



**HAL**  
open science

## Synthesis and Biological Evaluation of Methylenecyclopropane Analogues of Nucleosides

Germain Obame, Paul Brémond, Christophe Pannecouque, Gérard Audran

► **To cite this version:**

Germain Obame, Paul Brémond, Christophe Pannecouque, Gérard Audran. Synthesis and Biological Evaluation of Methylenecyclopropane Analogues of Nucleosides. *Synthesis: Journal of Synthetic Organic Chemistry*, 2013, 45 (18), pp.2612–2618. 10.1055/s-0033-1339311 . hal-01460478

**HAL Id: hal-01460478**

**<https://amu.hal.science/hal-01460478>**

Submitted on 31 May 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# Synthesis and Biological Evaluation of Methylenecyclopropane Analogues of Nucleosides

Germain Oboame,<sup>a</sup> Paul Brémond,<sup>a</sup> Christophe Pannecouque,<sup>b</sup> Gérard Audran<sup>\*a</sup>

<sup>a</sup> Aix-Marseille Université, CNRS ICR – UMR 7273, 13397 Marseille Cedex 20, France

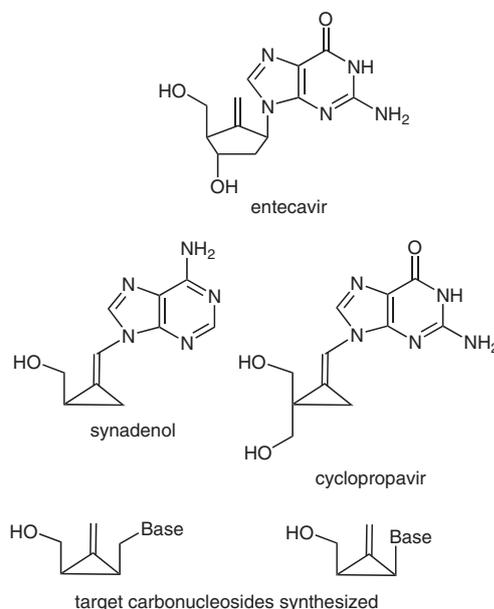
<sup>b</sup> Rega Institute for Medical Research, Katholieke Universiteit Leuven, 10 Minderbroedersstraat, 3000 Leuven, Belgium  
Fax +33(4)91288545; E-mail: g.audran@univ-amu.fr

Received: 13.05.2013; Accepted after revision: 04.06.2013

**Abstract:** Starting from a chiral methylenecyclopropane building block, readily obtained by enzymatic desymmetrization of a *meso*-diol, two types of methylenecyclopropane analogues of nucleosides were synthesized. The first type of nucleosides was obtained from the direct coupling of the chiral building block with 6-chloropurine under Mitsunobu reaction conditions followed by the functionalization of the purine base. The second type of nucleosides featured a Curtius rearrangement as the key step and the uracil heterocycle was then constructed by a linear methodology. These derivatives were evaluated as potential agents against important viral pathogens. None of the new compounds had significant antiviral activity at a concentration of 100 µg/mL, which was the highest concentration tested.

**Key words:** stereoselective synthesis, Curtius rearrangement, carbocyclic nucleosides, methylenecyclopropane carbonucleosides, antiviral agents

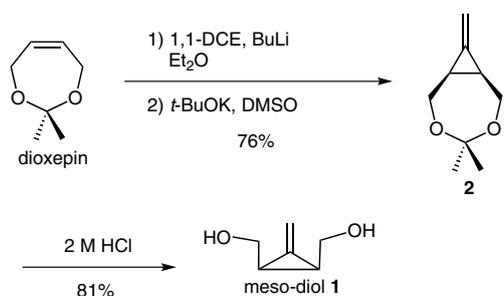
Nucleoside analogues represent an important class of therapeutic agents and show a remarkable wide spectrum of antiviral chemotherapy.<sup>1</sup> Among them, carbocyclic nucleosides are nucleoside analogues in which a carbon atom has replaced the oxygen atom of the furanose ring. They have been extensively studied including carbovir,<sup>2</sup> abacavir<sup>3</sup> (Ziagen<sup>®</sup>), and some cyclopentanic nucleosides.<sup>4</sup> In fact, they can display similar biological activity while presenting better stability as they are not prone to the action of the glycosylases that cleave the glycosidic bond of the natural nucleosides. As an example, entecavir<sup>5</sup> (Baraclude<sup>®</sup>), a carbanucleoside possessing a methylenecyclopentane skeleton, has been approved for the treatment of HBV infection (Figure 1). Moreover, in the course of the synthesis of novel antiviral nucleoside analogues, structural modifications of the heterocyclic bases and/or modifications on the sugar moiety have been attempted.<sup>6</sup> As a consequence, novel nucleosides containing a cyclopropane moiety have been found to have potent antiviral activity. Thus, methylenecyclopropane analogues of nucleosides,<sup>7</sup> such as synadenol<sup>8</sup> and cyclopropavir,<sup>9</sup> have been established as antiviral agents against  $\beta$ -herpes viruses and  $\gamma$ -herpes viruses.<sup>10</sup> In this paper, we report the synthesis and biological evaluation, with full experimental details, of novel methylenecyclopropane analogues of nucleosides.



**Figure 1** The structures of entecavir (Baraclude<sup>®</sup>), synadenol, cyclopropavir, and the methylenecyclopropane nucleosides synthesized in this work

We recently published a short paper on the synthesis and the enzymatic desymmetrization of *meso*-diol<sup>11</sup> **1** (Scheme 1) that is used herein for the synthesis of novel types of methylenecyclopropane nucleosides. The synthesis of *meso*-diol **1** was accomplished in 64% yield in three steps starting from 2,2-dimethyl-4,7-dihydro-1,3-dioxepin, which is easily prepared according to a literature procedure.<sup>12</sup> First, addition of methylchlorocarbene,<sup>13</sup> generated in situ from 1,1-dichloroethane and butyllithium in hexanes at  $-35$  °C, to the dioxepin gave a 4:1 (by <sup>1</sup>H NMR) *trans/cis* mixture of the expected diastereomeric chlorocyclopropanes. Then, dehydrochlorination of the chlorocyclopropanes with potassium *tert*-butoxide in dimethyl sulfoxide afforded methylenecyclopropane **2** in 76% yield, which was hydrolyzed with 2 M hydrochloric acid to give the diol **1** in 81% yield.

After screening commercial lipases, (–)-**4** was obtained on a large scale in 86% yield and an enantioselectivity of 98% ee by using lipase AK (from *Pseudomonas fluorescens*, PFL) and vinyl acetate in diisopropyl ether (Scheme 2). The high enantiomeric purity of (–)-**4** was determined by HPLC (Figure 2). Moreover, the stereostructure of **4**



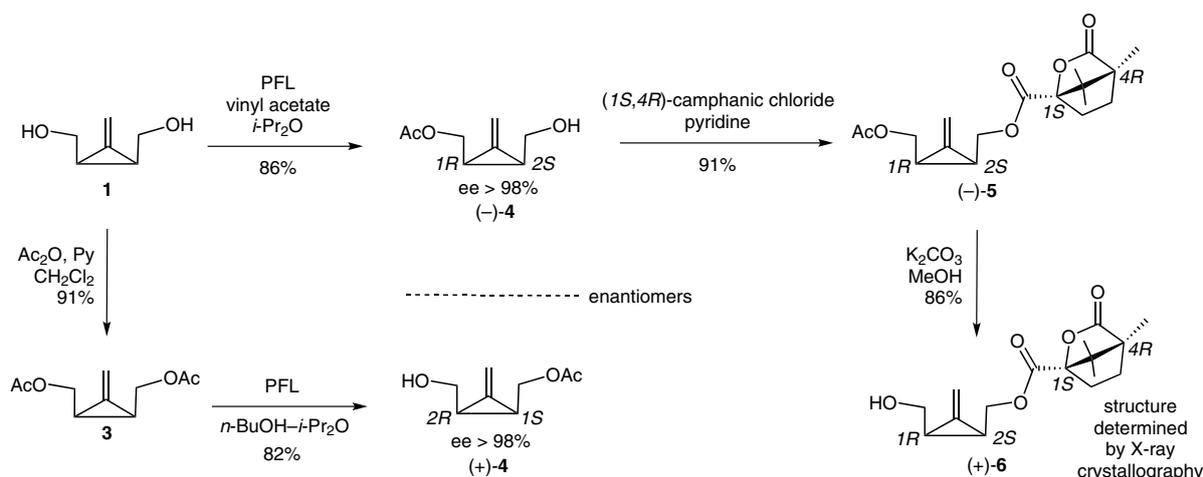
**Scheme 1**

was secured by single crystal X-ray diffraction of the corresponding camphanate ester derivative used. As depicted in Scheme 2, the reaction of (–)-4 with (1*S*,4*R*)-camphanic chloride<sup>14</sup> afforded the derivative (–)-5 in 91% yield, which was obtained as an oil. To solve this problem we performed the selective hydrolysis of the acetate group. Thus, treatment of (–)-5 with potassium carbonate in methanol afforded the crystalline alcohol (+)-6 in 86% yield. The ORTEP view of (+)-6 is shown in Figure 2.<sup>15</sup> The synthesis of the enantiomer (+)-4, by desymmetrization of diacetate 3, was also accomplished. Thus, treatment of 1 with acetic anhydride and pyridine gave the *meso*-diacetate 3 in 91% yield. Treatment of 3 with PFL

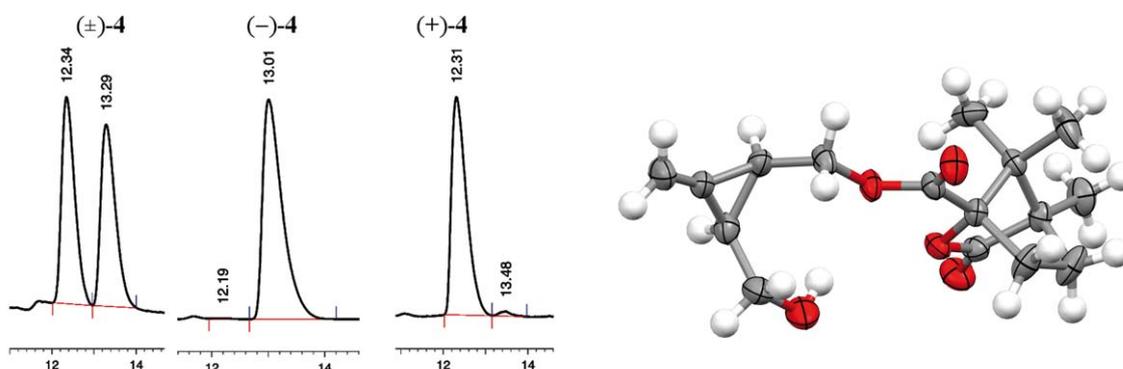
in the presence of butanol in diisopropyl ether afforded (+)-4 in 82% yield and with >98% ee. The high enantiomeric purity of (+)-4 was also checked by HPLC (Figure 2). This methodology provides a very simple and practical tool to access the two enantiomers of a versatile building block used to synthesize the target nucleosides, both on a large scale and with high enantiomeric excess.

The syntheses of methylenecyclopropane analogues of nucleosides are outlined in Scheme 3. Derivative (–)-4 was treated with 6-chloropurine in the presence of diisopropyl azodicarboxylate (DIAD) and triphenylphosphine to give the corresponding chloropurine (+)-7 in 86% yield.<sup>16</sup> One-pot ammonolysis and deprotection of the acetyl group of (+)-7 by treatment with saturated methanolic ammonia solution at 100 °C in a stainless steel pressure vessel for 10 hours provided 92% yield of aminopurine (–)-8. Alternatively, treatment of (+)-7 with cyclopropylamine followed by cleavage of the acetyl protecting group with methanolic ammonia produced the target aminopurine (–)-9 in 89% yield for two steps.

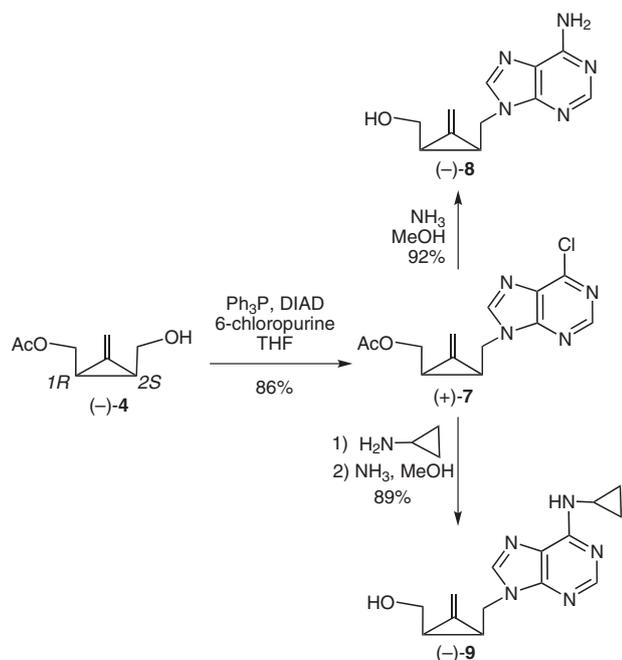
The methodology for the synthesis of another type of methylenecyclopropane analogue of nucleosides used the Curtius reaction<sup>17</sup> as a key step in order to remove a carbon atom and therefore to attach the heterocyclic base di-



**Scheme 2**



**Figure 2** Chiral HPLC diagrams of (±)-4, (–)-4 and (+)-4 and ORTEP view of chiral camphanate derivative (+)-6



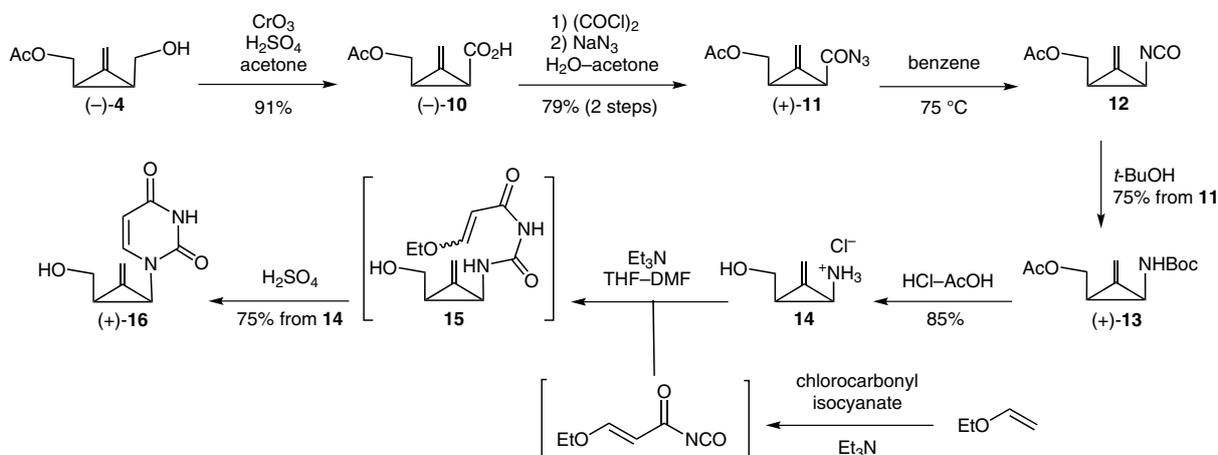
Scheme 3

rectly to the carbasugar (Scheme 4). Thus, Jones' reagent was employed to oxidize the alcohol (-)-4 in acetone at 0 °C to the corresponding carboxylic acid (-)-10 in 91% yield.<sup>18</sup> Direct transformation of carboxylic acid to the acyl azide (+)-11 with diphenylphosphoryl azide and triethylamine in dichloromethane failed and no reaction was observed.<sup>19</sup> The carboxylic acid (-)-10 was then converted into the acid chloride with oxalyl chloride at 0 °C and then to the acyl azide (+)-11 by using sodium azide in a water–acetone mixture.<sup>20</sup> Then, Curtius rearrangement of acyl azide (+)-11 to the corresponding isocyanate **12** was conducted in benzene, but the temperature should be kept below 75 °C as we observed decomposition of this formed isocyanate derivative and this resulted in lower yields. As isocyanate **12** is unstable, the addition under neutral, acidic, and basic conditions of water,<sup>21</sup> methanol,<sup>17b</sup> or butanol<sup>22</sup> were attempted directly with the crude

isocyanate **12**, but all these reactions were unsuccessful and led to decomposition of the starting material.

Fortunately, addition of *tert*-butyl alcohol to the crude isocyanate **12** at room temperature, followed by heating of the reaction mixture at 75 °C gave the carbamate (+)-13 in 75% yield for the two steps after purification by flash chromatography on silica gel.<sup>23</sup> Then, the simultaneous deprotection of the carbamate and acetate functions of (+)-13 was conducted in acidic conditions to afford the hydrochloride salt of amine **14** in 85% yield.<sup>19a</sup> After the completion of the synthesis of the carbocyclic aminosugar bearing the methylenecyclopropane moiety, the final stage involved the introduction of the heterocyclic base. All attempts to provide methylenecyclopropane analogues of nucleosides by construction of the purine base failed. Indeed, the condensation of **14** with 4,6-dichloropyrimidin-2-amine in the presence of diisopropylethylamine in butanol at reflux did not give the expected pyrimidine intermediate.<sup>24</sup> As a consequence, we investigated the synthesis of pyrimidine heterocyclic base as the precursor needed to react with the carbasugar is much more reactive, and so the coupling reaction could be realized under mild conditions. Then, the uracil base was constructed with a previously adapted methodology.<sup>25</sup> Ethyl vinyl ether was reacted with chlorocarbonyl isocyanate and the reaction mixture was treated with triethylamine to provide the highly reactive isocyanate intermediate. Condensation at -40 °C of this isocyanate with the hydrochloride salt **14** in the presence of triethylamine gave the preformed uracil base (+)-15. Finally, treatment of the (+)-15 with 0.5 M sulfuric acid provided the uracil derivative (+)-16. This two-step sequence gave (+)-16 in 75% yield from **14** after purification by column chromatography on silica gel. The enantioselective synthesis of the methylenecyclopropane (+)-16 with a uracil moiety as heterocyclic base was accomplished in eight steps in 34% overall yield from the chiral building block (-)-4.

Compounds **8**, **9**, and **16** were evaluated for their antiviral activity in human embryonic lung (HEL) cells [herpes simplex virus type 1 (HSV-1, strain KOS), herpes simplex virus type 2 (HSV-2, strain G), vaccinia virus, vesicular



Scheme 4

stomatitis virus, thymidine kinase-deficient (TK-) HSV-1 (strain KOS, ACV<sup>r</sup>), Vero cells (parainfluenza type 3 virus, reovirus type 1, Sindbis virus, Coxsackie B4 virus, Punta Toro virus), HeLa cells (vesicular stomatitis virus, Coxsackie B4 virus, respiratory syncytial virus), and Madin Darby canine kidney cells (influenza A H3N2, influenza A H1N1 and influenza B). In no case was significant antiviral activity or cytotoxicity witnessed at a concentration of 100 µg/mL, which was the highest concentration tested.

In summary, the enantioselective synthesis of methylenecyclopropane analogues of nucleosides **8**, **9**, and **16** was achieved starting from acetate **4** obtained by desymmetrization of a *meso*-diol. Thus, the nucleosides were synthesized by a direct coupling of the chiral building block under Mitsunobu conditions or by Curtius rearrangement followed by a linear methodology to construct the uracil heterocycle. Synthesized compounds were tested as potential antiviral agents; none of these compounds showed antiviral activity.

All air and/or H<sub>2</sub>O sensitive reactions were performed under an argon atmosphere with dry, freshly distilled solvents using standard syringe-cannula/septa techniques; all glassware was oven-dried (80 °C) and/or carefully dried in line with a flameless heat gun. All solvents were distilled under an argon atmosphere: THF from a blue soln of Na/benzophenone ketyl radical prior to use; CH<sub>2</sub>Cl<sub>2</sub> and DMF from CaH<sub>2</sub>, benzene and Et<sub>2</sub>O from LiAlH<sub>4</sub>. Routine monitoring of reactions was performed using Merck Silica gel 60 F<sub>254</sub>, aluminum-supported TLC plates; spots were visualized using UV light and ethanolic acidic *p*-anisaldehyde soln or ethanolic phosphomolybdic soln, followed by heating. Purification by column chromatography was performed with silica gel 60 (230–400 mesh) and gradients of Et<sub>2</sub>O–petroleum ether or CH<sub>2</sub>Cl<sub>2</sub>–MeOH, unless otherwise stated. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded in CDCl<sub>3</sub>, MeOH-*d*<sub>4</sub>, or DMSO-*d*<sub>6</sub> on a Bruker Avance DPX-300 spectrometer; residual nondeuterated solvent was used as internal reference. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Melting points are uncorrected. HRMS were performed using a SYNAPT G2 HDMS (Waters) mass spectrometer equipped with a pneumatically assisted atmospheric pressure ionization. The sample was ionized in positive mode electrospray under the following conditions: electrospray voltage (ISV): 2800 V; orifice voltage (OR): 20 V; nebulizing gas flow (N<sub>2</sub>): 800 L/h. The mass spectrum was obtained using a time of flight analyzer (TOF). The measure was realized in triplicate, with double internal standardization. The sample was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (450 µL) then diluted (dilution factor 1/10<sup>3</sup>) in a methanolic soln of NH<sub>4</sub>OAc (3 mM). The sample soln was infused in the ionization source at a 10 µL/min flow rate. Lipase AK (from *Pseudomonas fluorescens*, PFL) was gifted by Amano Pharmaceutical (Nagoya, Japan).

#### 4,4-Dimethyl-8-methylene-3,5-dioxabicyclo[5.1.0]octane (**2**)

A soln of 2,2-dimethyl-4,7-dihydro-1,3-dioxepin (20.0 g, 156 mmol) and 1,1-dichloroethane (13.0 mL, 156 mmol) in anhyd Et<sub>2</sub>O (100 mL) was cooled at –35 °C. Then, 2.5 M BuLi in hexane (61.6 mL, 156 mmol) was added to the mixture over a period of 3 h, during which time the reaction temperature was maintained between –40 and –35 °C. The mixture was stirred at –35 °C for 14 h, and then it was warmed to 0 °C and quenched with H<sub>2</sub>O. The aqueous layer was extracted with Et<sub>2</sub>O, and the combined Et<sub>2</sub>O extracts were dried, filtered, and concentrated. The oily residue was used in the next reaction without further purification.

To this crude product (26.7 g, 140 mmol) dissolved in anhyd DMSO (100 mL), *t*-BuOK (15.3 g, 140 mmol) was added and the resulting mixture was stirred at 70 °C for 1 h. The soln was then cooled to r.t., diluted with brine, followed by repeated extraction with Et<sub>2</sub>O. The combined organic layers were dried (anhyd MgSO<sub>4</sub>), filtered, and concentrated. The crude product was purified by flash chromatography to give methylenecyclopropane **2** (18.3 g, 76%) as a colorless oil.

IR (neat): 3046, 1651, 1244, 1132 cm<sup>-1</sup>.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 5.43 (m, 2 H), 4.15–4.04 (m, 2 H), 3.84–3.71 (m, 2 H), 1.89–1.82 (m, 2 H), 1.37 (s, 3 H), 1.50 (s, 3 H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 137.4 (C), 103.1 (CH<sub>2</sub>), 102.6 (C), 61.3 (2 CH<sub>2</sub>), 24.5 (2 CH), 20.5 (2 CH<sub>3</sub>).

HRMS (ESI): *m/z* [M + Na]<sup>+</sup> calcd for C<sub>9</sub>H<sub>14</sub>NaO<sub>2</sub>: 177.0886; found: 177.0880.

#### [2-(Hydroxymethyl)-3-methylenecyclopropyl]methanol (**1**)

A soln of compound **2** (10.0 g, 64.9 mmol) in THF (100 mL) was cooled at 0 °C, and aq 2 M HCl soln (50 mL) was added. The resulting soln was stirred for 2 h at r.t. The mixture was then cooled, neutralized with Amberlyst IRA-67, filtered, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel) gave the *meso*-diol **1** (6.01 g, 81%) as a colorless oil.

IR (neat): 3379, 3076, 1262, 1158 cm<sup>-1</sup>.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 5.36 (m, 2 H), 4.05–3.97 (m, 2 H), 3.81 (m, 2 H), 3.42–3.27 (m, 2 H), 2.06–2.00 (m, 2 H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 135.3 (C), 105.1 (CH<sub>2</sub>), 60.3 (2 CH<sub>2</sub>), 22.5 (2 CH).

HRMS (ESI): *m/z* [M + Na]<sup>+</sup> calcd for C<sub>6</sub>H<sub>10</sub>NaO<sub>2</sub>: 137.0573; found: 137.0573.

#### (–)-(1R,2S)-2-(Hydroxymethyl)-3-methylenecyclopropylmethyl Acetate [(–)-**4**]

The *meso*-diol **1** (6.00 g, 52.6 mmol), PFL (600 mg), and vinyl acetate (10 mL) in *i*-Pr<sub>2</sub>O (50 mL) were magnetically stirred at r.t. (TLC monitoring). After 1 h, the mixture was filtered, the solvent was removed in vacuo and the residue was purified by column chromatography (silica gel) to give monoacetate (–)-**4** (7.09 g, 86%) as a colorless oil.

[α]<sub>D</sub><sup>25</sup> –5.7 (*c* 1.0, CHCl<sub>3</sub>).

IR (neat): 3381, 3061, 1748, 1259, 1152 cm<sup>-1</sup>.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 5.45 (s, 2 H), 4.45 (dd, *J* = 12.4, 5.1 Hz, 1 H), 3.90 (dd, *J* = 12.3, 7.9 Hz, 1 H), 3.88 (d, *J* = 12.4 Hz, 1 H), 3.45 (dd, *J* = 12.3, 9.6 Hz, 1 H), 2.23 (br s, 1 H), 2.12–2.05 (m, 1 H, partially overlapped), 2.09 (s, 3 H), 2.03–1.96 (m, 1 H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 171.2 (C), 133.5 (C), 105.6 (CH<sub>2</sub>), 62.5 (CH<sub>2</sub>), 60.6 (CH<sub>2</sub>), 23.2 (CH), 21.2 (CH), 18.9 (CH<sub>3</sub>).

HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>8</sub>H<sub>13</sub>O<sub>3</sub>: 157.0859; found: 157.0857.

#### (–)-2-(Acetoxymethyl)-3-methylenecyclopropylmethyl 4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate [(–)-**5**]

To a soln of (–)-**4** (100 mg, 0.64 mmol) and DMAP (11.7 mg, 0.1 mmol) in pyridine (15 mL) at 5 °C under an argon atmosphere, was added (–)-(1*S*,4*R*)-camphanic acid chloride (160 mg, 0.70 mmol). The cooling bath was removed and the soln was stirred at r.t. (TLC monitoring) and the reaction was complete within 1 h. The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> and then it was sequentially washed with H<sub>2</sub>O, aq 1 M HCl soln, aq 1 M NaHCO<sub>3</sub> soln, and brine. The organic layer was dried (anhyd MgSO<sub>4</sub>), filtered, and concentrated in vacuo. The crude mixture was subjected to column chromatography to afford (–)-**5** (196 mg, 91%) as a colorless oil.

[α]<sub>D</sub><sup>25</sup> –13.4 (*c* 1.0, CHCl<sub>3</sub>).

IR (neat): 3058, 1741, 1728, 1174 cm<sup>-1</sup>.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 5.47 (s, 2 H), 4.42 (dd, *J* = 11.7, 6.8 Hz, 1 H), 4.38 (dd, *J* = 11.7, 5.1 Hz, 1 H), 4.10 (dd, *J* = 11.7, 8.2 Hz, 1 H), 3.91 (dd, *J* = 11.7, 8.6 Hz, 1 H), 2.43 (ddd, *J* = 12.1, 8.6, 4.6 Hz, 1 H), 2.03 (s, 3 H), 2.06–1.90 (m, 4 H), 1.63 (ddd, *J* = 12.3, 9.3, 4.6 Hz, 1 H), 1.07 (s, 3 H), 1.03 (s, 3 H), 0.94 (s, 3 H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 178.1 (C), 170.9 (C), 167.5 (C), 132.8 (C), 106.3 (CH<sub>2</sub>), 91.1 (C), 63.6 (CH<sub>2</sub>), 62.0 (CH<sub>2</sub>), 54.8 (C), 54.2 (C), 30.7 (CH<sub>2</sub>), 28.9 (CH<sub>2</sub>), 21.0 (CH<sub>3</sub>), 19.1 (CH), 18.6 (CH), 16.8 (2 CH<sub>3</sub>), 9.7 (CH<sub>3</sub>).

HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>18</sub>H<sub>25</sub>O<sub>6</sub>: 337.1646; found: 337.1646.

**(+)-2-(Hydroxymethyl)-3-methylenecyclopropylmethyl 4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate [(+)-6]**

To a soln of (–)-5 (100 mg, 0.30 mmol) in MeOH (10 mL) was added K<sub>2</sub>CO<sub>3</sub> (50.0 mg, 0.40 mmol). The mixture was stirred for 24 h at r.t., and then it was concentrated to remove MeOH, diluted with Et<sub>2</sub>O, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography gave (+)-6 (76 mg, 86%) as a solid. Recrystallization in Et<sub>2</sub>O–pentane gave (+)-6 as single crystals, suitable for X-ray diffraction; mp 81–83 °C.

[α]<sub>D</sub><sup>25</sup> +9.0 (*c* 1.0, CHCl<sub>3</sub>).

IR (KBr): 3369, 3026, 1784, 1749, 1731, 1172 cm<sup>-1</sup>.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 5.44 (s, 2 H), 4.52 (m, 1 H), 4.08 (dd, *J* = 11.8, 9.1 Hz, 1 H), 3.84 (br d, *J* = 13.5 Hz, 1 H), 3.47 (dd, *J* = 12.1, 8.9 Hz, 1 H), 2.49 (br s, 1 H), 2.32 (dd, *J* = 8.9, 4.6 Hz, 1 H), 2.01–1.92 (m, 4 H), 1.62 (ddd, *J* = 12.3, 9.2, 4.5 Hz, 1 H), 1.11 (s, 3 H), 1.02 (s, 3 H), 0.93 (s, 3 H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 177.8 (C), 167.5 (C), 133.4 (C), 105.6 (CH<sub>2</sub>), 91.0 (C), 63.9 (CH<sub>2</sub>), 60.3 (CH<sub>2</sub>), 54.7 (C), 54.3 (C), 30.7 (CH<sub>2</sub>), 28.9 (CH<sub>2</sub>), 22.9 (CH), 18.3 (CH), 16.7 (2 CH<sub>3</sub>), 9.7 (CH<sub>3</sub>).

HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>16</sub>H<sub>23</sub>O<sub>5</sub>: 295.3547; found: 295.3548.

**2-(Acetoxymethyl)-3-methylenecyclopropylmethyl Acetate (3)**

To a stirred soln of *meso*-diol **1** (1.00 g, 8.76 mmol) in pyridine (50 mL) was added Ac<sub>2</sub>O (2.00 mL, 18.4 mmol) and the mixture was stirred for 24 h at r.t. The mixture was poured into H<sub>2</sub>O and extracted with EtOAc. The combined organic layers were washed with aq 10% CuSO<sub>4</sub> soln, H<sub>2</sub>O, and brine, and then dried (anhyd MgSO<sub>4</sub>). Concentration of the organic layer in vacuo followed by purification of the residue by column chromatography (silica gel) gave **3** (1.58 g, 91%) as a colorless oil.

IR (neat): 3039, 1779, 1261, 1171 cm<sup>-1</sup>.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 5.48 (t, *J* = 2.2 Hz, 2 H), 4.48 (dd, *J* = 11.1, 7.5 Hz, 2 H), 3.95 (dd, *J* = 11.1, 8.5 Hz, 2 H), 2.11 (br s, 8 H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 170.7 (2 C), 133.4 (C), 105.8 (CH<sub>2</sub>), 62.3 (2 CH<sub>2</sub>), 20.9 (2 CH), 18.8 (2 CH<sub>3</sub>).

HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>10</sub>H<sub>15</sub>O<sub>4</sub>: 199.2261; found: 199.2263.

**(+)-(1*S*,2*R*)-2-(Hydroxymethyl)-3-methylenecyclopropylmethyl Acetate [(+)-4]**

To a soln of diacetate **3** (1.00 g, 5.04 mmol) in *i*-Pr<sub>2</sub>O (50 mL) and BuOH (10 mL) was added PFL (100.0 mg). The mixture was stirred at r.t. for 18 h. Then, the mixture was filtered through a pad of Celite. Concentration of the organic layer in vacuo followed by purification by column chromatography (silica gel) gave (+)-4. IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, and HRMS data are identical with those described for (–)-4. [α]<sub>D</sub><sup>25</sup> +5.9 (*c* 1.0, CHCl<sub>3</sub>).

**(+)-(1*R*,2*S*)-2-(6-Chloropurin-9-ylmethyl)-3-methylenecyclopropylmethyl Acetate [(+)-7]**

DIAD (379 μL, 1.87 mmol) was added dropwise to a soln of Ph<sub>3</sub>P (504 mg, 1.87 mmol) in anhyd THF (15 mL) under an argon atmosphere at 0 °C. The mixture was stirred for 30 min and then 6-chloropurine (297 mg, 1.87 mmol) was added. The mixture was stirred for an additional 30 min and then a soln of alcohol (–)-4 (200 mg, 1.28 mmol) in anhyd THF (15 mL) was slowly added. The cooling bath was removed and the mixture was stirred at r.t. for 12 h. The volatiles were evaporated in vacuo and the resulting residue was purified by column chromatography to give the carbonucleoside (+)-7 (322 mg, 86%) as a foam.

[α]<sub>D</sub><sup>25</sup> +13.0 (*c* 1.0, CHCl<sub>3</sub>).

IR (neat): 3029, 1758, 1241, 1136 cm<sup>-1</sup>.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 8.68 (s, 1 H), 8.23 (s, 1 H), 5.52 (t, *J* = 2.0 Hz, 1 H), 5.43 (t, *J* = 2.0 Hz, 1 H), 4.50 and 3.84 (ABX, *J* = 12.3, 10.2, 5.1 Hz, 2 H), 4.38 and 4.28 (ABX, *J* = 14.7, 8.5, 6.8 Hz, 2 H), 2.36–2.25 (m, 1 H), 2.16–2.07 (m, 1 H), 1.91 (s, 3 H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 170.6 (C), 151.9 (CH), 151.8 (C), 150.9 (C), 145.0 (CH), 132.2 (C), 131.5 (C), 106.9 (CH<sub>2</sub>), 61.6 (CH<sub>2</sub>), 42.5 (CH<sub>2</sub>), 20.8 (CH), 19.4 (CH), 19.2 (CH<sub>3</sub>).

HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>13</sub>H<sub>14</sub>N<sub>4</sub>O<sub>2</sub>Cl: 293.0800; found: 293.0802.

**(–)-(1*R*,2*S*)-[2-(6-Aminopurin-9-ylmethyl)-3-methylenecyclopropylmethyl]methanol [(–)-8]**

A soln of (+)-7 (100 mg, 0.34 mmol) in sat. methanolic NH<sub>3</sub> (20 mL) was heated at 100 °C for 10 h in a Parr stainless steel sealed reaction vessel. Then, the reaction mixture was allowed to cool to r.t. and concentrated in vacuo. The residue was purified by column chromatography to give carbonucleoside (–)-8 (72.3 mg, 92%) as a white solid; mp 170–172 °C.

[α]<sub>D</sub><sup>25</sup> –35.4 (*c* 1.0, MeOH).

IR (KBr): 3387, 3031, 1603, 1274, 1181 cm<sup>-1</sup>.

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ = 8.22 (s, 1 H), 8.17 (s, 1 H), 7.28 (s, 2 H), 5.41 (s, 1 H), 5.32 (s, 1 H), 5.04 (t, *J* = 5.3 Hz, 1 H), 4.30 and 4.21 (ABX, *J* = 14.7, 8.1, 6.4 Hz, 2 H), 3.78 (dt, *J* = 11.3, 5.4 Hz, 1 H), 3.46 (m, 1 H, partially overlapped), 2.16 (m, 1 H), 1.97 (m, 1 H).

<sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>): δ = 156.0 (C), 152.3 (CH), 149.4 (C), 140.9 (CH), 135.3 (C), 118.7 (C), 104.4 (CH<sub>2</sub>), 58.5 (CH<sub>2</sub>), 40.8 (CH<sub>2</sub>), 22.8 (CH), 19.3 (CH).

HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>11</sub>H<sub>14</sub>N<sub>5</sub>O: 232.2645; found: 232.2644.

**(–)-(1*R*,2*S*)-[2-[6-(Cyclopropylamino)purin-9-ylmethyl]-3-methylenecyclopropylmethyl]methanol [(–)-9]**

A soln of (+)-7 (65.0 mg, 0.22 mmol) and cyclopropylamine (1.0 mL) in MeOH (5.0 mL) was stirred at r.t. for 12 h under argon. The reaction mixture was allowed to cool to r.t. and concentrated in vacuo. Then, the resulting residue was dissolved into sat. methanolic NH<sub>3</sub> (15 mL) in a flask fitted with a rubber stopper at r.t. for 5 h. After evaporation of the solvent in vacuo, the residue was purified by column chromatography to give (–)-9 (53.6 mg, 89%) as a white solid; mp 184–185 °C.

[α]<sub>D</sub><sup>25</sup> –26.4 (*c* 1.0, MeOH).

IR (KBr): 3406, 3017, 1598, 1249, 1173 cm<sup>-1</sup>.

<sup>1</sup>H NMR (300 MHz, MeOH-*d*<sub>4</sub>): δ = 8.26 (s, 1 H), 8.19 (s, 1 H), 5.46 (t, *J* = 2.0 Hz, 1 H), 5.37 (t, *J* = 2.0 Hz, 1 H), 4.37 and 4.23 (ABX, *J* = 14.6, 8.2, 5.9 Hz, 2 H), 3.93 (dd, *J* = 12.1, 5.2 Hz, 1 H), 3.57 (dd, *J* = 12.1, 9.3 Hz, 1 H), 2.97–2.90 (m, 1 H), 2.23–2.12 (m, 1 H), 2.11–2.01 (m, 1 H), 0.90–0.82 (m, 2 H), 0.66–0.59 (m, 2 H).

$^{13}\text{C}$  NMR (75 MHz, MeOH- $d_4$ ):  $\delta$  = 157.0 (C), 153.4 (CH), 149.6 (C), 142.4 (CH), 135.5 (C), 120.4 (C), 105.4 (CH<sub>2</sub>), 60.2 (CH<sub>2</sub>), 42.5 (CH<sub>2</sub>), 24.6 (CH), 24.1 (CH), 20.7 (CH), 7.6 (2 CH<sub>2</sub>).

HRMS (ESI):  $m/z$  [M + H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>18</sub>ON<sub>5</sub>: 272.1506; found: 272.1505.

#### (–)-(1*S*,2*R*)-2-(Acetoxymethyl)-3-methylenecyclopropanecarboxylic Acid [(–)-10]

A soln of Jones reagent [prepared by mixing CrO<sub>3</sub> (26.7 g) with concd H<sub>2</sub>SO<sub>4</sub> (23 mL), followed by dilution with H<sub>2</sub>O to a final volume of 100 mL] was added to a soln of alcohol (–)-**4** (4.00 g, 25.6 mmol) in acetone (100 mL). Addition of Jones reagent (ca. 20 mL) was continued at 0 °C until the reddish color persisted for at least 5 min. The resulting soln was stirred for a further 1 h at r.t., and the excess oxidizing reagent was quenched with *i*-PrOH. The resulting soln was then diluted with H<sub>2</sub>O followed by repeated extraction with EtOAc. The combined organic phases were washed with 10% aq NaOH soln and the aqueous extracts were acidified to pH <2 with aq 6 M HCl soln. The resulting soln was extracted with EtOAc. The organic phases were combined, dried, and concentrated in vacuo to give acid (–)-**10** (3.96 g, 91%) as a colorless oil.

$[\alpha]_{\text{D}}^{25}$  –19.3 (*c* 1.0, CHCl<sub>3</sub>).

IR (neat): 3252, 3061, 1736, 1710, 1249, 1150 cm<sup>–1</sup>.

$^1\text{H}$  NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 10.3 (br s, 1 H), 5.63 and 5.61 (AB,  $J$  = 2.1 Hz, 2 H), 4.52 (m, 1 H), 4.22 (m, 1 H), 2.51–2.49 (m, 2 H), 2.12 (s, 3 H).

$^{13}\text{C}$  NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 176.4 (C), 171.1 (C), 130.5 (C), 106.8 (CH<sub>2</sub>), 60.8 (CH<sub>2</sub>), 23.2 (CH), 21.7 (CH), 20.8 (CH<sub>3</sub>).

HRMS (ESI):  $m/z$  [M + H]<sup>+</sup> calcd for C<sub>8</sub>H<sub>11</sub>O<sub>4</sub>: 171.0651; found: 171.0653.

#### (+)-(1*R*,2*S*)-2-(Azidocarbonyl)-3-methylenecyclopropylmethyl Acetate [(+)-11]

A soln of compound (–)-**10** (500 mg, 2.93 mmol) was cooled at 0 °C, and oxalyl chloride (1.00 g, 5.86 mmol) was added. The soln was allowed to warm to r.t. and stirred for 1 h. The soln was concentrated at reduced pressure and the resulting residue was taken up in acetone (16 mL) and transferred dropwise to a vigorously stirred soln of NaN<sub>3</sub> (773.0 mg, 11.8 mmol) in H<sub>2</sub>O (35 mL) at 0 °C. The resulting soln was maintained at 0 °C for 15 min, at which time it was partitioned between EtOAc and H<sub>2</sub>O. After separation, the aqueous layer was extracted with EtOAc and the combined organic layers were washed with H<sub>2</sub>O and brine, and then dried (anhyd MgSO<sub>4</sub>) and concentrated in vacuo to provide acyl azide (+)-**11** (453.0 mg, 79%) as a colorless oil.

$[\alpha]_{\text{D}}^{25}$  +29.0 (*c* 1.0, CHCl<sub>3</sub>).

IR (neat): 3064, 2132, 1749, 1238, 1157 cm<sup>–1</sup>.

$^1\text{H}$  NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 5.60 and 5.58 (AB,  $J$  = 2.4 Hz, 2 H), 4.53 (m, 1 H), 4.16 (m, 1 H), 2.55–2.41 (m, 2 H), 2.04 (s, 3 H).

$^{13}\text{C}$  NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 176.7 (C), 170.8 (C), 130.8 (C), 107.3 (CH<sub>2</sub>), 60.3 (CH<sub>2</sub>), 24.8 (CH), 24.1 (CH), 20.8 (CH<sub>3</sub>).

#### (+)-(1*R*,2*S*)-2-(*tert*-Butoxycarbonylamino)-3-methylenecyclopropylmethyl Acetate [(+)-13]

A soln of acyl azide (+)-**11** (400 mg, 2.04 mmol) in benzene (20 mL) was heated at 75 °C until the evolution of gas ceased (~3 h), and the mixture was cooled to r.t. The resulting isocyanate was dissolved in anhyd *t*-BuOH (2.0 mL) and the soln was refluxed for 4 h. The mixture was cooled to r.t. and the solvent was removed in vacuo. The residue was purified by flash chromatography to give carbamate (+)-**13** (395 mg, 75%) as a colorless oil.

$[\alpha]_{\text{D}}^{25}$  +41.4 (*c* 1.0, CHCl<sub>3</sub>).

IR (neat): 3340, 3053, 1759, 1717, 1143 cm<sup>–1</sup>.

$^1\text{H}$  NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 5.72 (s, 1 H), 5.55 (s, 1 H), 4.89 (br d,  $J$  = 5.9 Hz, 1 H), 4.18 and 4.03 (ABX,  $J$  = 10.7, 10.3, 5.5 Hz, .05 (s, 3 H), 1.44 (s, 9 H).

$^{13}\text{C}$  NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 171.1 (C), 156.3 (C), 132.5 (C), 108.3 (CH<sub>2</sub>), 79.7 (C), 61.0 (CH<sub>2</sub>), 29.1 (CH), 27.8 (3 CH<sub>3</sub>), 21.3 (CH), 21.1 (CH<sub>3</sub>).

HRMS (ESI):  $m/z$  [M + H]<sup>+</sup> calcd for C<sub>12</sub>H<sub>20</sub>O<sub>3</sub>N: 226.2965; found: 226.2970.

#### [2-(Hydromethyl)-3-methylenecyclopropylmethyl]ammonium Chloride (**14**)

A soln of (+)-**13** (200.0 mg, 0.77 mmol) in aq 1.2 M HCl soln–glacial AcOH (10 mL (1:1.5)) was stirred at r.t. for 12 h. After removal of the volatiles, the residue was triturated with Et<sub>2</sub>O. After filtration, the solid residue was placed under vacuum and gave product **14** (89.6 mg, 85%) as a brown oil. The chlorohydrate salt **14** was sufficiently pure to be used in the next step without purification.

IR (neat): 3386, 3296, 3058, 1247, 1172 cm<sup>–1</sup>.

$^1\text{H}$  NMR (300 MHz, MeOH- $d_4$ ):  $\delta$  = 4.32 (br s, 1 H), 4.17 (t,  $J$  = 2.0 Hz, 1 H), 2.41 (dd,  $J$  = 12.0, 4.7 Hz, 1 H), 2.16 (dd,  $J$  = 12.0, 7.0 Hz, 1 H), 1.76 (m, 1 H), 0.68–0.61 (m, 1 H).

$^{13}\text{C}$  NMR (75 MHz, MeOH- $d_4$ ):  $\delta$  = 129.9 (C), 110.7 (CH<sub>2</sub>), 59.4 (CH<sub>2</sub>), 28.3 (CH), 23.4 (CH).

HRMS (ESI):  $m/z$  [M]<sup>+</sup> calcd for C<sub>5</sub>H<sub>10</sub>NO: 100.0757; found: 100.0753.

#### (+)-(1*S*,2*S*)-1-[2-(Hydromethyl)-3-methylenecyclopropyl]-1*H*-pyrimidine-2,4-dione [(+)-16]

To a soln of chlorocarbonyl isocyanate (75.0  $\mu\text{L}$ , 0.88 mmol) in THF (2.0 mL) was slowly added a soln of ethyl vinyl ether (110  $\mu\text{L}$ , 1.04 mmol) in THF (2.0 mL) at 0 °C. The resulting soln was stirred for 20 min at 0 °C and Et<sub>3</sub>N (130  $\mu\text{L}$ , 0.88 mmol) in THF (2.0 mL) was then slowly added. The resulting suspension was stirred for 5 min at 0 °C then cooled down to –40 °C. A soln of chlorohydrate salt **14** (100 mg, 0.74 mmol) in DMF (2.0 mL) was rapidly added to the mixture and the suspension was allowed to slowly warm up to r.t. Then, volatiles were evaporated and the residue was dissolved in dioxane (5.0 mL). To this soln was added aq 0.5 M H<sub>2</sub>SO<sub>4</sub> soln (9.0 mL) and the mixture was heated at 80 °C for 2 h. Then the soln was cooled to r.t. and basified with aq 3 M NH<sub>3</sub> soln (7.0 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 to afford (+)-**16** (107 mg, 75%) as a white solid; mp 183–184 °C.

$[\alpha]_{\text{D}}^{25}$  +10.0 (*c* 1.0, MeOH).

IR (KBr): 3305, 3074, 1685, 1254, 1146 cm<sup>–1</sup>.

$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  = 11.3 (s, 1 H), 7.51 (d,  $J$  = 7.9 Hz, 1 H), 6.02 (s, 1 H), 5.80 (s, 1 H), 5.51 (d,  $J$  = 7.9 Hz, 1 H), 4.56 (d,  $J$  = 5.6 Hz, 1 H), 3.82 (d,  $J$  = 7.8 Hz, 1 H), 3.39–3.18 (m, 2 H, partially overlapped with DOH), 2.25–2.10 (m, 1 H).

$^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ):  $\delta$  = 163.0 (C), 151.4 (C), 144.1 (CH), 130.0 (C), 110.3 (CH<sub>2</sub>), 99.8 (CH), 57.3 (CH<sub>2</sub>), 33.7 (CH), 24.3 (CH).

HRMS (ESI):  $m/z$  [M + H]<sup>+</sup> calcd for C<sub>9</sub>H<sub>11</sub>O<sub>3</sub>N<sub>2</sub>: 195.0760; found: 195.0760.

## Acknowledgment

G.O. thanks the government of Gabon for a grant. The authors are grateful to Amano Pharmaceuticals for the kind gift of PFL. The authors are also thankful to Dr. N. Vanthuyne for HPLC analyses, to Dr. M. Giorgi for X-ray diffraction analyses and to CNRS and Aix-Marseille Université for their financial support. P. Fournier is gratefully acknowledged for the English revision of the manuscript.

**Supporting Information** for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synlett>.

## References

- (1) (a) De Clercq, E. *Antiviral Res.* **2005**, *67*, 56. (b) De Clercq, E. *Curr. Opin. Microbiol.* **2005**, *8*, 552. (c) Mathé, C.; Gosselin, G. *Antiviral Res.* **2006**, *71*, 276. (d) Field, H. J.; De Clercq, E. *Antiviral Chem. Chemother.* **2008**, *19*, 51. (e) De Clercq, E.; Field, H. J. *Antiviral Chem. Chemother.* **2008**, *19*, 63.
- (2) (a) Vince, R.; Hua, M.; Brownell, J.; Daluge, S.; Lee, F.; Shannon, W. M.; Lavelle, G. C.; Qualls, J.; Weislow, O. S.; Kiser, R.; Canonico, P. G.; Schultz, R. H.; Narayanan, V. L.; Mayo, J. G.; Shoemaker, R. H.; Boyd, M. R. *Biochem. Biophys. Res. Commun.* **1988**, *156*, 1046. (b) Vince, R.; Hua, M. *J. Med. Chem.* **1990**, *33*, 17.
- (3) (a) Daluge, S. M. US 5034394, **1991**. (b) Good, S. S.; Daluge, S. M.; Ching, S. V.; Ayers, K. M.; Mahony, W. B.; Faletto, M. B.; Domin, B. A.; Owens, B. S.; Dornsife, R. E.; McDowell, J. A.; Lafon, S. W.; Symonds, W. T. *Antiviral Res.* **1995**, *26*, A229.
- (4) For some representative examples, see: (a) Rao, J. R.; Schinazi, R. F.; Chu, C. K. *Bioorg. Med. Chem.* **2007**, *15*, 839. (b) Liu, L. J.; Ko, O. H.; Hong, J. H. *Bull. Korean Chem. Soc.* **2008**, *29*, 1723. (c) Abejón, P.; Blanco, J. M.; Caamaño, O.; Fernández, F.; García, M. D.; García-Mera, X.; Rodríguez-Borges, J. E.; Balzarini, J.; De Clercq, E. *Synthesis* **2009**, 2766. (d) Ugliarolo, E. A.; Lantaño, B.; Moltrasio, G. Y.; Moglioni, A. G. *Tetrahedron: Asymmetry* **2009**, *20*, 1848.
- (5) For reviews, see: (a) Ferrero, M.; Gotor, V. *Chem. Rev.* **2000**, *100*, 4319. (b) Agrofoglio, L. A.; Gillaizeau, I.; Saito, Y. *Chem. Rev.* **2003**, *103*, 1875. (c) Rodriguez, J. B.; Comin, M. J. *Mini-Rev. Med. Chem.* **2003**, *3*, 95. For a recent book, see: (d) *Modified Nucleosides in Biochemistry, Biotechnology and Medicine*; Herdewijn, P., Ed.; Wiley-VCH: Weinheim, **2008**.
- (6) Bisacchi, G. S.; Chao, S. T.; Bachard, C.; Daris, J. P.; Innaïmo, S.; Jacobs, G. A.; Kocy, O.; Lapointe, P.; Martel, A.; Merchant, Z.; Slusarchyk, W. A.; Sundeen, J. E.; Young, M. G.; Colonna, R.; Zahler, R. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 127.
- (7) For a review: Zemlicka, J. *Adv. Antiviral Drug Des.* **2007**, *5*, 113.
- (8) (a) Qiu, Y.-L.; Ksebati, M. B.; Ptak, R. G.; Fan, B. Y.; Breitenbach, J. M.; Lin, J.-S.; Cheng, Y.-C.; Kern, E. R.; Drach, J. C.; Zemlicka, J. *J. Med. Chem.* **1998**, *41*, 10. (b) Qiu, Y.-L.; Ptak, R. G.; Fan, B. Y.; Breitenbach, J. M.; Lin, J.-S.; Cheng, Y.-C.; Kern, E. R.; Drach, J. C.; Zemlicka, J. *Antiviral Chem. Chemother.* **1998**, *9*, 341. (c) Qiu, Y.-L.; Zemlicka, J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1441. (d) Guan, H.-P.; Ksebati, M. B.; Cheng, Y.-C.; Drach, J. C.; Kern, E. R.; Zemlicka, J. *J. Org. Chem.* **2000**, *65*, 1280. (e) Wang, R.; Ksebati, M. B.; Corbett, T. H.; Earl, R. K.; Drach, J. C.; Zemlicka, J. *J. Med. Chem.* **2001**, *44*, 4019.
- (9) (a) Zhou, S.; Breitenbach, J. M.; Borysko, K. Z.; Drach, J. C.; Kern, E. R.; Gullen, E.; Cheng, Y.-C.; Zemlicka, J. *J. Med. Chem.* **2004**, *47*, 566. (b) Kushner, N. L.; Williams-Aziz, S. L.; Hartline, C. B.; Harden, E. A.; Zhou, S.; Yan, Z.; Zemlicka, J.; Kern, E. R. *Antiviral Res.* **2004**, *62*, A68. (c) Zhaohua, Y.; Kern, E. R.; Gullen, E.; Cheng, Y.-C.; Drach, J. C.; Zemlicka, J. *J. Med. Chem.* **2005**, *48*, 91.
- (10) Zemlicka, J. *Adv. Antiviral Drug Des.* **2007**, *5*, 113.
- (11) Obame, G.; Pellissier, H.; Vanthuynne, N.; Bongui, J.-B.; Audran, G. *Tetrahedron Lett.* **2011**, *52*, 1082.
- (12) Elliott, W. J.; Fried, J. *J. Org. Chem.* **1976**, *41*, 2469.
- (13) (a) Binger, P.; Arora, S. *Synthesis* **1974**, 801. (b) Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 589. (c) de Meijere, A.; Becker, H.; Stolle, A.; Kozhushkov, S. I.; Bes, M. T.; Salaün, J.; Noltemeyer, M. *Chem. Eur. J.* **2005**, *11*, 2471.
- (14) (a) Gerlach, H. *Helv. Chim. Acta* **1985**, *68*, 1815. (b) Gerlach, H.; Kappes, D.; Boekman, K. Jr.; Maw, G. N. *Org. Synth.* **1993**, *71*, 48.
- (15) CCDC-785043 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at [www.ccdc.cam.ac.uk/conts/retrieving.html](http://www.ccdc.cam.ac.uk/conts/retrieving.html) [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033; e-mail: [deposit@ccdc.cam.ac.uk](mailto:deposit@ccdc.cam.ac.uk)].
- (16) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Jenny, T. F.; Previsani, N.; Benner, S. A. *Tetrahedron Lett.* **1991**, *32*, 7029. (c) Wachtmeister, J.; Classon, B.; Samuelsson, B. *Tetrahedron* **1995**, *51*, 2029. (d) Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229.
- (17) (a) Curtius, T. *Chem. Ztg.* **1912**, *35*, 249. (b) Tanaka, M.; Norimine, Y.; Fujita, T.; Suemune, H. *J. Org. Chem.* **1996**, *61*, 6952. (c) Aggarwal, V. K.; de Vicente, V.; Bonnert, R. V. *Org. Lett.* **2001**, *3*, 2785. (d) Banthorpe, D. V. *Rearrangements Involving Azido Groups*, In *The Chemistry of the Azido Group*; Patai, S., Ed.; Wiley: New York, **1971**, 397–340.
- (18) (a) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, D. C. L. *J. Chem. Soc.* **1946**, 39. (b) Luzzio, F. A.; Guziec, F. S. Jr. *Org. Prep. Proced. Int.* **1988**, *20*, 533. (c) Luzzio, F. A. *Org. React.* **1998**, *53*, 1. (d) Li, D.; Agnihotri, G.; Dakoiji, S.; Oh, E.; Lantz, M.; Liu, H.-w. *J. Am. Chem. Soc.* **1999**, *121*, 9034.
- (19) (a) Kazuta, Y.; Hirano, K.; Natsume, K.; Yamada, S.; Kimura, R.; Matsumoto, S.-I.; Furuichi, K.; Matsuda, A.; Shuto, S. *J. Med. Chem.* **2003**, *46*, 1980. (b) Kedrowski, B. L. *J. Org. Chem.* **2003**, *68*, 5403.
- (20) (a) Weinstock, J. *J. Org. Chem.* **1961**, *26*, 3511. (b) Jaafar, I.; Francis, G.; Danion-Bougout, R.; Danion, D. *Synthesis* **1993**, 56. (c) Vallgård, J.; Appelberg, U.; Arvidsson, L.-E.; Hjorth, S.; Svensson, B. E.; Hacksell, U. *J. Med. Chem.* **1996**, *39*, 1485.
- (21) Neutral conditions: (a) Murata, K.; Wang, S.-Z.; Morizawa, Y.; Oharu, K. *J. Fluorine Chem.* **2006**, *127*, 1125. Acidic conditions: (b) Cho, T. P.; Long, Y. F.; Gang, L. Z.; Yang, W.; Jun, L. H.; Yuan, S. G.; Hong, F. J.; Lin, W.; Liang, G. D.; Lei, Z.; Jing, L. J.; Shen, G. A.; Hong, S. G.; Dan, W.; Ying, F.; Ke, Y. P.; Ying, L.; Jun, F.; Tai, M. X. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3565. (c) Johnson, D. J.; Forbes, I. T.; Watson, S. P.; Garzya, V.; Stevenson, G. I.; Walker, G. R.; Mudhar, H. S.; Flynn, S. T.; Wyman, P. A.; Smith, P. W.; Murkitt, G. S.; Lucas, A. J.; Mookherjee, C. R.; Watson, J. M.; Gartlon, J. E.; Bradford, A. M.; Brown, F. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5434. Basic conditions: (d) Neufellner, E.; Kapeller, H.; Griengl, H. *Tetrahedron* **1998**, *54*, 11043.
- (22) Gajcy, K.; Pękala, J.; Frąckowiak-Wojtasek, B.; Librowski, T.; Lochyński, S. *Tetrahedron: Asymmetry* **2010**, *21*, 2015.
- (23) (a) Zhao, Y.; Yang, T.; Lee, M.; Lee, D.; Newton, M. G.; Chu, C. K. *J. Org. Chem.* **1995**, *60*, 5236. (b) Yoshida, S. Y.; Meyer, O. G. J.; Rosen, T. C.; Haufe, G.; Ye, S.; Sloan, M. J.; Kirk, K. L. *J. Med. Chem.* **2004**, *47*, 1796.
- (24) (a) Montgomery, J. A.; Temple, C. Jr. *J. Am. Chem. Soc.* **1957**, *79*, 5238. (b) Shealy, Y. F.; Clayton, J. D. *J. Am. Chem. Soc.* **1966**, *88*, 3885. (c) Shealy, Y. F.; Clayton, J. D. *J. Am. Chem. Soc.* **1969**, *91*, 3075. (d) Arita, M.; Adachi, K.; Ito, Y.; Sawai, H.; Ohno, M. *J. Am. Chem. Soc.* **1983**, *105*, 4049.
- (25) (a) Shealy, Y. F.; O'Dell, C. A. *J. Heterocycl. Chem.* **1976**, *13*, 1015. (b) Lin, T.-S.; Zhang, X.-H.; Wang, Z.-H.; Prusoff, W. H. *J. Med. Chem.* **1988**, *31*, 484. (c) Gosselin, G.; Griffe, L.; Meillon, J.-C.; Storer, R. *Tetrahedron* **2006**, *62*, 906.