Chiral Synthons from the Iridoid Glucoside Antirrhinoside − Synthesis of a Carbocyclic Homonucleoside Analogue[‡]

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The synthetic modification of the natural cyclopentanoid monoterpene glucoside antirrhinoside is reported. Some stereoselective modifications have been performed on the bicyclic iridoidic ring, resulting in opening of the dihydropyran ring. A series of chiral synthons having a highly oxygenated cyclopentanoid ring has been prepared, which could be used in the synthesis of nucleoside analogues. We describe herein the synthesis of an acyclovir derivative (DA-146) as an example.

Introduction

The cyclopentane ring is a template present in several natural products of biological interest, e.g. prostaglandins and similar derivatives. It has been introduced in the molecular structure of nucleosides[1−4] in place of the furanose moiety of ribose and deoxyribose.

The carbocyclic nucleoside analogues are important as antiviral agents, particularly against HIV infection. They belong to the class of reverse transcriptase (RT) inhibitors,[1−5] but they are, compared to other classical compounds of this group, well-suited for solving the problems associated with the hydrolytic lability of glycosidic bonds, which renders drugs metabolically unstable, and the low selectivity with respect to DNA cellular polymerases. Changing a furanose ring to a cyclopentanoid ring solves both of these problems; this is the first step en route to carbocyclic inhibitors, of which Carbovir, as well as aristeromycin and neoplacin A, are the best known examples.[1−5] The design of these inhibitors stems from the understanding of virus structure and of its replication mode.

Through studying the action of RT,[6−9] it is possible to understand the mechanism of interaction of the inhibitors. The RT enzyme uses the single viral stranded RNA as a template for the synthesis of the double-helix DNA. First of all, the RT links the template primer; in the second step, it links a new deoxyribonucleoside triphosphate (dNTP). The chain elongation reaction catalyzed by DNA polymerase is a nucleophilic attack of the 3′-OH terminus of the primer on the innermost phosphorus atom of a dNTP. A phosphodiester bridge is formed with the concomitant release of pyrophosphate.

The role of nucleoside carbocyclic analogues is to act as competitive inhibitors; at the same time, these analogues act as chain terminators as they lack the 3′-OH function.

Iridoids are characterized by the presence of a diversely functionalized cyclopentanoid ring and have been employed for the synthesis of prostaglandins[10] and carbocyclic nucleoside analogues.[11−14] In particular, aucubin,[15−24] asperuloside,[25] and catalpol[26−29] have been used in the synthesis of prostaglandin analogues, while aucubin constituted the chiral starting material in the synthesis of two carbocyclic nucleosides.[11−14] All of these are iridoids that are present in large quantities in plants and they are easily extracted and purified.[10] In the Mediterranean area, one other iridoid, namely antirrhinoside **1**, can easily be isolated in large quantities from several plants of the *Scrophulariaceae* family. Based on these considerations, we have studied chemical modifications of this natural glucoside, with the aim of preparing cyclopentanoid chiral derivatives that may be used in subsequent syntheses of new nucleoside analogues.

Results and Discussion

The first step in the transformation of an iridoid glucoside into a cyclopentanoid synthon is the opening of the dihydropyran ring present in these monoterpenes. The dihydropyran ring of antirrhinoside (**1**) was opened using a reductive synthetic strategy, as depicted in Scheme 1.

Three protocols were used. The first one (protocol A) is based on mercuriation of the double bond at C-3 and C-4 with $Hg(OAc)_2$ followed by reductive demercuriation with $NaBH_4$; the second (protocol B) is based on enzymatic hydrolysis of the glucoside followed by reduction of the hemiacetal derivative. Both of these strategies give compound **2**. The third (protocol C) involves ozonolysis of the C-3/C-4 double bond followed by reduction; it allows access to the lower homologue of compound **2**, namely the cyclopentane derivative **3**.

[‡] For preliminary communications, see refs.[30,33]

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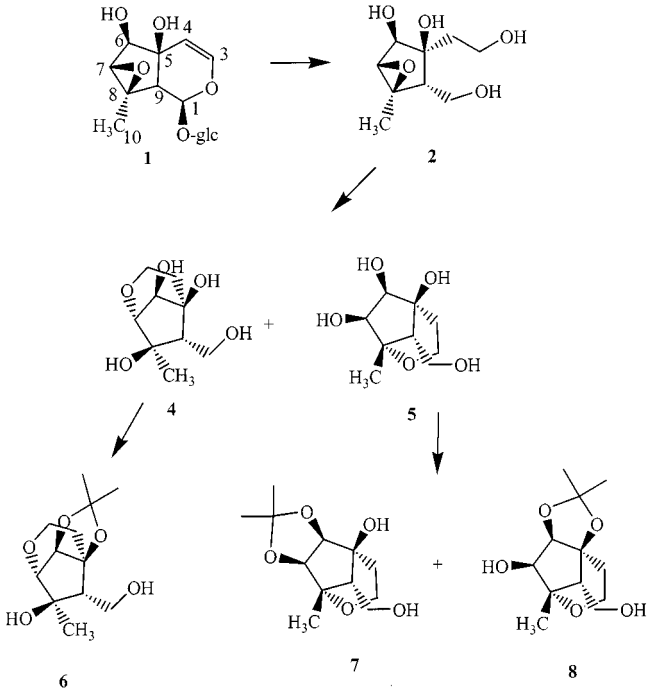
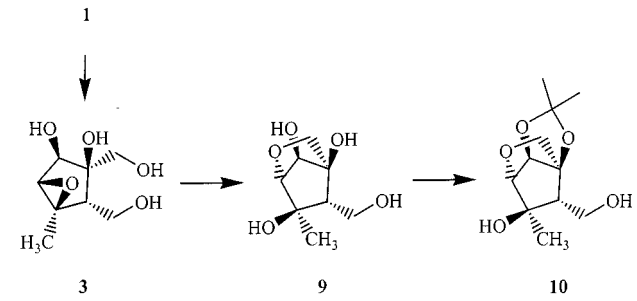


Scheme 1

These two compounds (**2** and **3**) retain the original cyclopentanoid skeleton and constitute suitable intermediates for elaboration to give carbocyclic analogues.

Compound **2** readily undergoes quantitative acid-catalyzed rearrangement; the primary 3-OH function, attached to the linear chain at C-5 in a position α with respect to the ring plane, takes part in an S_NI reaction from the back of the ring plane to C-7 and C-8 of the epoxide. This ring is opened in one of two different positions, leading to a mixture of two structural isomers (**4** and **5**), both of which have a bicyclic structure (see Scheme 1).

The outcome of this reaction has been confirmed by protection of compounds **4** and **5** to give the corresponding isopropylidene derivatives using 2,2′-dimethoxypropane in acetone under anhydrous acidic conditions. We obtained only one isopropylidene derivative (**6**) from compound **4**, blocking the hydroxyls at C-5 and C-6 in a *syn* fashion. On the other hand, we obtained a mixture of two isopropylidene derivatives (**7** and **8**) from compound **5** under the same protection conditions (Scheme 2), of which compound **8** has been reported previously.[30]



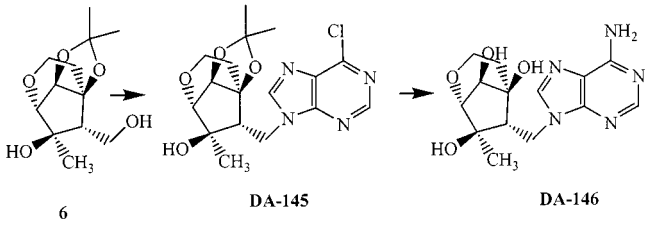
Scheme 2

The structures of compounds **6**, **7**, and the already known **8**[30] were established on the basis of their ^1H and ^{13}C NMR spectra (see Exp. Section), from which it could readily be deduced where the acetonide had been formed.

In the meantime, we noticed that the lower cyclopentanoid homologue (**3**) undergoes an acid-catalyzed rearrangement, but that it leads to only one product (**9**) through opening of the epoxide at C-7 (Scheme 2). We confirmed its structure by blocking the *syn* hydroxyls at C-5 and C-6, forming the corresponding isopropylidene derivative (compound **10**).[31,32]

Compound **6**, having a free primary hydroxyl group, is amenable to a coupling reaction with a heterocyclic base to produce a compound that may be classified as a conformationally restricted carbocyclic homonucleoside analogue. We decided to employ the Mitsunobu methodology[33] to link the base and the synthon **6**. We chose 6-chloropurine as it is commercially available and the substitution of chloride by ammonia to give adenine is well-known.[34]

We obtained the carbocyclic analogue **DA-146**, as outlined in Scheme 3. The structure of **DA-145** was ascertained from its ^1H NMR spectrum, which shows the expected shift for the 1-H proton as a result of H-bond formation between C-1 and N-9 of the chloropurine residue. Substitution of the chloro substituents of **DA-145** with an amine was carried out using ammonia, furnishing, after removal of the protecting group, the final acyclovir analogue **DA-146**.



Scheme 3

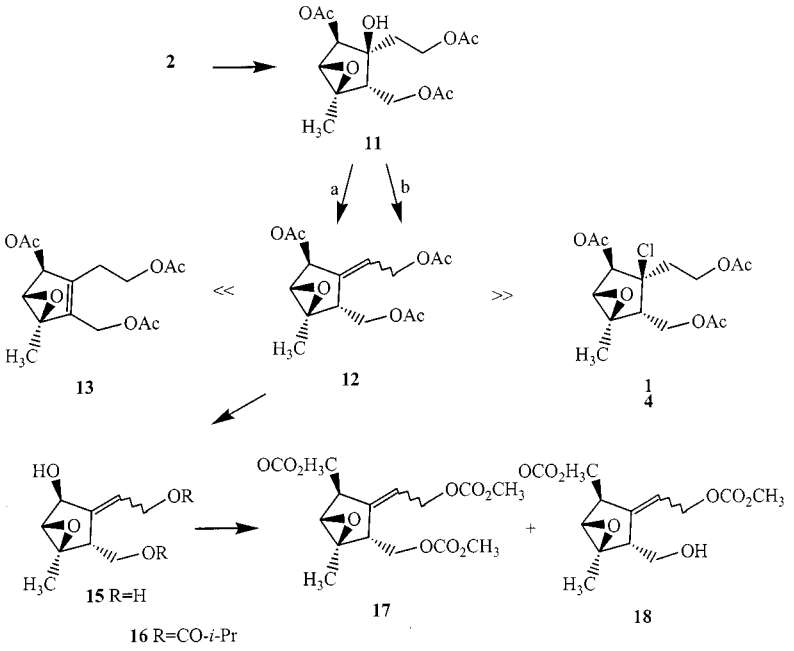
Other structural modifications have been performed on compound **2** (Scheme 4) so as to generate different chiral synthons.

The two primary hydroxyls and one secondary hydroxyl at C-1, C-3, and C-6 were protected by acetylation with acetic anhydride in pyridine to afford triacetate **11**. The free tertiary hydroxyl at C-5 of this compound was removed using a 9:1 mixture of pyridine and thionyl chloride.

We obtained, as the principal product, a 1:1 mixture of configurational isomers [(*E*)- and (*Z*)-**12**]. This mixture could be separated by chromatography (see Exp. Section), but, for the purpose of the preliminary reaction tests, we preferred working on the mixture.

The outcome of this reaction was found to depend on the conditions used. In fact, we observed two secondary products, the amount of which formed depended on the pyridine/thionyl chloride ratio (Scheme 4).

Using a higher proportion of pyridine, an additional dehydrated product (**13**) was obtained, stemming from a *syn*



Scheme 4

elimination of the tertiary hydroxyl with the 9-H proton. On the contrary, using a greater amount of the pyridine/$SOCl_2$ mixture, a chloride derivative (**14**) was also detected,[35] the stereochemistry of which was hypothesized on the basis of known reaction mechanisms involving $SOCl_2$.

Compound **12** was deprotected by a base-catalyzed transesterification using MeONa to afford compound **15**.

By judicious choice of the reaction conditions and a suitable acyl residue, it was possible to selectively protect the primary hydroxyl function in **15** using isobutyric anhydride in pyridine (Scheme 4). We obtained a diester derivative, compound **16**, bearing a free secondary hydroxyl group. This result was confirmed by a simple examination of the ^1H NMR spectrum of the product.

On the contrary, we succeeded in protecting the allylic hydroxyl functions by employing methyl chloroformate in pyridine and dichloromethane under DMPA catalysis (Scheme 4). We obtained the expected dicarbonate (**18**) together with the tricarbonate derivative (**17**). The allylic hydroxyls proved to be more reactive than the primary hydroxyl under these conditions.

Our aim is to use compound **16** as a synthon in the synthesis of a carbocyclic homonucleoside analogue following Mitsunobu's methodology. We are also trying to use this methodology for the synthesis of a carbocyclic homonucleoside analogue starting from compound **18**. In the meantime, we have used compound **17**, which would appear to be suitable for applying Trost's methodology as it bears allylic hydroxyl functions.[36–44]

Experimental Section

General: ^1H and ^{13}C NMR spectra were recorded on Varian Gemini 200 MHz and Varian XL 300 spectrometers; chemical shifts are expressed in ppm downfield from TMS. – Products were purified by solid-liquid column chromatography on Merck 0.0623–0.20 mm silica gel; eluent mixtures were chosen case by case. – Elemental analyses gave satisfactory results for all the described compounds. – TLC on plates precoated with Kiesel-Gel 60 F_{254} (Merck) was used to monitor the progress of the reactions; spots were developed by spraying with 2 N H_2SO_4 and heating to 120 °C for 2 min.

Syntheses

Compound 2: Antirrhinoside **1** was isolated from plants belonging to *Linaria* genus, according to the protocol described in refs.[10,45]

Protocol A: Antirrhinoside **1** (350 mg) was dissolved in water (10 mL) and then $Hg(OAc)_2$ (300 mg) was added to the stirred solution at room temperature. Once a clear mixture had been obtained, a tenfold excess of $NaBH_4$ was added. The reaction was monitored by TLC using chloroform/methanol (8:2) as eluent. When the reaction was complete, the mixture was neutralized with 2% citric acid solution. The resulting solution was filtered and the filtrate was treated with charcoal (5.11 g) to adsorb organic materials, which were tested for using H_2SO_4. The obtained suspension was filtered through a gooch funnel washing first with water to remove salts, and then with methanol. The methanolic filtrate was concentrated in vacuo to give compound **2** (150 mg), which was sufficiently pure for use in the following synthetic steps. – ^1H NMR (D_2O): δ = 1.43 (s, 3 H, CH_3), 1.82 (m, 2 H, 4-H), 2.16 (m, 1 H, 9-H), 3.57 (br. s, 1 H, 7-H), 3.70 (m, 2 H, 3-H), 3.78 (m, 2 H, 1-H), 4.05 (m, 1 H, 6-H). – ^{13}C NMR (D_2O): δ = 17.6 (CH_3), 38.7 (C-4), 56.8 (C-9), 60.4 (C-1), 60.5 (C-3), 67.5 (C-8), 69.4 (C-7), 79.1 (C-6), 80.5 (C-5).

Protocol B: Antirrhinoside **1** (566 mg) was dissolved in water (4.5 mL) and β-glucosidase (EC 3.2.1.21, Sigma Almond Meal, 566 mg) was added to the solution. This mixture was left at 32 °C for 24 h. The reaction was monitored by TLC using chloroform/methanol (8:2) as eluent. The reaction mixture was filtered through a gooch funnel, and the filtrate was extracted three times with EtOAc. The

combined organic layers were dried with anhydrous Na_2SO_4, filtered, and the solvents were evaporated in vacuo. The isolated product (269 mg) was immediately redissolved in water (9 mL) and a tenfold excess of $NaBH_4$ was added portionwise to the stirred solution. After 20 min, the reaction was complete, as shown by TLC using chloroform/methanol (8:2) as the eluent. The solution was neutralized with CO_2 gas. Charcoal was then added to the solution to absorb organic materials, which were tested for using H_2SO_4. The resulting suspension was filtered on a gooch and washed first with water to eliminate salts, and then with methanol. The methanolic solution was concentrated in vacuo and the product **2** (195 mg) was purified by chromatography, eluting with chloroform/methanol (9:1). The product was obtained as a yellow oil (175 mg).

Compound 3. − Protocol C: Antirrhinoside **1** (1.0 g) was dissolved in methanol (6 mL). The solution was cooled in an acetone bath at −75 °C and was then subjected to a flow of ozone under stirring. After 1 h, the reaction was quenched by adding a tenfold excess of $NaBH_4$ at −74 °C and its progress was checked by TLC eluting with $CHCl_3$/MeOH (8:2). The solution was neutralized with CO_2 gas and the solvents were evaporated in vacuo. The residue was dissolved in water and charcoal was added to absorb organic compounds, which were tested for using H_2SO_4. The resulting suspension was filtered through a gooch funnel and the solid was washed first with water to remove salts, and then with hot methanol. The methanolic solution was concentrated to dryness in vacuo to leave compound **3** (496 mg, 95% yield), which was sufficiently pure for use in the next synthetic steps. − ^{1}H NMR (D_2O): δ = 1.42 (s, 3 H, CH_3), 2.24 (m, 1 H, 9-H), 3.60 (3 H, 1-H, 7-H), 3.79 (m, 2 H, 4-H), 3.99 (br. s, 1 H, 6-H). − ^{13}C NMR (D_2O): δ = 17.3 (CH_3), 55.3 (C-9), 60.9 (C-1), 66.0 (C-4), 66.9 (C-8), 69.4 (C-7), 73.9 (C-5), 76.4 (C-6).

Compounds 4 and 5: Compound **2** (30 mg) was dissolved in 1 N H_2SO_4 (0.5 mL) and the resulting solution was left at room temperature overnight. Complete reaction was confirmed by TLC using $CHCl_3$/MeOH (7:3) as eluent. Two new spots appeared, while the starting material was completely consumed. The mixture was neutralized with $BaCO_3$, filtered, and the solid was washed with water. The aqueous phase was collected and the solvents were evaporated in vacuo. The mixture was separated by chromatography eluting with chloroform/methanol (7:3). Compound **4** was obtained as a colorless oil (7 mg); compound **5** is also colorless (5 mg). − Compound **4**: ^{1}H NMR (D_2O): δ = 1.3 (s, 3 H, CH_3), 1.60−2.05 (m, 2 H, 4-H), 2.1 (m, 1 H, 9-H), 3.69 (m, 1 H, 7-H), 3.72 (m, 2 H, 3-H), 3.70−3.85 (m, 2 H, 1-H), 4.0 (m, 1 H, 6-H). − ^{13}C NMR (D_2O): δ = 25.8 (CH_3), 40.6 (C-4), 60.5 (C-1), 60.8 (C-9), 65.6 (C-3), 78.0 (C-6), 81.3−81.4 (C-5 and C-8), 82.0 (C-7). − Compound **5**: ^{1}H NMR (D_2O): δ = 1.11 (s, 3 H, CH_3), 1.20−1.35 (m, 1 H, 4-H), 1.60−1.85 (2 H, 4-H and 9-H), 3.40−3.55 (m, 1 H, 3-H), 3.61−3.85 (3 H, 7-, 3-, and 1-H), 3.91 (m, 1 H, 6-H). − ^{13}C NMR (D_2O): δ = 21.8 (CH_3), 32.4 (C-4), 52.0 (C-9), 59.1 (C-3), 62.2 (C-1), 75.6 (C-6), 76.4 (C-7), 79.4 (C-8), 85.8 (C-5).

Compound 6: To a solution of compound **4** (7 mg) in anhydrous acetone (0.3 mL) were added 2,2′-dimethoxypropane (0.1 mL) and PPTS (17 mg), and the mixture was stirred at room temperature. The reaction was complete after 1 h, as shown by TLC control using chloroform /methanol (8:2) as eluent. The mixture was neutralized with Et_3N and the volatile materials were evaporated in vacuo. Compound **6** was purified by chromatography eluting first with chloroform, and then with chloroform /methanol (9:1). It was obtained as a colorless oil (1.6 mg). − ^{1}H NMR (D_2O): δ = 1.25 (s, 3 H, CH_3), 1.30−1.61 (isopropylidene), 1.90−2.12 (3 H, 4-H and 9-H), 3.59 (m, 1 H, 7-H), 3.8−4.15 (3 H, 1-H and 3-H), 4.49 (m, 1 H, 6-H).

Compounds 7 and 8: To a solution of compound **5** (5 mg) in anhydrous acetone (0.24 mL) were added 2,2′-dimethoxypropane (0.07 mL) and PPTS (14.5 mg). The reaction was terminated when two new spots were seen on TLC analysis eluting with chloroform/methanol (8:2). Work-up was carried out as described in the case of compound **6**. Chromatography eluting with chloroform/methanol (95:5) furnished the product **8** (1.7 mg, yellow oil) together with a small quantity of compound **7** (0.3 mg, yellow oil). − Compound **8**: ^{1}H NMR ([D_6]acetone): δ = 1.29 (s, 3 H, CH_3), 1.90−2.25 (3 H, 4-H and 9-H), 3.49−3.8 (4 H, 1-H and 3-H), 3.85 (m, 1 H, 7-H), 4.25 (m, 1 H, 6-H). − Compound **7**: ^{1}H NMR ([D_6]acetone): δ = 1.31 (s, 3 H, CH_3), 1.8−2.2 (3 H, 4-H and 9-H), 3.6−3.9 (4 H, 1-H and 3-H), 3.62 (m, 1 H, 7-H), 4.38 (m, 1 H, 6-H).

Compounds DA-145 and DA-146: To a solution of compound **6** (16 mg) in anhydrous THF (0.5 mL) under argon were added 6-chloropurine (46 mg) and Ph_3P (100.5 mg). After 10 min, a solution of DEAD (0.1 mL) in anhydrous THF (0.5 mL) was added at room temperature, maintaining an anhydrous atmosphere. After 18 h, the reaction was complete, as shown by TLC eluting with hexane/ethyl acetate (1:1). The solution was then concentrated to dryness in vacuo. The oily residue was purified by chromatography using hexane/ethyl acetate (1:1) as eluent. The product **DA-145** (12.6 mg) was obtained as a white powder. − ^{1}H NMR ($CDCl_3$): δ = 1.30 (s, 3 H, CH_3), 2.2 (3 H, 4-H and 9-H), 4.0 (4 H, 1-H and 3-H), 4.61 (m, 1 H, 6-H), 8.12 (s, 1 H, 8-H), 8.85 (s, 1 H, 2-H).

To a solution of **DA-145** (10 mg) in MeOH (1 mL) in a pressure reactor cooled in a liquid nitrogen bath was added liquid ammonia (3 mL). The reactor was then sealed and the mixture was heated at 75 °C for 24 h. The solvent was subsequently evaporated and the crude reaction product was directly treated with 2% aq. acetic acid. Work-up afforded the final compound **DA-146** (5.1 mg) as a colorless material. − ^{1}H NMR (D_2O): δ = 1.18 (s, 3 H, CH_3), 2.2−2.3 (3 H, 4-H and 9-H), 4.0−4.2 (4 H, 1-H and 3-H), 4.55 (m, 1 H, 6-H), 7.21 (s, 1 H, 8-H), 7.75 (s, 1 H, 2-H).

Compound 9: Compound **3** (25 mg) was dissolved in 1 N H_2SO_4 (0.5 mL) and the resulting solution was left at room temperature overnight. Complete reaction was confirmed by TLC eluting with chloroform/methanol (7:3). The mixture was then neutralized with $BaCO_3$, filtered, and the solid was washed with water. The aqueous phase was collected and the solvents were evaporated in vacuo. The crude product was separated by chromatography eluting with chloroform/methanol (7:3). Compound **9** was obtained as a colorless oil (18 mg). − ^{1}H NMR (D_2O): δ = 1.20 (s, 3 H, CH_3), 1.96 (s, 2 H, 4-H), 3.21 (t, 1 H, 9-H), 3.45 (d, 1 H, 7-H), 3.59 (d, 1 H, 6-H), 3.66 (d, 2 H, 1-H). − ^{13}C NMR (D_2O): δ = 19.2 (CH_3), 40.7 (C-4), 60.1 (C-3), 60.0 (C-9), 76.1 (C-5), 77.5 (C-7), 81.4 (C-8).

Compound 10: To a solution of compound **9** (100 mg) in anhydrous acetone (3 mL) were added 2,2′-dimethoxypropane (1 mL) and PPTS (200 mg) and the mixture was stirred at room temperature. After 5 h, the reaction was complete, as shown by TLC control eluting with chloroform/methanol (95:5). Work-up was carried out as described in the case of compound **6**. Compound **10** was obtained as a colorless oil (58 mg). − ^{1}H NMR ($CDCl_3$): δ = 1.19 (s, 3 H, CH_3), 1.32−1.49 (2 s, 6 H, 2 × CH_3), 3.21 (s, 2 H, 4-H), 3.73 (d, 2 H, 1-H), 3.89 (t, 1 H, 9-H), 3.94 (d, 1 H, 7-H), 4.20 (d, 1 H, 6-H).

Compound 11: To a stirred solution of compound **2** (20 mg) in anhydrous pyridine (0.2 mL) at room temperature was added acetic

anhydride (0.4 mL).After 12 h, the reaction was complete, as shown by TLC control eluting with chloroform/methanol (9:1). Work-up involved azeotropic removal of the pyridine by co-evaporation with methanol in vacuo. The residue was purified by chromatography eluting with chloroform/diethyl ether (1:1). Compound **11** (100% yield) was obtained as a yellow oil. − ^{1}H NMR ($CDCl_3$): δ = 1.40 (s, 3 H, CH_3), 1.78 (m, 2 H, 4-H), 1.81−2.15 (3 s, 9 H, CH_3CO), 2.3 (m, 1 H, 9-H), 3.43 (s, 1 H, 5-OH), 3.60 (s, 1 H, 7-H), 4.08−4.22 (m, 2 H, 3-H), 4.25 (d, 2 H, 1-H), 4.97 (s, 1 H, 6-H).

Compounds 12 and 13: To a solution of compound **11** (27 mg) in pyridine (2.5 mL), 0.1 mL of a mixture of pyridine/$SOCl_2$ (9:1) was added under argon at 0 °C. After 1 h, the reaction was complete, as shown by TLC eluting with chloroform/diethyl ether (8:2). Work-up involved diluting with EtOAc (100 mL), neutralizing the pyridine with 6 N HCl (5 mL), and washing the organic phase with saturated aq. $NaHCO_3$ solution and brine; the organic layer was dried with anhydrous Na_2SO_4 and the solvents were evaporated in vacuo. The residue was purified by chromatography eluting first with chloroform/diethyl ether (8:2) and then with diethyl ether/hexane (96:4). Compound **12** (isomeric mixture, 5 mg) was obtained as a yellow oil, while compound **13** (1 mg) is colorless. − Compound **12**: ^{1}H NMR ($CDCl_3$): δ = 1.45 (s, 1 H, CH_3), 1.51 (s, 1 H, CH_3), 2.01−2.22 (m, 6 H), 3.05 and 3.29 (m, 1 H, 9-H_2), 3.60−3.70 (s, 1 H, 7-H_2), 4.35 (m, 2 H, 1-H), 4.60 (m, 2 H, 3-H), 5.45 (m, 1 H, 6-H), 5.61−5.85 (m, 1 H, 4-H_2). − ^{13}C NMR ($CDCl_3$): δ = 15.4 (CH_3), 20.5−21.0 (CH_3CO), 44.2 (C-9), 48.1 (C-9′), 60.3 (C-3), 61.0−61.1 (C-3′), 64.0 (C-1), 65.5 (C-1′), 69.2 (C-7), 79.5 (C-6), 75.4 (C-6′), 123.5 and 126.1 (C-4 and C4′), 139.8 and 140.1 (C-5 and C-5′). − Compound **13**: ^{1}H NMR ($CDCl_3$): δ = 1.53−1.55 (2 s, 6 H, CH_3 and CH_3'), 2.00 (m, 2 H, 4-H), 2.01−2.19 (3 s, CH_3CO), 3.68 (m, 1 H, 7-H), 4.27 (m, 4 H, 1-H and 3-H), 5.55 (m, 1 H, 6-H).

Compounds 12 and 14: To a solution of compound **11** (40.7 mg) in pyridine (0.5 mL) under argon at 0 °C was added a 9:1 mixture of pyridine/$SOCl_2$ (0.15 mL). Under these conditions, we obtained the chloro derivative **14** (4.4 mg), but the main product remained compound **12** (22.5 mg). − Compound **14**: ^{1}H NMR ($CDCl_3$): δ = 1.55 (s, 3 H, CH_3), 1.82 (m, 2 H, 4-H), 1.99−2.25 (m, 9 H, CH_3CO), 2.7 (m, 1 H, 9-H), 4.25 (m, 1 H, 7-H), 4.33 (m, 4 H, 1-H and 3-H), 5.58 (d, 1 H, 6-H). − ^{13}C NMR (200 MHz, $CDCl_3$): δ = 21.2−21.8 (CH_3), 30.2−31.6 (3 CH_3CO), 47.9 (C-4), 59.9 (C-9), 60.0 (C-3), 68.0 (C-1), 76.9−78.1 (C-6), 84.5 (C-7), 90.8 (C-5), 92.6 (C-8), 170.4−171.0 (CO).

Compound 15: To a stirred solution of compound **12** (23.2 mg) in anhydrous methanol (1 mL) at room temperature was added freshly prepared 1 N sodium methoxide solution in methanol (0.7 mL). After 90 min, the reaction was complete, as shown by TLC eluting with chloroform/methanol (8:2). Work-up involved neutralizing with CO_2 gas and evaporation of the solvents in vacuo. The residue was purified by chromatography eluting with chloroform/methanol (8:2). The product **15** (15 mg) was obtained as a colorless oil. − ^{1}H NMR (D_2O): δ = 1.40 (s, 3 H, CH_3), 1.43 (s, 3 H, CH'_3), 2.79 (m, 1 H, 9-H), 3.04 (m, 1 H, 9′-H), 3.57 (m, 1 H, 7-H), 3.65 (m, 2 H, 1-H), 3.69 (m, 2 H, 3-H), 4.09 (m, 2 H, 3-H), 4.23 (1 H, 6-H and 6′-H), 5.68 (m, 2 H, 4-H).

Compound 16: To a stirred solution of compound **15** (0.6 mg) in pyridine (0.1 mL) at 0 °C was added isobutyric anhydride (2 μL). After 105 min, the reaction was complete, as shown by TLC control eluting with chloroform/diethyl ether (1:1). EtOAc was then added and work-up involved neutralizing with 6 N HCl (0.2 mL) and washing with saturated aq. $NaHCO_3$ solution and brine. The organic phase was dried with Na_2SO_4 and the solvents were evaporated in vacuo. The residue was purified by chromatography eluting with chloroform/diethyl ether (8:2) to afford compound **16** (0.48 mg). This was further purified by chromatography eluting with hexane to give 0.40 mg of **16** as a colorless oil. − ^{1}H NMR ($CDCl_3$): δ = 1.48 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3), 2.48−2.81 (isobutyryl), 3.11 (m, 1 H, 9-H), 3.99 (m, 1 H, 9′-H), 3.59 (s, 1 H, 7-H), 4.11 (d, 2 H, 1-H), 4.21 (m, 2 H, 3-H), 4.62 (m, 1 H, 6-H), 5.71 (1 H, 4-H and 4′-H).

Compounds 17 and 18: A solution of compound **15** (3.8 mg) in pyridine (0.01 mL) was diluted with dichloromethane (1 mL) at 0 °C and methyl chloroformate (0.024 mL) was added with stirring as the mixture was allowed to warm to room temperature. After 10 min, a catalytic amount of DMAP was added to the solution. After 1 h, the dicarbonate had formed and dichloroformate (0.02 mL) was added. After a further 1 h, the tricarbonate had also been formed, as shown by TLC eluting with ethyl acetate/hexane (9:1). The di- and tricarbonate were generated in a 1:1 ratio. Work-up involved adding dichloromethane (50 mL) to the solution and washing with brine (2−3 mL). The organic layer was dried with anhydrous Na_2SO_4 and the solvents were evaporated in vacuo. The residue was purified by chromatography eluting with ethyl acetate/hexane (7:3). The tricarbonate **17** (7.2 mg, colorless oil) and the dicarbonate **18** (3 mg, colorless) were obtained. − Compound **17**: ^{1}H NMR ($CDCl_3$): δ = 1.51 (s, 3 H, CH'_3), 1.60 (s, 3 H, CH_3), 3.09 (m, 1 H, 9′-H), 3.35 (m, 1 H, 9-H), 3.67 (s, 1 H, 7-H), 3.79 (s, 1 H, 7′-H), 3.85 (m, 9 H, 3-CH′′), 4.25 (m, 2 H, 1-H), 4.72 (m, 2 H, 3-H), 5.58 (m, 1 H, 6-H), 5.70 (m, 1 H, 6′-H), 5.80 (m, 1 H, 4′-H and 4-H). − Compound **18**: ^{1}H NMR ($CDCl_3$): δ = 1.51 (s, 3 H, CH'_3), 1.65 (s, 3 H, CH_3), 2.90 (m, 1 H, 9′-H), 3.19 (m, 1 H, 9-H), 3.65 (m, 1 H, 7′-H), 3.75 (s, 1 H, 7-H), 3.85 (m, 2 H, 1-H), 4.72 (m, 2 H, 3-H), 5.60 (1 H, 6-H and 6′-H), 5.72−5.85 (2 H, 4-H and 4′-H).

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