 27.5, 40.5, 60.9, 61.4, 76.5, 80.1, 118.7, 140.7, 150.0, 151.8, 155.8; HRMS(FAB) Calcd $[M+H]^-$ ($C_{12}H_{18}N_5O_3$): 280.1410, found: 280.1417.

4.1.16. (+/−)-(1β,2β,3β,5α)-1,2-Dihydroxy-1-methyl-3-(benzyloxymethyl)-5-amino-cyclopentane (20). The preparation was carried out as described for **10**, using **17** in place of **4**. Cyclopentylamine **20** was obtained as a brown oil and directly used in the next step without purification: TLC R_f=0.13 (C).

4.1.17. (+/−)-2′-*C*-Methyl-4′-epi-carbocyclic uridine (21). The preparation was carried out as described for **15**, using **17** in place of **4**. Carbocyclic nucleoside **21** was obtained in 27% yield (4 steps from **17**) as a white powder: TLC R_f=0.29 (C); mp 195.5–196.4 °C; UV (H_2O) λ_{max}= 267 nm (ε=10,400); ^{1}H NMR (200 MHz, DMSO) δ 1.00 (s, 3H), 1.87 (m, 2H), 2.31 (m, 1H), 3.40 (dd, 1H, J=6.8, 10.5 Hz), 3.60 (m, 2H), 4.49 (m, 2H), 4.82 (d, 1H, J= 4.2 Hz), 4.89 (m, 1H), 5.54 (d, 1H, J=8.0 Hz), 7.67 (d, 1H, J=8.0 Hz), 11.23 (br, 1H); ^{13}C NMR (75.5 MHz, DMSO) δ 20.4, 27.1, 40.5, 60.7, 61.0, 76.5, 79.9, 100.3, 143.5, 151.4, 162.9; HRMS(FAB) Calcd $[M+H]^-$ ($C_{11}H_{17}N_2O_5$): 257.1137, found: 257.1140.

4.2. X-ray crystallographic data

Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 284302 and 284303.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.10.037

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RAPID ACCESS TO 2′-BRANCHED-CARBOCYCLIC NUCLEOSIDES AND THEIR 4′-EPIMERS FROM 2-ALKYL-CYCLOPENTENE-1-ONES

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- *2-Methyl-2-cyclopentene-1-one was used as starting material in a novel route toward 2′-branched-carbocyclic nucleosides. This methodology was efficiently adapted to the preparation of 4′-epi-carbocycles. A series of this new class of molecules was synthesized as potential antiviral compounds.*

Keywords 2′-*C*-Methyl Branched Nucleosides, Carbocyclic Nucleosides, Cyclopentenones

INTRODUCTION

Modified nucleosides are currently the object of a huge effort in medicinal chemistry as they remain amongst the most promising molecules for potential antiviral activity. For instance telbivudine (L-dT), the L enantiomer of natural 2′-deoxythymidine, is a powerful new drug candidate selective against hepatitis B virus.[1,2] Furthermore, 2′-*C*-methyl ribonucleosides were recently shown to possess very interesting potential for hepatitis C chemotherapy.[3,4] These observations prompted us to consider the preparation of carbocyclic analogs of 2′-*C*-branched ribonucleosides. In general, carbocycles show increased stability in vivo when compared to nucleosides,[5,6] coupled with biological activity in some examples

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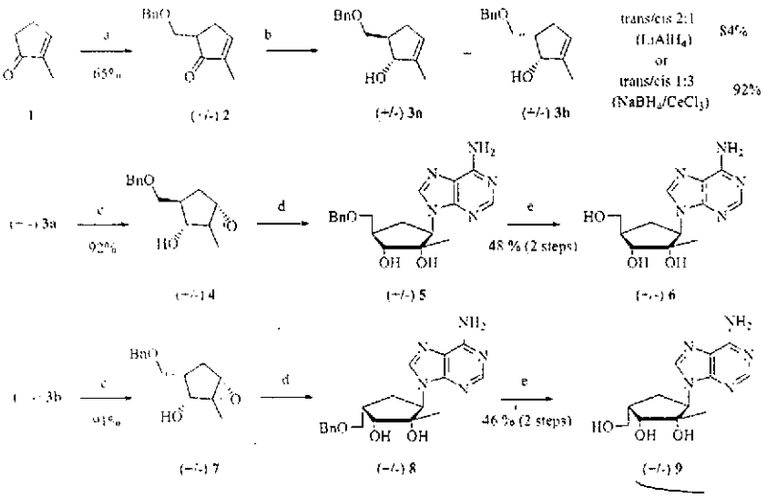


SCHEME 1 Reagents: (a) Lithium diisopropylamide (LDA), benzylbromomethyl ether, THF, −78 to −50°C; (b) $LiAlH_4$, ether, −78 to −60°C or $CeCl_3.7\ H_2O$, $NaBH_4$, MeOH, 0°C; (c) 3-chloroperoxybenzoic acid (*m*-CPBA), methylene chloride, 0°C; (d) NaH, adenine, DMF, 100°C; (e) palladium hydroxide on charcoal, cyclohexene, MeOH, reflux.

(*e.g.*, carbovir).[7] Since 2′-branched carbocycles* had not been reported when this work was initiated, a need for the design of a new synthetic route giving rapid access to this class of molecules became obvious.

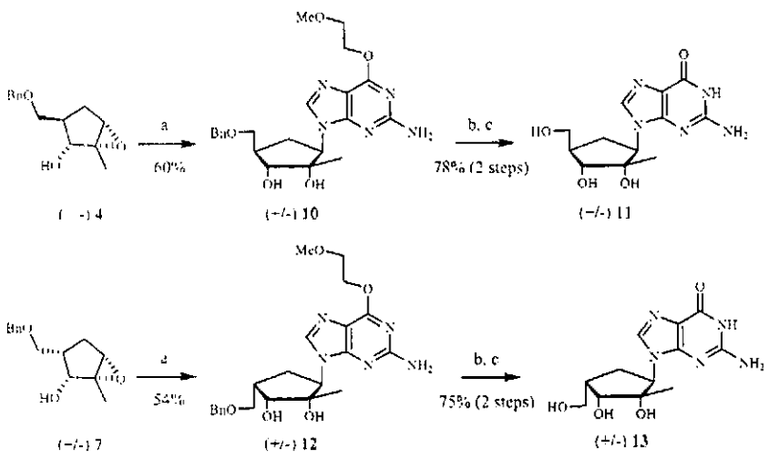
In this article, we wish to present the shortest synthesis of racemic carbocyclic nucleosides reported to date using 2-alkyl-cyclopentenones as versatile starting materials.

CHEMISTRY

Since both enantiomers of 2′-methyl-branched nucleosides were our initial targets, the choice of the starting material was oriented toward achiral 5-membered-rings already bearing a methyl group. The commercially available 2-methyl-2-cyclopentene-1-one **1** possesses the desired features and was our preferred starting material.

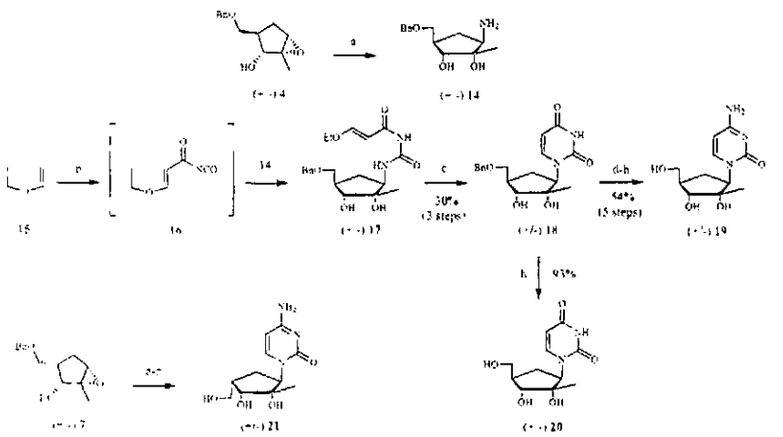
As they are prone to self-condensation, cyclopentenones are reported as challenging substrates for α-alkylation reactions.[8,9] Indeed, we encountered some difficulties in introduction of a hydroxymethyl group on the ketone **1**. For instance, an attempt with gaseous formaldehyde following the procedure of Jernow et al.[10] gave disappointing results, but, fortunately, **1** could be cleanly alkylated in acceptable yield using freshly prepared benzylbromomethyl ether[11] (Scheme 1). Ketone **2** was reduced with $LiAlH_4$ to get an easily separable 2:1 mixture of diols

*In this poster, numbers are given by analogy with the parent ribonucleosides.



SCHEME 2 Reagents: (a) NaH, 2-amino-6-(methoxyethoxy)-purine, DMF, 120°C; (b) 3N HCl, dioxane, 80°C; (c) palladium hydroxide on charcoal, cyclohexene, MeOH, reflux.

3a and **3b** favoring the *trans* isomer. The ratio of diols could be dramatically modified by a simple change of the reducing agent, $NaBH_4$ in presence of $CeCl_3$ giving **3b** as the major product in a 3:1 ratio. Both **3a** and **3b** were epoxidized to get **4** and **7**, which were submitted to the same chemistry: the epoxides were opened with the sodium salt of adenine, and the carbocycles **5** and **8** were then deprotected to obtain 2′-methyl-aristeromycin **6** and its 4′-epimer **9** in 5 steps.



SCHEME 3 Reagents: (a) NH_3, MeOH, 130°C; (b) *N*-(chlorocarbonyl)-isocyanate, THF, 0°C; then Et_3N, 0°C; then **14**, −40°C; (c) 1N H_2SO_4, dioxane, 100°C; (d) *p*-toluenesulfonic acid, 2,2-dimethoxypropane, acetone, RT; (e) trifluoroacetic anhydride, *N*-methylpyrrolidine; then *p*-nitrophenol, MeCN, 0°C; (f) NH_3, MeOH, 60°C; (g) trifluoroacetic acid 90%, 0°C; (h) palladium hydroxide on charcoal, cyclohexene, MeOH, reflux.

In a similar fashion, guanosine analogues **11** and **13** were prepared from **4** and **7** respectively using protected guanine.[12] We then focused our attention on pyrimidine nucleosides. Even though uracil salts were shown to react slowly with epoxides[13] we found it more advantageous to build the pyrimidine ring starting from the amine **14**. Epoxide **4** was opened with ammonia with perfect regio-and stereoselective control. Resulting cyclopentylamine **14** was used without purification in a uracil ring-construction process adapted from previously described procedures,[14,15] isocyanate **16** being condensed in situ with **14**. Compound **17** was then cyclized under acidic conditions to afford carbocycle **18**. The latter was used for the preparation of both cytidine and uridine derivatives **19** and **20**. Compound **19** was synthesized by adaptation of the method of Miah et al.[16] Again, it was possible to use epoxide **7** in the same route to get the 4′-epimers of **19** and **20** (Schemes 2 and 3).

CONCLUSION

A new synthetic method for the preparation of carbocyclic nucleosides has been developed from 2-alkyl-cyclopentenones, giving a rapid access to racemic 2′-branched carbocycles. The versatility of this method allows the preparation of seldom reported 4′-epi-carbocyclic nucleosides.[17] This method is adaptable to the synthesis of a large number of potential antiviral targets through the key intermediates **4** and **7**. Furthermore, introduction of various 2′-branching-groups can be achieved by using the appropriate ketone as a starting material.

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