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Palladium Catalysed Tandem Allylic Substitution Methodology in the Synthesis of a Component of Civet

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PALLADIUM CATALYSED TANDEM ALLYLIC SUBSTITUTION METHODOLOGY IN THE SYNTHESIS OF A COMPONENT OF CIVET

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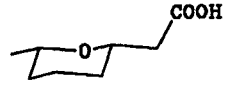
ABSTRACT: A facile synthesis of a component of civet 1 is reported in which the key step involves palladium catalysed introduction of the acetic acid substituent in the C-1 position of a pseudorhamnal derivative.

Nature produces many simple compounds which may be regarded as modified C-glycosides.[1] Many diverse methods have therefore been developed for the introduction of carbon substituents into the C-1 position of glycosides and related compounds.[2] We have recently described, without experimental details, an efficient Pd catalysed C-1 substitution of suitable pseudoglycals.[3] Herein this method is applied in the synthesis of (2*S*,6*S*-6-methyltetrahydropyran-2-yl)acetic acid (1), a component of civet[4] (which is a glandular secretion of the civet cat *Viverra civetta*) starting from di-*O*-acetyl-L-rhamnal (2).[5] This is a more direct route than alternative chiral syntheses.[6,7]



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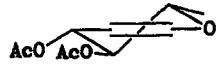

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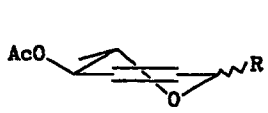
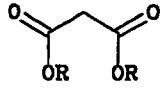
*To whom correspondence should be directed.

Di-*O*-acetyl-L-rhamnal (**2**) was converted to the pseudorhamnal (**3**, 80%) by brief reflux in water.[8] Since carbonates enhance the regioselectivity of the substitution at the anomeric position,[3] **3** was acylated with benzyl chloroformate by *N,N*-dimethylaminopyridine catalysis, furnishing the pseudorhamnal (**4**) in a $\alpha:\beta$ mixture of 8:1. The α-anomer was obtained pure in 80% yield by crystallization from ether/hexane. The α-anomeric structure was evidenced in the ^{1}H NMR spectrum of the compound by the large $^3J_{4,5}$ coupling constant (9.4 Hz) indicative of an exclusively *trans*-diaxial interaction.[9] The difference in the fine structure of the signals of H-2 and H-3 confirms the anomeric structure.[10]

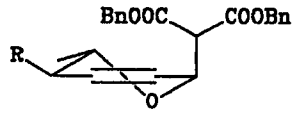
The anion of dibenzyl malonate (**5**) was selected as an ideal $^{\ominus}CH_2COOH$ equivalent in the $Pd(PPh_3)_4$[11] catalysed substitution of the anomeric position of **4** yielding the C-2 substituted dihydropyran (**6**, 80%). It is of interest to note that the anions of di-*tert*-butyl malonate (**7**) and Trost's reagent (**8**)



3 R=OH
4 R=α-OCOOBn



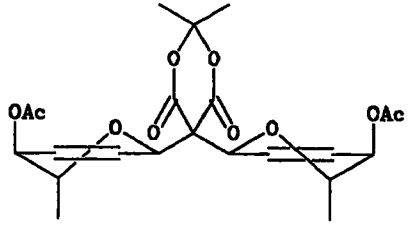
5 R=Bn
7 R=^{t}Bu
9 R,R=CMe_2



6 R=OAc
11 R=H

$PhSO_2CH_2CO_2Me$

8



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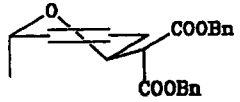
resulted in little or no substitution, while the anion of Meldrum's acid (**9**) reacted with two equivalents of **4** producing the C_2 symmetric bispyranoid derivative (**10**). The ^{1}H NMR spectrum of the product **6** is consistent with the assigned structure in which C-1 substitution occurs with retention of configuration.[12] The H-1 resonance appears as a doublet with $^3J_{4,5} = 6.3$ Hz. The magnitude of the coupling indicates an equilibrium between conformations in which the relevant proton (H-1 and H-2) have alternatively *trans*-diaxial and -die-quatorial relationships. This phenomenon is confirmed by similar fine structure in the signals of H-3 and H-4.[10]

The second palladium catalysed nucleophillic allylic substitution reaction consists of the replacement of the acetate group of the dihydropyran (**6**) with hydride. Exposure of **6** to a mixture of diphenylsilane, zinc chloride and a catalytic amount of $Pd(PPh_3)_4$ (10 mol %)[13] gave an inseparable mixture of dihydropyrans **11** and **12** (84%, 3:1 resp. by ^{1}H NMR). The generation of this mixture was of no concern in this synthesis since the next process entailed the simultaneous hydrogenation of the olefinic bonds and the reductive debenzylation of the esters of **11** and **12** with hydrogen, catalysed by palladium on carbon, furnishing the tetrahydropyranyl malonic acid (**13**)[14] as common product in almost quantitative yield. Decarboxylation of **13** either by distillation (150°C/300 mTorr) or flash thermolysis (150°C) resulted in isomerization (probably by a reversible ring opening *via* β-alkoxy elimination



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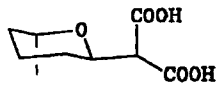

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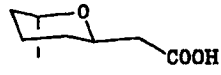

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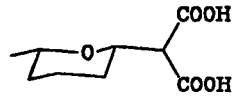
followed by or in concert with decarboxylation) at the tetrahydropyranoid 2-position, favouring the product of inverted configuration, the desired component of civet (**2**, 5:1 by ^{1}H NMR relative to diastereomer **14**). Similar decarboxylation of the *cis*-pyranosyl malonate **15** yielded a 9:1 mixture of **2** and **14** respectively.[14]

We are currently investigating the use of α-nitro acetate esters as nucleophiles for the primary palladium catalysed allylic substitution reaction. This allows the retention of stereochemistry at the tetrahydropyranoid 2-position when the nitro group is homolytically removed,[15] availing methodology for the synthesis of *trans*-2,6-disubstituted tetrahydropyranoid derivatives to complement this methodology for the synthesis of the *cis*-derivatives.



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Experimental

The preparation of solvents and reagents, and general laboratory and separation techniques and the instrumentation used is described in the preceding article.[5] Ether was distilled off a sodium/potassium liquid alloy as described in the preceding article. Absolute EtOH was distilled off $Mg(OEt)_2$.

4-O-Acetyl-L-pseudorhamnal (3).[8] – Di-*O*-acetyl-L-rhamnal (**2**) (250 mg, 1.17 mmol) was suspended in water (20 ml) and refluxed for 15 min with the exclusion of light. Monitoring the reaction by TLC (EtOAc/hexane-1:3) was imperative to determine the optimum point of reaction where product gains

no longer outweighed losses to byproducts. The solution was cooled down to ambient temperature and extracted with $CHCl_3$ (3x30 ml), the combined extracts dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was flash chromatographed (EtOAc/hexane-1:3) furnishing *4-O-acetyl-L-pseudorhamnal* (**3**) (160 mg, 79%); $[\alpha]_D^{23}$ -136.1° ±1.9 (*c* 1.00, $CHCl_3$); υ_{max} ($CHCl_3$) 3593 (OH unbonded) and 1745 cm^{-1} (C=O); in an α:β anomer distribution of 71:29 by NMR: α anomer: ^1H NMR δ1.21 (d, 3H, $^3J_{Me,5}$ = 6.3 Hz, CH_3), 2.07 (s, 3H, CH_3CO_2), 3.08 (bs, 1H, OH), 4.03 (dq, 1H, $^3J_{5,4}$ = 9.1 and $^3J_{5,Me}$ = 6.4 Hz, H-5), 5.02 (dd, 1H, $^3J_{4,5}$ = 9.0 and $^3J_{4,2\ or\ 3}$ = 1.4 Hz, H-4), 5.37 (bs, 1H, H-1) and 5.83-5.87 (m, 2H, H-2 and H-3); ^{13}C NMR (assignments made by HETCORR) δ17.91 (q, CH_3), 21.03 (q, CH_3CO_2), 64.93 (d, C-5), 70.66 (d, C-4), 88.74 (d, C-1), 128.42 and 129.69 (2xd, C-2 and C-3) and 170.54 (s, CH_3CO_2); β anomer: ^1H NMR δ1.28 (d, 3H, $^3J_{Me,5}$ = 6.4 Hz, CH_3), 2.06 (s, 3H, CH_3CO_2), 3.20 (d, 1H, $^3J_{OH,1}$ = 8.0 Hz, OH), 3.79 (dq, 1H, $^3J_{5,4}$ = 7.7 and $^3J_{5,Me}$ = 6.4 Hz, H-5), 5.06 (dd, 1H, $^3J_{4,5}$ = 7.8 and $^3J_{4,2\ or\ 3}$ = 1.4 Hz, H-4), 5.37 (bs, 1H, H-1) and 5.83-5.87 (m, 2H, H-2 and H-3); ^{13}C NMR (assignments made by HETCORR) δ18.44 (q, CH_3), 21.03 (q, CH_3CO_2), 64.94 (d, C-4), 71.59 (d, C-5), 91.38 (d, C-1), 128.57 and 131.16 (2xd, C-2 and C-3) and 170.42 (s, CH_3CO_2); *m/z* (EI, 70 eV) 155 (M^+-OH, 5.5%), 95 (34) and 42 (100).

Benzoxycarbonyl 4-O-acetyl-6-deoxy-α-L-erythrohex-2-enopyranoside (4).– 4-*O*-Acetyl-L-pseudorhamnal (**3**) (1.78 g, 10.3 mmol) and *N,N*-dimethylaminopyridine (235 mg, 1.92 mmol) were dissolved in CH_2Cl_2 (70 ml) and cooled down to -50°C. Pyridine (3.50 ml, 43.4 mmol) and benzyl chloroformate (13.0 ml of a 50% solution in toluene, 38.9 mmol) were then added, forming a

suspension. The reaction mixture was stirred for 30 min after which it was allowed to thaw to ambient temperature. At *ca* 0°C the suspension had dissolved completely. Triethylamine (100 μl) and flash silica gel (*ca* 4 g) were added and the volatiles removed *in vacuo*. The adsorbed residue was brought onto a flash chromatography column (deactivated by pre-elution with 2% triethylamine in 1:3-EtOAc/hexane) and flash chromatographed (EtOAc/hexane-1:3) furnishing *benzoxycarbonyl 4-O-acetyl-6-deoxy-α-L-erythrohex-2-enopyranoside* (4) (3.23 g) as a mixture of anomers (α:β-89:11 by NMR). The α anomer was obtained by crystallization (ether/hexane) (2.52 g, 80%) mp 66-67°C; $[\alpha]_D^{23}$ -53.9° ±2.0 (*c* 1.00, $CHCl_3$); υ_{max} ($CHCl_3$) 1747 (C=O) and 1258 and 1252 cm^{-1} (C–O); ^1H NMR δ1.22 (d, 3H, $^3J_{Me,5}$ = 6.2 Hz, CH_3), 2.07 (s, 3H, CH_3CO_2), 3.97 (dq, 1H, $^3J_{5,4}$ = 9.4 and $^3J_{5,Me}$ = 6.2 Hz, H-5), 5.08 (dq, 1H, $^3J_{4,5}$ = 9.4 and $^3J_{4,3} \approx {}^4J_{4,2} \approx {}^5J_{4,1} \approx$ 1.7 Hz, H-4), 5.18 (s, 2H, 2xH'), 5.81 (ddd, 1H, $^3J_{2,3}$ = 10.2, $^3J_{2,1}$ = 2.8 and $^4J_{2,4}$ = 2.0 Hz, H-2), 5.98 (dd, 1H, $^3J_{3,2}$ = 10.2 and $^3J_{3,4}$ = 1.3 Hz, H-3), 6.14 (d, 1H, $^3J_{1,2}$ = 2.0 Hz, H-1) and 7.32-7.39 (m, 5H, Ph); ^{13}C NMR (assignments made by HETCORR) δ17.73 (q, CH_3), 20.96 (q, CH_3CO_2), 67.15 (d, C-5), 69.81 (t, C'), 70.01 (d, C-4), 91.76 (d, C-1), 124.98 (d, C-2), 131.75 (d, C-3), 128.40 (d, *o*-Ph), 128.59 (d, *m*- and *p*-Ph), 134.93 (s, *ipso*-Ph), 154.01 (s, OCO_2) and 170.27 (s, CH_3CO_2); *m/z* (EI, 70 eV) 306 (M^+, 0.15%), 262 (1.8), 246 (9.9), 155 (42), 95 (96) and 91 (100).

Dibenzyl (2R,5R,6S-5-acetoxy-6-methyl-5,6-dihydro-2H-pyran-2-yl)malonate (6).– Dibenzyl malonate (5) (1.00 ml, 4.00 mmol) in THF (20 ml) was deprotonated at 0°C with NaH (80% suspension in oil, 100 mg, 3.33 mmol) and allowed to warm to ambient temperature. Benzoxycarbonyl 4-*O*-acetyl-

6-deoxy-α-L-erythrohex-2-enopyranoside (4) (1.00 g, 3.26 mmol) and $Pd(PPh_3)_4$ (400 mg, 346 μmol) were then added consecutively, addition of latter producing a suspension which rapidly dissolved again. After 10 min the reaction mixture was partially concentrated *in vacuo* and then washed (EtOAc/hexane-1:4) through a bed of silica gel to eliminate most of the catalyst. The solvent was removed from the filtrate *in vacuo* and the residue flash chromatographed (2% EtOAc/benzene) furnishing *dibenzyl (2R,5R,6S-5-acetoxy-6-methyl-5,6-dihydro-2H-pyran-2-yl)malonate* (6) (1.20 g, 84%); $[\alpha]_D^{23}$ -66.3° ±1.6 (*c* 1.00, $CHCl_3$); ν_{max} ($CHCl_3$) 1740 (C=O) and 1150 cm^{-1} (C–O); ^1H NMR δ1.10 (d, 3H, $^3J_{Me,6}$ = 6.5 Hz, CH_3), 2.03 (s, 3H, CH_3CO_2), 3.78 (q_n, 1H, $^3J_{6,5} \approx {}^3J_{6,Me}$ = 6.3 Hz, H-6), 3.80 (d, 1H, $^3J_{2',2}$ = 9.9 Hz, H-2') 4.82 (dq, 1H, $^3J_{2,2'}$ = 9.9 and $^3J_{2,3} \approx {}^4J_{2,4} \approx {}^5J_{2,5} \approx$ 2.2 Hz, H-2), 4.91 (dddd, 1H, $^3J_{5,6}$ = 6.3, $^3J_{5,4}$ = 2.9, $^5J_{5,2}$ = 2.0 and $^4J_{5,3}$ = 1.4 Hz, H-5), 5.13 (d, 1H, $^2J_{H'H'}$ = 12.3 Hz, H'b), 5.13 (s, 2H, 2xH"), 5.22 (d, 1H, $^2J_{H'H'}$ = 12.5 Hz, H'a), 5.79 [ddd, 1H, $^3J_{4,3}$ = 10.4, $^3J_{4,5}$ = 2.8 and $^4J_{4,2}$ = 1.9 Hz, H-4 (or H-3)], 6.00 [ddd, 1H, $^3J_{3,4}$ = 10.4, $^3J_{3,2}$ = 2.5 and $^4J_{3,5}$ = 1.4 Hz, H-3 (or H-4)], and 7.23-7.36 (m, 10H, 2xPh); ^{13}C NMR (assignments made by HETCORR) δ17.16 (q, CH_3), 21.07 (q, CH_3CO_2), 55.79 (d C-2'), 67.29 (t, C' and C"), 68.60 (d, C-6), 69.44 (d, C-5), 69.69 (d, C-2), 125.91 and 129.99 (2xd, C-3 and C-4) 128.13 and 128.17 (2xd, 4x*o*-Ph), 128.29 and 128.43 (2xd, *p*-Ph), 128.48 and 128.56 (2xd, 4x*m*-Ph), 135.00 and 135.27 (2xs, *ipso*-Ph), 166.36 and 166.43 [2xs, $CH(CO_2Bn)_2$] and 170.49 (s, CH_3CO_2); *m/z* (EI, 70 eV) 438 (M^+, 0.24%), 394 (19), 378 (6.1), 155 (3.0) and 91 (100).

A mixture of dibenzyl (2R,6S-6-methyl-5,6-dihydro-2H-pyran-2-yl)malonate (11) and dibenzyl (2S,6R-2-methyl-5,6-dihydro-2H-pyran-6-yl)malonate (12).–

A solution of dibenzyl (2*R*,5*R*,6*S*-5-acetoxy-6-methyl-5,6-dihydro-2*H*-pyran-2-yl)malonate (1.00 g, 2.28 mmol) in a mixture of diphenylsilane (1.30 ml, 7.00 mmol) and THF (20 ml) was treated with $ZnCl_2$ (1.00 g, 7.34 mmol) followed by $Pd(PPh_3)_4$ (300 mg, 260 μmol) at ambient temperature for 12 h. The reaction mixture was then washed (EtOAc/hexane-1:3) through a bed of silica gel to eliminate most of the catalyst. The solvent was removed from the filtrate *in vacuo* and the residue redissolved in THF (20 ml). Anhydrous Bu_4NF (the trihydrate 1.75 g, 5.55 mmol dried azeotropically by refluxing in 30 ml toluene through a Dean-Stark separator) was added and the mixture stirred for 5 h to fluorinate the diphenylsilane derivatives. The solvent was removed *in vacuo* and the residue flash chromatographed (EtOAc/hexane-1:8) furnishing a 3:1 mixture by ^1H NMR of *dibenzyl (2R,6S-6-methyl-5,6-dihydro-2H-pyran-2-yl)malonate* (11) and *dibenzyl (2S,6R-2-methyl-5,6-dihydro-2H-pyran-6-yl)malonate* (12) (728 mg, 84%); υ_{max} ($CHCl_3$) 1742 (C=O) and 1158 cm^{-1} (C—O); ^1H NMR component of the major isomer (11): δ1.08 (d, 3H, $^3J_{Me,6}$ = 6.2 Hz, CH_3), 1.89-1.97 (m, 2H, H-5's), 3.74 (m, 1H, H-6), 3.82 (d, 1H, $^3J_{2',2}$ = 10.2 Hz, H-2'), 4.86 (ddd, 1H, $^3J_{2,2'}$ = 10.2, $^3J_{2,3\text{ or }4}$ = 2.5 and $^4J_{2,4\text{ or }3}$ = 1.7 Hz, H-2), 5.13-5.18 (m, 4H, 2xH' and 2xH''), 5.78 (dm, 1H, $^3J_{3,4}$ = 10.4 Hz, H-3), 5.87 (dm, 1H, $^3J_{4,3}$ = 10.3 Hz, H-4) and 7.21-7.36 (m, 10H, 2xPh); ^1H NMR component of the minor isomer (12): δ1.13 (d, 3H, $^3J_{Me,2}$ = 6.8 Hz, CH_3), 2.02-2.11 (m, 2H, H-5's), 3.64 (d 1H, $^3J_{6',6}$ = 9.6 Hz, H-6'), 3.99 (m, 1H, H-2), 4.87 (ddd, 1H, $^3J_{6,6'}$ = 9.7, $^3J_{6,5ax}$ = 8.3 and $^3J_{6,5eq}$ = 3.8 Hz, H-6), 5.13-5.18 (m, 4H, 2xH' and 2xH''), 5.58-5.76 (m, 2H, $^3J_{4,3}$ = 10.6 Hz, H-3 and H-4) and 7.21-7.36 (m, 10H, 2xPh); ^{13}C NMR component of the major isomer (11): δ20.98 (q, CH_3), 31.81 (t, C-5), 56.60 (d, C-2'), 64.95 (d, C-6), 67.14 (t, C' and C''), 126.08 and 126.67

(2xd, C-3 and C-4) 128.15-128.53 (*o*-, *m*- and *p*-Ph), 135.14 and 135.46 (2xs, *ipso*-Ar-C) and 166.67 and 166.77 [2xs, $CH(CO_2Bn)_2$]; ^{13}C NMR component of the minor isomer (x): δ19.42 (q, CH_3), 28.10 (t, C-5), 57.26 (d C-6'), 66.61 and 69.04 (2xd, C-2 and C-6), 67.14 (t, 2x$PhCH_2$), 71.31 (d, C-2), 122.31 and 130.65 (2xd, C-3 and C-4) 128.10-128.53 (*o*-, *m*- and *p*-Ar-C), 134.28 and 134.39 (2xs, *ipso*-Ar-C) and 166.65 and 166.84 [2xs, $CH(CO_2Bn)_2$]; *m/z* (EI, 70 eV) 380 (M^+, 1.3%), 289 (4.6), 245 (51), 201 (2.8), 97 (92) and 91 (100).

(2R,6S-6-Methyltetrahydropyran-2-yl)malonic acid (13).[14]– A mixture of dibenzyl (2*R*,6*S*-6-methyl-5,6-dihydro-2*H*-pyran-2-yl)malonate (**11**) and dibenzyl (2*S*,6*R*-2-methyl-5,6-dihydro-2*H*-pyran-6-yl)malonate (**12**) (3:1, 250 mg, 657 μmol) were dissolved in absolute EtOH (5 ml) and treated with 3% Pd/C (75 mg, 21.1 μmol) and stirred under 3 atmospheres of H_2 for 12 h. The catalyst was filtered off through Celite and the filtrate evaporated *in vacuo* furnishing *(2R,6S-6-methyltetrahydropyran-2-yl)malonic acid* (**13**) (130 mg, 98%); ^1H NMR (DMSO-d_6) δ1.01 (d, 3H, $^3J_{Me,6}$ = 6.1 Hz, CH_3), 0.97-1.75 (m, 6H, $CH_2CH_2CH_2$), 3.10 (d, 1H, $^3J_{2',2}$ = 8.8 Hz, H-2'), 3.27-3.53 (m, 1H, H-6) and 3.76 (td, 1H, $^3J_{2,2'} \approx {}^3J_{2,3ax} \approx$ 9.0 and $^3J_{2,3eq}$ = 1.5 Hz, H-2); ^{13}C NMR (DMSO-d_6) δ21.98 (q, CH_3), 22.85 (t, C-4), 28.42 (t, C-5), 32.57 (t, C-3), 58.05 (d, C-2'), 73.48 (d, C-6), 74.95 (d, C-2) and 169.05 [s, $CH(CO_2H)_2$].

(2S,6S-6-Methyltetrahydropyran-2-yl)acetic acid (2) (the component of civet).– (2*R*,6*S*-6-Methyltetrahydropyran-2-yl)malonic acid (**13**) (40 mg, 198 μmol) was decarboxylatively distilled in a preheated Kugelrohr (150°C/300 mTorr) furnishing an 83:17 mixture by NMR of *(2S,6S-6-methyltetrahydropyran-2-*

yl)acetic acid (2) and *(2R,6S-6-methyltetrahydropyran-2-yl)acetic acid* (14) (29 mg, 93%); ^{1}H NMR[16] δ1.16 (d, 3H, $^3J_{Me,6}$ = 6.2 Hz, CH_3), 1.09-1.35, 1.45-1.70 and 1.70-1.90 (3xm, 2H, 3H and 1H respectively, $CH_2CH_2CH_2$), 2.45 (dd, 1H, $^2J_{2',2'}$ = 15.7 Hz and $^3J_{2'b,2}$ = 5.4, H-2'b), 2.58 (dd, 1H, $^2J_{2',2'}$ = 15.8 Hz and $^3J_{2'a,2}$ = 7.5, H-2'a), 3.51 (dqd, 1H, $^3J_{6,5ax}$ = 10.8, $^3J_{6,Me}$ = 6.2 and $^3J_{6,5eq}$ = 1.9 Hz, H-6), 3.75 (dddd, 1H, $^3J_{2,3ax}$ = 11.0, $^3J_{2,2'a}$ = 7.5, $^3J_{2,2'b}$ = 5.4 and $^3J_{2,3eq}$ 2.0 Hz, H-2) and 5.85-6.80 (br s, 1H, CO_2H; ^{13}C NMR[7] δ21.97 (q, CH_3), 23.10 (t, C-4), 30.72 (t, C-3), 32.72 (t, C-5), 41.11 (t, C-2'), 73.95 (d, C-6), 74.62 (d, C-2) and 174.27 (s, CO_2H).

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