A new stereoselective route to the carbocyclic nucleoside cyclobut-A

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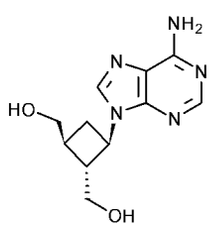
A new synthesis of cyclobut-A, a carbocyclic nucleoside analogue of oxetanocin is described. The key step involves a stereoselective intramolecular [2+2] photocycloaddition to provide a trisubstituted cyclobutane derivative with the desired stereochemistry. The nucleoside linkage was established through nucleophilic displacement of an acetate group by adenine.

Introduction

Nucleoside analogues are extremely useful for the development of therapeutic agents to control viral diseases and cancer. Replacement of the furanose ring oxygen of a nucleoside by a CH_2 unit results in carbocyclic nucleoside analogues.[1] Carbocyclic nucleosides have emerged as targets of intense investigation due to their potent biological activity and greater metabolic activity than the corresponding carbohydrate counterpart. Aristeromycin, neplanocin, and carbovir are a few cyclopentyl nucleosides that have been shown to be inhibitors of HIV. Cyclobut-A, **1**, a cyclobutyl nucleoside analogue of the naturally occurring oxetanocin-A, **2**,[2] was first synthesised by Honjo.[3a] The remarkable antiviral activity[4] exhibited by cyclobut-A has prompted the synthesis[3] of cyclobut-A and its related compounds.



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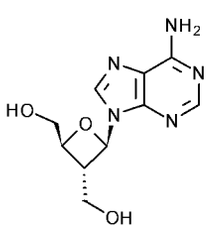
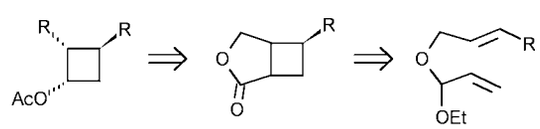


2

Recently we have developed efficient strategies for the synthesis of functionalised cyclobutane derivatives[5] based on [2+2] photocycloaddition. We have also demonstrated[6] that appropriately constructed cyclobutane derivatives undergo facile ring expansion to produce cyclopentane derivatives. Based on these methodologies we have initiated a programme for the synthesis of cyclobutyl and cyclopentyl nucleosides. Herein, we describe a stereoselective route to cyclobut-A.

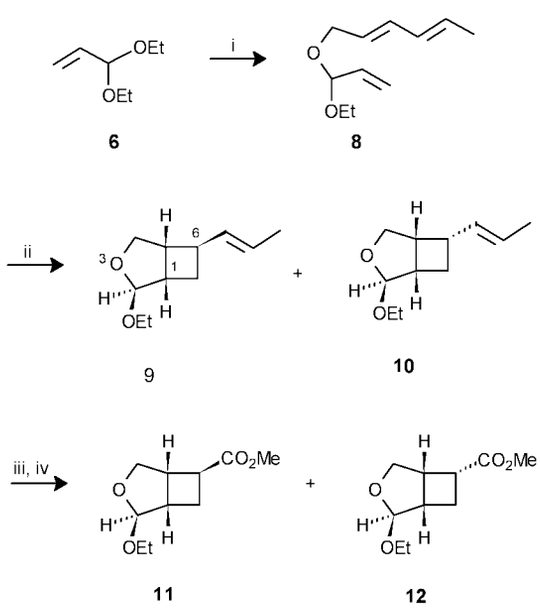
Results and discussion

One of the widely used methods of constructing carbocyclic nucleosides involves nucleophilic displacement[1] of a suitable derivative of a hydroxy group in an appropriately constructed carbocycle by a heterocyclic base. Thus, displacement of the acetate group in the cyclobutane derivative **3** (R is either a hydroxymethyl derivative or a group that can be converted to hydroxymethyl group) by adenine should afford an adduct with the desired stereochemistry for conversion to cyclobut-A. Retrosynthetically, the acetate **3** may be available from the bicyclic lactone **4**, which in turn will be obtained from [2+2] cycloaddition of the diene **5**. It is the cycloaddition step that will set the relative stereochemistry of the three contiguous centres on the four-membered ring for cyclobut-A.



3 **4** **5**

The triene **8** was chosen as the equivalent of the diene **5**. Transacetalisation of acrolein diethyl acetal **6** with hexa-2,4-dienol **7** afforded the triene **8**[5] in 77% yield (Scheme 1). Photocycloaddition was effected by irradiation of the triene **8** in



6 **8**

9 **10**

11 **12**

Scheme 1 *Reagents and conditions*: (i) **7**, PPTS, C_6H_6, Δ, 77%; (ii) *hv*, CuOTf, Et_2O, 5 h, 70%; (iii) $RuCl_3$–$NaIO_4$, CCl_4–CH_3CN–H_2O, rt, 1 h, 88%, (iv) CH_2N_2, ether, rt, 84%.

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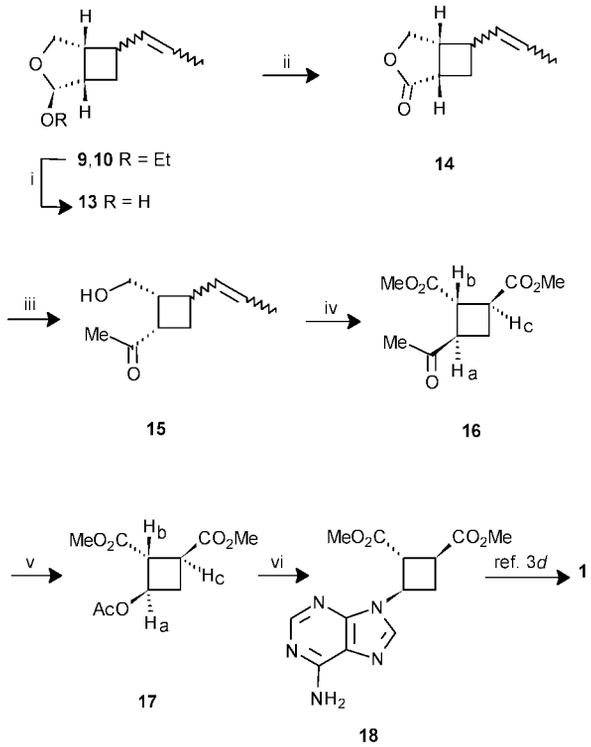
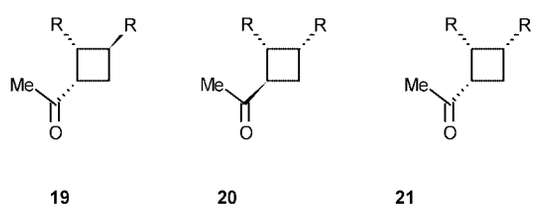
diethyl ether solution in the presence of copper(I) trifluoromethane sulfonate (CuOTf) as catalyst. An inseparable mixture of four adducts was obtained in 70% yield in 2.5 : 5 : 1 : 1.5 ratio as indicated by the presence of four singlets at δ 4.97, 4.95, 4.85 and 4.83 for the C_2-protons and four signals at δ 107.5, 107.7, 108.4 and 108.5 for the C_2-methine carbons. The gross structure of the photoadducts as **9** and **10** along with the corresponding *Z*-isomers was clearly discernible from ^{1}H and ^{13}C NMR spectra. Further structural support was obtained from the following transformation. Oxidative cleavage of the olefinic chain of this four-component mixture followed by esterification (CH_2N_2) of the resulting acids led to a 4 : 1 mixture of the methyl esters **11** and **12** as indicated by the appearance of two singlets at δ 4.90 and 4.76 for the C_2-protons. This confirmed that the two components of the four photoadducts were *Z*-isomers of the adducts **9** and **10**. When the mixture of the methyl esters **11** and **12** was equilibrated with 2% NaOMe–MeOH under reflux, the minor peak at δ 4.76 reduced gradually leading finally to a mixture with a 14 : 1 ratio. Thus, the component in which the C_2–H appeared at δ 4.90 had the thermodynamically more stable *exo* orientation of the COOMe group as depicted in structure **11**. Accordingly the minor component in the mixture had the structure **12**. Thus, the four components in the photoadduct had the structures **9** and **10** and the corresponding *Z*-isomers, with **9** as the major product.

The *exo* stereochemical assignment of the OEt group in the photoadducts **9** and **10** was based on comparison of the coupling constant of C_2–H with those reported[7] for analogous *exo*- and *endo*-2-substituted-3-oxabicyclo[3.2.0]heptanes. In the *exo*-isomer the C_2–H *trans* to C_1–H exhibits a much lower coupling constant (J ~ 1 Hz) than that (J ~ 5–6 Hz) in the corresponding *endo*-structures in which C_2–H is *syn* to C_1–H. The C_2–H signal in each of the photoadducts appeared as a singlet. Thus, C_2- and C_1-hydrogens bear a *trans* relationship to each other as depicted in structures **9** and **10**.

After determining that the required *anti* relationship of the C_3-substituent to the 1,2 substituents on the cyclobutane ring can be established through intramolecular photocycloaddition–epimerisation, we focussed our attention on completion of the synthesis. The photoadduct mixture on treatment with 80% aqueous acetic acid at 80 °C led to the thermodynamically more stable lactol mixture **13** in 70% yield (Scheme 2). Retention of stereochemistry at C_2 during deprotection follows from the appearance of the C_2–H's as singlets. Oxidation of the lactol mixture **13** with Jones reagent afforded the lactone **14** as a mixture in 71% yield. The lactone **14** was then converted to the hydroxy-ketone **15** in 68% yield through methylenation using the procedure developed by Petasis[8] followed by acid hydrolysis of the resulting enol ether. Oxidation of the hydroxy-ketone **15** with RuO_4 followed by treatment of the resulting dicarboxylic acid with diazomethane gave the keto-diester **16** in 63% yield. The structure of the keto-diester **16** was established by its transformation to the acetate **17** through Baeyer–Villiger oxidation using TFAA and urea–H_2O_2 adduct[9] in 70% yield. Chemical shift assignment to the protons H_a, H_b, and H_c of the acetate **17** was made through proton decoupling experiments in ^{1}H NMR. The *syn* orientation of the OAc group with the COOMe group at C_3 was determined through an NOE experiment. Thus, irradiation of H_c gave a 1.4% enhancement of H_a. The formation of **16** from the hydroxy-olefin **15** probably proceeds through epimerisation during RuO_4 oxidation. AM1 calculations[10] (using MOPAC, version 1.10) indicate that the methyl ester **16** (R = COOMe) (E = −2936.8269 kcal mol^{-1}) is more stable than the isomeric methyl esters **19** (R = COOMe) (E = −2935.7300 kcal mol^{-1}), **20** (R = COOMe) (E = −2934.7834 kcal mol^{-1}) and **21** (R = COOMe) (E = −2930.9233 kcal mol^{-1}) in the gas phase. Thus rapid isomerisation of the initially formed dicarboxylic acids **19** and **21** (R = COOH) to the most stable isomer leading to the ester **16** after esterification is quite expected.



Scheme 2 *Reagents and conditions*: (i) AcOH–H_2O, 80 °C, 3.5 h, 70%; (ii) Jones reagent, 0 °C–rt, 1 h, 71%; (iii) Cp_2TiMe_2, toluene, 65–70 °C, 16 h, 68%; (iv) $RuCl_3$–$NaIO_4$, CCl_4–CH_3CN–H_2O, rt, 0.5 h, 63%; (v) TFAA, urea–H_2O_2, KH_2PO_4, CH_2Cl_2, 0 °C–rt, 22 h, 70%; (vi) adenine, K_2CO_3, DMF, 90 °C, 12 h, 30%.



The acetate **17** was then treated with adenine in the presence of K_2CO_3 in DMF at 90 °C to afford mainly the known nucleoside derivative **18**, mp 190–193 °C, in 30% yield. ^{1}H NMR characteristics of this sample were found to be identical with those reported in literature[3d] for compound **18**. The 1,3-*syn* relationship between the heterocyclic ring and the COOMe group at the 3′ position was established by a 2.2% NOE of 3′-H when 1′-H was irradiated. The nucleoside derivative **18** may arise through direct displacement[3d] of the acetoxy group in **17** or elimination of the acetoxy group followed by 1,4 addition of adenine with epimerisation to the thermodynamically more stable 1,3-*syn* cyclobutane structure. It is difficult to say which path is operative in this case. The compound **18** has already been transformed[3d] to cyclobut-A through $LiAlH_4$ reduction. Thus with the synthesis of the compound **18**, a formal synthesis of cyclobut-A is accomplished.

Experimental

The compounds described here are all racemates. All reactions were carried out under an atmosphere of N_2. Column chromatography was performed on silica gel (60–120 mesh). Petroleum refers to the fraction of petroleum ether bp 60–80 °C. Ether refers to diethyl ether. Organic extracts were dried over anhydrous Na_2SO_4. IR spectra were recorded for thin films. Unless otherwise stated, ^{1}H and ^{13}C NMR spectra were

recorded for samples in $CDCl_3$ solution at 300 MHz and 75 MHz, respectively.

3-Ethoxy-4-oxadeca-1,6,8-triene 8

A mixture of hexa-2,4-dien-1-ol **7** (1 g, 10.20 mmol), acrolein diethyl acetal **6** (3.3 g, 25.6 mmol), PPTS (5 mg) and benzene (15 cm^3) was heated under reflux in an oil bath for 1 h with azeotropic removal of ethanol. On cooling the reaction mixture was washed with aqueous $NaHCO_3$ (2 × 3 cm^3, 5%) dried and then concentrated under vacuum. The residual mass was chromatographed (ether–petroleum 1 : 19) to afford the triene **8** (1.4 g, 77%). (Found C, 72.89; H, 9.81. $C_{11}H_{18}O_2$ requires C, 72.49; H, 9.95%); δ_H: 1.22 (3H, t, *J* 6.9 Hz), 1.75 (3H, d, *J* 6.6 Hz), 3.40–3.67 (2H, m), 4.04–4.13 (2H, m), 4.93 (1H, d, *J* 3 Hz), 5.27–5.43 (2H, m), 5.65–5.85 (3H, m), 6.05–6.25 (2H, m); δ_C: 15.2 (CH_3), 18.1 (CH_3), 61.0 (CH_2), 65.7 (CH_2), 100.8 (CH), 118.3 (CH_2), 126.4 (CH), 129.9 (CH), 130.9 (CH), 133.0 (CH), 135.4 (CH).

exo-2-Ethoxy-6-(prop-1′-enyl)-3-oxa[3.2.0]heptanes 9 and 10 and the corresponding *Z*-isomers

A solution of the triene **8** (2 g, 10.8 mmol) in ether (250 cm^3) containing CuOTf (0.2 g, 0.94 mmol) was irradiated internally with a 450 W medium pressure mercury vapour lamp (Hanovia) through a double walled water cooled quartz immersion well for 5 h. The reaction mixture was then washed with ice cold aqueous NH_4OH (2 × 20 cm^3, 35%), dried and concentrated under vacuum. The residual oil was chromatographed (ether–petroleum 1 : 19) to afford the cyclobutane derivatives **9** and **10** along with the corresponding *Z*-isomers (1.4 g, 70%). (Found C, 72.10; H, 9.99. $C_{11}H_{18}O_2$ requires C, 72.49; H, 9.95%); δ_H (for the major diastereoisomer): 1.14 (3H, t, *J* 7.2 Hz), 1.65 (3H, d, *J* 6 Hz), 1.87–1.92 (2H, m), 2.69–2.73 (3H, m), 3.39–3.44 (1H, m), 3.68–3.84 (3H, m), 4.83, 4.85, 4.95, 4.97 (s, C_2-H), 5.32–5.57 (2H, m); δ_C (for the major diastereoisomer): 15.6 (CH_3), 18.2 (CH_3), 27.5 (CH_2), 39.9 (CH), 41.4 (CH), 44.1 (CH), 62.5 (CH_2), 72.2 (CH_2), 108.7 (CH), 123.7 (CH), 135.6 (CH).

Methyl 2-ethoxy-3-oxa[3.2.0]heptane-6-carboxylates 11 and 12

To a solution of RuO_4 [generated from $RuCl_3$ (5 mg, 0.02 mmol), sodium metaperiodate (2.8 g, 13.5 mmol) in carbon tetrachloride (4 cm^3), acetonitrile (3 cm^3) and water (2 cm^3)], was added a solution of the photoadduct mixture as obtained above (500 mg, 2.7 mmol) in carbon tetrachloride (4 cm^3). The reaction mixture was allowed to stir at rt for 1 h. The white precipitate so formed was then filtered off. The filtrate was extracted with ethyl acetate (3 × 10 cm^3). The ethyl acetate extract was washed with saturated $NaHCO_3$ solution (3 × 2 cm^3). The $NaHCO_3$ washings were cooled in ice and acidified with cold 6 M HCl and extracted with ethyl acetate to afford the corresponding carboxylic acids (450 mg, 88%).

A solution of this crude carboxylic acid (100 mg, 0.53 mmol) in dry ether (2 cm^3) was treated with an excess of an ether solution of diazomethane. The residual mass on evaporation of the ether was filtered through a short column of neutral alumina to afford a mixture of the methyl esters **11** and **12** (90 mg, 84%) in 4 : 1 ratio.

The crude methyl esters **11** and **12** (150 mg, 0.75 mmol) were refluxed with a solution of NaOMe (10 cm^3, 2%) in MeOH for 4 h. The reaction mixture was then acidified with 6 M HCl and extracted with ether (3 × 10 cm^3). The ether extract was dried and concentrated and esterified with an excess of ethereal diazomethane to afford a mixture of the methyl esters **11** and **12** in a 14 : 1 ratio. The mixture was then chromatographed (ether–petroleum 1 : 19) to afford the ester **11** (100 mg, 67%) (Found C, 60.20; H, 8.14. $C_{10}H_{16}O_4$ requires C, 59.98; H, 8.05%); ν_{max}/cm^{-1} 1735.8; δ_H: 1.16 (3H, t, *J* 3.3 Hz), 1.90–1.99 (1H, m), 2.35–2.45 (1H, m), 2.79–2.88 (2H, m), 3.15 (1H, br s), 3.39–3.49 (1H, m), 3.69 (3H, s) overlapping with 3.62–3.78 (1H, m), 3.85 (2H, d, *J* 2.5 Hz), 4.98 (1H, s); δ_C: 15.5 (CH_3), 24.1 (CH_2), 40.3 (CH), 41.4 (CH), 42.1 (CH), 52.2 (OCH_3), 62.6 (OCH_2), 71.7 (OCH_2), 108.1 (CH), 175.9 (CO).

6-(Prop-1′-enyl)-3-oxabicyclo[3.2.0]heptan-2-ol 13

A solution of the photoadduct mixture **9**, **10** (1 g, 5.5 mmol) in 80% aqueous acetic acid (10 cm^3) was refluxed at 80 °C for 3.5 h. Most of the acetic acid was removed from the reaction mixture under vacuum. The residual mass was dissolved in ether (20 cm^3). The ether layer was washed with saturated aqueous $NaHCO_3$ (2 × 5 cm^3), dried and concentrated under vacuum. The residual mass was chromatographed (ether–petroleum 1 : 3) to afford the lactol **13**. (590 mg, 70%) (Found C, 70.30; H, 8.95. $C_9H_{14}O_2$ requires C, 70.10; H, 9.15%); δ_H (for the major isomer): 1.66 (3H, d, *J* 6.3 Hz), 1.91 (2H, m), 2.45 (1H, br s), 2.56–2.80 (3H, m), 3.84–4.05 (2H, m), 5.25–5.63 (3H, m); δ_C (for the major isomer): 18.2 (CH_3), 27.3 (CH_2), 39.8 (CH), 41.9 (CH), 44.1 (CH), 72.4 (CH_2), 103.5 (CH), 123.8 (CH), 135.5 (CH).

6-(Prop-1′-enyl)-3-oxabicyclo[3.2.0]heptan-2-one 14

To a magnetically stirred solution of the lactol **13** (500 mg, 3.3 mmol) in acetone (4 cm^3) cooled to 0 °C, was added dropwise Jones reagent (0.7 M). The reaction mixture was stirred at rt for 1 h, diluted with water (5 cm^3) and extracted with ether (3 × 10 cm^3). The ether extract was washed with saturated aqueous $NaHCO_3$ (4 cm^3), dried and concentrated under vacuum. The residual mass was chromatographed (ether–petroleum 1 : 5) to afford the lactone **14** (350 mg, 71%) (Found C, 71.12; H, 7.85. $C_9H_{12}O_2$ requires C, 71.03; H, 7.95%); ν_{max}/cm^{-1} 1768.6; δ_H (for the major isomer): 1.60 (3H, d, *J* 5.4 Hz), 2.19–2.28 (3H, m), 2.84–2.95 (2H, m), 4.15–4.28 (2H, m), 5.35–5.45 (2H, m); δ_C (for the major isomer): 17.9 (CH_3), 30.1 (CH_2), 35.0 (CH), 41.5 (CH), 41.6 (CH), 72.9 (CH_2), 125.7 (CH), 132.8 (CH), 182.0 (CO).

1α-Acetyl-2α-hydroxymethyl-3-(prop-1′-enyl)cyclobutane 15

To a magnetically stirred solution of the lactone **14** (160 mg, 0.95 mmol) in dry toluene (5 cm^3) was added Cp_2TiMe_2 (400 mg, 1.9 mmol), prepared from titanocene dichloride (2 g, 8 mmol) and methyllithium (12 cm^3, 19 mmol, 1.6 M in ether) under an argon atmosphere. The reaction mixture was stirred for 16 h in the dark at 65–70 °C. The brownish reaction mixture was concentrated and the remaining syrup was diluted with THF (2 cm^3). This was then treated with 4 M HCl (0.5 cm^3) and stirred for 4 h at rt. The reaction mixture was neutralised (saturated aqueous $NaHCO_3$) and then extracted with diethyl ether (3 × 5 cm^3). The organic extract was dried, filtered and concentrated. Column chromatography of the crude product (ether–petroleum 1 : 1) afforded pure compound **15** (120 mg, 68%) (Found C, 71.20; H, 9.90. $C_{10}H_{15}O_2$ requires C, 71.39; H, 9.58%); ν_{max}/cm^{-1} 1701.1; δ_H (for the major isomer): 1.62 (3H, d, *J* 6.3 Hz), 1.86 (2H, AB_q, *J* 10.2 Hz), 2.13 (3H, s), 2.25–2.63 (2H, m), 2.82–2.92 (1H, m), 3.57 (1H, dd, *J* 6.8, 9 Hz), 3.71 (1H, dd, *J* 4.7, 9 Hz), 5.37–5.45 (2H, m); δ_C (for the major isomer): 17.8 (CH_3), 27.6 (CH_3), 28.5 (CH_2), 35.8 (CH), 46.4 (CH), 47.0 (CH), 64.6 (CH_2), 125.2 (CH), 133.5 (CH), 210.5 (CO).

Dimethyl 1β-acetylcyclobutane-2α,3β-dicarboxylate 16

A solution of the hydroxy-ketone **15** (100 mg, 0.59 mmol) in carbon tetrachloride (2 cm^3) was added to a solution of RuO_4 [generated from $RuCl_3$ (5 mg), sodium metaperiodate (0.64 g, 2.98 mmol) in carbon tetrachloride (2 cm^3)–acetonitrile (1 cm^3)–water (1 cm^3)]. The reaction mixture was allowed to stir at room temperature for 0.5 h. The resulting white precipitate was filtered off. The filtrate was extracted with ethyl acetate

(3×10 cm^3). The organic extract was washed with saturated aqueous $NaHCO_3$ (3×2 cm^3). The basic washings on acidification with 6 M HCl were extracted with ether to afford the corresponding dicarboxylic acid. This was treated with an excess of an ether solution of diazomethane. The residue obtained on evaporation of the ether was filtered through a short column of neutral alumina to afford the dimethyl ester **16** (80 mg, 63%) (Found C, 56.31; H, 6.76. $C_{10}H_{14}O_5$ requires C, 56.07; H, 6.54%); ν_{max}/cm^{-1} 1718.5, 1733.9; δ_H: 2.15 (3H, s), 2.26–2.43 (2H, m), 3.30 (1H, H_c or H_a, q, *J* 9 Hz), 3.32 (1H, H_a or H_c, q, *J* 9 Hz), 3.60 (1H, H_b, t, *J* 9 Hz), 3.70 (3H, s), 3.73 (3H, s); δ_C: 24.9 (CH_2), 27.8 (CH_3), 36.5 (CH), 42.4 (CH), 44.9 (CH), 52.6 (CH_3), 52.7 (CH_3), 173.0 (CO), 173.3 (CO), 206.5 (CO).

Dimethyl 1β-acetoxycyclobutane-2α,3β-dicarboxylate 17

To a solution of the keto-diester **16** (80 mg, 0.37 mmol) in dry dichloromethane (8 cm^3) was added KH_2PO_4 (1.01 g, 7.48 mmol) and urea–H_2O_2 adduct (750 mg, 7.85 mmol) at 0 °C. To this trifluoroacetic anhydride (0.26 cm^3, 1.85 mmol) was added dropwise with stirring. After further stirring at room temperature for 22 h, the reaction was neutralised with saturated aqueous $NaHCO_3$ and extracted with dichloromethane (3×10 cm^3). The organic extract was dried over $CaCl_2$ and concentrated under vacuum. The residual mass was column chromatographed (ether–petroleum 1 : 4) to afford the acetate **17** (60 mg, 70%) (Found C, 52.45; H, 6.07. $C_{10}H_{14}O_6$ requires C, 52.17; H, 6.13%); ν_{max}/cm^{-1} 1735.8; δ_H: 2.05 (3H, s), 2.22 (1H, ddd, *J* 7.8, 8.3 and 11.5 Hz), 2.65 (1H, dt, *J* 7.8, 11.5 Hz), 3.03 (1H, H_c, q, *J* 9.1 Hz), 3.41 (1H, H_b, t, *J* 7.8 Hz), 3.72 (3H, s), 3.73 (3H, s), 5.02 (1H, H_a, q, *J* 7.8 Hz); δ_C: 21.1 (CH_3), 31.2 (CH), 33.7 (CH_2), 49.0 (CH), 52.6 (CH_3), 52.7 (CH_3), 66.6 (CH), 170.5 (CO), 171.7 (CO), 173.2 (CO).

9-[*t*-2′, *c*-3′-bis(methoxycarbonyl)cyclobut-1′-yl]adenine 18

To a solution of the acetate **17** (50 mg, 0.22 mmol) in DMF (2 cm^3), K_2CO_3 (35 mg, 0.25 mmol) and adenine (34 mg, 0.25 mmol) were added. The mixture was heated at 90 °C for 12 h. DMF was then distilled out under vacuum and the residue was extracted with chloroform (3×2 cm^3). The organic extract was concentrated under vacuum to afford a white solid **18** (20 mg, 30%); mp 190–193 °C (lit.[3d] 195–196 °C); ν_{max}/cm^{-1} 1571.9, 1598.9, 1672.2, 1718.5, 1741.6; δ_H: 2.81–3.03 (2H, m), 3.27 (1H, q, *J* 9.3 Hz), 3.72 (3H, s), 3.80 (3H, s), 4.16 (1H, t, *J* 9.1 Hz), 5.07 (1H, q, *J* 9.1 Hz), 5.78 (2H, br s), 7.94 (1H, s), 8.35 (1H, s); δ_C: 30.6 (CH_2), 35.1 (CH), 48.3 (CH), 48.4 (CH), 52.9 (CH_3), 139.3 (CH), 140.9 (C), 153.1 (C), 153.5 (CH), 155.9 (C), 171.4 (CO), 172.9 (CO).

Acknowledgements

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