Synthesis of Saturated Anacardic Acids, and Alkenyl and Alkynyl Analogues†

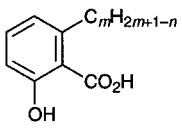
J. Chem. Research (S), 1997, 14–15
J. Chem. Research (M), 1997, 0228–0240

John H. P. Tyman* and Naina Visani

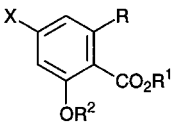
Department of Chemistry, Brunel University, Uxbridge, Middlesex UB8 3PH, UK

The *C*-alkylation of esters of 2-methoxy-6-methylbenzoic acid and of the 4-methyl isomers affords a route to homologous compounds of the natural anacardic acid series and of the unnatural isoanacardic acids respectively; ω-alkenyl and ω-alkynyl compounds suitable for synthesising other natural phenolic lipids or for structure–activity studies are also accessible.

C_{15} Anacardic acids (**1**; $m = 15$, $n = 0, 2, 4, 6$) occur in *Anacardium occidentale*,[2] C_{13} and C_{15} members (**1**; $m = 13, 15$, $n = 0, 2$) in *Pistacia vera*[3] and C_{17} members (**1**; $m = 17$, $n = 6$) in *Spondias mombin*,[4] to cite but a few sources of these widely distributed phenolic lipids which generally all possess methylene-interrupted unsaturation but at different positions in the side-chain.



1

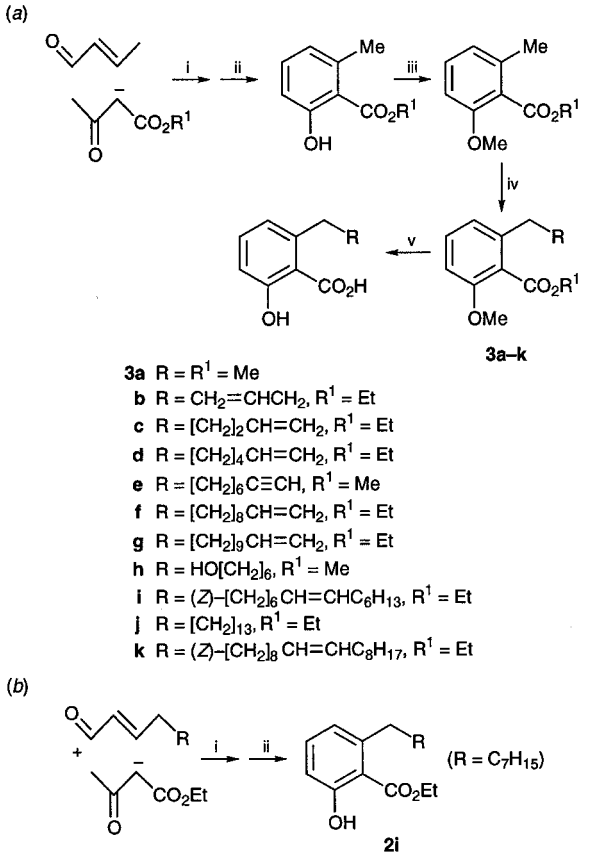


2a R = n-Alkyl, $R^1 = R^2$ = Me, X = H
b R = n-Alkyl, $R^1 = R^2$ = X = H
c R = n-Alkyl, R^1 = X = H, R^2 = Me
d R = $R^1 = R^2$ = Me, X = H
e R = *n*-Alkyl, $R^1 = R^2$ = Me, X = OH
f R = Me, $R^1 = R^2$ = X = H
g R = R^1 = Me, R^2 = X = H
h R = Me, R^1 = Bu^t, R^2 = X = H
i R = C_8H_{17}, R^1 = Et, R^2 = X = H
j R = Me, R^1 = Et, R^2 = Me, X = OMe

Their range of properties found over many years has been high-lighted in recent work on their action as inhibitory agents[5] towards methicillin-resistant *Staphylococcus aureus* (MRSA), prostaglandin synthase,[6] glycerol-3-phosphate dehydrogenase[7] and β-lactamase,[4] as molluscicides,[8] for the potential control of schistosomiasis,[9] for antimicrobial[10] and antitumour[11] activity and application to many technical problems.[2] Both the isolation of mixed anacardic acids (**1**; $m = 15$, $n = 0, 2, 4, 6$) from natural cashew nut-shell liquid extracted[12] from *Anacardium occidentale*, chromatographically by the use of ammoniated solvent systems,[13] organic base solvents[14] and the separation of the unsaturated constituents by argentation chromatography[15] or HPLC[8] are laborious. Thus their synthesis and that of analogues for structure–activity studies[16] has become of interest.

The preparation of methyl ester methyl ethers (**2a**) has been disclosed[17] from 1-methoxycyclohexa-1,4-diene, obtained by Birch reduction of methoxybenzene, conjugation of the product, and Diels–Alder reaction with homologous propiolic esters with loss of ethene from the adduct. The method derives from an earlier use by others of methyl propiolate. Thence, the homologous phenolic acids were obtained. This has prompted us to describe some of our own work on saturated, monoalkenyl dienyl compounds and analogues completed some years ago and briefly reviewed.[18]

Saturated anacardic acids (**2b**) were first synthesised in low to moderate yields by the thermolysis of basic copper salts of 2-alkylbenzoic acids.[19] From 2- or 3-fluoromethoxybenzene,[20] *O*-Me anacardic acids (**2c**) were readily obtained in improved yield, a method which was applied to the synthesis[21] of ginkgolic acid (**1**; $m = 15$, $n = 2$).



3a–k

3a R = R^1 = Me
b R = $CH_2{=}CHCH_2$, R^1 = Et
c R = $[CH_2]_2CH{=}CH_2$, R^1 = Et
d R = $[CH_2]_4CH{=}CH_2$, R^1 = Et
e R = $[CH_2]_6C{\equiv}CH$, R^1 = Me
f R = $[CH_2]_8CH{=}CH_2$, R^1 = Et
g R = $[CH_2]_9CH{=}CH_2$, R^1 = Et
h R = $HO[CH_2]_6$, R^1 = Me
i R = (*Z*)-$[CH_2]_6CH{=}CHC_6H_{13}$, R^1 = Et
j R = $[CH_2]_{13}$, R^1 = Et
k R = (*Z*)-$[CH_2]_8CH{=}CHC_8H_{17}$, R^1 = Et

2i

Scheme 1 *Reagents and conditions:* i, NaOEt, then HCl; ii, Br_2, heat; ii, Me_2SO_4, K_2CO_3, Me_2CO; iv, $LiNPr^i_2$, −70 °C, THF, HMPA, RX; H_3O^+; v, LiSBu^t

The synthesis of **2d** has been described[31] from but-2-enal and methyl acetoacetate by Michael addition and the alkylation of its carbanion appeared in our work to offer a route [Scheme 1(*a*)] to both saturated and unsaturated (alkenyl and alkynyl) anacardic acids in higher potential yields then by our original routes. The use of homologous α,β-unsaturated aldehydes in similar Michael addition reactions [Scheme 1(*b*)] has not been exploited, probably because the starting aldehydes are relatively inaccessible and the alkyl side chain is vulnerable to attack in the usual aromatisation step with bromine of the Michael adduct. For this reason also the alkylation route from **2d** is valuable since it permits the use of alkenyl and alkynyl halides. Thus in this way compounds **3a–k** were synthesised.

Although the methylation of **2d** presented no difficulty[37] the application of the alkylation initially to higher members proved initially to have no useful outcome and a wide variety of reaction conditions were examined. Of various aprotic co-solvents, HMPA proved the most useful. A low temperature to prevent self-reaction of the carbanion and avoidance of excessively concentrated reaction media were necessary. A 4–10% solution of the ester in THF itself containing 15%

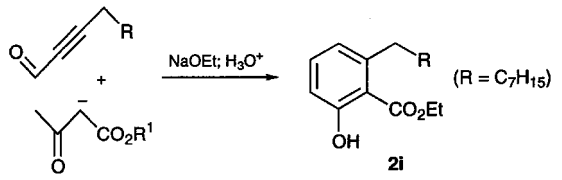
*To receive any correspondence.
†Long-chain Phenols, Part 33. Part 32 is ref. 1.

HMPA represented optimum conditions for the reaction mixture. In the alkylation of the carbanion of methyl or ethyl 2-methoxy-6-methylbenzoate with the halide (RX) the following yields (%) of compounds in the series (**3a–k**) were obtained. With MeI (87%; **3a**, R^1 = Et), CH_2=$CHCH_2Br$ (92%; **3b**, R^1 = Et), CH_2=$CH[CH_2]_2Br$ (87%; 27% without HMPA; **3c**, R^1 = Et), CH_2=$CH[CH_2]_4Br$ (60%; **3d**, R^1 = Et), CH_2=$CH[CH_2]_8Br$ (94%; **3f**, R^1 = Et), CH_2=$CH[CH_2]_9Br$ (76%; **3g**, R^1 = Et), CH_2=$CH[CH_2]_9OTs$ (45%), $EtO(Me)CHO[CH_2]_6Cl$ (78%; **3h**, R^1 = Me), HC≡$C[CH_2]_6Br$ (44%, **3e**, R^1 = Me), C_3H_7C≡CCH_2C≡$C[CH_2]_6I$ (78%), (*Z*)-C_3H_7CH=$CH[CH_2]_9I$ (37%), (*Z*)-$C_6H_{13}CH$=$CH[CH_2]_6I$ (30%; **3i**, R^1 = Et), (*Z*)-$C_8H_{17}CH$=$CH[CH_2]_8I$ (25%; **3k**, R^1 = Et), and $C_{14}H_{29}Br$ (34%; **3j**, R^1 = Et).

In the alkylation of the carbanion from ethyl dimethylorsellinate (**2j**) with pentadecyl bromide under a variety of conditions a yield of 5% resulted. Thus in that case it had proved essential to employ the Michael addition procedure for the synthesis of 2,4-dihydroxy-6-pentadecylbenzoic acid.[38]

An attempt was made (Scheme 2) to use an α,β-alkynal, undec-2-ynal, in a Michael addition with the anion of ethyl acetoacetate to eliminate the aromatisation step for the formation of **2i**. Although the required product was formed the procedure was erratic and it could not be repeated.

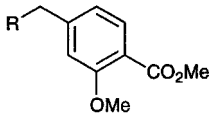
Hydrolysis of the alkylation products with aqueous etha-



Scheme 2

nolic potassium hydroxide afforded low to moderate yields with much unchanged material. Potassium *tert*-butoxide[39] proved too mild and simultaneous ester cleavage and demethylation was finally affected with lithium *tert*-butyl thiolate[40] as shown in Scheme 1(*a*).

The isomeric methyl 2-methoxy-4-methylbenzoate (**8a**),



8a R = H
b R = $[CH_2]_9CH$=CH_2

obtained by esterification of 2-hydroxy-4-methylbenzoic acid followed by methylation under anhydrous conditions with dimethyl sulfate, was similarly alkylated. Thus, 11-bromoundec-1-ene afforded methyl 4-(dodec-11-en-1-yl)-2-methoxybenzoate (**8b**), a compound in the unnatural iso-anacardic acid series,[2] members of which can also be semi-synthesised by carbonation of natural 3-alkyl- and alkenyl-phenols.[2]

The alkylation only succeeds with 4-methyl and 2-methyl compounds bearing an activating alkoxycarbonyl group electron-withdrawing substituent and 3-methyl isomers are unaffected unless they have an electron-withdrawing substituent, or thio-activation, on the methyl group, both of which are superfluous requirements for the 2- and 4-methyl series. With alternative electron-withdrawing groups such as nitro or cyano in these two series the range of synthetic utility could probably be extended.

The ω-hydroxyalkyl and ω-alkynyl compounds accessible by the application of the alkylation procedure described offer potential routes to a wide range of polyunsaturated phenolic lipids with side-chains differing in length and position of unsaturation.

Techniques used: ^{1}H NMR, MS, TLC, flash chromatography

References: 49

Received, 8th August 1996; Accepted, 11th October 1996
Paper E/6/05538I

References cited in this synopsis

1 A. Kozubek and J. H. P. Tyman, *Chem. Phys. Lipids*, 1995, **78**, 29.
2 J. H. P. Tyman, *Chem. Soc. Rev*., 1979, **8**, 499; J. H. P. Tyman, in *Studies in Natural Products Chemistry*, ed. Atta-ur-Rahman, Elsevier, Amsterdam, 1991, vol. 9, p. 313; J. H. P. Tyman, *Synthetic and Natural Phenols*, Elsevier, Amsterdam, 1996.
3 M. Yalpani and J. H. P. Tyman, *Phytochemistry*, 1983, **22**, 2263.
4 N. J. Coates, M. L. Gilpin, M. N. Gwynn, D. E. Lewis, P. H. Milner, S. R. Spear and J. W. Tyler, *J. Nat. Prod*., 1994, **57**, 654; S. S. Arogba, Ph.D. Thesis, Brunel University, 1987.
5 H. Muroi and I. Kubo, *Biosci., Biotechnol., Biochem*., 1994, **58**, 1925; I. Kubo and M. Sukigara, PCT Int. Appl. WO 0530417.
6 R. Grazzini, D. Hesk, E. Heininger, G. Hildebrandt, C. C. Reddy, D. Cox-Foster, J. Medford, R. Craig and R. O. Mumma, *Biochem. Biophys. Res. Commun*., 1991, **176**, 775.
7 J. Irie, M. Murata and S. Homma, *Biosci., Biotechnol., Biochem*., 1996, **60**, 240.
8 J. T. Sullivan, C.S. Richards, H. A. Lloyd and G. Krishna, *Planta Med*., 1982, **44**, 175.
9 I. Kubo, S. Komatsu and M. Ochi, *J. Agric. Food Chem*., 1986, **34**, 970.
10 I. Kubo, H. Muroi, M. Himejima, Y. Yamgiwa, H. Mera, K. Tokushima, S. Ohta and T. Kamikawa, *J. Agric. Food Chem*., 1993, **41**, 1016.
11 I. Kubo, M. Ochi, P. C. Vieira and S. Komatsu, *J. Agric. Food Chem*., 1993, **41**, 1012.
12 J. H. P. Tyman, R. A. Johnson, M. Muir and R. Rokhgar, *J. Am. Oil Chem. Soc*., 1989, **68**, 553.
13 J. H. P. Tyman and L. J. Morris, *J. Chromatogr*., 1967, **27**, 287.
14 K. S. Nagabhushana and B. Ravindranath, *J. Agric. Food Chem*., 1995, **43**, 2381.
15 N. Jacobs and J. H. P. Tyman, *J. Chromatogr*., 1971, **54**, 83.
16 I. Kubo, H. Muroi and A. Kubo, *Biorg. Med. Chem*., 1995, **3**, 873.
17 R. Zehnter and H. Gerlach, *Liebigs Ann. Chem*., 1995, 2009.
18 J. H. P. Tyman and N. Visani, in *Topics in Lipid Research*, ed., R. Klein and B. Schmitz, Royal Society of Chemistry, London, 1986; N. Visani, Ph.D. Thesis, Brunel University, 1988.
19 A. A. Durrani and J. H. P. Tyman, *J. Chem. Soc*., *Perkin Trans. 1*, 1989, 2069.
20 A. A. Durrani and J. H. P. Tyman, *J. Chem. Soc*., *Perkin Trans. 1*, 1979, 2079.
21 J. H. P. Tyman, *J. Org. Chem*., 1976, **41**, 894.
31 F. M. Hauser and S. A. Pogany, *Synthesis*, 1980, 814.
37 J. A. Carpenter, G. E. Evans, F. J. Leeper, J. Staunton and M. R. Wilkinson, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1043.
38 I. Bruce, J. H. P. Tyman and R. N. Spencer, *J. Chem. Res*., 1992, (*S*) 224; (*M*) 1773.
39 P. G. Gassman and W. N. Schenk, *J. Org. Chem*., 1977, **42**, 918.
40 S. Wolfe, J. B. Ducep and J. D. Greenhorn, *Can. J. Chem*., 1975, **53**, 3435.