Cannabis XVIII*
Isolation and synthesis of olivetol derivatives formed in the pyrolysis of cannabidiol

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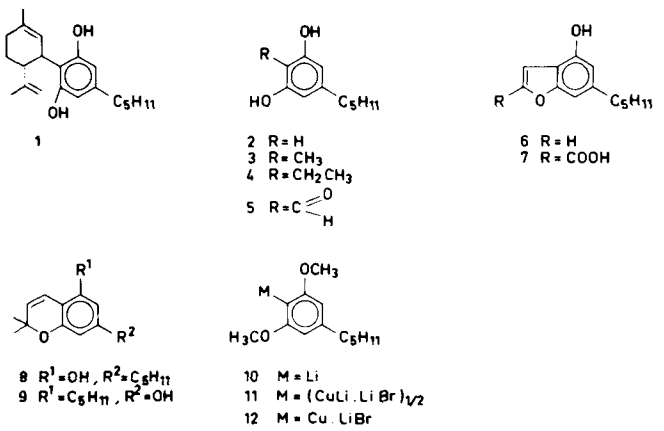
Abstract. Pyrolysis of cannabidiol results in the formation of several new cannabinoids and cracking products. In an earlier paper several structures were proposed for the cracking products based on GCMS measurements. In this paper the isolation and synthesis of the majority of these cracking products – which are in general $C_{(2)}$-substituted olivetol derivatives – is described. 2,6-Dimethoxy-4-pentylphenyl-lithium and the cuprates derived therefrom proved to be very promising intermediates for the synthesis of olivetol derivatives specifically substituted at $C_{(2)}$. The versatility of these reagents is illustrated by several examples.

Introduction

Since cannabis products are generally administered by smoking, we prefer to study the components formed by pyrolysis of cannabinoids rather than those present in the plant-material. Pyrolysis of cannabidiol (CBD, **1**) affords a complex mixture of volatile (cracking) products and new cannabinoidal compounds. The structures of several of these cannabinoids formed during pyrolysis of CBD have been described in previous articles[1–5]. In a preceeding paper *Küppers* et al.[3] analysed the volatiles using GCMS combined with silylation-experiments. In order to obtain a definitive proof for the structures proposed, the isolation and synthesis of these cracking products were undertaken.



Furthermore, biochemical studies of these products required more material which could be provided by their synthesis.

Results

The volatiles were separated from the pyrolysate mixture by preparative GLC; the components eluating before CBD were collected separately. This sample was further fractionated by repeated preparative TLC; the results are summarised in Table I.

Table I Analysis of the fractions obtained by preparative TLC.

fraction	Rf – zone	yield (mg)	GLC and GCMS analysis*
1	0.57–0.71	3.6	80% Rx = 0.62: "$^{314}/_{231}$"
2	0.44–0.52	8.5	75% CBD
3	0.30–0.38	22	75% Rx = 0.23: "$^{246}/_{231}$"
4	0.21–0.30	2.5	85% Rx = 0.13: "$^{204}/_{147}$"
5	0.11–0.17	5.8	95% Rx = 0.15: "$^{194}/_{138}$"
6	0.01–0.05	30	98% Rx = 0.13: "$^{180}/_{124}$"

* Components are indicated by their molecular ion and most abundant ion.

The spectroscopical data of the components "$^{180}/_{124}$", "$^{194}/_{138}$", "$^{204}/_{147}$" and "$^{246}/_{231}$" are in excellent agreement with the structures proposed by *Küppers* et al.[3]: olivetol (**2**), 2-methylolivetol (**3**), 4-hydroxy-6-pentylbenzofuran (**6**) and 2,2-dimethyl-5-hydroxy-7-pentylchromene (**8**), respectively. Product "$^{314}/_{231}$" is identical with cannabicitran – described earlier by *Crombie* et al.[6] and *Bercht* et al.[7] – and is probably formed by *trans-cis*-isomerisation of $C_{(3)}$–$C_{(4)}$ in CBD in combination with a ring-closure of both the phenolic OH-groups with $C_{(1)}$ and $C_{(8)}$, respectively.

Further proof for the correctness of the proposed structures was obtained by their synthesis. 2,6-Dimethoxy-4-pentylphenyllithium (**10**) and the cuprates **11** and **12** derived therefrom proved to be very promising intermediates for the specific introduction of substituents at $C_{(2)}$ of olivetol. Compound **10** is prepared in quantitative yield by metallation of olivetol dimethyl ether with *n*-butyllithium. Reaction of **10** with methyl iodide followed by demethylation with borium tribromide gave 2-methylolivetol (**3**) in 75% yield. This product was identical with the isolated cracking product "$^{194}/_{138}$". More examples of coupling reactions with **10** are given in Table II.

In several cases the use of the homocuprate **11**, which can be obtained by the addition of half an equivalent of cuprous bromide to **10**, proved to be advantageous. Condensation of homocuprate **11** with a mixture of the vinylic bromide **13**

* Part XVII, see ref. 9.

[1] *F. J. E. M. Küppers, R. J. J. Ch. Lousberg, C. A. L. Bercht, C. A. Salemink, J. K. Terlouw, W. Heerma* and *A. Laven*, Tetrahedron **29**, 2797 (1973).

[2] *F. J. E. M. Küppers, C. A. L. Bercht, C. A. Salemink, R. J. J. Ch. Lousberg, J. K. Terlouw* and *W. Heerma*, Tetrahedron **31**, 1513 (1975).

[3] *F. J. E. M. Küppers, C. A. L. Bercht, C. A. Salemink, R. J. J. Ch. Lousberg, J. K. Terlouw* and *W. Heerma*, J. Chromatogr. **108** (2), 375 (1975).

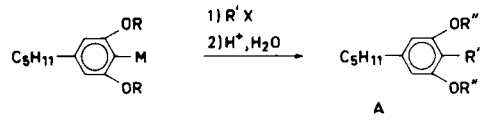
[4] *H. J. W. Spronck* and *R. J. J. Ch. Lousberg*, Experientia **33**, 705 (1977).

[5] *H. J. W. Spronck*, Thesis, University of Utrecht, The Netherlands (1976).

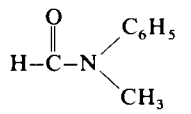
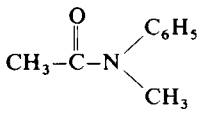
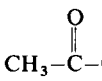
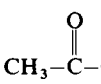
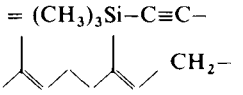
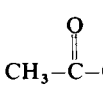
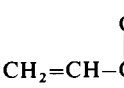
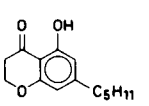
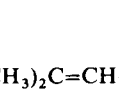
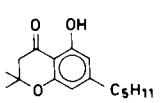
[6] *L. Crombie* and *R. Ponsdorf*, J. Chem. Soc. (C) 796 (1971).

[7] *C. A. L. Bercht*, Thesis, University of Utrecht, The Netherlands (1973).

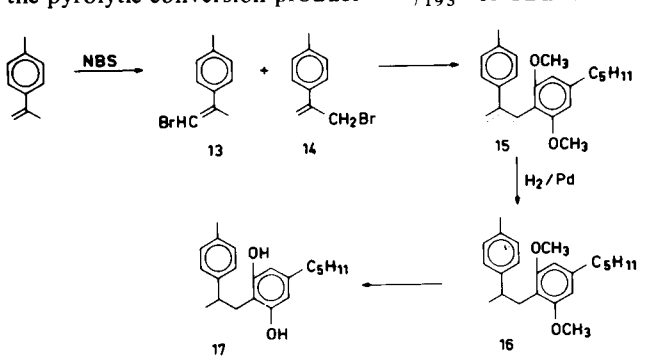
Table II Condensation reactions with metallated olivetol ethers.



A

R'X	M	R	product	yield (GLC)
CH_3I	Li	CH_3	A : R″ = CH_3, R′ = CH_3–	97%
CH_2=CH–CH_2Br	Li	CH_3	A : R″ = CH_3, R′ = CH_2=CH–CH_2–	98%
	Li	CH_3	A : R″ = CH_3, R′ = H–CO–	92%
	Li	CH_3	–	0%
	Li	CH_3	A : R″ = CH_3, R′ = CH_3CO–	25%
CH_3–CH_2–I	$(CuLi.LiBr)_{\frac{1}{4}}$	CH_3	A : R″ = CH_3, R′ = CH_3CH_2–	80%
1 bromo-2-*p*-tolylpropene 3 bromo-2-*p*-tolylpropene	$(CuLi,LiBr)_{\frac{1}{4}}$	CH_3	A : R″ = CH_3, R′ = 2-*p*-tolylpropen-1 (and 3) yl.	100%
H–C≡C–CH_2–Br	$(CuLi.LiBr)_{\frac{1}{4}}$	CH_3	A : R″ = CH_3, R′ = H–C≡C–CH_2–	60%
	Cu.LiBr	CH_3	A : R″ = CH_3, R′ = CH_3CO–	80%
$(CH_3)_3$Si–C≡C–I	Cu.LiBr	CH_3	A : R″ = CH_3, R′ = $(CH_3)_3$Si–C≡C–	75%
geranylbromide	Cu.LiBr	CH_3	A : R″ = CH_3, R′ = 	95%
	Cu.LiBr	THP	A : R″ = H, R′ = CH_3–CO–	80%
	Cu.LiBr	THP		20%
	Cu.LiBr	THP		99%

and the allylic bromide **14** (Scheme 1 and Table II) resulted in a quantitative formation of the double bond isomers **15**, which, after hydrogenation and demethylation, gave 2-(2-{*p*-tolyl}propyl)olivetol (**17**). This product is identical with the pyrolytic conversion product "$^{312}/_{193}$" of CBD[9].



Scheme 1

If **10** is converted into the corresponding cuprate **12** – by the addition of one equivalent of cuprous bromide – a versatile reagent is obtained for condensation with acyl halides[8] (Table II). Thus reaction of **12** with acetyl chloride gave **2**-aceto-olivetol dimethyl ether which by Wolff-Kishner reduction and demethylation was converted into 2-ethyl-olivetol (**4**) in good yield. This product proved to be identical with the cracking product "$^{208}/_{152}$", which is formed almost exclusively under air-pyrolysis of CBD[3,5]. More examples of condensation reactions of **12** are give in Table II; in some cases the tetrahydropyranyl (THP) ether of olivetol was used instead of the dimethyl ether since this protective group can be removed under very mild conditions, in contrast to the methyl group which can be hydrolysed only under drastic conditions.

2,2-Dimethyl-5-hydroxy-7-pentylchromene (**8**) was prepared according to the pyridine catalysed chromene synthesis described by *Bandaranayake* et al.[10]. Coupling of 3-hydroxy-3-methylbutanal dimethyl acetal with olivetol gave **8** as the

[8] *E.g.: J. F. Normant*, Synthesis 63 (1972).

[9] *H. J. W. Spronck* and *C. A. Salemink*, Recl. Trav. Chim., preceeding paper.

[10] *W. M. Bandaranayake, L. Crombie* and *D. A. Whiting*, J. Chem. Soc. (C), 811 (1971).

main product accompanied by smaller amounts of the isomer **9** and the corresponding disubstituted product. Product **8** was isolated by preparative TLC and proved to be identical with the cracking product "$^{246}/_{231}$" described above.

5-Hydroxy-7-pentylbenzofuran (**6**) was obtained in a way similar to the benzofuran synthesis described by *Tanaka*[11] by condensation of 2-formylolivetol (**5**) with diethyl bromomalonate, followed by decarboxylation of the intermediate coumarilic acid **7**. At first the synthesis of the starting material **5** was tried by a Gattermann-Adams formylation of olivetol as described by *Jen* et al.[12]; this procedure, however, yielded almost exclusively 4-formylolivetol. When 4-ethoxycarbonylolivetol[13] was formylated by the same procedure followed by saponification and decarboxylation, **5** was obtained easily and in good yield[14].

In view of the structural resemblance of the above mentioned cracking products to olivetol – which is a very potent inhibitor of prostaglandin biosynthesis[15] – these products were tested for their inhibitory activity. Especially 2-methyl- and 2-ethylolivetol proved to be very strong inhibitors. The results of these experiments will be the subject of a forthcoming publication[16]. Since these cracking products represent a substantial amount (25–40%) of the total pyrolysate of CBD this finding may be of importance.

Experimental

Instrumentation: Pyrolysis was carried out according to the procedure described in part VIII of this series[1]. GLC and GCMS were carried out on the same instruments and under the same conditions as described in preceeding papers[1,3].

Isolation of several cracking products: 1.75 g Nitrogen pyrolysate of CBD was subjected to preparative GLC. The column effluent with Rx < 1 (Rx CBD ≡ 1) was collected and submitted to repeated preparative TLC on SiO_2 plates (Merck PSC). Elution with hexane-ether 4 : 1 followed by removal of small zones of adsorbent and extraction with ether resulted in the fractions listed in Table 1.

2-Methylolivetol (**3**). *General procedure for condensation reactions with 2,6-dimethoxy-4-pentyl-phenyllithium* (**10**):

To a solution of 4.16 g (0.02 mol) olivetol dimethyl ether in 20 ml dry ether in a nitrogen atmosphere 10.5 ml 2M n-butyllithium was added. After stirring for 4 hours the flask was placed in an ice bath and 3 g (0.021 mol) methyl iodide was added slowly. Diluted hydrochloric acid was added and the mixture was extracted with ether. The combined organic layers were dried over magnesium sulphate and the solvent was evaporated. The residue was dissolved in 30 ml methylene chloride and cooled to −40°C. A solution of 5.2 g boron tribromide in 20 ml methylene chloride was added with stirring and the temperature was allowed to rise to room temperature (2 hrs). The solution was poured into ice. After neutralisation the organic layer was separated and the aqueous layer extracted with methylene chloride. Drying of the organic layers and evaporation of the solvent, followed by recrystallisation of the crude 2-methylolivetol from heptane afforded 2.9 g of **3** (75%), m.p. 72.4°C.

MS (70eV): *m/e* 194 (18%), 152 (7%), 151 (10%), 139 (10%), 138 (100%), 137 (37%), 123 (12%), 91 (8%). PMR (60 MHz, $CDCl_3$): 0.85 (t, J = 6 Hz, 3H), 1.0–1.8 (br, 6H), 2.04 (s, 3H), 2.44 (t, J = 7 Hz, 2H), 4.71 (s, 2H), 6.20 (s, 2H) ppm.
IR (KBr): 3390 (s, br), 2960 (s), 2930 (s), 2860 (s), 1625 (s), 1590 (s), 1425 (s), 1160 (m), 1070 (s), 990 (mw), 930 (m), 830 (ms), 740 (m), 720 (mw) cm^{-1}.

2-(2-{p-Tolyl}propyl)olivetol (**17**). *General procedure for condensation reactions with olivetol dimethyl ether homocuprate* (**11**):

1.98 g of *p*-Isopropenyltoluene and 20 g of *N*-bromosuccinimide were refluxed in CCl_4. On completion of the reaction the succinimide was removed by filtration and the filtrate was distilled. The fraction boiling between 79° and 82°C (1 mm Hg) contained a mixture of the allylic bromide **14** (55%) and the vinylic bromide **13** (45%).

4.5 g of this mixture was condensed with olivetol dimethyl ether homocuprate (**11**) which was prepared by adding 1.28 g (9 mmol) of dry cuprous bromide to a solution of 2,6-dimethoxy-4-pentylphenyllithium (**10**) – which was prepared from 3.7 g (18 mmol) of olivetol dimethyl ether – in 30 ml of dry THF.

After the bromides **13** and **14** had been added, the mixture was allowed to stand overnight, 40 ml of 4*N* hydrochloric acid was added and the organic layer separated. The aqueous layer was extracted and the combined organic layers were dried (Na_2SO_4) and concentrated. This mixture was dissolved in 30 ml of glacial acetic acid and reduced with 0.5 g of 10% Pd/C (H_2, 5 atm, 80°, 60 h). After filtration, 50 ml of water were added and the solution was extracted with ether. After neutralisation with saturated sodium bicarbonate solution, drying (Na_2SO_4), filtration and concentration 3.2 g of crude **16** were obtained.

This product was added to a methylmagnesium iodide solution (prepared from 2 g of magnesium and 16 g of methyl iodide) in ether. The ether was evaporated and the residue was heated in a nitrogen atmosphere at 180–210°C during 6 hours. After cooling, 20 ml ether was added, followed by 50 ml 10% ammonium chloride solution and the mixture was acidified with 20% hydrochloric acid. The organic phase was separated and the water layer extracted with 50 ml ether. The combined ethereal layers were neutralised ($NaHCO_3$), dried (Na_2SO_4) and concentrated. The residue was chromatographed on Florisil (Roth, 200 g), Elution with ether-hexane (1 : 10) gave a yellow oil (350 mg), giving spectroscopical as well as GLC data identical with those of the isolated[9] pyrolysis product "312/193".

2-Acetylolivetol dimethyl ether. General procedure for condensation reactions of 2,6-dimethoxy-4-pentylphenylcopper (**12**):

To a solution of 20.8 g (0.10 mol) of olivetol dimethyl ether in 200 ml of dry THF in a nitrogen atmosphere 60 ml of 2 *M* butyllithium were added. After stirring for 4 hours the reaction flask was placed in an ice bath and 14.4 g of cuprous bromide were added slowly with stirring. The cuprous bromide dissolved readily. To the ice-cooled solution, 7.9 g (0.10 mol) of acetyl chloride dissolved in 200 ml of dry THF was added. The mixture was stirred for 2–4 hours while the temperature was allowed to rise to room temperature. 150 ml of 4*N* HCl were added followed by 100 ml of ether. The organic layer was separated and the aqueous layer was extracted with two 100 ml portions of ether. The combined organic layers were dried over anhydrous sodium sulphate and concentrated. Distillation of the residue afforded 20 g (80%) of 2-acetylolivetol dimethyl ether b.p. 127–130°C (0.005 mm Hg).

2-Ethylolivetol (**4**)

20 g 2-Acetylolivetol dimethyl ether was refluxed for 2 hours with 50 ml of absolute ethanol and 10 g of hydrazine hydrate.

The ethanol was evaporated, 20 g of powdered potassium hydroxide was added and the mixture was heated for 1 hr. at 230°C in a nitrogen atmosphere. After cooling, water was added and the mixture was extracted with two 100 ml portions of ether. The combined ethereal layers were dried over anhydrous magnesium sulphate. Evaporation of the solvent yielded 18 g of 2-ethylolivetol dimethyl ether. Demethylation was carried out as described for 2-methylolivetol. Yield 11 g **4** (70%).

MS (70 eV): *m/e* 208 (16%), 166 (11%), 165 (17%), 153 (8%), 152 (100%), 151 (11%), 123 (18%), 91 (10%).
PMR (60 MHz, $CDCl_3$): 0.88 (t, J = 6 Hz, 3H), 1.17 (t, J = 8 Hz, 3H), 1.1–1.8 (br, 6H), 2.43 (t, J = 8 Hz, 2H), 2.65 (q, J = 8 Hz, 2H), 5.28 (s, br, 2H), 6.30 (s, 2H) ppm.
IR (CCl_4): 3620 (vs), 3480 (w, br), 3030 (vw), 2960 (vs), 2940 (vs), 2880 (s), 2860 (s), 1630 (s), 1590 (s), 1440 (vs), 1380 (w), 1340 (m), 1300 (w), 1285 (w), 1235 (vs), 1160 (s), 1090 (vs), 990 (s), 965 (m) cm^{-1}.

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[11] *S. Tanake*, J. Amer. Chem. Soc. **73**, 872 (1951).
[12] *T. Y. Jen, G. A. Hughes* and *H. Smith*, US patent 3,462,459 (1969).
[13] *T. Kato* and *T. Hozumi*, Chem. Pharm. Bull. **20**, 1574 (1972).
[14] *W. B. Whalley*, J. Chem. Soc. 3278 (1949).
[15] *S. Burstein, E. Levin* and *C. Varanelli*, Biochem. Pharmacol. **22**, 2905 (1973).
[16] *H. J. W. Spronck, J. M. Luteijn, C. A. Salemink* and *D. Nugteren*, Biochem. Pharmacol. **27**, 607 (1978).

2,2-Dimethyl-5-hydroxy-7-pentylchromene (**8**)

A mixture of 1.8 g of olivetol and 1.34 g of 1,1-dimethoxy-3-hydroxy-3-methylbutane in 790 mg of pyridine was refluxed in a nitrogen atmosphere for 4 hours. Next a second 1.34 g portion of 1,1-dimethoxy-3-hydroxy-3-methylbutane was added and the mixture was heated until the reaction had come to an end (60 hours). The pyridine and the excess reagent were distilled off and the dark brown residue was chromatographed on silica gel using benzene-chloroform (4 : 1) as eluent. Yield 350 mg of **8** and 150 mg of 2,2-dimethyl-7-hydroxy-5-pentylchromene (**9**).

8: MS (70 eV): *m/e* 246 (11%), 232 (14%), 231 (100%), 189 (5%), 187 (9%), 175 (8%), 174 (30%), 173 (5%). PMR (60 MHz, $CDCl_3$), 0.84 (t, J = 6 Hz, 3H), 1.39 (s, 6H), 1.0–1.7 (br, 6H), 2.41 (t, J = 9 Hz, 2H), 5.48 (d, J = 10 Hz, 1H), 5.45 (s, br, 1H), 6.15 (d, J = 2 Hz, 1H), 6.26 (d, J = 2 Hz, 1H), 6.61 (d, J = 10 Hz, 1H) ppm. IR (CCl_4): 3610 (s), 3460 (m, br), 3050 (w), 2960 (vs), 2930 (vs), 2860 (s), 1625 (vs), 1570 (s), 1430 (s), 1380 (m), 1360 (m), 1250 (ms), 1115 (ms), 1050 (s) cm^{-1}.

9: MS identical with MS of **8**. PMR (60 MHz, $CDCl_3$): 0.86 (t, J = 6 Hz, 3H), 1.36 (s, 6H), 1.0–1.7 (br, 6H), 2.48 (t, J = 9 Hz, 2H), 5.45 (d, J = 10 Hz, 1H), 6.23 (s, 2H), 6.45 (d, J = 10 Hz, 1H), 7.10 (s, br, 1H) ppm. IR (CCl_4): 3605 (s), 3470 (m, br), 3040 (w), 2960 (vs), 2870 (s), 2860 (s), 1610 (vs), 1580 (m), 1465 (m), 1445 (m), 1375 (m), 1360 (m), 1145 (s), 1130 (s), 1120 (s) cm^{-1}.

2-Formylolivetol (**5**)

40 g of Aluminium chloride, dissolved in 250 ml of ether were added slowly with stirring to a solution of 26.5 g of 4-ethoxycarbonyl-olivetol and 35 g of zinc cyanide in 250 ml of ether at 0°C. Hydrogen chloride was then bubbled through the cooled mixture for 5 hours. After standing for 24 hours at room temperature the mixture was concentrated and the residue heated with 500 ml of water on a steam bath during 20 minutes. After cooling, the solution was extracted with chloroform, dried and concentrated. Recrystallisation from methanol afforded slightly yellow crystals, 22 g (74%), m.p. 35°C. This product was boiled under reflux in 300 ml of 4*N* potassium hydroxide solution during 3 hours. After cooling, the solution was acidified and extracted with ether. The ethereal layers were dried and concentrated. Recrystallisation from benzene/hexane afforded 10 g (66%) of 2-formylolivetol, m.p. 56°–57°C.

4-Hydroxy-6-pentylbenzofuran (**6**)

A mixture of 2.08 g of 2-formylolivetol, 4 g of ethyl bromomalonate, 2 g of anhydrous potassium carbonate and 10 ml of methyl ethyl ketone was refluxed for 5 hours on a steam bath. The solvent was evaporated and the residue mixed with water, acidified and extracted with ether. The ether was evaporated and the residue dissolved in alcoholic potash (10%) and refluxed on a steam bath for 1 hour. The ethanol was evaporated and the residue was dissolved in water and acidified. The crystals thus formed were collected by filtration, yielding 0.50 g crude 4-hydroxy-6-pentylcoumarilic acid (**7**).

The acid **7** and copper powder (0.1 g) were refluxed in 5 ml of quinoline during 30 min. After cooling, ether was added and the copper was removed by filtration. The ethereal solution was washed 3 times with dilute hydrochloric acid in order to remove quinoline. After shaking with sodium bicarbonate solution the ether extract was concentrated and the oily residue was chromatographed on Florisil (Roth, 50 g). Elution with hexane – ether (4 : 1) yielded 0.34 g of 5-hydroxy-7-pentylbenzofuran as a slightly yellow oil.

MS (70 eV): *m/e* 204 (35%), 162 (5%), 161 (15%), 149 (14%), 148 (80%), 147 (100%), 91 (35%). PMR (90 MHz, CCl_4): 0.86 (t, J = 7 Hz, 3H), 1.0–1.7 (br, 6H), 2.52 (t, J = 7 Hz, 2H), 5.86 (br, 1H), 6.34 (s, 1H), 6.71 (d, J = 2.5 Hz, 1H), 6.86 (s, 1H), 7.36 (d, J = 2.5 Hz, 1H) ppm. IR (CCl_4): 3610 (s), 3440 (br), 3040 (w), 2960 (s), 2930 (vs), 2860 (s), 1600 (vs), 1495 (s), 1468 (m), 1427 (s), 1370 (m), 1250 (m), 1051 (vs) cm^{-1}.

Acknowledgement

We thank the Dutch Department of Public Health and Environmental Hygienics for supporting one of us *(H. S.)*.