Tetrahedron Vol. 37, pp. 2085 to 2089, 1981
Printed in Great Britain.

0040-4020/81/112085-05$02.00/0
Pergamon Press Ltd.

IRIDOIDS : NOVEL TOTAL SYNTHESIS OF (±)-ISOIRIDOMYRMECIN AND OF (±)-VERBENALOL

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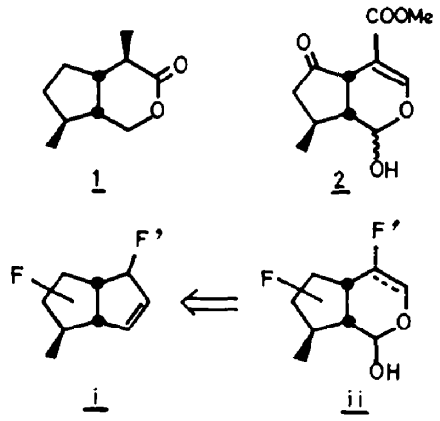
(Received in the UK 3 April 1981)

Abstract - A novel synthesis of the iridoids (±)-isoiridomyrmecin 1 and (±)-verbenalol 2 is described starting from the tricyclo |3.3.0.$0^{2,8}$|octan-3-one 3, using cis fused bicyclo|3.3.0|octenes as intermediates. The heterocyclic ring of the iridoids was formed in the final stages of the syntheses.

In the foregoing paper we have described an efficient entry for several polyfunctionalized cis bicyclo|3.3.0|octanes and adumbrated their transformation to the cyclopentanopyran structural unit (ii) of the iridoid monoterpenes (scheme 1).



1 2 i ii

Scheme 1

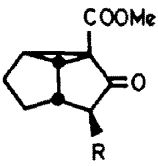
It is indeed appropriate to construct the sensitive heterocyclic iridoid system from a more stable cis-bicyclo|3.3.0|octene precursor only in the final stages of the synthesis. Furthermore, this strategy ensures the desired cis fusion in the iridoid ringsystem. Although this approach has been applied in several iridoid syntheses[1-5], it suffered from the lack of general methods for constructing suitably functionalized bicyclo|3.3.0|oct-2-enes such as i. Only recently increasing efforts have been devoted to the synthesis of polyquinane systems[6]. Amongst these methods we want to mention the recent approaches where the link between bicyclo|3.3.0|octenes and iridoids is straightforward.

Whitesell has exploited the transannular cyclization of cyclooctadiene derivatives to construct the diquinane ringsystem[7,8] and developed a new method to introduce β,γ-unsaturated esters[9,10]. Recently Isoe reported[11] an approach very similar to ours, including an intramolecular carbenoid cyclopropanation followed by a solvolytic opening of the resulting 4-methyltricyclo|3.3.0.$0^{2,8}$|octan-3-one.

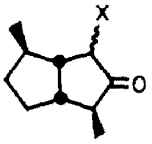
In the present paper we want to illustrate the synthetic potential of 3 and 8 with the syntheses of (±)-isoiridomyrmecin 1[12] and (±)-verbenalol 2[13], members of two different iridoid subclasses[14]. Verbenalol, the aglucon of the naturally occuring glucoside verbenalin, is a representative of the largest class characterized by the typically substituted dihydropyran ring in 2.

In the foregoing paper[15] we have described the synthesis of 3 and its application by stereocontrolled manipulations using nucleophiles and electrophiles. The methylation of 3, using diisopropylamide as the base led to a stereohomo-

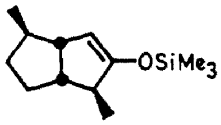
geneous product 4 (85 %); the configuration of 4 is proven by its transformation into (±)-isoiridomyrmecin 1, a well established structure (scheme 2).



3 , R = H
4 ; R = Me



5 ; X = COOMe
6 ; X = H



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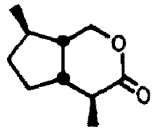


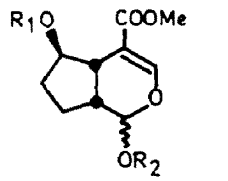
1

Scheme 2

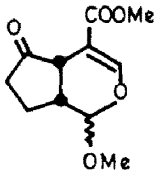
Since this relative configuration is the thermodynamically more stable one in the target molecule, the present stereoselectivity is not of absolute necessity. The β orientation of the other methylgroup is of a more stringent nature and was obtained by nucleophilic opening of the cyclopropane ring which occurs with inversion of configuration[16]. Reaction of 4 with dimethylcopperlithium afforded keto ester 5; hydrolysis and decarboxylation led to a single ketone 6 (87 % overall). The stage was now set for the transformation to the iridoid skeleton. The kinetic enolate derived from ketone 6 was trapped with trimethylsilyl chloride. The crude enol silylether 7 was subjected to ozonolysis followed by reductive workup with sodium borohydride[17] and afforded directly (±)-isoiridomyrmecin 1, which gave spectroscopic data in accord with those obtained by Whitesell*. Most significantly, the fingerprint region of the IR spectrum, as well as the ^{13}C NMR spectrum were identical.

ing point, two different approaches were examined. In compound 8, which is readily accessible[15] from 3; the methoxycarbonylgroup at C-2 has already the oxidation state present in the target molecule; the additional methyl group of the iridoid skeleton has to be introduced at C-6. It is obvious that the acetoxyfunction in 8 has to serve as a handle for this purpose and that an α,β-unsaturated ketone has to be envisaged as an intermediate. One possible solution is to carry out this transformation on the preformed 6-nor-iridoid 9 (scheme 3). Indeed, as already described 9 is easily available from 8 via a reaction sequence modifying the cyclopentene ring. Simultaneous transesterification of the acetate and protection of the hemi acetal upon sulfuric acid catalyzed treatment with methanol afforded 10 (85 %). Jones oxidation of 10 led to ketone 11 in 66 % yield. However our efforts to introduce the desired double bond met with complete failure.

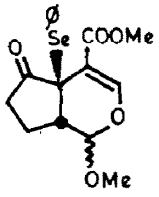
A variety of standard methods to bring about this transformation turned out to be uncompatible with the presence of the heterocyclic ring, a problem we already alluded to above. Only reaction of the lithium enolate, formed by



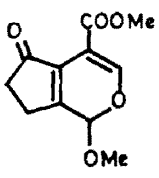
9 ; R1 = Ac ; R2 = H
10 ; R1 = H ; R2 = Me



11



12



13

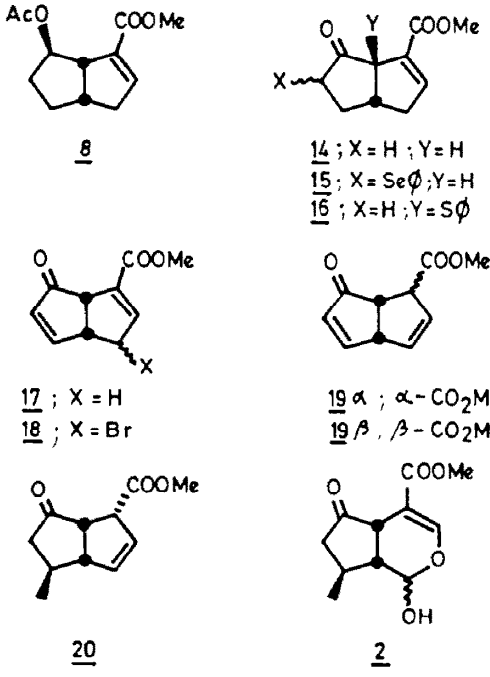
Scheme 3

We then turned our attention to the synthesis of (±)-verbenalol 2. With 8 as a common start- kinetic deprotonation of 11, with phenylselenenylbromide[18] led to an isolable product 12. The structure of this unexpected compound 12 is supported by its clean transformation to the pyrane 13, using the mild oxidation-elimination

* We thank Prof. J.K. Whitesell for kindly providing copies of the spectra.

process[19].

A better opportunity for double bond formation was present at the stage of ketone 14 (scheme 4) which was obtained from 8 by methanolysis and subsequent Jones oxidation of the intermediate alcohol (63 % overall).



Scheme 4

Treatment of 14 with one equivalent of phenylselenenyl chloride in ethyl acetate[20] led to the desired α-phenylselenide 15 (81 %). Although subsequent oxidation and elimination afforded enone 17, the low yield (40 %) incited us to investigate an alternative method.

Convinced that this low yield was primarily due to side reactions frequently encountered with the fragmentation of α-keto-selenoxides[21], we decided to try the usually cleaner sulfoxide elimination.

However, sulfenylation of the kinetic enolate (lithium diisopropylamide in tetrahydrofuran) from 14 with phenyl benzene thiosulfonate[22] afforded the angular sulfide 16 (70 % after crystallization; m.p. 80°).

The selenenylation experiment had suggested that the enolisation of ketone 14 towards the methylene side is thermodynamically favoured. Indeed, treatment of 14 with trimethylsilyl chloride and triethylamine dimethylformamide[23] afforded the desired enolsilylether which was directly oxidized with palladium acetate to 17 (55 % overall)[24].

The double bond migration of the unsaturated ester 17 was now undertaken using a slight variation of Sutherland's method[25] via allylic bromination (NBS) to 18 and subsequent reduction with zinc in acetic acid yielding a mixture of the C-2 epimers (6:1) (63 %) of 19 next to starting compound 17 (12 %). As both C-2 epimers could be separated by column chromatography, the subsequent conjugate addition with dimethylcopperlithium was performed on the major isomer 19α (α-COOMe) yielding the stereohomogeneous compound 20 (86 %).

The double bond in 20 was cleaved with ozone; workup with zinc-acetic acid afforded (±)-verbenalol 2 (72 %) as an epimeric mixture at the hemi acetal function; 2 was characterized by the expected spectral data[13]. Verbenalol has already been synthesized by Sakan and Abe[1].

EXPERIMENTAL

The m.ps. are uncorrected. The NMR spectra were recorded at 90 MHz (Varian EM-390) or at 360 MHz (WH-Brucker) in $CDCl_3$ unless otherwise stated with TMS as internal standard. Chemical shifts (δ) are expressed in ppm. The MS data were recorded on an AEI MS-50 spectrometer. Rf values are quoted for Merck silica gel 60 GF_{254} the plates of thickness 0.25 mm with EtOAc-isooctane (ratio given between brackets) as eluent unless otherwise stated. Reaction products were isolated by the addition of water and extraction. The combined extracts were washed with saturated brine and dried over $MgSO_4$. The solvent was removed from the filtered soln on a rotary evaporator. Column chromatographic separations were performed on silica gel with EtOAc-isooctane (ratio given between brackets) as eluent unless otherwise stated.

3β-Methoxycarbonyl-4β-methyltricyclo [3.3.0.0^{2,8}]-3 octan-2-one (4)

To a soln of LDA (22 mmol) in THF (20 mL) were added at -80° successively 3 (3.6 g; 20 mmol) in THF (20 mL), HMPA (3.6 mL; 20 mmol) and a soln of MeI (5.68 g; 40 mmol) in THF (10 mL). The mixture was stirred at -30° for 1 1/2 hr and was then poured into 10 % HCl-ice. Workup and distillation (b.p. 90°C; 15 mm Hg) afforded 4 (3.3 g; 85 %). Rf (3:7) 0.24; IR (film) 1760-1730 cm^{-1}; NMR (360 MHz) 3.73 (s, 3), 3.16 (t, J = 6.0 Hz, 1), 2.76 (t, J = 6.6 Hz, 1), 2.47 (t, J = 6.0 Hz, 1), 2.22-1.94 (m, 3), 1.70-1.55 (m, 2), 1.18 (d, J = 7.6 Hz, 3); MS m/z 194 (M^+, 24) 79 (100).

2β,8β-Dimethyl-cis-bicyclo [3.3.0 octan-3-one (5)

To Me_2CuLi (15.0 mmol) in ether (15 mL) at -40° was added in 10 min a soln of 4 (1.94 g; 10 mmol) in ether (5 mL). After stirring at -30° for 90 min, the mixture was poured in a cold 10 % HCl soln. Isolation with ether (4 x 25 mL) and workup afforded 5 (2.1 g; 100 %) which was dissolved in a 1 % H_2SO_4 soln in HOAc (15 mL). After heating at reflux for 5 hr the mixture was cooled, poured in ice water (150 mL) and 6 was isolated with ether (5 x 50 mL). Workup and distillation (b.p. 70°C at 16 mm Hg) afforded 6 (1.32 g; 87 %). Rf (ether/hexane 1:1) 0.55; IR (film) 1740 cm^{-1}; NMR 2.7-0.8 (m, 10), 1.05 (d, J = 6.9 Hz, 3), 1.02 (d, J = 6.0 Hz, 3);

^{13}C NMR 222.1, 50.5, 48.6, 46.2, 41.8. 41.5, 35.2, 30.9, 18.9, 13.8; MS m/z 152 (M^+, 61), 95 (100).

(±)-Isoiridomyrmecin (1).

To a soln of LDA (1.1 mmol) in THF (2 mL) at -80° was slowly added a soln of 6 (152 mg; 1.0 mmol). After 30 min a soln of TMSCl (326 mg; 3.0 mmol) and HMPA (537 mg; 3.0 mmol) in THF (1 mL) was added. The mixture was warmed up and stirred at 20° for 30 min. Quenching with a cold sat. $NaHCO_3$ aq. and isolation with pentane yielded 7. Crude 7 was dissolved in dry MeOH (10 mL), cooled to -80° and treated with O_3. Excess O_3 was blown out with N_2 and $NaBH_4$ (150 mg; 5.0 mmol) was added. After 1 hr the mixture was acidified with 10 % HCl. MeOH was removed in vacuo and ether (10 mL) was added. This two phase system was stirred at 20° for 5 hr. Workup and column chromatography (benzene-ether 9:1) yielded 1 (70 mg; 42 %).

Rf (benzene/ether 9:1) 0.23; IR (film), 1740 cm^{-1}; NMR (360 MHz) 4.34 (dd, J = 11.00 and 6.25 Hz, 1), 3.96 (t, J = 11.00 Hz, 1), 2.32 (m, J = 30.0 Hz, 1), 2.18-1.61 (m, 5), 1.39-1.19 (m, 2), 1.19 (d, J = 6.5 Hz, 3), 1.06 (d, J = 6.5 Hz, 3); ^{13}C NMR 176.5, 69.5, 45.4, 43.3, 39.1, 38.3, 35.7, 33.1, 19.2, 14.0; HRMS m/z (4 %) 168.1146; calc. for $C_{10}H_{16}O_2$, 168.1150.

Alcohol 10

To a soln of 9 (256 mg; 1.0 mmol) in MeOH (5 ml) was added at 20° a 2 % H_2SO_4 soln in MeOH (1 mL). After stirring for 2 hr at 20° and 3 hr at reflux, the mixture was cooled (0°) and Et_3N (0.3 mL) was added. After evaporation in vacuo, the residue was taken up in ether (20 mL). Workup and column chromatography (Et_2O/hexane 1:1) yielded epimeric (2:1) 10 (194 mg; 85 %).

Rf (ether) 0.47 and 0.45; IR (film) 3600-3300, 1710, 1685, 1640, 1630 cm^{-1}; NMR (CCl_4) 7.35 (d, J = 1.2 Hz) and 7.32 (d, J = 1.0 Hz) 1, 4.77 (d, J = 3.6 Hz) and 4.48 (d, J = 5.4 Hz) 1, 3.82 (m, 1), 3.71 (s, 3), 3.58 (bs, 1), 3.43 (s) and 3.40 (s) 3, 2.71-1.40 (m, 6); MS m/z 228 (M^+, 0.1), 71 (100).

Non-iridoid 11

To a soln of 10 (480 mg; 2.1 mmol) in acetone (20 mL) at 0° was added excess Jones oxidans. After 1 hr the reaction was quenched with i PrOH (1 mL). The solvent was removed in vacuo and water was added. Extraction with CH_2Cl_2 (5 x 20 mL), workup and column chromatography (1:1) afforded epimeric 11 (316 mg; 66 %). Rf (1:1) 0.23 and 0.20; IR (film) 1750, 1710, 1635 cm^{-1}; NMR (CCl_4) 7.34 (d, J = 1.2 Hz) and 7.24 (d, J = 1.2 Hz) 1, 4.96 (d, J = 4.5 Hz) and 4.38 (d, J = 7.8 Hz) 1, 3.70 (s, 3), 3.57 (s) and 3.40 (s) 3, 3.50-3.20 (m, 2), 2.50-1.80 (m, 4); MS m/z 226 (M^+, 0.1), 139 (100).

Pyrane 12

To LDA (0.76 mmol) in THF (1 mL) at -80° was dropwise added a soln of 11 (144 mg; 0.63 mmol) in THF (1 mL). After 30 min a 2.4 M soln of PhSeBr in THF (315 µL; 0.75 mmol) was added. Stirring was continued at -80° for 10 min, followed by quenching with sat NH_4Cl aq Workup and column chromatography (benzene/EtOAc 9:1) afforded 12 (155 mg; 54 %). To selenide 12 (155 mg; 0.4 mmol) in CH_2Cl_2 (1 mL) at -80° was added a soln of mCPA (81 mg; 0.4 mmol) in CH_2Cl_2 (0.5 mL). After stirring for 15 min at -60°, the soln was injected in CH_2Cl_2 (15 mL) and Et_3N (15 mL) at 20°. Workup and column chromatography (1:1) afforded 13 (52 mg; 57 %).

Rf (1:1) 0.18; IR (film) 1735, 1720-1700, 1630, 1590 cm^{-1}; NMR 7.45 (bs, 1), 5.82 (bs, 1), 3.75 (s, 3), 3.51 (s, 3), 2.8-2.1 (m, 4); MS m/z 224 (M^+, 12), 192 (100).

2-Methoxycarbonyl-cis-bicyclo[3.3.0]oct-2-en-8-one (14)

To a soln of 8 (1.12 g; 5 mmol) in dry MeOH (25 mL) was added solid K_2CO_3 (140 mg; 1 mmol). The mixture was stirred for 16 hr at 20° and was then neutralised with 5 % HCl. Workup and column chromatography (ether-hexane 5:5) yielded the corresponding alcohol (800 mg; 90 %). To a soln of the latter (728 mg; 4.0 mmol) in acetone (140 mL) at -10° , was added dropwise Jones-oxidans. After stirring 1 hr at -10° and 1 hr at 20° iPrOH (2 mL) was added. Water (50 mL) was added and the organic solvents were evaporated in vacuo. Workup and column chromatography (ether/hexane 1:1) yielded ketone 14 (504 mg; 69 %). Rf (ether/benzene 1:1) 0.42; IR (KBr) 1740, 1725, 1720-1690, 1615 cm^{-1}; NMR (360 MHz) 6.78 (q, J = 2.33 Hz, 1), 3.78 (s, 3), 3.56 (bd, J = 8.8 Hz, 1), 3.21 (m, ΣJ = 34.3 Hz, 1), 2.89 (dddd, J = 19.0, 9.3, 2.5 and 1.5 Hz, 1), 2.39 (ddt, J = 19.0, 4.5 and 2.8 Hz, 1), 2.40-2.23 (m, 2), 2.18 (dq, J = 13.0 and 8.3 Hz, 1), 1.73 (m, ΣJ = 32.5 Hz, 1); HRMS m/z (100 %) 180.0791; calc. for $C_{10}H_{12}O_3$, 180.0786

2-Methoxycarbonyl-cis-bicyclo[3.3.0]octa-2,6-dien-8-one (17)

A soln of ketone 14 (90 mg; 0.5 mmol), TMSCl (317 µl; 2.5 mmol) and Et_3N (505 mg; 5.0 mmol) at 130°, was stirred for 6 hr. The mixture was poured in hexane (25 mL) and washed successively with a cold 5 % HCl soln and sat. $NaHCO_3$ aq. Drying on $MgSO_4$ and evaporation yielded the silyl enolether. A soln of the latter in acetonitrile (1.75 mL) was added dropwise to a soln of $Pd(OAc)_2$ (120 mg; 0.53 mmol) in acetonitrile (1 mL); stirring was continued for 2 hr. Filtration on silica gel-celite, concentration in vacuo and column chromatography (ether/hexane 7:3) yielded 17 (49 mg; 55 %). Rf (ether) 0.27; IR (film) 1740-1690, 1625, 1590 cm^{-1}; NMR (360 MHz) 7.63 (dd, J = 5.8 and 2.6 Hz, 1), 6.68 (m, ΣJ = 6.8 Hz, 1) 6.17 (dd, J = 5.8 and 1.6 Hz, 1), 3.84 (s, 3), 3.84-3.80 (m, 2), 2.91 (ddt, J = 9.8, 5.2 and 1.4 Hz, 1), 2.49 (dq, J = 9.8 and 1.7 Hz, 1); HRMS m/z (100 %) 178.0634; calc. for $C_{10}H_{10}O_3$, 178.0629.

2-Methoxycarbonyl-cis-bicyclo[3.3.0]octa-3,6-dien-8-one (19)

A mixture of 17 (267 mg; 1.5 mmol), NBS (347 mg; 2.0 mmol) and AIBN (trace) in CCl_4 (15 mL) was refluxed for 5 min. After cooling to 0° the succinimide was filtered off and was washed with cold CCl_4 (10 mL). After evaporation in vacuo at 20°, the residue 18 was taken up in CH_2Cl_2 (12 mL). At -10° HOAc (5 mL) and Zn powder (130 mg; 2.0 mmol) were added. The mixture was stirred for 1 hr at 0° and 1 hr at 20°. Ether (40 mL) was added and the mixture was filtered. Workup and column chromatography (ether: hexane 1:1) yielded 19α (143 mg; 54 %), 19β (24 mg, 9 %) and 17 (32 mg; 12 %).

19α : Rf (ether) 0.56; IR (film) 1740-1730, 1705-1695, 1580 cm^{-1}; NMR (360 MHz) 7.79 (dd, J = 5.8 and 3.0 Hz, 1), 6.09 (dd, J = 5.8 and 2.0 Hz, 1), 5.91 (dt, J = 5.6 and 2.3 Hz, 1), 5.68 (dt, J = 5.6 and 2.3 Hz, 1), 4.12 (m, ΣJ = 18.0 Hz, 1), 3.74 (s, 3), 3.72 (p, J = 2.8 Hz, 1), 3.48 (dd, J = 5.6 and 2.8 Hz, 1); MS m/z 178 (M^+, 4), 119 (100).

19β : Rf (ether) 0.35; IR (film) 1740-1730, 1705-1695, 1585 cm^{-1}; NMR (360 MHz) 7.75 (dd, J = 6.0 and 3.0 Hz, 1), 6.10 (dd, J = 6.0 and 2.0 Hz, 1), 6.00 (dt, J = 5.75 and 2.40 Hz, 1), 5.64 (dt, J = 5.75 and 2.1 Hz, 1), 4.06 (m, ΣJ = 17.5 Hz, 1), 3.90 (dq, J = 11.25 and 2.25 Hz, 1), 3.71 (s, 3), 3.31 (dd, J = 11.25 and 6.0 Hz, 1); MS m/z 178 (M^+, 40), 119 (100).

2α-Methoxycarbonyl-6β-methyl-cis-bicyclo [3.3.0]oct-3-en-8-one (20)
To Me_2CuLi (1.9 mmol) in ether (7 mL) at -60° was added enone 19α (112 mg; 0.63 mmol) in ether (5 mL) over a period of 5 min. After stirring for 10 min the mixture was poured into a sat NH_4OH-NH_4Cl (1:1) aq (20 mL) Workup and column chromatography (ether/hexane 3:7) yielded 20 (104 mg; 86 %).
Rf (ether/hexane 3:7) 0.28; IR (film) 1740-1730 cm^{-1}; NMR (360 MHz) 5.85 (dt, J = 5.6 and 2.0 Hz, 1), 5.72 (dt, J = 5.6 and 2.6 Hz, 1), 3.69 (s, 3), 3.67 (p, J = 2.2 Hz, 1), 3.31-3.21 (m, 2), 2.38-1.98 (m, 3), 1.14 (~d, J = 7.4 Hz, 3); MS m/z 194 (M^+, 12), 69 (100).

(±)-Verbenalol (2)
Through a soln of 20 (60 mg; 0.3 mmol) in CH_2Cl_2 (6 mL) at -40° was passed O_3. After removal of the solvent at reduced pressure, the residue was dissolved in HOAc (3 mL) and Zn powder (65 mg; 1.0 mmol) was added in one portion. After stirring at 20° for 45 min and heating at 80° for 90 min, the mixture was cooled and added to a sat $NaHCO_3$ aq (100 mL). Extraction with Et_2O (4 x 25 mL) and workup yielded 2 (51 mg; 72 %) after column chromatography (3:7). Rf (ether/hexane 4:1) 0.25; IR (film) 3550-3250, 1740, 1730, 1710, 1690, 1630 cm^{-1}; NMR (360 MHz) 7.44 (d, J = 1.2 Hz) and 7.39 (d, J = 1.2 Hz) 1, 5.55 (d, J = 3.0 Hz) and 4.89 (d, J = 8.0 Hz), 1, 3.78 (s) and 3.77 (s), 3, 3.76-3.34 (m, 2), 2.66-1.85 (m, 4), 1.27 (d, J = 7.2 Hz) and 1.26 (d, J = 7.0 Hz), 3; HRMS m/z 226.0846; calc. for $C_{11}H_{14}O_5$. 226.0841.

Acknowledgements : We thank the N.F.W.O. and the "Ministerie voor Wetenschapsbeleid" for financial help to the laboratory. P.C. and R.O. are indepted to the I.W.O.N.L. for a graduate scolarship.

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