A Study on the Allylic Substitution of (1*R*,5*R*,8*R*)- and (1*R*,5*R*,8*S*)-8-Hydroxy-2-oxabicyclo[3.3.0]oct-6-en-3-one Derivatives − Preparation of (1*S*,2*R*,3*R*)-9-[2-Hydroxy-3-(2-hydroxyethyl)cyclopent-4-en-1-yl]-9*H*-adenine[‡]

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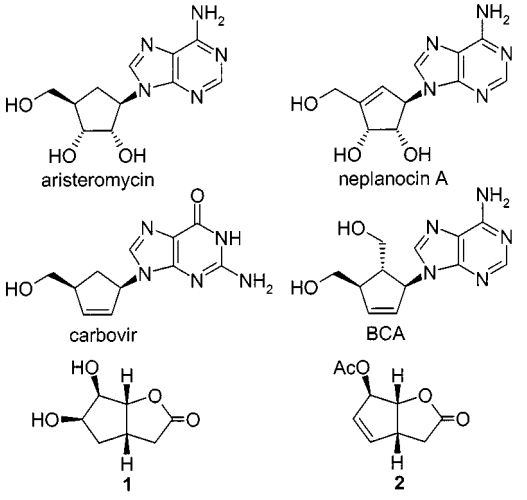
Keywords: Allylic substitution / Carbocycles / Catalysis / Lactones / Mitsunobu substitution / Nucleosides / Palladium

The palladium-catalyzed substitution of acylated (1*R*,5*R*,8*R*)- and (1*R*,5*R*,8*S*)-8-hydroxy-2-oxabicyclo[3.3.0]oct-6-en-3-ones has been studied using a number of C- and N-nucleophiles. In all cases, the *exo* derivatives (8*R*) were found to be more reactive than the corresponding *endo* derivatives (8*S*). The reaction was found to give good yields and a single product when sodium dimethyl malonate was used as the nucleophile. However, when less reactive C- and N-nucleophiles were employed, the reaction gave inseparable mixtures of both C-6 and C-8 substituted products, thus limiting the synthetic use of the reaction with these nucleophiles. Additionally, Mitsunobu substitution of (1*R*,5*R*,8*R*)-8-hydroxy-2-oxabicyclo[3.3.0]oct-6-en-3-one (**3**) with 6-chloropurine, followed by reduction of the lactone moiety and treatment with liquid ammonia, gave the carbocyclic nucleoside (1*S*,2*R*,3*R*)-9-[2-hydroxy-3-(2-hydroxyethyl)cyclopent-4-en-1-yl]-9*H*-adenine (**19**), which can be viewed as an analogue of the carbocyclic nucleoside BCA.

Introduction

During the last 20 years the field of carbocyclic nucleosides has been the subject of an immense research effort amongst chemists and biologists.[1−6] This is especially due to the antitumor and antiviral activities displayed by this class of compounds, coupled with their increased metabolic stability towards phosphorylase enzymes.[1] In particular, research effort has been directed towards finding compounds displaying activity against viral diseases such as HIV and HSV. Examples of compounds displaying antiviral activities include the naturally occurring aristeromycin and neplanocin A, as well as synthetic compounds like carbovir and BCA, which both show *anti*-HIV activity.[1−6] Abacavir, which is the cyclopropylamine derivative of carbovir, has now entered into clinical use for treatment of HIV.

Our approach to the area of carbocyclic nucleosides and carbasugars is based on the short and efficient synthesis of bicyclic *cis*-fused cyclopentane lactones, such as **1**, developed in our laboratories.[7,8] Starting from bromodeoxyaldonolactones, very useful synthons themselves for a number of applications,[9] these bicyclic lactones have been converted into a number of carbasugars and aminopolyhydroxycyclopentanes.[7,8,10,11] In particular, we have utilized the lactone **2** for the synthesis of carbasugars functionalized at all five ring carbon atoms.[10]



A number of groups have utilized bicyclic lactones similar to **2** for the synthesis of carbocyclic nucleosides. Examples include the syntheses of (−)-aristeromycin and (−)-carbodine,[12] carbovir,[13,14] abacavir,[14] homo-carbovir and homo-abacavir,[15] epinor-BCA,[16] and carbocyclic nikkomycin C.[17,18] Palladium(0)-catalyzed allylic substitution, pioneered by Tsuji and Trost,[19] is one of the most important methods for the substitution of allylic systems. However, only a few studies have been made on the palladium-catalyzed allylic substitution of unsaturated bicyclic lactones like **2**, and these have all been carried out on systems having the lactone group itself as the leaving group.[17,18,20]

On this basis, we decided to investigate the allylic substitution of the bicyclic lactone **2** and related derivatives, with the aim not only of synthesizing carbocyclic nucleosides, but also of introducing nitrogen and carbon substituents for the possible synthesis of compounds such as aminocyclopentitols and prostaglandins. In this paper, we report on

[‡] Synthesis of Carbasugars from Aldonolactones, III. − Part II: Ref.[10]

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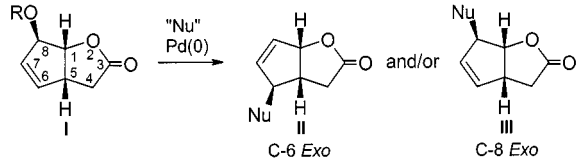
the palladium-catalyzed allylic substitution of C-8 substituted 2-oxabicyclo[3.3.0]oct-6-en-3-ones **2**, **4**, **7**, and **8**. We also report on the synthesis of (1*S*,2*R*,3*R*)-9-[2-hydroxy-3-(2-hydroxyethyl)cyclopent-4-en-1-yl]-9*H*-adenine (**19**) by Mitsunobu substitution.

Results and Discussion

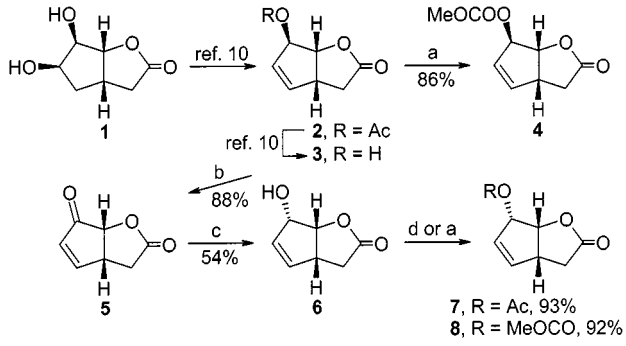
Palladium(0)-catalyzed allylic substitution normally favors attack at the sterically less hindered allylic position. However, in the case of the allylic system **I**, this rule is of little help as the C-6 and C-8 positions are sterically equivalent, and the substitution might therefore lead to products substituted at either C-6 or C-8 (**II** and **III**, respectively) (Scheme 1). The only difference between the two positions is the substitution pattern on the neighboring carbon atoms: C-1 substituted by an oxygen atom and C-5 by a methylene group. It is, however, difficult to predict in which way an electronic effect will affect the substitution.



Scheme 1. Possible products of the palladium(0)-catalyzed allylic substitution of **I**

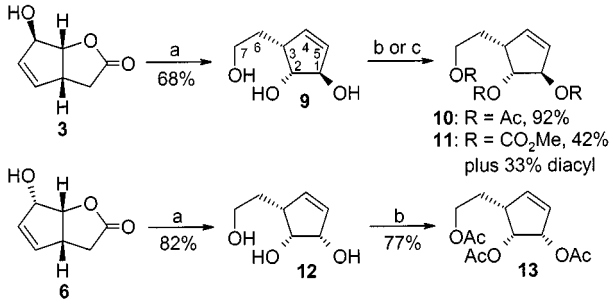
Preparation of Substrates

Previously, we have described an efficient method for the synthesis of (1*R*,5*R*,8*R*)-8-acetoxy-2-oxabicyclo[3.3.0]oct-6-en-3-one (**2**) on a multi-gram scale.[10] In order to investigate the effect of the bicyclic system, we decided to prepare both the acetate and the more reactive carbonate derivative, as well as the C-8 epimeric acetate and carbonate. Thus, the allylic acetate **2** was deprotected by treatment with acidic methanol to give the allylic alcohol **3** (Scheme 2). Standard acylation with methyl chloroformate gave the carbonate **4** in 86% yield. In order to invert the stereochemistry at C-8, the allylic alcohol **3** was oxidized by treatment with PCC to give the conjugated ketone **5** in 88% yield; this was then reduced under Luche conditions to give the allylic alcohol **6** (54%). Standard acetylation and acylation then gave the acetate **7** (93%) and the carbonate **8** (92%), respectively.



Scheme 2. Preparation of the allylic substrates **4**, **7**, and **8**: a) MeOCOCl, pyridine, DCM; b) PCC, DCM; c) $NaBH_4$, $CeCl_3$, MeOH; d) Ac_2O, pyridine

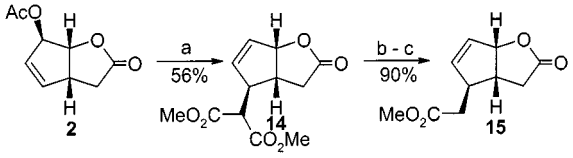
We also decided to prepare the corresponding monocyclic compounds for comparison against the regioselectivity imposed by the bicyclic system. The monocyclic compounds, moreover, were believed to be more reactive substrates than the bicyclic system for the allylic substitution, due to reduced steric hindrance. Thus, the lactone moiety of the allylic alcohol **3** was reduced using calcium borohydride in THF to give the cyclopentene **9** (68%), which was then acetylated and acylated to give the acetate **10** (92%) and the carbonate **11** (42% plus 33% diacylated), respectively (Scheme 3). Similarly, **6** was reduced to the cyclopentene **12** (82%) and then acetylated to give **13** in 77% yield.



Scheme 3. Preparation of the allylic substrates **10**, **11**, and **13**: a) $Ca(BH_4)_2 \cdot 2THF$, THF; b) Ac_2O, pyridine; c) MeOCOCl, pyridine, DCM

Substitution Reactions

The first Pd-catalyzed reaction investigated was the substitution of the acetate **2** using the dimethyl malonate anion, chosen for its high reactivity and irreversible addition, as the nucleophile. Thus, when **2** was treated with 2 equiv. of sodium dimethyl malonate and 5 mol-% of $Pd(PPh_3)_4$, a single product was formed and isolated in a moderate yield (56%) (Scheme 4). The structure was determined by H,H- and C,H-correlated NMR spectroscopy to be consistent with the C-6 *exo* malonate derivative **14**. Decarboxylation and subsequent esterification gave **15** in excellent yield (90%). A method for introduction of a 2-carbon unit onto the cyclopentane ring has hence been developed.



Scheme 4. Alkylation of the lactone **2** with sodium dimethyl malonate: a) $CH_2(CO_2Me)_2$, NaH, $Pd(PPh_3)_4$, THF; b) HCl, MeOH/H_2O; c) HCl, MeOH, DMP

When Pd-catalyzed substitution of the acetate **2** was performed using other nucleophiles (lithium salt of phenylsulfonylnitromethane, lithium azide, potassium phthalimide, and sodium 6-chloropurine), however, only low or no conversion of the starting material was observed. On the other hand, when the corresponding carbonate **4** was submitted to the same reaction conditions using these nucleophiles, we found to our satisfaction that full conversion occurred in

Table 1. Palladium-catalyzed allylic substitution of **4**

Entry	Nucleophile/conditions[a]	Product ratio C-6/C-8	Total yield[b]
1	$CH_2(CO_2Me)_2$, NaH	3:2	69%
2	$LiCH(NO_2)SO_2Ph$, 3 h	not determined[c]	70%
3	LiN_3	5:1[d]	51%
4	PhthNK	3:2	66%
5	6-chloropurine, NaH	2:1	42%[e]

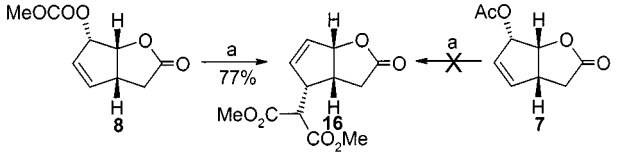
[a] General conditions: 5% $Pd(PPh_3)_4$ in THF at room temp. for 16 h unless otherwise stated. – [b] Combined yield of chromatographed products. – [c] Formation of four isomers due to formation of a new stereocenter.[30] – [d] Also formation of the C-6 *endo* and C-8 *endo* retention products. – [e] 37% recovered starting material.

all cases but one (Table 1). We observed, however, that both the C-6 and C-8 substituted products were formed.

Treatment of the carbonate **4** with sodium dimethyl malonate gave a 3:2 mixture of the C-6 *exo* product **14** and the regioisomeric C-8 *exo* product in good total yield (Entry 1). The products could not, however, be separated by flash chromatography. Likewise, the same lack of regioselectivity was observed when **4** was treated with the lithium salt of phenylsulfonylnitromethane, potassium phthalimide, or the sodium salt of 6-chloropurine (Entries 2, 4–5), resulting in mixtures of the C-6 and C-8 products. In none of these cases could the products be separated by chromatography.

When lithium azide was used as the nucleophile, the corresponding retention (*endo*) products were also formed. It was possible to separate the two *endo* azides from the mixture by careful chromatography, and this made it possible to accomplish the complete assignment of the ^1H and ^{13}C NMR spectra for all four isomeric azides. The reaction is, however, of little synthetic use. The formation of a complex mixture of allylic azides was anticipated, as allylic azides are known to be very reactive and easily undergo [3,3]-sigmatropic rearrangements.[21] Likewise, the formation of retention-type products has been described previously.[20,22]

The C-8 epimeric lactones **7** and **8**, with the acyloxy substituent in an *endo* orientation, were found to be less reactive than the corresponding lactones **2** and **4**, possessing *exo* substituents. No reaction occurred when the acetate **7** was treated with sodium dimethyl malonate (Table 2, Entry 1). When the corresponding carbonate **8** was treated under the same conditions, the C-6 *endo* product **16** could be isolated in good yield (77%) as the only product (Entry 2) (Scheme 5).



Scheme 5. Treatment of **7** and **8** with sodium dimethyl malonate: a) $CH_2(CO_2Me)_2$, $Pd(PPh_3)_4$, NaH, THF

When **8** was treated with lithium azide, all four possible isomeric azides were obtained; an outcome similar to that observed with the *exo* lactone **4** (Entry 3). On the other hand, no reaction occurred when 6-chloropurine was employed as the nucleophile in the substitution of **8**, even when the reaction was attempted at reflux temperatures (Entry 4). This observation again confirms that the *endo* substituent makes the bicyclic lactones less susceptible to palladium-catalyzed substitution than the compounds with the leaving group in the *exo* orientation.

We then investigated the Pd-catalyzed substitution of the monocyclic cyclopentene derivatives **10**, **11**, and **13**. When the cyclopentene acetate **10** was treated with dimethyl malonate under standard conditions, no reaction took place. This observation was very surprising, as the monocyclic system was expected to be more reactive than the bicyclic system, which had reacted under these conditions. Currently we have no explanation for this behavior. In contrast, when the carbonate **11** was treated with dimethyl malonate under the same conditions, full conversion was observed. The product consisted of an inseparable mixture of both possible products in a 2:1 ratio. On the other hand, no reaction was observed when **11** was treated with 6-chloropurine at reflux temperatures, which again is puzzling as the carbonate **4** reacted under milder conditions. Finally, the epimeric cyclopentene acetate **13** was treated with dimethyl malonate under standard conditions and was found to give a complex mixture of products and starting material, with one major product. Apparently, in the monocyclic case, the "*endo*" derivatives are more reactive than the "*exo*" derivatives. This is in stark contrast to the bicyclic series, where the *exo* lactones were far more reactive than the *endo* lactones.

Mitsunobu Substitution

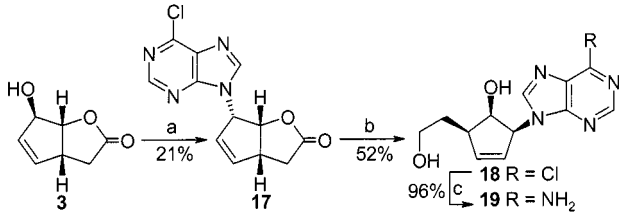
To complement the palladium-catalyzed substitutions, we also wished to investigate the Mitsunobu substitution[23] of the allylic alcohol **3** with 6-chloropurine as the nucleophile. In contrast to the palladium-catalyzed substitution, the Mitsunobu reaction in general leads to products with inverted stereochemistry at the substituted carbon atom. The formation of both retention- (via allylic rearrangements) and inversion-type products in the Mitsunobu substitution of allylic alcohols have been reported in the literature.[24]

Thus, the allylic alcohol **3** was treated with 6-chloropurine under Mitsunobu conditions (Scheme 6). After workup, ^1H NMR showed the presence of one major product along with at least five minor ones, among which were some possible N-7 alkylated products. The major product could be isolated by recrystallization, in 21% yield, and was identified as the nucleoside analogue **17** on the basis of 1D and H,H- and C,H-correlated NMR spectroscopy.[25]

Table 2. Palladium-catalyzed allylic substitution of **7** and **8**

Entry	Nucleophile/conditions[a]	Product ratio C-6/C-8	Total yield[b]
1 (**7**)	$CH_2(CO_2Me)_2$, NaH	no reaction	0%
2 (**8**)	$CH_2(CO_2Me)_2$, NaH	1:0	77%
3 (**8**)	LiN_3	3:1[c]	55%
4 (**8**)	6-chloropurine, NaH, reflux	no reaction	0%

[a] General conditions: 5% $Pd(PPh_3)_4$ in THF at room temp. for 16 h unless otherwise stated. − [b] Combined yield of chromatographed products. − [c] Also formation of the C-6 *exo* and C-8 *exo* retention products.



Scheme 6. Synthesis of the carbocyclic nucleoside **19**: a) DEAD, Ph_3P, 6-chloropurine, THF. b) $Ca(BH_4)_2$, 2 THF; c) NH_3 (liq.)

Finally, compound **17** was converted into the carbocyclic nucleoside **19**. Reduction of the lactone moiety was performed using calcium borohydride to give **18** in a moderate yield (52%); this was then converted into **19** by treatment with liquid ammonia in 96% yield. This carbocyclic nucleoside can be viewed as an analogue of the biologically interesting carbocyclic nucleoside BCA.[16,26]

Conclusion

Four bicyclic lactones − the C-8 *exo* acetate **2** and carbonate **4**, together with the C-8 epimeric acetate **7** and carbonate **8** − were investigated in palladium(0)-catalyzed substitution reactions, using five different C- and N-nucleophiles.

In all cases it was found that the *exo* derivatives were more reactive than the corresponding *endo* derivatives. The reactions with sodium dimethyl malonate as the nucleophile generally gave good yields and a single product, whereas less reactive C- and N-nucleophiles gave inseparable mixtures of both C-6 and C-8 substituted products, imposing a limitation on the synthetic use of the reaction with these nucleophiles. For the monocyclic systems the results were more ambiguous, with no reaction occurring in some cases and mixtures obtained in others.

Reaction of the *exo*-hydroxylactone **3** with 6-chloropurine under Mitsunobu conditions gave the carbocyclic nucleoside derivative **17**, isolated by recrystallization. This was then converted into the BCA analogue **19** by reduction of the lactone moiety and treatment with liquid ammonia.

In summary, we have probed the scope and limitations of the palladium-catalyzed substitution of the (1*R*,5*R*,8*R* or 8*S*)-8-hydroxy-2-oxabicyclo[3.3.0]oct-6-en-3-one system, as well as preparing the carbocyclic nucleoside (1*S*,2*R*,3*R*)-9-[2-hydroxy-3-(2-hydroxyethyl)cyclopent-4-en-1-yl]-9*H*-adenine (**19**).

Experimental Section

General Remarks: Reactions carried out under nitrogen were performed in flame-dried glassware. $Pd(PPh_3)_4$,[27] lithium azide,[28] and potassium phthalimide[29] were prepared according to literature procedures. $Ca(BH_4)_2$·2THF was purchased from Fluka Chemie AG. DEAD was distilled and stored under argon, THF was distilled from sodium/benzophenone, and dichloromethane from calcium hydride under nitrogen. Melting points are uncorrected. − Specific rotations were measured with a Perkin−Elmer 241 polarimeter and the concentrations are given in g/100 mL. − NMR spectra were recorded with Varian Inova 500 and Mercury 300 spectrometers. Chemical shifts (δ) were measured in ppm and coupling constants (*J*) in Hz. For NMR spectra in deuterated solvents, the solvent peak was used as reference ($CDCl_3$: δ = 7.27 for ^1H, δ = 76.93 for ^{13}C; [D_4]methanol: δ = 3.31 for ^1H, δ = 49.0 for ^{13}C; [D_6]acetone: δ = 2.05 for ^1H, δ = 29.8 for ^{13}C). When necessary, NMR spectroscopic data were assigned using H,H- and C,H-correlated spectra. − Elemental analyses were performed by the Institute of Physical Chemistry, University of Vienna and the Department of Chemistry, University of Copenhagen. HRMS (FAB) was performed by the Department of Chemistry, University of Copenhagen. TLC was performed on Merck 60 F_{254} precoated silica plates and spots were detected by spraying with a solution of cerium ammonium molybdate [1.5% $(NH_4)_6Mo_7O_{24}$·$4H_2O$, 1% $Ce(SO_4)_2$·$4H_2O$ and 10% H_2SO_4] or by dipping in a solution of potassium permanganate (1.5 g $KMnO_4$, 10 g K_2CO_3, 2.5 mL 5% aq. NaOH and 150 mL water), followed in both cases by charring. Flash chromatography was performed using silica gel 60 (Grace AB Amicon, 35−70 μm). Solvent removal was performed with a rotary evaporator at a temperature below 40 °C.

Methyl (1*R*,5*R*,8*R*)-3-Oxo-2-oxabicyclo[3.3.0]oct-6-en-8-yl Carbonate (4): Pyridine (5 mL) and methyl chloroformate (1.22 mL, 15.85 mmol) were added to a solution of compound **3**[10] (739 mg, 5.28 mmol) in dichloromethane (50 mL) at 0 °C and the mixture was stirred for 30 min. Water (10 mL) was then added, and the mixture was stirred for 10 min, followed by addition of more water (15 mL). The phases were separated and the aqueous phase extracted with dichloromethane (3 × 50 mL). The combined organic phases were washed with sat. aq. $CuSO_4$ (3 × 25 mL) and the combined aqueous phases reextracted with dichloromethane (20 mL). The combined organic phases were washed with brine (25 mL), followed by drying ($MgSO_4$) and concentration. Purification by flash chromatography (EtOAc/hexane, 1:1) gave the title compound **4** as a colorless oil (900 mg, 86%). − $[\alpha]_D$ = −238.3 (*c* = 0.72, $CHCl_3$). − ^1H NMR (300 MHz, $CDCl_3$): δ = 2.40 (dd, 1 H, $J_{4',5}$ = 2.0, $J_{4,4'}$ = 18.5, 4′-H), 2.78 (dd, 1 H, $J_{4,5}$ = 10.0, $J_{4,4'}$ = 18.5, 4-H), 3.68−3.77 (m, 1 H, 5-H), 3.78 (CH_3OCO), 4.95 (1 H, $J_{1,5}$ = 5.5, 1-H), 5.55 (s, 1 H, 8-H), 5.94 (1 H, dt, *J* = 2.0, *J* = 2.0, $J_{6,7}$ = 5.5, 6-H or 7-H), 6.01 (1 H, dt, *J* = 1.5, *J* = 1.5, $J_{6,7}$ = 5.5, 6-H or 7-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.8 (C-4), 43.6 (C-5),

54.8 (*CH*$_3$OCO), 84.9 (C-1), 85.1 (C-8), 128.1, 139.7 (C-6 + C-7), 154.5 (CH$_3$O*CO*), 174.8 (C-3). − $C_9H_{10}O_5$ (198.18): calcd. C 54.55, H 5.09; found C 54.36, H 4.99.

(1*R*,5*R*)-2-Oxabicyclo[3.3.0]oct-6-ene-3,8-dione (5): PCC (722 mg, 3.35 mmol) and Celite (760 mg) were suspended in dichloromethane (15 mL), and a solution of compound **3** (313 mg, 2.23 mmol) in dichloromethane (10 mL) was added over 1 h using a syringe pump. The mixture was stirred for 16 h at room temp., followed by filtration through a pad of Celite and concentration. The black residue was filtered through a short pad of silica (EtOAc), and then purified by flash chromatography (EtOAc/hexane, 9:1) to give the title compound **5** as a colorless oil (270 mg, 88%). − $[\alpha]_D$ −143.4 (c = 0.85, $CHCl_3$). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.50 (m, 1 H, 4′-H), 2.95 (m, 1 H, 4-H), 3.77 (s, 1 H, 5-H), 4.73 (s, 1 H, 1-H), 6.35 (s, 1 H, 6-H or 7-H), 7.67 (s, 1 H, 6-H or 7-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.5 (C-4), 39.3 (C-5), 77.5 (C-1), 132.8, 164.1 (C-6 + C-7), 174.7 (C-3), 201.2 (C-8). − $C_7H_6O_3$ (138.12): calcd. C 60.87, H 4.38; found C 60.60, H 4.20.

(1*R*,5*R*,8*S*)-8-Hydroxy-2-oxabicyclo[3.3.0]oct-6-en-3-one (6): A solution of compound **5** (340 mg, 2.46 mmol) and $CeCl_3$·7H_2O (975 mg, 2.62 mmol) in methanol (15 mL) was cooled to 0 °C. $NaBH_4$ (101 mg, 3.70 mmol) was added, and the mixture was stirred for 10 min. The solution was then quenched with 1 N HCl (5 mL), stirred for 1.5 h, and concentrated to a residue, which was dissolved in water (10 mL) and extracted with ethyl acetate (6 × 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to give a residue. Flash chromatography (EtOAc) gave a crude crystalline product (256 mg, 74%), which was purified by recrystallization (EtOAc) to give the title compound **6** as colorless crystals (187 mg, 54%), m.p. 122−123 °C. − $[\alpha]_D$ = −51.5 (c = 0.35, $CHCl_3$). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.30 (br s, 1 H, OH), 2.49 (dd, 1 H, $J_{4',5}$ = 2.0, $J_{4,4'}$ = 18.0, 4′-H), 2.82 (dd, 1 H, $J_{4,5}$ = 10.0, $J_{4,4'}$ = 18.0, 4-H), 3.39−3.44 (m, 1 H, 5-H), 4.90 (br d, 1 H, $J_{1,8}$ = 5.5, 8-H), 5.01 (t, 1 H, $J_{1,5}$ = 5.5, $J_{1,8}$ = 5.5, 1-H), 5.74 (1 H, dt, J = 2.0, J = 2.0, $J_{6,7}$ = 6.0, 6-H or 7-H), 5.90 (1 H, dt, J = 2.0, J = 2.0, $J_{6,7}$ = 6.0, 6-H or 7-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.6 (C-4), 43.4 (C-5), 76.9 (C-8), 81.5 (C-1), 131.9, 134.2 (C-6 + C-7), 175.7 (C-3). − $C_7H_8O_3$ (140.14): calcd. C 60.00, H 5.75; found C 59.87, H 5.74.

(1*R*,5*R*,8*S*)-8-Acetoxy-2-oxabicyclo[3.3.0]oct-6-en-3-one (7): Pyridine (2 mL) and acetic anhydride (1 mL) were added to a solution of compound **6** (122 mg, 0.87 mmol) in dichloromethane (20 mL) at 0 °C, and the mixture was stirred for 16 h at room temp. Water (10 mL) was added and the mixture stirred for 1 h. The phases were separated and the aqueous phase was extracted with dichloromethane (3 × 25 mL). The combined organic phases were then washed with 1 N HCl (20 mL), sat. aq. $NaHCO_3$ (20 mL), and brine (20 mL), followed by drying ($MgSO_4$) and concentration. Purification by flash chromatography (EtOAc/hexane, 1:1) gave the title compound **7** as a colorless oil, which crystallized upon standing (148 mg, 93%). Recrystallization (Et_2O) gave crystals of m.p. 63−64 °C. − $[\alpha]_D$ = −152.7 (c = 1.49, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.02 (s, 3 H, CH_3CO), 2.34 (dd, 1 H, $J_{4',5}$ = 3.0, $J_{4,4'}$ = 18.0, 4′-H), 2.71 (dd, 1 H, $J_{4,5}$ = 10.0, $J_{4,4'}$ = 18.0, 4-H), 3.38−3.45 (m, 1 H, 5-H), 5.11 (t, 1 H, $J_{1,5}$ = 6.0, $J_{1,8}$ = 6.0, 1-H), 5.56 (1 H, dq, J = 1.5, J = 1.5, J = 1.5, $J_{1,8}$ = 6.0, 8-H), 5.77 (1 H, dt, J = 2.0, J = 2.0, $J_{6,7}$ = 6.0, 6-H or 7-H), 5.85 (1 H, dt, J = 2.0, J = 2.0, $J_{6,7}$ = 6.0, 6-H or 7-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.4 (*CH*$_3$CO), 33.6 (C-4), 43.3 (C-5), 77.2 (C-8), 79.2 (C-1), 129.4, 134.8 (C-6 + C-7), 170.0 (CH$_3$*CO*), 175.5 (C-3). − $C_9H_{10}O_4$ (182.18): calcd. C 59.34, H 5.53; found C 59.04, H 5.38.

Methyl (1*R*,5*R*,8*S*)-3-Oxo-2-oxabicyclo[3.3.0]oct-6-en-8-yl carbonate (8): Compound **6** (96 mg, 0.69 mmol) was treated according to the procedure for preparation of **4**. Purification by flash chromatography (EtOAc/hexane, 1:1) gave the title compound **8** as colorless crystals (125 mg, 92%). Recrystallization (EtOAc/hexane,) gave crystals of m.p. 103.5−104 °C. − $[\alpha]_D$ = −149.7 (c = 0.90, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.37 (dd, 1 H, $J_{4',5}$ 3.5, $J_{4,4'}$ 18.0, 4′-H), 2.74 (dd, 1 H, $J_{4,5}$ = 10.0, $J_{4,4'}$ = 18.0, 4-H), 3.41−3.49 (m, 1 H, 5-H), 3.76 (CH_3OCO), 5.15 (t, 1 H, $J_{1,5}$ = 6.0, $J_{1,8}$ = 6.0, 1-H), 5.52 (d, 1 H, $J_{1,8}$ = 6.0, 8-H), 5.83 (1 H, ddd, J = 1.5, J = 2.0, $J_{6,7}$ = 6.0, 6-H or 7-H), 5.90 (1 H, dt, J = 2.0, J = 2.0, $J_{6,7}$ = 6.0, 6-H or 7-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.0 (C-4), 43.8 (C-5), 55.3 (*CH*$_3$OCO), 79.5, 80.6 (C-1 + C-8), 129.4, 136.8 (C-6 + C-7), 155.2 (CH$_3$O*CO*), 176.7 (C-3). − $C_9H_{10}O_5$ (198.18): calcd. C 54.55, H 5.09; found C 54.52, H 4.90.

(1*R*,2*R*,3*R*)-1,2-Dihydroxy-3-(2-hydroxyethyl)cyclopent-4-ene (9): A solution of compound **3** (210 mg, 1.50 mmol) in THF (5 mL) was added under nitrogen to a solution of $Ca(BH_4)_2$·2THF (565 mg, 2.64 mmol) in THF (10 mL), and the mixture was stirred for 16 h at room temp. Ethanol (10 mL) was added and the mixture stirred for another 3.5 h, followed by concentration. The crystalline residue was filtered through a short plug of silica, eluting with methanol, and then purified by flash chromatography (EtOAc/MeOH, 9:1) to give the title compound **9** as a hygroscopic, colorless oil (146 mg, 68%); $[\alpha]_D$ = −198.1 (c = 0.88, MeOH). − ^{1}H NMR (300 MHz, [D$_4$]methanol): δ = 1.46−1.57 (m, 1 H, 6′-H), 1.82−1.94 (m, 1 H, 6-H), 2.83−2.91 (m, 1 H, 3-H), 3.56−3.69 (m, 2 H, 7-H + 7′-H), 4.06 (dd, 1 H, J = 4.0, J = 7.0, 2-H), 4.52−4.55 (m, 1 H, 1-H), 5.71 (1 H, dt, J = 2.0, J = 2.0, $J_{4,5}$ = 6.0, 5-H), 5.87 (1 H, ddd, J = 1.0, J = 2.5, $J_{4,5}$ = 6.0, 4-H). − ^{13}C NMR (75 MHz, [D$_4$]methanol): δ = 32.6 (C-56, 46.3 (C-3), 61.8 (C-7), 81.1 (C-2), 83.4 (C-1), 132.6 (C-5), 137.7 (C-4).

(1*R*,2*R*,3*R*)-1,2-Diacetoxy-3-(2-acetoxyethyl)cyclopent-4-ene (10): Compound **9** (146 mg, 1.01 mmol) was treated according to the procedure for preparation of **7** (reaction time 64 h). Purification by flash chromatography (EtOAc/hexane, 3:7) gave the title compound **10** as a colorless oil (251 mg, 92%). − $[\alpha]_D$ = −209.8 (c = 0.74, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.43−1.55 (m, 1 H, 6′-H), 1.69−1.80 (m, 1 H, 6-H), 1.95 (s, 3 H, CH_3CO), 1.96 (s, 3 H, CH_3CO), 2.00 (s, 3 H, CH_3CO), 2.99−3.07 (m, 1 H, 3-H), 3.94−4.06 (m, 2 H, 7-H + 7′-H), 5.24 (dd, 1 H, J = 4.0, J = 7.0, 2-H), 5.55−5.58 (m, 1 H, 1-H), 5.71 (1 H, dt, J = 2.0, J = 2.0, $J_{4,5}$ = 6.0, 5-H), 5.95 (1 H, ddd, J = 1.0, J = 2.5, $J_{4,5}$ = 6.0, 4-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.5, 20.6, 20.7 (3 × *CH*$_3$CO), 27.8 (C-6), 42.6 (C-3), 62.3 (C-7), 77.9 (C-2), 82.1 (C-1), 128.1 (C-5), 137.7 (C-4), 170.1, 170.5 (3 × CH$_3$*CO*). − $C_{13}H_{18}O_6$ (270.28): calcd. C 57.77, H 6.71; found C 57.55, H 6.61.

(1*R*,2*R*,3*R*)-1,2-Dimethoxycarbonyl-3-[2-(methoxycarbonyl)-ethyl]cyclopent-4-ene (11): Compound **9** (130 mg, 0.93 mmol) was treated according to the procedure for preparation of **4** (reaction time 2 h). Purification by flash chromatography (EtOAc/hexane, 3:7) gave the title compound **11** as a colorless oil (121 mg, 42%), together with the 1,7-diacylated compound (78 mg, 33%).

Compound 11: $[\alpha]_D$ = −161.1 (c = 1.48, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.64 (1 H, ddt, $J_{6',7}$ = 6.5, $J_{6',7'}$ = 6.5, $J_{3,6'}$ = 9.0, $J_{6,6'}$ = 14.0, 6′-H), 1.91 (1 H, ddt, $J_{6,7}$ 6.5, $J_{6,7'}$ = 6.5, $J_{3,6}$ = 8.0, $J_{6,6'}$ = 14.0, 6-H), 3.11−3.21 (m, 1 H, 3-H), 3.73 (s, 3 H, CH_3OCO), 3.74 (s, 3 H, CH_3OCO), 3.77 (s, 3 H, CH_3OCO), 4.11−4.17 (m, 2 H, 7-H + 7′-H), 5.21 (dd, 1 H, J = 4.0, J = 7.0, 2-H), 5.55−5.60 (m, 1 H, 1-H), 5.81 (1 H, dt, J = 2.0, J = 2.0, $J_{4,5}$ = 6.0, 5-H), 6.04 (dd, 1 H, J = 2.0, $J_{4,5}$ = 6.0, 4-H). − ^{13}C

NMR (75 MHz, $CDCl_3$): δ = 27.8 (C-6), 42.6 (C-3), 54.6, 54.7, 55.0 (3 × *CH*$_3$OCO), 66.0 (C-7), 81.1 (C-2), 85.3 (C-1), 127.6 (C-5), 138.5 (C-4), 155.0, 155.5 (3 × CH_3O*CO*). − $C_{13}H_{18}O_9$ (318.28) calcd. C 49.06, H 5.70; found C 48.94, H 5.56.

1,7-Diacylated Compound: $[\alpha]_D$ = −105.1 (*c* = 1.17, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.61−1.74 (m, 1 H, 5′-H), 20.1−2.13 (m, 1 H, 5-H), 3.11−3.21 (m, 2 H, 4-H + OH), 3.74 (s, 3 H, CH_3OCO), 3.77 (s, 3 H, CH_3OCO), 4.18−4.24 (m, 2 H, 6-H + 6′-H), 4.33 (dd, 1 H, *J* = 4.0, *J* = 7.0, 3-H), 5.33−5.37 (m, 1 H, 2-H), 5.72 (1 H, dt, *J* = 2.5, *J* = 2.5, $J_{1,4a}$ = 6.0, 1-H), 6.00 (1 H, ddd, *J* = 1.0, *J* = 2.5, $J_{1,4a}$ = 6.0, 4a-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.9 (C-5), 44.3 (C-4), 54.6, 54.8 (2 × *CH*$_3$OCO), 66.8 (C-6), 77.4 (C-3), 89.8 (C-2), 126.9 (C-1), 139.4 (C-4a), 155.6, 156.3 (2 × CH_3O*CO*).

(1*S*,2*R*,3*R*)-1,2-Dihydroxy-3-(2-hydroxyethyl)cyclopent-4-ene (12): Compound **6** (80 mg, 0.57 mmol) was treated according to the procedure for preparation of **9**. Purification by flash chromatography (EtOAc/MeOH, 9:1) gave the title compound **12** as a hygroscopic, colorless oil (67 mg, 82%). − $[\alpha]_D$ = −4.9 (*c* = 0.61, MeOH). − ^{1}H NMR (300 MHz, [D$_4$]methanol): δ = 1.56−1.68 (m, 1 H, 6′-H), 1.82−1.94 (m, 1 H, 6-H), 2.61−2.71 (m, 1 H, 3-H), 3.64−3.69 (m, 2 H, 7-H + 7′-H), 4.17 (t, 1 H, *J* = 6.5, *J* = 6.5, 2-H), 4.48−4.52 (m, 1 H, 1-H), 5.74 (1 H, dt, *J* = 2.0, *J* = 2.0, $J_{4,5}$ = 6.0, 5-H), 5.85 (1 H, dt, *J* = 1.5, *J* = 1.5, $J_{4,5}$ = 6.0, 4-H). − ^{13}C NMR (75 MHz, [D$_4$]methanol): δ = 33.6 (C-6), 46.2 (C-3), 61.6 (C-7), 73.8 (C-2), 77.0 (C-1), 132.4 (C-5), 137.2 (C-4).

(1*S*,2*R*,3*R*)-1,2-Diacetoxy-3-(2-acetoxyethyl)cyclopent-4-ene (13): Compound **12** (50 mg, 0.35 mmol) was acetylated according to the procedure for preparation of **7** (reaction time 64 h). Purification by flash chromatography (EtOAc/hexane, 3:7) gave the title compound **13** as a colorless oil (72 mg, 77%). − $[\alpha]_D$ = +28.3 (*c* = 0.71, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.70 (1 H, ddt, $J_{6',7}$ = 6.5, $J_{6',7'}$ = 6.5, $J_{3,6'}$ = 8.5, $J_{6,6'}$ = 14.0, 6′-H), 1.87−1.99 (m, 1 H, 6-H), 2.04 (s, 3 H, CH_3CO), 2.05 (s, 3 H, CH_3CO), 2.08 (s, 3 H, CH_3CO), 2.83−2.93 (m, 1 H, 3-H), 4.10−4.16 (m, 2 H, 7-H + 7′-H), 5.37 (dd, 1 H, $J_{1,2}$ 6.0, *J* = 6.5, 2-H), 5.65 (1 H, ddd, *J* = 1.0, *J* = 2.0, $J_{1,2}$ = 6.0, 1-H), 5.87 (1 H, dt, *J* = 2.0, *J* = 2.0, $J_{4,5}$ = 6.0, 5-H), 6.11 (1 H, ddd, *J* = 1.0, *J* = 2.5, $J_{4,5}$ = 6.0, 4-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.5, 20.8 (3 × *CH*$_3$CO), 29.0 (C-5), 42.7 (C-3), 62.6 (C-7), 72.4 (C-2), 75.1 (C-1), 128.0 (C-5), 138.5 (C-4), 170.0, 170.1, 170.9 (3 × CH_3*CO*). − $C_{13}H_{18}O_6$ (270.28): calcd. C 57.77, H 6.71; found C 57.49, H 6.60.

(1*R*,5*R*,6*S*)-8-[Bis(methoxycarbonyl)methyl]-2-oxabicyclo[3.3.0]oct-7-en-3-one (14): To a suspension of pentane-washed NaH (25 mg, 1.04 mmol) in THF (3 mL) under nitrogen was slowly added dimethyl malonate (0.135 mL, 1.22 mmol) over 5 min, resulting in a clear solution. To this was added a solution of $Pd(PPh_3)_4$ (31 mg, 0.03 mmol) and compound **2**[10] (101 mg, 0.55 mmol) in THF (2 mL), and the resulting yellow reaction mixture was stirred for 16 h at room temp. The now brown reaction mixture was quenched with 10% aqueous acetic acid (5 mL) and stirred for 15 min. The mixture was concentrated and the residue was taken up into dichloromethane (50 mL) and washed with water (2 × 10 mL). The combined aqueous phases were reextracted with dichloromethane (20 mL) and then the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), and concentrated. Purification by flash chromatography (EtOAc/hexane, 1:1) gave the title compound **14** as a colorless oil (78 mg, 56%). − $[\alpha]_D$ = −150.3 (*c* = 1.61, $CHCl_3$). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.32 (dd, 1 H, $J_{4',5}$ 2.0, $J_{4,4'}$ 18.0, 4′-H), 2.74 (dd, 1 H, $J_{4,5}$ 10.0, $J_{4,4'}$ 18.0, 4-H), 3.51−3.53 (m, 2 H, 6-H + 9-H), 3.56−3.66 (m, 1 H, 5-H), 3.72 (s, 3 H, CH_3OCO), 3.73 (s, 3 H, CH_3OCO), 5.11 (d, 1 H, $J_{1,5}$ = 6.0, 1-H), 5.69 (dd, 1 H, *J* = 1.0, $J_{7,8}$ = 5.5, 7-H or 8-H), 5.74 (1 H, dt, *J* = 1.5, *J* = 1.5, $J_{7,8}$ = 5.5, 7-H or 8-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.3 (C-4), 44.9 (C-5), 51.9, 53.1 (C-6 + C-9), 52.5, 52.6 (2 × *CH*$_3$OCO), 85.1 (C-1), 130.3, 134.2 (C-7 + C-8), 167.9, 168.0 (2 × CH_3*CO*), 176.0 (C-3). − $C_{12}H_{14}O_6$ (254.24): calcd. C 56.69, H 5.55; found C 56.40, H 5.64.

(1*R*,5*R*,6*S*)-8-(Methoxycarbonylmethyl)-2-oxabicyclo[3.3.0]oct-7-en-3-one (15): A solution of compound **14** (46 mg, 0.18 mmol) in methanol/4 N HCl (1 mL + 4 mL) was heated to reflux for 16 h. Concentration gave the free acid, which was dissolved in acidic methanol (3 mL, 1% v/v acetyl chloride in methanol). 2,2-Dimethoxypropane (3 mL) was added and the mixture stirred for 16 h at room temp. Concentration and purification by flash chromatography (EtOAc/hexane, 1:1) gave the title compound **15** as a colorless oil (32 mg, 90%). − $[\alpha]_D$ = −134.5 (*c* = 0.53, $CHCl_3$). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.24−2.28 (m, 2 H, 9-H + 9′-H), 2.35 (dd, 1 H, $J_{4',5}$ = 2.0, $J_{4,4'}$ = 18.0, 4′-H), 2.69 (dd, 1 H, $J_{4,5}$ = 10.0, $J_{4,4'}$ = 18.0, 4-H), 3.20−3.26 (m, 1 H, 6-H), 3.50−3.58 (m, 1 H, 5-H), 3.63 (s, 3 H, CH_3OCO), 4.83 (dd, 1 H, *J* = 0.5, $J_{1,5}$ = 6.0, 1-H), 5.56 (1 H, dt, *J* = 1.5, *J* = 1.5, $J_{7,8}$ = 5.5, 7-H or 8-H), 5.72 (1 H, ddt, *J* = 0.5, *J* = 2.5, *J* = 2.5, $J_{7,8}$ = 5.5, 7-H or 8-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.6, 36.6 (C-4 + C-9), 44.5, 48.4 (C-5 + C-6), 51.7 (*CH*$_3$OCO), 86.7 (C-1), 132.2, 132.8 (C-7 + C-8), 171.5 (CH_3O*CO*), 176.0 (C-3).

Treatment of 4 with Sodium Dimethyl Malonate: Compound **4** (113 mg, 0.57 mmol) was treated according to the procedure for **14**. Purification by flash chromatography (EtOAc/hexane, 1:1) gave a 3:2 regioisomeric mixture of compound **14** and the C-8 isomer as a colorless oil (100 mg, 69%).

C-8 Isomer: ^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.4 (C-4), 39.7 (C-5), 52.4, 55.0 (C-6 + C-9), 52.5, 52.6 (2 × *CH*$_3$OCO), 88.3 (C-1), 131.2, 137.3 (C-7 + C-8), 167.9, 168.1 (2 × CH_3O*CO*), 176.4 (C-3).

Treatment of 4 with Lithium Phenylsulfonylnitromethane: A solution of $Pd(PPh_3)_4$ (30 mg, 0.03 mmol) in THF (1 mL) was added under nitrogen to a solution of compound **4** (101 mg, 0.51 mmol) and lithium phenylsulfonylnitromethane (161 mg, 0.78 mmol) in THF (3 mL), and the mixture was stirred for 16 h at room temp. The now brown reaction mixture was quenched and worked up according to the procedure for **14**. Purification by flash chromatography (EtOAc/hexane, 1:1) gave a complex mixture of the four possible regio- and stereoisomeric phenylsulfonylnitromethanes as a colorless oil (117 mg, 70%).

Treatment of 4 with Lithium Azide: A solution of $Pd(PPh_3)_4$ (34 mg, 0.03 mmol) in THF (1 mL) was added under nitrogen to a solution of compound **4** (107 mg, 0.54 mmol) and LiN_3 (55 mg, 1.12 mmol) in THF (3 mL), and the mixture was stirred for 16 h at room temp. Dichloromethane (25 mL) was added to the now orange reaction mixture, which was washed with water (10 mL) followed by re-extraction of the aqueous phase with dichloromethane (10 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), and concentrated, after which purification by flash chromatography (EtOAc/hexane, 1:1) gave a mixture of the four possible regio- and stereoisomeric azides in an 18:6:4:1 ratio (45 mg, 51%).

C-6 *exo* Azide: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.46 (dd, 1 H, $J_{4',5}$ = 2.0, $J_{4,4'}$= 18.5, 4′-H), 2.83 (dd, 1 H, $J_{4,5}$ = 10.0, $J_{4,4'}$ = 18.5, 4-H), 3.67−3.72 (m, 1 H, 5-H), 4.48 (1 H, br s, 6-H), 5.64 (d, 1 H, $J_{1,5}$ = 5.5, 1-H), 5.94 (1 H, dt, *J* = 3.0, *J* = 3.0, $J_{7,8}$ = 5.5, 7-H or 8-H), 6.04 (1 H, ddd, *J* = 1.0, *J* = 2.0, $J_{7,8}$ = 5.5, 7-H or

8-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 32.0 (C-4), 44.2 (C-5), 69.9 (C-8), 85.7 (C-1), 128.4, 137.9 (C-6 + C-7), 174.6 (C-3).

C-8 *exo* Azide: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.40 (dd, 1 H, $J_{4',5}$ = 6.5, $J_{4,4'}$ = 18.5, 4′-H), 2.93 (dd, 1 H, $J_{4,5}$ = 11.0, $J_{4,4'}$ = 18.5, 4-H), 3.05−3.10 (m, 1 H, 5-H), 4.31 (1 H, br s, 8-H), 5.64 (1 H, dt, J = 1.0, J = 1.0, $J_{1,5}$ = 7.0, 1-H), 6.15 (dd, 1 H, J = 2.0, $J_{6,7}$ = 5.5, 6-H or 7-H), 6.26 (1 H, dt, J = 1.5, J = 1.5, $J_{6,7}$ = 5.5, 6-H or 7-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.4 (C-4), 42.9 (C-5), 71.8 (C-8), 87.2 (C-1), 134.0, 134.9 (C-6 + C-7), 175.2. (C-3).

C-6 *endo* Azide: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.62 (dd, 1 H, $J_{4,5}$ = 10.5, $J_{4,4'}$ = 19.0, 4-H), 2.78 (dd, 1 H, $J_{4',5}$ = 6.5, $J_{4,4'}$ = 19.0, 4′-H), 3.35−3.41 (m, 1 H, 5-H), 4.68 (1 H, br d, $J_{5,6}$ = 7.0, 6-H), 5.34 (1 H, dt, J = 1.0, J = 1.0, $J_{1,5}$ = 7.0, 1-H), 6.11 (1 H, dt, J = 1.0, J = 1.0, $J_{7,8}$ = 5.5, 7-H or 8-H), 6.17 (1 H, dt, J = 2.0, J = 2.0, $J_{7,8}$ = 5.5, 7-H or 8-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.3 (C-4), 40.1 (C-5), 66.1 (C-6), 85.8 (C-1), 132.8, 134.6 (C-7 + C-8), 176.7 (C-3).

C-8 *endo* Azide: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.49 (dd, 1 H, $J_{4',5}$ = 3.5, $J_{4,4'}$ = 18.0, 4′-H), 2.81 (dd, 1 H, $J_{4,5}$ = 10.0, $J_{4,4'}$ = 18.0, 4-H), 3.48−3.53 (m, 1 H, 5-H), 4.39 (1 H, br d, $J_{1,8}$ = 5.0, 8-H), 5.12 (t, 1 H, $J_{1,5}$ 5.5, $J_{1,8}$ = 5.5, 1-H), 5.91 (1 H, dt, J = 1.5, J = 1.5, $J_{6,7}$ = 5.5, 6-H or 7-H), 5.94 (1 H, dt, J = 2.0, J = 2.0, $J_{6,7}$ = 5.5, 6-H or 7-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.6 (C-4), 44.2 (C-5), 66.8 (C-8), 81.8 (C-1), 131.5, 136.0 (C-6 + C-7), 176.0 (C-3).

Treatment of 4 with Potassium Phthalimide: A solution of $Pd(PPh_3)_4$ (37 mg, 0.03 mmol) in THF (1 mL) was added under nitrogen to a solution of compound **4** (99 mg, 0.50 mmol) and potassium phthalimide (190 mg, 1.03 mmol) in THF (5 mL), and the mixture was stirred for 16 h at room temp. The reaction mixture was quenched and worked up according to the procedure for **14**. Purification by flash chromatography (EtOAc/hexane, 1:1) gave a 3:2 mixture of phthalimides as colorless crystals (90 mg, 66%).

Compound Substituted at C-6: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.47 (dd, 1 H, $J_{4',5}$ 2.0, $J_{4,4'}$ 18.0, 4′-H), 2.83 (dd, 1 H, $J_{4,5}$ = 10.5, $J_{4,4'}$ = 18.0, 4-H), 4.97−4.12 (m, 1 H, 5-H), 5.18 (dd, 1 H, J = 1.0, $J_{1,6}$ = 7.0, 1-H), 5.39 (1 H, br s, 8-H), 5.64 (1 H, dt, J = 2.5, J = 2.5, $J_{7,8}$ = 5.5, 7-H or 8-H), 5.99 (1 H, dt, J = 2.0, J = 2.0, $J_{7,8}$ = 5.5, 7-H or 8-H), 7.69−7.73 (m, 2 H, Ar-H), 7.78−7.82 (m, 2 H, Ar-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.8 (C-4), 45.5 (C-5), 60.4 (C−N), 85.7 (C-1), 123.2 (Ar-C), 126.6 (C-6 or C-7), 134.1 (Ar-C), 137.7 (C-6 or C-7), 167.1, 167.4 (Ar-C), 175.6 (C-3).

Compound Substituted at C-8: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.50 (dd, 1 H, $J_{4',5}$ 6.5, $J_{4,4'}$ 18.5, 4′-H), 2.83 (dd, 1 H, $J_{4,5}$ = 10.5, $J_{4,4'}$ = 18.5, 4-H), 3.23−3.30 (m, 1 H, 5-H), 5.20 (t, 1 H, J = 2.0, J = 2.0, 8-H), 5.92 (dd, 1 H, J = 2.5, $J_{1,5}$ = 5.5, 1-H), 5.92 (1 H, dt, J = 2.0, J = 2.0, $J_{6,7}$ = 5.5, 6-H or 7-H), 6.22 (1 H, dt, J = 2.0, J = 2.0, $J_{6,7}$ = 5.5, 6-H or 7-H), 7.69−7.73 (m, 2 H, Ar-H), 7.78−7.82 (m, 2 H, Ar-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 34.3 (C-4), 40.9 (C-5), 60.9 (C−N), 88.9 (C-1), 123.2 (Ar-C), 131.5, 132.9 (C-6 + C-7), 134.1 (Ar-C), 167.1, 167.4 (Ar-C), 175.7 (C-3).

Treatment of 4 with 6-Chloropurine: To a suspension of pentane-washed NaH (25 mg, 1.04 mmol) in THF (3 mL) under nitrogen was added 6-chloropurine (160 mg, 1.04 mmol) and the mixture was stirred for 0.5 h, resulting in a clear solution. To this was added a solution of $Pd(PPh_3)_4$ (64 mg, 0.06 mmol) and compound **4** (108 mg, 0.55 mmol) in THF (2 mL), and the mixture was stirred for 5 d. Concentration gave a residue, which was filtered and washed with acetone to give a crude product. Purification by flash chromatography (EtOAc) first gave recovered starting material (40 mg, 37%), followed by a 2:1 mixture of purines as a colorless oil also containing Ph_3P (78 mg, 42% corrected for Ph_3P).

Compound Substituted at C-6: ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 2.57 (dd, 1 H, $J_{4',5}$ 2.0, $J_{4,4'}$ 18.0, 4′-H), 3.05 (dd, 1 H, $J_{4,5}$ = 10.0, $J_{4,4'}$ = 18.0, 4-H), 4.16−4.24 (m, 1 H, 5-H), 5.28 (1 H, dq, J = 0.5, J = 0.5, J = 0.5, J = 6.0, 1-H or 6-H), 5.85−5.89 (m, 1 H, 1-H or 6-H), 6.12 (1 H, ddt, J = 1.0, J = 2.5, J = 2.5, $J_{7,8}$ = 5.5, 7-H or 8-H), 6.37 (1 H, dt, J = 1.5, J = 1.5, $J_{7,8}$ = 5.5, 7-H or 8-H), 8.41 (s, 1 H, Ar-H), 8.66 (s, 1 H, Ar-H). − ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 32.3 (C-4), 46.0 (C-5), 66.6 (C-6), 86.4 (C-1), 127.2, 129.6, 132.5, 132.7, 141.4, 145.8, 152.3 (C-6 + C-7+ Ar-C), 175.7 (C-3).

Compound Substituted at C-8: ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 2.81 (dd, 1 H, $J_{4',5}$ = 5.5, $J_{4,4'}$ = 18.5, 4′-H), 3.05 (dd, 1 H, $J_{4,5}$ = 11.0, $J_{4,4'}$ = 18.5, 4-H), 3.48−3.57 (m, 1 H, 5-H), 5.93 (1 H, quintet, 8-H), 5.98 (1 H, ddt, J = 1.0, J = 2.0, J = 2.0, $J_{1,5}$ = 7.0, 1-H), 6.39 (1 H, ddd, J = 1.0, J = 2.0, $J_{6,7}$ = 5.5, 6-H or 7-H), 6.45 (1 H, dt, J = 2.0, J = 2.0, $J_{6,7}$ = 5.5, 6-H or 7-H), 8.55 (s, 1 H, Ar-H), 8.69 (s, 1 H, Ar-H). − ^{13}C NMR (125 MHz, [D$_6$]acetone): δ = 34.2 (C-4), 44.1 (C-5), 67.6 (C-8), 88.6 (C-1), 132.6, 133.7, 134.5, 134.6, 136.6, 145.7, 152.1 (C-6 + C-7 + Ar-C), 175.9 (C-3).

Treatment of 8 with Sodium Dimethyl Malonate. − (1*R*,5*R*,6*R*)-8-[Bis(methoxycarbonyl)methyl]-2-oxabicyclo[3.3.0]oct-7-en-3-one (16): Compound **8** (57 mg, 0.29 mmol) was treated according to the procedure for **14**. Purification by flash chromatography (EtOAc/hexane, 4:6) gave the title compound **16** as a colorless oil (56 mg, 77%). − $[\alpha]_D$ −72.5 (c = 1.75, $CHCl_3$). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.29 (dd, 1 H, $J_{4',5}$ = 9.0, $J_{4,4'}$ = 18.0, 4′-H), 2.45 (dd, 1 H, $J_{4,5}$ 10.0, $J_{4,4'}$ 18.0, 4-H), 3.40 (d, 1 H, $J_{6,9}$ = 11.5, 9-H), 3.39−3.46 (m, 1 H, 5-H), 3.55−3.61 (m, 1 H, 6-H), 3.72 (s, 3 H, CH_3OCOO), 3.79 (s, 3 H, CH_3OCOO), 5.50 (1 H, br. d, $J_{1,5}$ = 7.5, 1-H), 5.91 (1 H, br d, $J_{7,8}$ = 6.0, 7-H or 8-H), 5.94 (1 H, dt, J = 1.5, J = 1.5, $J_{7,8}$ = 6.0, 7-H or 8-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.5 (C-4), 39.5 (C-5), 45.7, 52.5, 52.8 (C-6 + C-9 + 2 × CH_3OCOO), 87.8 (C-1), 130.5, 135.5 (C-7 + C-8), 168.0, 168.1 (2 × CH_3OCOO), 175.9 (C-3). − $C_{12}H_{14}O_6$ (254.24): calcd. C 56.69, H 5.55; found C 56.29, H 5.48.

Treatment of 8 with Lithium Azide: Compound **8** (55 mg, 0.28 mmol) was treated according to the procedure for treatment of **4** with lithium azide. Concentration gave a 3:1:11:3 mixture of the four isomeric azides. Separation by flash chromatography (EtOAc/hexane, 4:6) first gave a 2:1 mixture of the two *exo*-substituted azides (6 mg, 13%) followed by the C-6 *endo* compound (15 mg, 33%) and then the C-8 *endo* compound (4 mg, 9%).

(1*R*,5*R*,8*S*)-8-(6-Chloropurin-9-yl)-2-oxabicyclo[3.3.0]oct-6-en-3-one (17): A solution of **3** (438 mg, 3.13 mmol), Ph_3P (980 mg, 3.74 mmol), and 6-chloropurine (580 mg, 3.75 mmol) in THF at −20 °C under nitrogen was stirred for 0.5 h. DEAD (0.25 mL, 1.61 mmol) was then added dropwise over 15 min, and the reaction mixture was stirred for a further 1 h at −20 °C. Concentration gave a black residue, which was subjected to flash chromatography (EtOAc). The fractions containing **17** were combined (510 mg) and recrystallized (EtOAc) to give the title compound **17** as colorless crystals (182 mg, 21%, m.p. 193−196 °C). Further recrystallization gave crystals of m.p. 194−195 °C (EtOAc). − $[\alpha]_D$ = −215.6 (c = 0.13, acetone). − ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 2.59 (1 H, dt, J = 2.0, $J_{4',5}$ = 2.0, $J_{4,4'}$ = 18.0, 4′-H), 2.95 (1 H, ddd, J = 2.0, $J_{4,5}$ = 10.0, $J_{4,4'}$ = 18.0, 4-H), 3.84−3.89 (m, 1 H, 5-H), 5.42 (1 H, dt, J = 1.5, $J_{1,5}$ = 5.5, $J_{1,8}$ = 5.5, 1-H), 6.15 (1 H, dt, J =

1.5, J = 1.5, $J_{1,8}$ = 5.5, 8-H), 6.21 (dd, 1 H, J = 1.5, $J_{6,7}$ = 5.5, 6-H or 7-H), 6.26 (dd, 1 H, J = 2.5, $J_{6,7}$ = 5.5, 6-H or 7-H), 8.35 (d, 1 H, J = 2.0, Ar-H), 8.74 (d, 1 H, J = 2.0, Ar-H). − ^{13}C NMR (125 MHz, [D$_6$]acetone): δ = 33.8 (C-4), 45.9 (C-5), 62.9 (C-8), 81.0 (C-1), 128.3, 129.4, 132.6, 132.7, 137.8, 146.7, 152.4 (C-6 + C-7 + Ar-C), 175.4 (C-3). − $C_{12}H_9ClN_4O_2$ (276.68): calcd. C 52.09, H 3.28, N 20.25, Cl 12.81; found C 51.92, H 3.36, N 19.95, Cl 13.11.

6-Chloro-9-[(1*S*,2*R*,3*R*)-2-hydroxy-3-(2-hydroxyethyl)cyclopent-4-en-1-yl]-9*H*-purine (18): A solution of compound **17** (64 mg, 0.23 mmol) in THF (2 mL) was added under nitrogen to a solution of Ca(BH$_4$)$_2$·2THF (93 mg, 0.43 mmol) in THF (5 mL). The reaction mixture was stirred for 1.5 h, then quenched with MeOH (3 mL) and concentrated. Purification by flash chromatography (CHCl$_3$/MeOH, 9:1) gave the title compound **18** as colorless crystals (34 mg, 52%, m.p. 167−170 °C). − [α]$_D$ −79.5 (c = 0.28, MeOH). − ^{1}H NMR (300 MHz, [D$_4$]methanol): δ = 1.74−1.87 (m, 1 H, 6′-H), 1.89−1.99 (m, 1 H, 6-H), 2.88−3.12 (m, 1 H, 3-H), 3.69−3.73 (m, 2 H, 7-H + 7′-H), 4.57 (t, 1 H, J = 5.0, J = 5.0, 1-H), 5.82 (m, 1 H, 2-H), 5.95 (1 H, dt, J = 2.0, J = 2.0, $J_{4,5}$ = 6.0, 4-H or 5-H), 6.19 (1 H, dt, J = 2.0, J = 2.0, $J_{4,5}$ = 6.0, 4-H or 5-H), 8.37 (s, 1 H, Ar-H), 8.73 (s, 1 H, Ar-H). − ^{13}C NMR (75 MHz, [D$_4$]methanol): δ = 32.3 (C-6), 48.1 (C-3), 61.8 (C-7), 64.9 (C-1), 73.6 (C-2), 126.8, 132.5, 140.5, 148.7, 151.0, 153.0, 153.7 (C-1 + C-5 + Ar-C). − $C_{12}H_{13}ClN_4O_2$ (280.7133): calcd. for [M + H] 281.0803, found 281.0804.

(1*S*,2*R*,3*R*)-9-[2-Hydroxy-3-(2-hydroxyethyl)cyclopent-4-en-1-yl]-9*H*-adenine (19): Liquid ammonia (ca. 10 mL) was added to compound **18** (19 mg, 0.07 mmol), and the mixture was sealed in a steel tube at 80 °C for 3 d. After cooling to room temp., the tube was opened and the ammonia was allowed to evaporate, leaving a brown residue. This was dissolved in methanol (10 mL), filtered, and concentrated to a crude product. Purification by flash chromatography (CHCl$_3$/MeOH, 8:2) gave the title compound **19** as colorless crystals (17 mg, 96%, m.p. 184−187 °C). − [α]$_D$ = −78.4 (c = 0.98, MeOH). − ^{1}H NMR (300 MHz, [D$_4$]methanol): δ = 1.73−1.84 (m, 1 H, 6′-H), 1.86−1.97 (m, 1 H, 6-H), 2.90−3.03 (m, 1 H, 3-H), 3.69−3.73 (m, 2 H, 7-H + 7′-H), 4.52 (t, 1 H, J = 5.0, J = 5.0, 1-H), 5.62−5.66 (m, 1 H, 2-H), 5.94 (1 H, dt, J = 2.5, J = 2.5, $J_{4,5}$ = 6.0, 4-H or 5-H), 6.14 (1 H, dt, J = 2.0, J = 2.0, $J_{4,5}$ = 6.0, 4-H or 5-H), 7.98 (s, 1 H, Ar-H), 8.21 (s, 1 H, Ar-H). − ^{13}C NMR (75 MHz, [D$_4$]methanol): δ = 32.3 (C-6), 47.9 (C-3), 61.7 (C-7), 64.4 (C-1), 73.9 (C-2), 127.4, 139.8, 143.0, 151.0, 153.7, 157.0, 157.4 (C-4 + C-5 + Ar-C). − $C_{12}H_{15}N_5O_2$ (261.2828): calcd. for [M + H] 262.1301, found 262.1286.

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