A new stereoselective route to the carbocyclic nucleoside cvclobut-A

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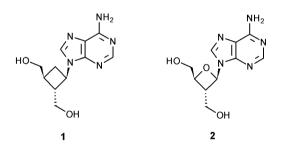
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A new synthesis of cyclobut-A, a carbocyclic nucleoside analogue of oxetanocin is described. The key step involves a stereoselective intramolecular [2+2] photocycloaddition to provide a trisubstituted cyclobutane derivative with the desired stereochemistry. 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 CH₂ 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 activity⁴ exhibited by cyclobut-A has prompted the synthesis³ of cyclobut-A and its related compounds.



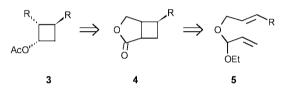
Recently we have developed efficient strategies for the synthesis of functionalised cyclobutane derivatives ⁵ based on [2+2] photocycloaddition. We have also demonstrated ⁶ that appropriately constructed cyclobutane derivatives undergo facile ring expansion to produce cyclopentane derivatives. Based 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

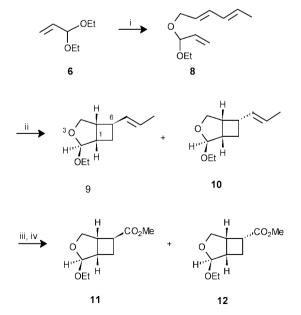
One of the widely used methods of constructing carbocyclic nucleosides involves nucleophilic displacement¹ of a suitable derivative of a hydroxy group in an appropriately constructed carbocycle by a heterocyclic base. Thus, displacement of the acetate group in the cyclobutane derivative **3** (R is either a hydroxymethyl derivative or a group that can be converted to hydroxymethyl group) by adenine should afford an adduct

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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.



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



Scheme 1 Reagents and conditions: (i) **7**, PPTS, C_6H_6 , Δ , 77%; (ii) *hv*, CuOTf, Et₂O, 5 h, 70%; (iii) RuCl₃–NaIO₄, CCl₄–CH₃CN–H₂O, rt, 1 h, 88%, (iv) CH₂N₂, ether, rt, 84%.

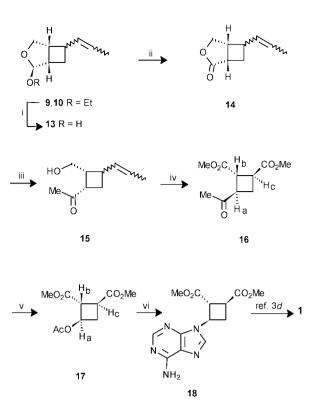
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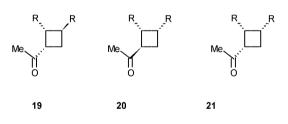
diethyl ether solution in the presence of copper(I) trifluoromethane sulfonate (CuOTf) as catalyst. An inseparable mixture of four adducts was obtained in 70% yield in 2.5 : 5 : 1 : 1.5 ratio as indicated by the presence of four singlets at δ 4.97, 4.95, 4.85 and 4.83 for the C₂-protons and four signals at δ 107.5, 107.7, 108.4 and 108.5 for the C2-methine carbons. The gross structure of the photoadducts as 9 and 10 along with the corresponding Z-isomers was clearly discernible from ¹H and ¹³C 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 (CH₂N₂) 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 C₂-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 C₂-H with those reported ⁷ for analogous *exo*- and *endo*-2-substituted-3-oxabicyclo[3.2.0]heptanes. In the *exo*-isomer the C₂-H *trans* to C₁-H exhibits a much lower coupling constant ($J \sim 1$ Hz) than that ($J \sim 5$ -6 Hz) in the corresponding *endo*-structures in which C₂-H is *syn* to C₁-H. The C₂-H signal in each of the photoadducts appeared as a singlet. Thus, C₂- and C₁-hydrogens bear a *trans* relationship to each other as depicted in structures **9** and **10**.

After determining that the required anti relationship of the C₃-substituent to the 1,2 substituents on the cyclobutane ring can be established through intramolecular photocycloadditionepimerisation, 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 C2 during deprotection follows from the appearance of the C2-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 Petasis⁸ followed by acid hydrolysis of the resulting enol ether. Oxidation of the hydroxy-ketone 15 with RuO₄ 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-H₂O₂ adduct⁹ 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 ¹H NMR. The syn orientation of the OAc group with the COOMe group at C3 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 RuO₄ oxidation. AM1 calculations¹⁰ (using MOPAC, version 1.10) indicate that the methyl ester 16 (R = COOMe) ($E = -2936.8269 \text{ kcal mol}^{-1}$) is more stable than the isomeric methyl esters 19 (R = COOMe) (E =-2935.7300 kcal mol⁻¹), **20** (R = COOMe) (E = -2934.7834kcal 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–H₂O, 80 °C, 3.5 h, 70%; (ii) Jones reagent, 0 °C–rt, 1 h, 71%; (iii) Cp₂TiMe₂, toluene, 65–70 °C, 16 h, 68%; (iv) RuCl₃–NaIO₄, CCl₄–CH₃CN–H₂O, rt, 0.5 h, 63%; (v) TFAA, urea–H₂O₂, KH₂PO₄, CH₂Cl₂, 0 °C–rt, 22 h, 70%; (vi) adenine, K₂CO₃, DMF, 90 °C, 12 h, 30%.



The acetate 17 was then treated with adenine in the presence of K₂CO₃ in DMF at 90 °C to afford mainly the known nucleoside derivative 18, mp 190–193 °C, in 30% yield. ¹H 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 3^{d} 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 LiAlH₄ 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 N₂. 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 Na₂SO₄. IR spectra were recorded for thin films. Unless otherwise stated, ¹H and ¹³C NMR spectra were

recorded for samples in CDCl₃ 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 cm³) 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 NaHCO₃ (2 × 3 cm³, 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. C₁₁H₁₈O₂ requires C, 72.49; H, 9.95%); $\delta_{\rm H}$: 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); $\delta_{\rm C}$: 15.2 (CH₃), 18.1 (CH₃), 61.0 (CH₂), 65.7 (CH₂), 100.8 (CH), 118.3 (CH₂), 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 cm³) 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 NH₄OH (2×20 cm³, 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. C₁₁H₁₈O₂ requires C, 72.49; H, 9.95%); $\delta_{\rm H}$ (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, C₂-H), 5.32–5.57 (2H, m); $\delta_{\rm C}$ (for the major diastereoisomer): 15.6 (CH₃), 18.2 (CH₃), 27.5 (CH₂), 39.9 (CH), 41.4 (CH), 44.1 (CH), 62.5 (CH₂), 72.2 (CH₂), 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 cm³), acetonitrile (3 cm³) and water (2 cm³)], was added a solution of the photoadduct mixture as obtained above (500 mg, 2.7 mmol) in carbon tetrachloride (4 cm³). 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 cm³). The ethyl acetate extract was washed with saturated NaHCO₃ solution (3 × 2 cm³). The NaHCO₃ 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 cm³) 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 cm³, 2%) in MeOH for 4 h. The reaction mixture was then acidified with 6 M HCl and extracted with ether (3 × 10 cm³). 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. C₁₀H₁₆O₄ requires C, 59.98; H, 8.05%); v_{max} cm⁻¹ 1735.8; $\delta_{\rm H}$: 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); $\delta_{\rm C}$: 15.5 (CH₃), 24.1 (CH₂), 40.3 (CH), 41.4 (CH), 42.1 (CH), 52.2 (OCH₃), 62.6 (OCH₂), 71.7 (OCH₂), 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 cm³) 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 cm³). The ether layer was washed with saturated aqueous NaHCO₃ (2 × 5 cm³), 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. C₉H₁₄O₂ requires C, 70.10; H, 9.15%); $\delta_{\rm H}$ (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); $\delta_{\rm C}$ (for the major isomer): 18.2 (CH₃), 27.3 (CH₂), 39.8 (CH), 41.9 (CH), 44.1 (CH), 72.4 (CH₂), 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 cm³) 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 cm³) and extracted with ether (3 × 10 cm³). The ether extract was washed with saturated aqueous NaHCO₃ (4 cm³), 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. C₉H₁₂O₂ requires C, 71.03; H, 7.95%); ν_{max}/cm^{-1} 1768.6; $\delta_{\rm H}$ (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); $\delta_{\rm C}$ (for the major isomer): 17.9 (CH₃), 30.1 (CH₂), 35.0 (CH), 41.5 (CH), 41.6 (CH), 72.9 (CH₂), 125.7 (CH), 132.8 (CH), 182.0 (CO).

1a-Acetyl-2a-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 cm³) was added Cp₂TiMe₂ (400 mg, 1.9 mmol), prepared from titanocene dichloride (2 g, 8 mmol) and methyllithium (12 cm³, 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 cm³). This was then treated with 4 M HCl (0.5 cm³) and stirred for 4 h at rt. The reaction mixture was neutralised (saturated aqueous NaHCO₃) and then extracted with diethyl ether $(3 \times 5 \text{ cm}^3)$. 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. C₁₀H₁₅O₂ requires C, 71.39; H, 9.58%); v_{max}/cm^{-1} 1701.1; $\delta_{\rm H}$ (for the major isomer): 1.62 (3H, d, J 6.3 Hz), 1.86 (2H, AB_a, 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); $\delta_{\rm C}$ (for the major isomer): 17.8 (CH₃), 27.6 (CH₃), 28.5 (CH₂), 35.8 (CH), 46.4 (CH), 47.0 (CH), 64.6 (CH₂), 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 cm³) was added to a solution of RuO₄ [generated from RuCl₃ (5 mg), sodium metaperiodate (0.64 g, 2.98 mmol) in carbon tetrachloride (2 cm³)–acetonitrile (1 cm³)–water (1 cm³)]. 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 cm³). The organic extract was washed with saturated aqueous NaHCO₃ (3 × 2 cm³). 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. C₁₀H₁₄O₅ requires C, 56.07; H, 6.54%); v_{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 (CH₂), 27.8 (CH₃), 36.5 (CH), 42.4 (CH), 44.9 (CH), 52.6 (CH₃), 52.7 (CH₃), 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 cm³) was added KH₂PO₄ (1.01 g, 7.48 mmol) and urea–H₂O₂ adduct (750 mg, 7.85 mmol) at 0 °C. To this trifluoroacetic anhydride (0.26 cm³, 1.85 mmol) was added dropwise with stirring. After further stirring at room temperature for 22 h, the reaction was neutralised with saturated aqueous NaHCO₃ and extracted with dichloromethane (3 × 10 cm³). The organic extract was dried over CaCl₂ 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. C₁₀H₁₄O₆ requires C, 52.17; H, 6.13%); v_{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, Hz), 3.72 (3H, s), 3.73 (3H, s), 5.02 (1H, H_a, q, *J* 7.8 Hz); δ_{C} : 21.1 (CH₃), 31.2 (CH), 33.7 (CH₂), 49.0 (CH), 52.6 (CH₃), 52.7 (CH₃), 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 cm³), 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 $(3 \times 2 \text{ cm}^3)$. 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); v_{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 (CH₂), 35.1 (CH), 48.3 (CH), 48.4 (CH), 52.9 (CH₃), 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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