Selective Synthesis of Monomethyltocols *via* η-Allylnickel Complexes

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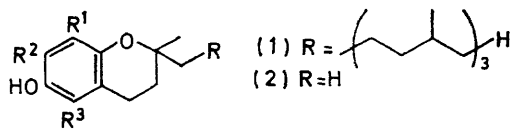
A new synthesis of the monomethyltocols (1a—c) and the 2,2-dimethylchroman-6-ol models (2a—c), using the di-μ-bromobis-(1—3-η-3-alkylbut-2-enylnickel) complexes (9a and b), is described. Reaction of the η-allylnickel complexes (9a and b) with the bromo-*p*-diacetoxytoluenes (3a—c) gave the corresponding alkyl substituted *p*-diacetoxytoluenes (10a—c) and (11a—c) in high yield, and these were converted into the chromanols (1a—c) and (2a—c) by hydrolysis–cyclisation with tin(II) chloride and hydrochloric acid, also in high yield.

AMONG the tocopherols, the vitamin E factor, there are three isomeric monomethyltocols (1a—c), and only 8-methyltocol (1a) has been found in nature.[1]

The reported syntheses of the tocols (1a—c) mainly involve condensation of toluquinone or its derivatives with phytol under acidic conditions.[2-5] These methods, however, have little regioselectivity and consequently yield mixtures of isomeric tocols or so-called double chromans, in statistical amounts, which are difficult

[1] R. A. Morton, 'Biochemistry of Quinones,' Academic Press, New York, 1965, ch. 8.
[2] P. Karrer and H. Fritzsche, *Helv. Chim. Acta*, 1939, **22**, 260.
[3] D. McHale, P. Mamalis, J. Green, and S. Marcinkiewicz, *J. Chem. Soc.*, 1958, 1600.
[4] D. McHale, P. Mamalis, S. Marcinkiewicz, and J. Green, *J. Chem. Soc.*, 1959, 3358.
[5] J. Green, D. McHale, P. Mamalis, and S. Marcinkiwiecz, *J. Chem. Soc.*, 1959, 3374.

to separate. Nilson *et al.* prepared the monomethyltocol models (2a—c) by unambiguous routes, but the synthetic sequences were very long.[6]



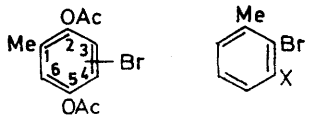
(1) R =

(2) R=H

	R^1	R^2	R^3
a	Me	H	H
b	H	Me	H
c	H	H	Me

To avoid these disadvantages, regiospecific alkylation is needed. For this purpose, a η-allylnickel complex, derived from tetracarbonylnickel and an allyl halide, would be useful, since it could transform a carbon–halogen bond selectively to a carbon–carbon bond under mild conditions. Recently, the synthetic utility of η-allylnickel complexes has been recognised, and they have been used in the synthesis of several natural substances including α-santalene,[7] *epi*-β-santalene,[7] geranyl acetate,[8,9] coenzyme Q,[10] and vitamin K.[11]

We now describe a new synthesis of the monomethyltocols (1a—c) and their models (2a—c), involving allylation by η-allylnickel complexes.



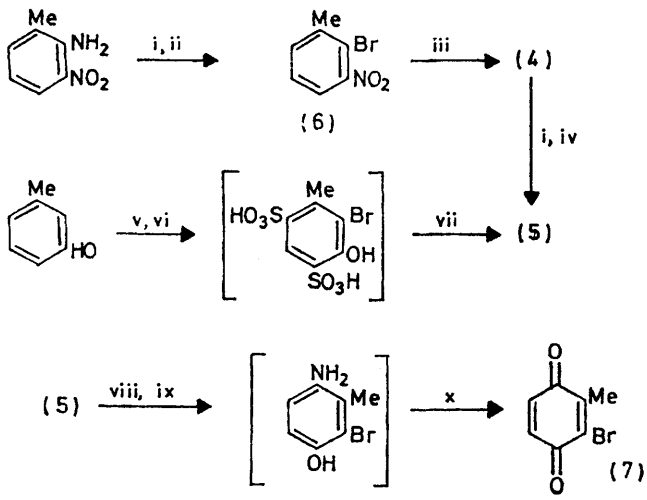
(3) a, 3-Br (4) X = NH_2

b, 4-Br (5) X = OH

c, 6-Br

2,5-Diacetoxy-3-bromotoluene (3a), the intermediate for 8-methyltocol (1a), is a known material [12] and was prepared from *o*-cresol *via* 4,6-dibromo-*o*-cresol [13] and 2-bromo-6-methyl-*p*-benzoquinone.[14] 2,5-Diacetoxy-4-bromotoluene (3b), the intermediate for 7-methyltocol (1b), was prepared by reductive acetylation of 2-bromo-5-methyl-*p*-benzoquinone [15] with zinc in acetic anhydride.

For the preparation of 2,5-diacetoxy-6-bromotoluene (3c), the intermediate for 5-methyltocol (1c), oxidation of 2-bromo-*m*-toluidine (4) or 2-bromo-3-methylphenol (5) to give 2-bromo-3-methyl-*p*-benzoquinone were considered as possible routes. 2-Bromo-3-nitrotoluene (6), prepared from 6-nitro-*o*-toluidine by a slight modification of Gibson's method,[16] was reduced with tin to afford the toluidine (4) (75%). When the toluidine (4) was oxidized by aqueous potassium dichromate in sulphuric acid solution, only a trace of sublimable quinone (4) was obtained (0·5%). Oxidation with Fremy's salt of the phenol (5) obtainable from *m*-cresol [17] or by diazotisation of the toluidine (4) followed by acidic hydrolysis, gave a tarry residue. The quinone (7) was eventually prepared *via* the *p*-aminophenol (Scheme). The diazonium salt of sulphanilic acid was allowed to



SCHEME

Reagents: i, $NaNO_2$; ii, Cu_2Br_2; iii, Sn–HCl; iv, H_3O^+; v, $ClSO_3H$; vi, Br_2; vii, H_3O^+–steam; viii, p-$\overset{+}{N}_2C_6H_4SO_3^-$; ix, $SnCl_2$–HCl; x, $FeCl_3$

react with the phenol (5) in aqueous sodium carbonate, then the crude product was reduced by tin(II) chloride to give the *p*-aminophenol, which was immediately oxidised by iron(III) chloride to afford the quinone (7) (24% overall). The quinone was converted into the diacetate (3c) by reductive acetylation (85%).

We then attempted the synthesis of the 8-methyltocol model (2a). Reaction of 1-bromo-3-methylbut-2-ene (8a) [18] with tetracarbonylnickel in benzene at 50° for 3 h under nitrogen afforded the dark red η-allylnickel complex (9a). This complex was treated with (3a) in hexamethylphosphoramide (HMPA) at 50°. The dark red solution turned deep green during 5 h and gave 2,5-diacetoxy-3-(3-methylbut-2-enyl)toluene (10a) in 77% yield. The diacetate (10a) was then treated with tin(II) chloride (to prevent aerial oxidation to the quinone) and hydrochloric acid in dioxan at reflux for

[6] J. L. G. Nilsson, H. Sievertsson, and H. Selander, *Acta Chem. Scand.*, 1968, **22**, 3160.

[7] E. J. Corey and M. F. Semmelhack, *J. Amer. Chem. Soc.*, 1967, **89**, 2755.

[8] K. Sato, S. Inoue, S. Ota, and Y. Fujita, *J. Org. Chem.*, 1972, **37**, 462.

[9] F. Guerrieri and G. P. Chiusoli, *Chim. Ind.* (*Milan*), 1969, **51**, 1252.

[10] K. Sato, S. Inoue, and R. Yamaguchi, *J. Org. Chem.*, 1972, **37**, 1889.

[11] (*a*) K. Sato, S. Inoue, and K. Saito, *J.C.S. Chem. Comm.*, 1972, 953; (*b*) K. Sato, S. Inoue, and K. Saito, *J.C.S. Perkin I*, 1973, 2289.

[12] L. C. Raiford, *J. Amer. Chem. Soc.*, 1910, **44**, 163.

[13] Th. Zincke and A. Hedenstrom, *Annalen*, 1906, **350**, 269.

[14] J. Cason and H. Rapoport, 'Laboratory Text in Organic Chemistry,' 2nd edn., Prentice Hall, Englewood Cliffs, 1962, p. 188.

[15] K. J. M. Andrews, D. H. Marrian, and D. R. Maxwell, *J. Chem. Soc.*, 1956, 1844.

[16] C. S. Gibson and J. D. A. Johnson, *J. Chem. Soc.*, 1929, 1229.

[17] R. A. Benkeser and W. E. Buting, *J. Amer. Chem. Soc.*, 1952, **74**, 3011.

[18] J. Tanaka, T. Katagiri, and S. Yamada, *Nippon Kagaku Zasshi*, 1966, **87**, 877.

8 h to afford directly 2,2,8-trimethylchroman-6-ol (2a) in 96% yield.

This procedure was extended to the synthesis of 8-methyltocol (1a). Phytyl bromide (8b), prepared from phytol by treatment with phosphorus tribromide in petroleum,[19] was allowed to react with tetracarbonylnickel in benzene at 52° to give the η-allylnickel complex (9b), which was isolated and treated with (3a) in HMPA at 50° for 5 h. The crude product was purified by column chromatography to give the phytyl diacetate (11a) in 86% yield. Conversion into the chromanol (1a) was carried out as for the model compound (2a) in 97% yield.

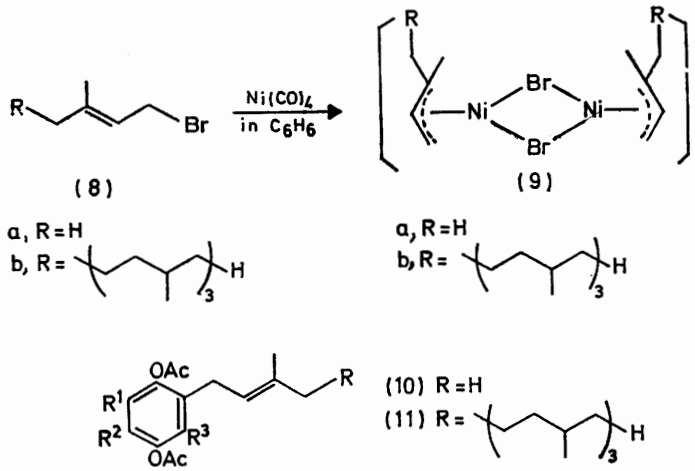


TABLE 1

Alkylation of the bromodiacetoxytoluenes (3a—c) with η-allylnickel complexes (9a or b)

Starting material	Product	Yield [a] (%)	M.p. (°C) $[n_D^{20}]$	Analysis [b] (%) C	H
(3a)	(10a)	77	[1·5093]	69·85	7·6
(3b)	(10b)	74	39·5—40·3	69·75	7·55
(3c)	(10c)	75	[1·5150]	69·05	7·4
(3a)	(11a)	86	[1·4884]	76·55	10·65
(3b)	(11b)	52	[1·4875]	76·3	10·55
(3c)	(11c)	93	[1·4898]	76·45	10·45

[a] Based on (3a—c) after isolation by silica gel column chromatography. [b] Compounds (10a—c) ($C_{16}H_{20}O_4$) require C, 69·55; H, 7·3%. Compounds (11a—c) ($C_{31}H_{50}O_4$) require C, 76·5; H, 10·35%.

TABLE 2

Hydrolysis–cyclisation of the alkenyldiacetoxytoluenes (10a—c) and (11a—c) to chromanols

Starting material	Product	Yield [a] (%)	M.p. (°C) $[n_D^{20}]$	Analysis [b] (%) C	H
(10a)	(2a)	96	84·6—85·5	74·7	8·6
(10b)	(2b)	84	87—88	75·1	8·65
(10c)	(2c)	83	60·5—61·3	74·8	8·65
(11a)	(1a)	97	[1·4938]	80·6	11·75
(11b)	(1b)	92	[1·5028]	80·45	11·4
(11c)	(1c)	78	[1·5059]	79·7	11·6

[a] Isolated yield after purification by silica gel column chromatography. [b] Compounds (2a—c) ($C_{12}H_{16}O_2$) require C, 74·95; H, 8·4%. Compounds (1a—c) ($C_{27}H_{46}O_2$) require C, 80·55; H, 11·5%.

[19] P. Karrer, A. Geiger, H. Rentschler, E. Zbinden, and A. Kugler, *Helv. Chim. Acta*, 1943, **26**, 1741.

The other tocols (1b and c) and their models (2b and c) were prepared similarly: these results are summarised in Tables 1 and 2. The methods described here could be extended to the synthesis of the other tocopherols.

EXPERIMENTAL

M.p.s were taken on a hot-stage apparatus. I.r. spectra were determined on a Hitachi 215 spectrophotometer, and n.m.r. spectra on a JEOL C-60 spectrometer for solutions of carbon tetrachloride or deuteriochloroform with tetramethylsilane as internal reference. 2,5-Diacetoxy-3-bromotoluene (3a),[12] 2-bromo-5-methyl-*p*-benzoquinone,[15] 2-bromo-3-nitrotoluene (6),[16] 2-bromo-3-methylphenol (5),[17] 1-bromo-3-methylbut-2-ene (8a),[18] phytyl bromide (8b),[19] and some other synthetic intermediates were prepared by the methods described in the literature and their physical properties agreed with those reported. All the reactions involving the η-allylnickel complexes (9a and b) were carried out under a stream of nitrogen or argon.

2,5-Diacetoxy-4-bromotoluene (3b).—To a hot solution (90—95°) of 2-bromo-5-methyl-*p*-benzoquinone (18·0 g) in acetic anhydride (90 ml) was added gradually powdered zinc (27·0 g) during 30 min. Anhydrous sodium acetate (7·2 g) was then added and the mixture was heated for 30 min. The solution was filtered, the residue washed with warm acetone, and the filtrate and washings were combined and poured onto ice. The precipitate gave the *diacetate* (3b) (23·8 g), as needles (from ethanol), m.p. 125·0—125·4° (Found: C, 45·75; H, 4·05. $C_{11}H_{11}BrO_4$ requires C, 46·0; H, 3·85%).

2-Bromo-m-toluidine (4).—To a stirred solution of 2-bromo-3-nitroluene (6) (2·5 g) and tin (flower) (2·8 g) in water (5 ml) was added conc. hydrochloric acid (12 ml) dropwise at 50°. After the addition was complete, the mixture was stirred for a further 2 h, then cooled. An oil which separated on addition of aqueous sodium hydroxide was extracted with ether, and the extracts were washed with water, dried ($MgSO_4$), and concentrated. Column chromatography on silica gel afforded 2-bromo-*m*-toluidine (4) (1·6 g, 15%), $\nu_{max.}$ (neat) 3460, 3375, 1025, and 770 cm^{-1}; *N-acetyl derivative*, m.p. 144·0—144·5° (Found: C, 47·35; H, 4·6. $C_9H_{10}BrNO$ requires C, 47·4; H, 4·4%).

2-Bromo-3-methylphenol (5).—To a stirred solution of the bromotoluidine (4) (2·2 g) in water (35 ml) and conc. sulphuric acid (5·8 ml) was added saturated aqueous sodium nitrite (1 g) at 0—5°. This mixture was filtered

and added dropwise to a hot solution (120°) of water (10 ml)–conc. sulphuric acid (5 ml), and the mixture was steam-distilled. The distillate gave 2-bromo-3-methylphenol (7) (0·93 g, 42%) as plates (from n-hexane), m.p. 60·7—61·5° (lit.,[17] 61·5—62·0°), identical (spectral data) with the sample derived from *m*-cresol.

*2-Bromo-3-methyl-*p*-benzoquinone* (7).—Sulphanilic acid (3·46 g) was dissolved in water (20 ml) containing anhydrous sodium carbonate (1·06 g) and cooled to 15°. To this solution was added sodium nitrite (1·49 g) in water (4 ml) and the mixture was poured into ice–water (24 g) containing conc. hydrochloric acid (4·3 ml) and kept at 0° for 30 min. To a stirred solution of 2-bromo-3-methylphenol (5) (2·94 g) in water (24 ml) containing sodium hydroxide (4·4 g) was added dropwise at 0° the diazonium salt solution prepared as before, and the mixture was left overnight. The orange coupling product precipitated on neutralisation with conc. hydrochloric acid (10 ml) and the mixture was then heated with tin(II) chloride (11 g) in conc. hydrochloric acid (8 ml) and gradually became homogeneous. After addition of iron(III) chloride (32 g), the mixture was immediately steam-distilled. The distillate gave the *bromoquinone* (7) (0·74 g, 24%), as yellow needles (from n-hexane), m.p. 65·4—65·7°, $\nu_{max.}$ (KBr) 1660 and 1595 cm^{-1} (Found: C, 42·25; H, 2·7. $C_7H_5BrO_2$ requires C, 41·85; H, 2·5%).

2,5-Diacetoxy-6-bromotoluene (3c).—The bromoquinone (7) (1·5 g) was reductively acetylated using zinc (2·25 g) and anhydrous sodium acetate (0·6 g) in acetic anhydride (10 ml) by the procedure described above. Recrystallisation from n-hexane gave the *diacetate* (3c), as plates, m.p. 96·0—96·3° (Found: C, 46·4; H, 4·05. $C_{11}H_{11}BrO_4$ requires C, 46·0; H, 3·85%).

2,5-Diacetoxy-3-(3-methylbut-2-enyl)toluene (10a).—To a stirred solution of tetracarbonylnickel (5·4 g) in benzene (40 ml) under nitrogen was added dropwise 1-bromo-3-methylbut-2-ene (8a) (3·2 g) in benzene (20 ml) at 50° during 1 h, and stirring was continued for 2 h at 50°. The dark red solution was concentrated under reduced pressure at below 10°, and the dark red residue was dissolved in hexamethylphosphoramide (HMPA) (50 ml), and the diacetate (3a) (4·3 g) was added. The mixture was heated at 50° for 5 h, and the solution turned from dark red to deep green, suggesting the end point of the coupling reaction. The mixture was poured into water containing a little conc. hydrochloric acid and extracted with petroleum–ether (1 : 1). The extract was washed with water, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was chromatographed on silica gel [eluant n-hexane–di-isopropyl ether (8 : 2)] to afford the *diacetate* (10a) (3·16 g); $\nu_{max.}$ (neat) 2930, 1760, 1600, 1475, 1370, 1210, 1170, 1030, and 910 cm^{-1}, δ (CCl_4) 6·08 (d) and 6·02 (d) (each 1H, ArH), 5·05 (1H, t, CH=), 3·05 (2H, d, CH_2), 2·16 (s) and 2·11 (s) (each 3H, Ac), 2·06 (3H, s, ArMe), and 1·71 (s) and 1·63 (s) (each 3H, olefinic Me).

2,5-Diacetoxy-4-(3-methylbut-2-enyl)toluene (10b).—This *compound* was prepared from (3b) and (9a) by the method just described, $\nu_{max.}$ (KBr) 2925, 1760, 1500, 1440, 1370, 1210, 1170, 1070, and 915 cm^{-1}, δ ($CDCl_3$) 6·87br (2H, s, ArH), 5·20 (1H, t, CH=), 3·18 (2H, d, CH_2), 2·28 (6H, s, Ac), 2·13 (3H, s, ArMe), and 1·74 (s) and 1·67 (s) (each 3H, olefinic Me).

2,5-Diacetoxy-6-(3-methylbut-2-enyl)toluene (10c).—This *compound* was similarly prepared from (3c) and (9a), $\nu_{max.}$ (neat) 2920, 1750, 1580, 1470, 1365, 1210, 1180, 1060, and 910 cm^{-1}, δ ($CDCl_3$) 6·78 (2H, s, ArH), 4·92 (1H, t, CH=), 3·20 (2H, d, CH_2), 2·25 (6H, s, Ac), 2·05 (3H, s, ArMe), and 1·72 (s) and 1·67 (s) (each 3H, olefinic Me).

2,5-Diacetoxy-3-phytyltoluene (11a).—The η-phytylnickel complex (9b) was prepared from tetracarbonylnickel (2·7 g) and phytyl bromide (8b) (4·2 g) in benzene at 52° for 3 h under nitrogen. After removal of benzene, the diacetate (3a) (2·15 g) and HMPA (40 ml) were added and heated at 50° for 5 h. The mixture was worked up as described above, and chromatography on a silica gel column afforded *2,5-diacetoxy-3-phytyltoluene* (11a) (3·12 g, 86%), $\nu_{max.}$ (neat) 2920, 1755, 1460, 1365, 1210, 1165, 1030, and 910 cm^{-1}, δ (CCl_4) 6·54br (2H, s, ArH), 5·08 (1H, t, CH=), 3·05 (2H, d, CH_2), 2·20 (s) and 2·15 (s) (each 3H, Ac), 2·08 (3H, s, ArMe), 1·62br (3H, s, olefinic Me), 1·18br (21H, s, methylene chain), and 0·86 (12H, d, side-chain Me).

2,5-Diacetoxy-4- and *-6-phytyltoluene* (11b) and (11c) were prepared by the reaction of (9b) with (3b) or (3c), respectively, and had the following spectral data: (11b), $\nu_{max.}$ (neat) 2925, 1760, 1500, 1460, 1370, 1215, 1185, 1160, 1015, and 915 cm^{-1}, δ ($CDCl_3$) 6·95 (2H, s, ArH), 5·25 (1H, t, CH=), 3·22 (2H, d, $ArCH_2$), 2·29 (6H, s, Ac), 2·14 (3H, s, ArMe), 1·67br (3H, s, olefinic Me), 1·23br (21H, s, methylene chain), and 0·89 (12H, d, side-chain Me); (11c), $\nu_{max.}$ (neat) 2900, 1760, 1585, 1465, 1370, 1220, 1180, 1010, and 910 cm^{-1}, δ ($CDCl_3$) 6·83 (2H, s, ArH), 4·94 (1H, t, CH=), 3·24 (2H, d, $ArCH_2$), 2·27 (s) and 2·23 (s) (each 3H, Ac), 2·07 (3H, s, ArMe), 1·70br (3H, s, olefinic Me), 1·19br (21H, s, methylene chain), and 0·88 (12H, d, side-chain Me).

2,2,8-Trimethylchroman-6-ol (2a).—To a solution of the diacetate (10a) (1·38 g) in dioxan (30 ml) was added tin(II) chloride (6·0 g) in conc. hydrochloric acid (6·0 ml). The mixture was refluxed for 8 h, then poured into water and extracted with ether. The extract was washed with water, dried ($MgSO_4$), and evaporated, and the residue was chromatographed on silica gel to give *2,2,8-trimethylchroman-6-ol* (2a) (0·92 g, 96%), $\nu_{max.}$ (KBr) 3270, 2960, 1600, 1460, 1365, 1220, 1200, 1155, 1120, and 920 cm^{-1}, δ (CCl_4) 6·15 (2H, m, ArH), 3·99br (1H, s, OH), 2·61 (t) and 1·68 (t) (each 2H, methylene in chroman ring), 2·02 (3H, s, ArMe), and 1·25 (6H, s, Me on chroman ring).

The other diacetates were converted into chromanols in the manner described above. The chromanols had the following spectral data.

2,2,7-Trimethylchroman-6-ol (2b); $\nu_{max.}$ (KBr) 3380, 2980, 2925, 1515, 1420, 1190, 885, and 875 cm^{-1}, δ ($CDCl_3$) 6·62 (s) and 6·53 (s) (each 1H, ArH), 4·68br (1H, s, OH), 2·68 (t) and 1·78 (t) (each 2H, methylene in chroman ring), 2·17 (3H, s, ArMe), and 1·30 (6H, s, Me on chroman ring).

2,2,5-Trimethylchroman-6-ol (2c); $\nu_{max.}$ (KBr) 3450, 2980, 1485, 1350, 1260, 1200, and 805 cm^{-1}, δ ($CDCl_3$) 6·45 (2H, s, ArH), 4·00br (1H, s, OH), 2·60 (t) and 1·79 (t) (each 2H, methylene in chroman ring), 2·10 (3H, s, ArMe), and 1·28 (6H, s, Me on chroman ring).

8-Methyltocol (1a); $\nu_{max.}$ (neat) 3310, 2920, 1600, 1460, 1370, 1215, 1140, and 845 cm^{-1}, δ (CCl_4) 6·15 (2H, m, ArH), 5·91br (1H, s, OH), 2·52 (t) and 1·64 (t) (each 2H, methylene in chroman ring), 1·99 (3H, s, ArMe), 1·17br (24H, s, methylene chain and Me on chroman ring), and 0·86 (12H, d, side-chain Me).

7-Methyltocol (1b); $\nu_{max.}$ (neat) 3400, 2900, 1460, 1375, 1170, 1005, and 865 cm^{-1}, δ ($CDCl_3$) 6·60 (s) and 6·50 (s) (each 1H, ArH), 3·75br (1H, s, OH), 2·68 (t) and 1·76

(t) (each 2H, methylene in chroman ring), 2·18 (3H, s, ArMe), 1·22br (24H, methylene chain and Me on chroman ring), and 0·88 (12H, d, side-chain Me).

5-Methyltocol (1c); $\nu_{max.}$ (neat) 3400, 2920, 1460, 1375, 1230, and 805 cm^{-1}, δ ($CDCl_3$) 6·50 (2H, s, ArH), 4·00br (1H, s, OH), 2·60 (t) and 1·80 (t) (each 2H, methylene in chroman ring), 2·10 (3H, s, ArMe), 1·18br (24H, s, methylene chain and Me on chroman ring), and 0·87 (12H, d, side-chain Me).

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