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Synthesis of new aliphatic and aromatic phytotoxic derivatives of 2α,4α-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one

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Abstract: Several new compounds with potential herbicidal activity were synthesized from 2α,4α-dimethyl-6,7-*exo*-isopropylidenedioxy-8-oxabicyclo[3.2.1]octan-3-one (4). Seven aromatic alcohols were prepared by reaction of (4) with aryllithium reagents, where the aryl groups were 4-ethoxyphenyl (5, 70% yield), 4-ethylphenyl (6, 82% yield), 4-butylphenyl (7, 78% yield), 4-*tert*-butylphenyl (8, 81% yield), 2,4-dimethoxyphenyl (9, 75% yield), 2-ethylphenyl (10, 12% yield) and *para*-(4-bromophenoxy)phenyl (11, 24% yield). Reaction of the acetonide (4) with Grignard reagents formed also four aliphatic alcohols where the alkyl groups are ethyl (13, 78%), butyl (14, 85%), hexyl (15, 81%) and octyl (25, 92%). The alcohols (5), (6), (7), (8), (13), (14), (15) and (25) were reacted with thionyl chloride in pyridine, forming their respective alkenes (17, 76%), (18, 74%), (19, 83%), (20, 73%), (22, 78%), (26, 62%), (23, 77%) and (24, 66%). The effect of these compounds, at the concentration of 5.5 μg g^{-1}, on the development of radicle and aerial parts of *Sorghum bicolor* (L) Moench, *Euphorbia heterophylla* L, *Brachiaria decumbens* and *Desmodium tortuosum* DC was evaluated.

Keywords: [3 + 4] cycloaddition; herbicides; weeds; oxabicyclo

1 INTRODUCTION

The chemical control of weed plants began in the 19th century with the use of large quantities of simple inorganic compounds with no selectivity. The industry of organic herbicides began in 1934, when indol-3-ylacetic acid (IAA), a plant growth hormone, was discovered. The discovery of IAA led to the development of synthetic growth regulators such as 2,4-dichlorophenoxyacetic acid (2,4-D) and 4-chloro-2-methylphenoxyacetic acid (MCPA), the first two effectively selective herbicides.[1]

Since the discovery of these herbicides, new classes have been synthesized, for example substituted ureas, triazines, uracils, pyridazinones, amides, triazinones, anilides and diphenyl ethers.[2] The agrochemical industry now invests great sums of money in research and development of new compounds with herbicidal activity.

The area of weed control requires constant research to cope with evolution of weed resistance to herbicides, and to develop compounds possessing broader weed-control spectra and better environmental behaviour. One approach to find potential herbicides is to use compounds with known phytotoxic activity as a model for the synthesis of new compounds.[2–4] Therefore 3-aryl-6,7-*exo*-isopropylidenedioxy-8-oxabicyclo[3.2.1]oct-2-ene was used as a model, because it had shown strong herbicidal activity against several crops and weeds.[5] In this work, we describe the synthesis and biological activity of various new aromatic and aliphatic derivatives of oxabicycloctenone (Fig 1).

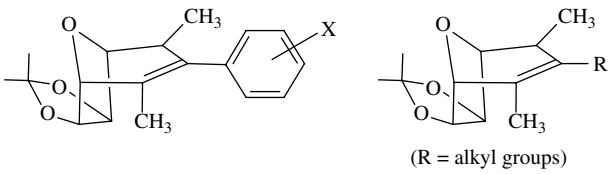

Figure 1. Generic structures for the herbicides prepared.

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2 MATERIALS AND METHODS

2.1 General procedures

Solvents were dried according to the usual procedures described in the literature.[6] Flash column chromatography was performed using silica gel 60 (63–230 μm). Melting points were determined on a electrothermal digital apparatus. Infrared spectra were recorded on a Perkin-Elmer Spectrum 1000 grating spectrometer, using a potassium bromide disc or sodium chloride liquid film, scanning from 625 to 4000 cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded in a Bruker DPX 200 (200 MHz) spectrometer. Tetramethylsilane was used as internal standard ($\delta = 0$) and deuterated chloroform as solvent. Mass spectra were recorded in a QP 5000 Shimadzu GC/MS instrument.

2.2 Synthetic procedures

*2.2.1 Synthesis of acetonide (**4**)*

The acetonide 2α,4α-dimethyl-6,7-*exo*-isopropylidenedioxy-8-oxabicyclo[3.2.1]octan-3-one (**4**) was prepared from pentan-3-one using the method described previously[7] and outlined in Fig 2.

*2.2.2 General procedure for the preparation of alcohols **5–11***

Aryl bromide (3.0 mmol) in dry THF (10 ml) was placed in a two-necked round-bottomed flask, and the system was kept under nitrogen atmosphere at −78 °C. To this solution was added butyllithium (1.6 M in hexane, 1.9 ml, 3 mmol) and the reaction mixture was stirred for 1 h before the addition of the acetonide **4** (600 mg, 2.65 mmol) in dry THF (5 ml). The resultant reaction mixture was stirred at room temperature for 3 h and then quenched by addition of water (20 ml). The organic solvents were removed in a rotary evaporator and the water layer was extracted with dichloromethane (5 × 20 ml). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give a yellow solid. This solid was purified by column chromatography using hexane + diethyl ether (2 + 1 by volume) and recrystallised from a mixture of hexane and dichloromethane. The yields for each reaction and some analytical data for the products are shown in Appendix Table A1.

*2.2.3 General procedure for the preparation of alcohols **13–15** and **25***

A mixture of magnesium (354 mg, 14.58 mmol), iodine crystals and dry THF (6 ml) was stirred under a nitrogen atmosphere in a three-necked round-bottomed flask. The alkyl bromide (13.25 mmol) in dry THF (12 ml) was added dropwise from a dropping funnel. When half of this solution had been added it was diluted with a further 12 ml of THF and the addition to the reaction mixture was completed over 90 min. The solution was stirred for a further 30 min and the acetonide **4** (600 mg, 2.65 mmol) dissolved in dry THF (12 ml) was added dropwise. The solution was stirred for 2 h and then quenched with saturated aqueous ammonium chloride (20 ml). The solid residue was removed by filtration and the filtrate was extracted with dichloromethane (5 × 20 ml). The combined organic extracts was washed with brine (20 ml), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The solid residue was purified by flash column chromatography and recrystallised from a mixture of hexane and dichloromethane. The yields for each reaction and some analytical data for the products are shown in Appendix Table A2.

*2.2.4 General procedure for the preparation of alkenes **17–20, 22–24** and **26***

To a solution of the alcohol (1.21 mmol) in pyridine (8.0 ml, 100 mmol) in a round-bottomed flask kept at 0 °C was added thionyl chloride (2.5 ml, 40 mmol). The solution was stirred for 2 h before the reaction was quenched with 10 drops of hydrochloric acid (2 M) and extracted with dichloromethane (5 × 20 ml). The combined organic layers was washed with brine (20 ml), dried over anhydrous magnesium sulfate and concentrated in a rotary evaporator to give a brown oil which was purified by flash column

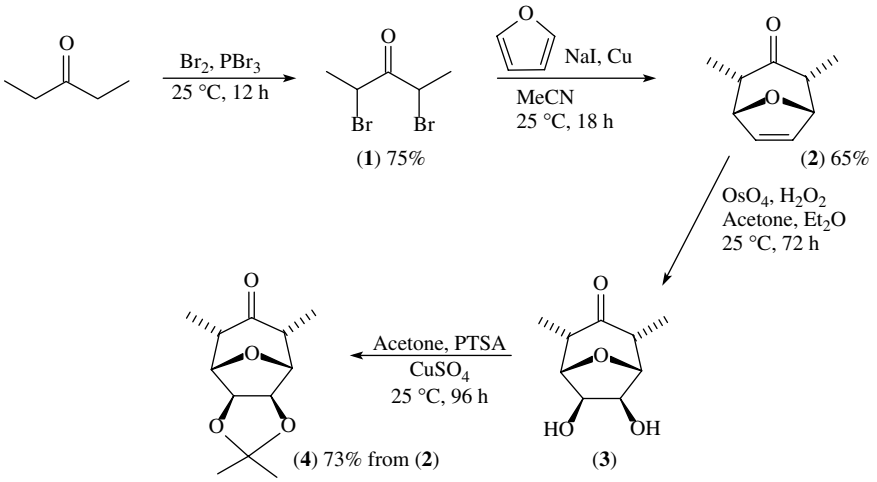

Figure 2. Synthetic scheme for the preparation of the acetonide **4**.

chromatography using hexane + diethyl ether (2 + 1 to 1 + 2 by volume). The yields for each reaction are shown in Appendix Table A3.

*2.2.5 General procedure for the preparation of alkene **21***
To a solution of the alcohol **9** (100 mg, 0.27 mmol) in dichloromethane (5 ml) was added $BF_3{\cdot}OEt_2$ (39 mg, 0.034 ml, 0.27 mmol). The reaction mixture was stirred for 16 h, quenched with distilled water (15 ml) and extracted with dichloromethane (5 × 20 ml). The combined organic layers were washed with brine (20 ml), dried over anhydrous magnesium sulfate and concentrated in a rotary evaporator to give a brown oil (70 mg). This residue was purified by flash column chromatography using hexane + diethyl ether (2 + 1 by volume) affording alkene **21** as an oil (9 mg, 10% yield).

2.3 Bioassays

The experiments were carried out in a greenhouse with *Sorghum bicolor* (L) Moench, *Euphorbia heterophylla* L, *Brachiaria decumbens* and *Desmodium tortuosum* DC.

The bioassays for herbicide activity were carried out for compounds **5**–**9**, **17**–**20**, **13**–**15** and **22**–**26** using plastic pots and the total growth of the test plants evaluated.

Test solutions were prepared by dissolving 5.0 mg of each compound in a mixture of xylene (60 µl), pentan-3-one (20 µl) and Tween 40 (polyoxyethylene-sorbitan monopalmitate, two drops). The volume of the resulting mixture was completed to 100 ml with distilled water to afford a solution of 5.5 µg g^{-1}. A solution with the same composition described above, but without the test compound, was used as a control.[8]

Ten seeds of each test plant were placed at 0.5 to 1.0 cm depth in 0.10 dm^3 plastic pots containing 164 g of washed sand soaked in 18 ml of the test solution. The pots were kept in a greenhouse at 25 °C, watered regularly to maintain the humidity at 12% w/w, and a solution containing the required nutrients was applied three times a week.

The test plants were harvested 20 days after sowing, and the radicle separated from the aerial parts. These parts were kept separately in paper bags and dried at 75 °C to constant weight and the mass of the dried matter determined. The data were analysed using Tukey's test at $P = 0.05$. All treatments were replicated four times in a completely randomized design. The percentage growth inhibition of roots and aerial parts were calculated in relation to the mass of the roots and aerial parts of the control, respectively.

3 RESULTS AND DISCUSSION

3.1 Synthesis

The present work involved the synthesis of new alcohols and alkenes derived from 2α,4α-dimethyl-6,7-*exo*-isopropylidenedioxy-8-oxabicyclo[3.2.1]octan-3-one (**4**; Fig 2). This was prepared in four steps from pentan-3-one in 36% overall yield following the methodology previously described.[7] The synthesis of the aromatic alcohols from the acetonide **4** can be done either by Grignard's reaction or addition of aryllithium compounds. We opted for the second reagent, as the aryllithium reaction was usually cleaner and gives better yields than Grignard's.[5] Reaction of the aryl bromide with butyllithium formed the aryllithium, which was reacted with the acetonide **4**. Five different substituted aryl bromides were used for the synthesis of the alcohols **5**–**9**.

The synthesis of the aliphatic alcohols was carried out by Grignard's reaction, as the synthesis of aliphatic organolithium from butyllithium is not viable. This methodology was employed to prepare three new aliphatic alcohols, **13**, **14** and **15**. Alcohol **25** had previously been prepared by reaction of the acetonide **4** with butyllithium in 43% yield,[8] but we managed to prepare this compound by Grignard's reaction in a much higher yield (92%).

The addition of aryl and alkyl on the carbonyl of the bicyclic system is exo selective, as this is the less crowded side of the molecule. The favoured exo addition led to the equatorial aryl and alkyl system. A NOE difference experiment with irradiation at $\delta \cong 5.0$ (H6, H7) resulted in an enhancement of the OH signal, and no effect was observed for the resonance of the alkyl and aryl groups on carbon 3.

Compounds **9** and **10** differ from the other alcohols in that they have a substituting group at the *ortho* position on the aromatic ring. The steric hindrance of this group could make the attack of the aryllithium on the carbonyl of the acetonide **4** difficult. This could explain the low yield for the synthesis of **10**. However, alcohol **9** was prepared in good yield (75%), which is similar to the yields for the syntheses of the alcohols with no group in the *ortho* position.

Alcohol **11** was prepared in low yield (24%) and was difficult to purify. Even after flash column chromatography and recrystallisation the melting point range was 125–155 °C, indicating that it was impure. The difficulty in this synthesis could be due to the bromine in the second aromatic ring favouring polymerisation during the aryllithium formation. The alcohol **11** showed the same R_f value as the starting material.

Alcohol **16** was isolated in 3% yield during the synthesis of alcohol **14**. In crowded ketones the addition of hydride to the carbonyl and the yield for the reduction is improved when the Grignard's reagent is also hindered.

Although alcohol **16** was not isolated during the synthesis of **13** and **15**, it could have been formed in small quantities.

All the alcohols previously prepared in adequate quantity were dehydrated with thionyl chloride in pyridine. This reaction was attempted for alcohols **5**–**8**, **13**–**15** and **25** to give their respective alkenes. The aliphatic and aromatic alcohols were dehydrated in good yield by reaction with thionyl chloride in pyridine. The thionyl chloride methodology was employed also for alcohol **9**, but it was not successful.

Therefore we decided to use $BF_3{\cdot}OEt_2$ as dehydrating agent[9] for this alcohol. However the yield was low (10%) even with $BF_3{\cdot}OEt_2$, which could be due to the methoxy group in the *ortho* position on the aromatic ring.

The absence of the hydroxyl band around 3500 cm^{-1} in the infrared spectra was very strong evidence for the formation of the alkenes. The formation of the alkenes is confirmed by the doublets in $\delta = 4.49–4.67$ and $\delta = 4.71–4.83$, assigned to H6 and H7 respectively. The alcohols presented only one singlet in $\delta = 4.95–5.07$ (H6 and H7) because of the symmetry of the molecule.

All compounds prepared were characterised by their spectroscopic and physical data (IR; ^{1}H NMR, ^{13}C NMR, MS). For **13**, **15** and **17** C, H, N analysis was also obtained. (Appendix Tables A4–A8).

3.2 Biological activity

The effect of the aromatic and aliphatic compounds at 5.5 μg g^{-1} on the development of the aerial parts and roots of *S*, *E heterophylla*, *B decumbens* and *D tortuosum* were evaluated and the results are shown in Tables 1 and 2. Compounds **10**, **11**, **16** and **21** were not prepared in sufficient quantity to be tested. The effect of compounds **25** and **26** on *S bicolor* and *E heterophylla* had been evaluated previously.[8]

For *S bicolor*, the aromatic alcohol **5** caused the best inhibition of the development of the aerial parts (70.11%) and roots (57.72%). Alcohols **6** and **8** and alkene **17** presented stimulatory effects on the roots of (−77.04%), (−78.68%) and (−80.33%), respectively. Nevertheless these results were not significantly different from the control. For the aliphatic compounds the aerial parts were inhibited by 65.21% and 61.24% by alkenes **23** and **24**, respectively.

For *E heterophylla*, the aromatic alkene **19** presented a good stimulation of the aerial parts (−77.78%), and it was significantly different from all the other compounds. The aliphatic compounds did not show any great activity, the means not being statistically different from one another.

For *B decumbens*, the aromatic alcohol **5** was the most active for both, inhibiting the aerial parts (44.12%) and roots (61.53%). The alcohol **6** and alkene **19** also showed significant root inhibition of 53.84% and 46.15%, respectively. The aliphatic alcohol **14** presented significant root inhibition (46.15%), and all the other aliphatic compounds also showed root inhibition.

For *D tortuosum*, the aromatic alcohol **5** showed significant inhibition of the development of the aerial parts (48.68%) and roots (68.00%). The aromatic compounds **7**, **9** and **18** also showed significant inhibition of aerial parts and roots. The aliphatic alcohols **13** and **14** presented significant root inhibition, 44.00% and 36.00%, respectively.

Table 1. Effect of aromatic compounds at 5.5 μg g^{-1} on the development of roots and aerial parts of four plant species using sand as substrate[a]

Treatment (products)	Aerial parts (mg)	Aerial parts (% inhibition)	Roots (mg)	Roots (% inhibition)
		Sorghum bicolor		
Control	18.9 ab	0.00	6.1 ab	0.00
5	5.6 b	70.11	2.6 b	57.72
6	20.8 a	−10.58	10.8 a	−77.04
7	19.3 a	−2.25	3.5 b	43.49
8	19.6 a	−3.48	10.9 a	−78.68
9	9.6 ab	49.47	6.1 ab	0.00
17	17.9 ab	5.03	11.0 a	−80.33
18	13.8 ab	26.98	5.2 ab	14.75
19	8.7 ab	54.10	3.5 b	42.28
20	11.5 ab	39.15	6.1 ab	0.00
CV (%)	36.4		36.9	
		Euphorbia heterophylla		
Control	9.9 b	0.00	2.5 bcde	0.00
5	8.7 b	12.12	1.9 de	25.20
6	8.8 b	11.11	2.6 bcde	−2.36
7	11.0 b	−11.11	2.7 bcd	−6.30
8	9.7 b	2.02	4.0 a	−57.48
9	5.4 b	45.45	1.4 e	44.88
17	10.6 b	−7.07	1.9 cde	25.20
18	10.3 b	−4.04	2.5 bcde	0.00
19	17.6 a	−77.78	2.0 cde	21.26
20	9.6 b	3.03	3.1 abc	−39.00
CV (%)	74.1		18.1	
		Brachiaria decumbens		
Control	3.4 ab	0.00	1.3 a	0.00
5	1.9 e	44.12	0.5 d	61.53
6	3.3 abc	2.94	0.6 cd	53.84
7	3.5 a	−2.94	1.0 abc	23.84
8	3.3 ab	2.94	0.9 abcd	30.77
9	2.7 cd	20.58	0.8 bcd	38.46
17	3.3 abc	2.94	1.2 ab	7.69
18	2.9 bcd	14.71	1.0 abc	23.84
19	2.6 d	23.53	0.7 cd	46.15
20	3.3 ab	2.94	1.0 abc	23.84
CV (%)	8.1		21.3	
		Desmodium tortuosum		
Control	7.6 a	0.00	2.5 ab	0.00
5	3.9 c	48.68	0.8 d	68.00
6	5.9 ab	22.37	1.7 c	32.00
7	5.3 bc	30.26	1.8 c	28.00
8	7.5 a	1.31	1.8 bc	28.00
9	4.9 bc	35.52	1.5 c	40.00
17	7.5 a	1.31	2.1 bc	16.00
18	5.4 bc	28.95	1.7 c	32.00
19	6.1 ab	19.73	1.8 bc	28.00
20	7.4 a	2.63	1.7 c	32.00
CV (%)	12.51		15.32	

[a] Means, in the same column, with the same letter are not significantly different at $P = 0.05$% by Tukey's test.

The compounds showed different inhibition for each plant, and the same product had different behaviour over the radicle and aerial parts, even on plants of the same species.

For the aliphatic compounds, it was not possible to establish the influence of the size of the aliphatic

Table 2. Effect of aliphatic compounds at 5.5 μg g^{-1} on the development of roots and aerial parts of four plant species using sand as substrate[a]

Treatment (products)	Aerial parts (mg)	Aerial parts (% inhibition)	Roots (mg)	Roots (% inhibition)
		Sorghum bicolor		
Control	18.9 ab	0.00	6.1 abc	0.00
13	15.6 abc	17.26	7.6 abc	−23.17
14	10.7 bc	43.38	4.6 abc	24.59
15	22.3 a	−17.86	7.8 abc	−27.24
22	16.8 abc	11.11	8.9 a	−42.68
23	6.7 c	65.21	2.9 c	53.85
24	7.3 c	61.24	3.4 bc	44.72
25	16.0 abc	15.08	4.0 bc	34.68
26	14.8 abc	21.43	3.7 bc	38.71
CV (%)	31.4		35.0	
		Euphorbia heterophylla		
Control	9.9 ab	0.00	2.5 a	0.00
13	6.4 b	35.35	2.4 a	5.51
14	10.2 ab	−3.03	2.3 a	9.45
15	8.2 ab	17.17	2.3 a	9.45
22	9.0 ab	9.09	2.4 a	5.51
23	10.4 ab	−5.05	3.6 a	−41.73
24	12.0 a	−21.21	3.7 a	−45.66
25	7.2 b	26.82	2.0 a	21.50
26	7.8 ab	21.24	2.8 a	−10.24
CV (%)	19.2		29.6	
		Brachiaria decumbens		
Control	3.4 ab	0.00	1.3 a	0.00
13	3.2 b	5.88	1.0 ab	23.08
14	3.1 b	8.82	0.7 b	46.15
15	4.7 a	−38.23	1.0 ab	23.08
22	2.8 b	17.65	0.9 ab	30.76
23	3.1 b	8.53	0.9 ab	30.76
24	3.0 b	11.76	0.8 ab	38.46
CV (%)	17.3		23.5	
		Desmodium tortuosum		
Control	7.6 ab	0.00	2.5 ab	0.00
13	5.6 b	26.31	1.4 d	44.00
14	5.5 b	27.63	1.6 cd	36.00
15	8.3 a	−9.21	1.8 bcd	28.00
22	7.5 ab	1.32	2.3 abc	8.00
23	6.3 ab	17.10	1.8 bcd	28.00
24	8.3 a	−9.21	2.0 bcd	20.00
CV (%)	13.61		16.18	

[a] Means, in the same column, with the same letter are not significantly different at $P = 0.05\%$ by Tukey's test.

chain on the herbicide activity. However, in general the aliphatic compounds were less active than the aromatics.

For the alkenes, compounds **23** and **24** were the most active, reducing the growth of the aerial parts of *S bicolor* by 65.21% and 61.24% respectively. Nevertheless, these compounds showed low phytotoxicity for the other plant species.

The aromatic alcohol **5** was the most active compound, inhibiting the development of the radicle and aerial parts of *S bicolor* (57.72% and 70.11%), *B decumbens* (61.53% and 44.12%), and *D tortuosum* (68.00% and 48.68%), showing a very potent herbicide activity.

Though it was not possible to establish a structure–activity relationship, it seems that the aromatic ether showed some activity. However the alcohols **5** and **9** were the most active compounds.

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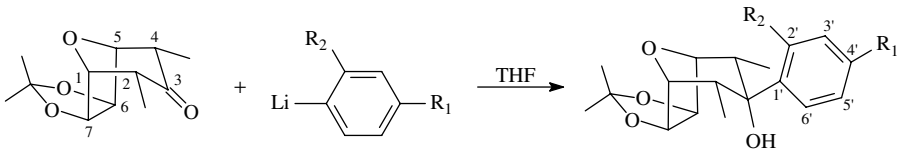
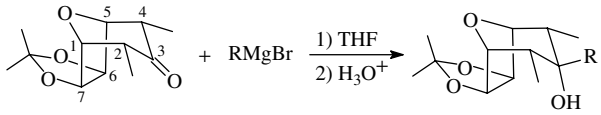
APPENDIX: PHYSICAL, ANALYTICAL AND SPECTROSCOPIC DATA

Table A1. Physical and analytical data for the synthetic aromatic alcohols **5–11**



Compound	R_1	R_2	Molecular formula	Yield (%)	Mp (°C)	MS, *m/z* (%)
5	$-OCH_2CH_3$	H	$C_{20}H_{28}O_5$	70	148–150	348 ($M^{+\bullet}$, 3), 330 (23), 207 (30), 178 (25), 150 (23), 149 (100), 121 (61), 113 (39), 97 (28), 83 (42), 77 (24), 55 (50), 43 (100)
6	$-CH_2CH_3$	H	$C_{20}H_{28}O_4$	82	193–195	317 ($[M-15]^+$, 17), 133 (91), 83 (24), 77 (24), 55 (27), 43 (100)
7	$-CH_2(CH_2)_2CH_3$	H	$C_{22}H_{32}O_4$	78	152–153	345 ($[M-15]^+$, 33), 219 (24), 161 (100), 112 (57), 83 (53), 43 (100)
8	$-C(CH_3)_3$	H	$C_{22}H_{32}O_4$	81	209–211	345 ($[M-15]^+$, 22), 175 (16), 161 (80), 91 (46), 57 (80), 43 (100)
9	$-OCH_3$	$-OCH_3$	$C_{20}H_{28}O_6$	75	163–164	364 ($M^{+\bullet}$, 1), 346 ($[M-18]^+$, 6), 223 (10), 165 (100), 55 (13), 43 (67)
10	H	$-CH_2CH_3$	$C_{20}H_{28}O_4$	12	130–150	317 ($[M-15]^+$, 22), 145 (13), 133 (68), 112 (20), 55 (22), 43 (100)
11	4-Bromphenoxy	H	$C_{27}H_{36}BrO_5$	24	125–155	459 ($[M-15]^+$, 2), 211 (25), 95 (7), 55 (14), 43 (100)

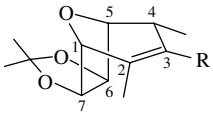
Table A2. Physical and analytical data for the synthetic aliphatic alcohols **13–16** and **25**



Compound	R	Molecular formula	Yield (%)	Mp (°C)	MS, *m/z* (%)
13	Ethyl	$C_{14}H_{24}O_4$	78	133–134	241 ($[M-15]^+$, 24), 123 (7), 97 (10), 83 (9), 69 (9), 57 (65), 55 (23), 43 (100)
14	Hexyl	$C_{18}H_{32}O_4$	85	124–126	297 ($[M-15]^+$, 14), 279 (5), 109 (6), 95 (9), 85 (7), 69 (6), 57 (16), 55 (23), 43 (100)
15	Octyl	$C_{20}H_{36}O_4$	81	94–96	325 ($[M-15]^+$, 14), 109 (7), 95 (12), 83 (7), 71 (11), 57 (29), 55 (32), 43 (100)
16[a]	H	$C_{12}H_{20}O_4$	3	151–152	213 ($[M-15]^+$, 23), 153 (12), 111 (6), 84 (8), 69 (17), 59 (19), 55 (22), 43 (100)
25	Butyl	$C_{16}H_{28}O_4$	92	131–132	269 ($[M-15]^+$, 100), 207 (33), 167 (15), 151 (11), 107 (15), 85 (36), 43 (71)

[a] Compound (**16**) was isolated during the synthesis of (**14**).

Table A3. Physical and analytical data for the synthetic alkenes **17–24** and **26**



Compound	R	Molecular Formula	Yield (%)	Mp (°C)	MS, *m/z* (%)
17	4-Ethoxyphenyl	$C_{21}H_{29}O_4$	76	145–146	330 ($M^{+\bullet}$, 33), 257 (14), 243 (30), 215 (25), 199 (15), 187 (14), 129 (18), 77 (14), 55 (19), 43 (100)

Table A3. Continued

Compound	R	Molecular Formula	Yield (%)	Mp (°C)	MS, *m/z* (%)
18	4-Ethylphenyl	$C_{21}H_{29}O_3$	74	Oil	314 ($M^{+\bullet}$, 32), 299 (16), 227 (44), 199 (36), 128 (19), 115 (17), 43 (100)
19	4-Butylphenyl	$C_{23}H_{33}O_3$	83	Oil	342 ($M^{+\bullet}$, 22), 327 (13), 255 (31), 227 (22), 199 (16), 181 (13), 57 (31), 43 (100)
20	4-*tert*-Butylphenyl	$C_{23}H_{33}O_3$	73	121–122	342 ($M^{+\bullet}$, 11), 327 (6), 255 (11), 227 (11), 57 (100), 43 (58)
21	2,4-Dimethoxyphenyl	$C_{21}H_{29}O_5$	10	Oil	346 ($M^{+\bullet}$, 28), 331 (8), 259 (31), 231 (30), 138 (31), 121 (18), 43 (100)
22	Ethyl	$C_{14}H_{22}O_3$	78	Oil	238 ($M^{+\bullet}$, 17), 223 (19), 165 (12), 151 (37), 123 (44), 95 (14), 81 (13), 43 (100)
23	Hexyl	$C_{18}H_{30}O_3$	77	Oil	294 ($M^{+\bullet}$, 7), 279 (8), 151 (12), 123 (13), 55 (19), 43 (100)
24	Octyl	$C_{20}H_{34}O_3$	66	Oil	322 ($M^{+\bullet}$, 9), 307 (6), 235 (8), 151 (17), 123 (16), 57 (28), 55 (22), 43 (100)
26	Butyl	$C_{16}H_{26}O_3$	62	Oil	294 ($M^{+\bullet}$, 7), 279 (8), 219 (4), 180 (7), 169 (8), 151 (12), 123 (13), 43 (100)

Table A4. Elemental analysis of **13**, **15** and **17**

	Calculated (%)			Found (%)		
Compound	C	H	O	C	H	O
13	65.60	9.44	24.97	65.53	9.50	25.17
15	70.55	10.66	18.79	70.11	10.73	19.16
17	72.70	7.93	19.37	72.70	8.08	19.22

Table A5. Spectroscopic data for the synthetic alcohols **5–11**

Compound	IR ν_{max} (cm^{-1})	^{1}H NMR ($CDCl_3$) δ	^{13}C NMR ($CDCl_3$) δ
5	3442, 3050, 1608, 1510 and 1458	0.72 (d, 6H, $J = 7.2$, 2 × Me), 1.37 (s, 3H, Me), 1.41 (t, 3H, $J = 7.0$, Me), 1.51 (s, 3H, Me), 1.59 (s, 1H, OH), 2.32 (dq, 2H, $J_{2,Me} = J_{4,Me} = 7.2$ and $J_{2,1} = J_{4,5} = 4.0$, H2 and H4), 4.02 (q, 2H, $J = 7.0$, CH_2), 4.09 (d, 2H, $J_{1,2} = J_{5,4} = 4.0$, H1 and H5), 5.05 (s, 2H, H6 and H7), 6.85 (d, 2H, $J = 8.9$, H3′ and H5′), 7.23 (d, 2H, $J = 8.9$, H2′ and H6′)	157.8 (C4′), 136.8 (C1′), 126.0 (C2′ and C6′), 114.0 (C3′ and C5′), 111.0 (CMe_2), 84.3 (C6 and C7), 80.7 (C1 and C5), 76.8 (C3), 63.4 (CH_2), 42.8 (C2 and C4), 26.2 (Me), 24.7 (Me), 14.9 (Me), 9.6 (2 × Me)
6	3454, 3050, 1508 and 1458	1.23 (t, 3H, $J = 7.6$, Me), 1.63 (s, 1H, OH), 2.64 (q, 2H, $J = 7.6$, CH_2), 7.16 (d, 2H, $J = 8.6$, H3′ and H5′), 7.24 (d, 2H, $J = 8.6$, H2′ and H6′)	142.8 (C4′), 142.0 (C1′), 127.6 (C2′ and C6′), 124.8 (C3′ and C5′), 28.2 (CH_2), 15.3 (Me)
7	3480, 3050, 1560 and 1508	0.92 (t, 3H, $J = 7.3$, Me), 1.25–1.43 (m, 2H, CH_2), 1.55–1.67 (m, 2H, CH_2), 1.63 (s, 1H, OH), 2.63 (dd, 2H, $J_a \cong J_b \cong 7.3$, CH_2), 7.14 (d, 2H, $J = 8.5$, H3′ and H5′), 7.23 (d, 2H, $J = 8.5$, H2′ and H6′)	142.0 (C4′), 141.5 (C1′), 128.2 (C2′ and C6′), 124.7 (C3′ and C5′), 35.0 (CH_2), 33.5 (CH_2), 22.4 (CH_2), 13.9 (Me)
8	3463, 3090, 1560 and 1508	1.31 (s, 9H, 3 × CH_3), 1.61 (s, 1H, OH), 7.23 (d, 2H, $J = 8.7$, H2′ and H6′), 7.34 (d, 2H, $J = 8.7$, H3′ and H5′)	149.7 (C4′), 141.7 (C1′), 125.0 (C2′ and C6′), 124.5 (C3′ and C5′), 34.4 (C), 31.3 (3 × Me)
9	3476, 3092, 1613, 1583 and 1502	1.61 (s, 1H, OH), 3.05–3.18 (m, 2H, H2 and H4), 3.83 (s, 6H, 2 × OMe), 6.48–6.58 (m, 2H, H3′ and H5′), 7.28 (d, 1H, $J = 7.2$, H6′)	160.1 (C4′), 156.6 (C2′), 128.2 (C6′), 124.3 (C1′), 103.3 (C5′), 99.5 (C3′), 55.3 (OMe), 55.1 (OMe), 37.9 (C2 and C4)

(*continued overleaf*)

Table A5. Continued

Compound	IR ν_{max} (cm^{-1})	^1H NMR ($CDCl_3$) δ	^{13}C NMR ($CDCl_3$) δ
10	3490, 3066 and 1458	0.71 (d, 2H, $J = 7.2$, 6H, 2 × Me), 1.21 (t, 3H, $J = 7.5$, Me), 1.64 (s, 1H, OH), 2.65–2.78 (m, 2H, H2 and H4), 2.88 (q, 2H, $J = 7.5$, CH_2), 7.10–7.45 (m, 4H, H3′, H4′, H5′ and H6′)	141.0 (C2′), 140.3 (C1′), 131.9 (C4′), 127.4 (C6′), 126.1 (C3′), 125.3 (C5′), 40.5 (C2 and C4), 26.4 (CH_2), 17.3 (Me)
11	3506, 3050, 1608, 1506 and 1458	1.61 (s, 1H, OH), 6.86–7.46 (m, 8H, H2′–H12′)	

Table A6. Spectroscopic data for the synthetic alcohols **13–16** and **25**

Compound	IR ν_{max} (cm^{-1})	^1H NMR ($CDCl_3$) δ	^{13}C NMR ($CDCl_3$) δ
13	3427, 2950, 1060 and 958	0.80 (t, 3H, $J = 7.5$, Me), 0.92 (d, 6H, $J = 7.2$, 2 × Me), 1.33 (s, 3H, Me), 1.47 (q, 2H, $J = 7.5$, CH_2), 1.48 (s, 3H, Me), 1.68 (s, 1H, OH), 2.02 (dq, 2H, $J_{2,Me} = J_{4,Me} = 7.2$ and $J_{2,1} = J_{4,5} = 4.1$, H2 and H4), 3.95 (d, 2H, $J_{1,2} = J_{5,4} = 4.1$, H1 and H5), 4.97 (s, 2H, H6 and H7)	110.9 (CMe_2), 84.5 (C6 and C7), 80.7 (C1 and C5), 74.4 (C3), 36.6 (C2 and C4), 30.3 (CH_2), 26.2 (Me), 24.7 (Me), 9.4 (2 × Me), 9.4 (Me)
14	3420, 2960, 1045 and 960	0.88 (t, 3H, $J = 6.8$, Me), 1.13–1.43 (m, 10H, 5 × CH_2), 1.67 (s, 1H, OH)	38.0 (CH_2), 37.4 (C2 and C4), 31.6 (CH_2), 29.7 (CH_2), 24.9 (CH_2), 22.6 (CH_2), 14.0 (Me)
15	3410, 2940, 1050 and 960	0.84 (t, 3H, $J = 6.7$, Me), 1.16–1.42 (m, 14H, 7 × CH_2), 1.68 (s, 1H, OH)	37.9 (CH_2), 37.3 (C2 and C4), 31.8 (CH_2), 30.0 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 24.9 (CH_2), 22.6 (CH_2), 14.1 (Me)
16	3400, 2990, 1050 and 950	1.68 (s, 1H, OH), 3.68 (t, 1H, $J = 3.3$, H3)	37.5 (C2 and C4)
25	3410, 2980, 1050 and 940	0.89 (t, 3H, $J = 6.9$, Me), 1.05–1.44 (m, 6H, 3 × CH_2), 1.63 (s, 1H, OH)	37.6 (CH_2), 37.3 (C2 and C4), 27.1 (CH_2), 23.1 (CH_2), 13.9 (Me)

Table A7. Spectroscopic data for the synthetic alkenes **17–21**

Compound	IR ν_{max} (cm^{-1})	^1H NMR ($CDCl_3$) δ	^{13}C NMR ($CDCl_3$) δ
17	3050, 2970, 1508, 1178 and 862	0.74 (d, 3H, $J = 7.5$, 4-Me), 1.36 (s, 3H, Me), 1.41 (t, 3H, $J = 7.0$, Me), 1.54 (s, 3H, Me), 1.56 (d, 3H, $J = 2.4$, 2-Me), 2.97–3.10 (m, 1H, H4), 4.02 (q, 2H, $J = 7.0$, CH_2), 4.24 (s, 1H, H1), 4.30 (d, 1H, $J = 5.5$, H5), 4.64 (d, 1H, $J = 5.8$, H6), 4.83 (d, 1H, $J = 5.8$, H7), 6.84 (d, 2H, $J = 8.9$, H3′ and H5′), 6.94 (d, 2H, $J = 8.9$, H2′ and H6′)	157.7 (C4′), 135.1 (C3), 130.8 (C2), 129.5 (C2′ and C6′), 129.1 (C1′), 114.1 (C3′ and C5′), 112.1 (CMe_2), 84.8 and 84.7 (C6 and C7), 81.9 and 80.6 (C1 and C5), 63.4 (CH_2), 35.6 (C4), 26.3 (Me), 25.0 (Me), 16.8 (2-Me), 14.9 (Me), 14.0 (4-Me)
18	3050, 2963, 1508, 1161 and 864	1.24 (t, 3H, $J = 7.6$, Me), 2.64 (q, 2H, $J = 7.6$, CH_2), 6.93 (d, 2H, $J = 8.6$, H2′ and H6′), 7.14 (d, 2H, $J = 8.6$, H3′ and H5′)	142.5 (C4′), 135.8 (C1′), 128.4 (C3′ and C5′), 127.5 (C2′ and C6′), 28.5 (CH_2), 25.0 (Me), 15.4 (Me)
19	3050, 2956, 1508, 1161 and 864	0.93 (t, 3H, $J = 7.2$, Me), 1.26–1.44 (m, 2H, CH_2), 1.50–1.73 (m, CH_2), 2.59 (t, 2H, $J = 7.6$, CH_2), 6.92 (d, 2H, $J = 8.0$, H2′ and H6′), 7.12 (d, 2H, $J = 8.0$, H3′ and H5′)	141.2 (C4′), 135.8 (C1′), 128.3 (C3′ and C5′), 128.1 (C2′ and C6′), 35.3 (CH_2), 33.5 (CH_2), 25.0 (Me), 22.4 (CH_2), 14.0 (Me)

Table A7. Continued

Compound	IR ν_{max} (cm^{-1})	^1H NMR ($CDCl_3$) δ	^{13}C NMR ($CDCl_3$) δ
20	3038, 2963, 1508, 1158 and 976	1.31 (s, 9H, 3 × Me), 6.93 (d, 2H, $J = 8.3$, H2′ and H6′), 7.31 (d, 2H, $J = 8.3$, H3′ and H5′)	149.4 (C4′), 135.4 (C1′), 128.1 (C2′ and C6′), 124.9 (C3′ and C5′), 34.0 (C), 31.3 (3 × Me), 25.0 (Me)
21	2964, 1609, 1578, 1506 and 979	0.66 (d, 3H, $J = 7.6$, 4-Me), 1.36 (s, 3H, Me), 1.56 (d, 3H, $J = 2.5$, 2-Me), 1.55 (s, 3H, Me), 2.80–2.95 (m, 1H, H4), 3.74 (s, 3H, OMe), 3.81 (s, 3H, OMe), 4.24–4.29 (m, 2H, H1 and H5), 4.65 (d, 1H, $J = 5.8$, H6), 4.81 (d, 1H, $J = 5.8$, H7), 6.34–6.47 (m, 2H, H3′ and H5′), 6.86 (d, 1H, $J = 8.7$, H6′)	160.2 (C4′) 157.9 (C2′), 130.3 (C3), 129.6 (C2), 129.1 (C6′), 119.5 (C1′), 111.1 (CMe_2), 103.7 (C5′), 98.5 (C3′), 85.0 and 84.9 (C6 and C7), 81.8 and 80.8 (C1 and C5), 55.4 (OMe), 55.3 (OMe), 33.7 (C4), 26.3 (Me), 25.0 (Me), 16.8 (2-Me), 14.1 (4-Me)

Table A8. Spectroscopic data for the synthetic alkenes **22**–**24** and **26**

Compound	IR ν_{max} (cm^{-1})	^1H NMR ($CDCl_3$) δ	^{13}C NMR ($CDCl_3$) δ
22	2974, 2878, 1654 and 978	0.92 (t, 3H, $J = 7.6$, Me), 0.99 (d, 3H, $J = 7.5$, 4-Me), 1.32 (s, 3H, Me), 1.51 (s, 3H, Me), 1.63 (d, 3H, $J = 2.4$, 2-Me), 1.77–2.17 (m, 2H, CH_2), 2.67–2.84 (m, 1H, H4), 4.10 (s, 1H, H1), 4.14 (d, 1H, $J = 5.5$, H5), 4.50 (d, 1H, $J = 5.8$, H6), 4.71 (d, 1H, $J = 5.8$, H7)	134.7 (C3), 126.4 (C2), 112.0 (CMe_2), 84.7 and 84.5 (C6 and C7), 81.9 and 80.6 (C1 and C5), 33.3 (C4), 26.3 (Me), 24.9 (Me), 21.2 (CH_2), 15.2 (2-Me), 13.1 (4-Me), 12.6 (Me)
23	2930, 2850, 1460 and 970	0.88 (t, 3H, $J = 6.7$, Me), 1.16–1.40 (m, 8H, 4 × CH_2), 1.93–2.08 (m, 2H, CH_2)	31.7 (CH_2), 29.9 (CH_2), 29.3 (CH_2), 27.8 (CH_2), 26.3 (Me), 25.0 (Me), 22.6 (CH_2), 14.1 (Me)
24	2920, 2840, 1450 and 970	0.88 (t, 3H, $J = 6.4$, Me), 1.07–145 (m, 12H, 6 × CH_2), 1.82–2.08 (m, 2H, CH_2)	31.9 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 28.1 (CH_2), 27.9 (CH_2) 26.3 (Me), 25.0 (Me), 22.7 (CH_2), 14.1 (Me)
26	2950, 2850, 1630 and 960	0.89 (t, 3H, $J = 6.5$, Me), 1.13–1.42 (m, 4H, 2 × CH_2), 1.82–2.12 (m, 2H, CH_2)	30.0 (CH_2), 27.8 (CH_2), 26.2 (Me), 24.9 (Me), 22.7 (CH_2), 14.0 (Me)