Journal of Natural Products
Vol. 53, No. 6, pp. 1463-1470, Nov-Dec 1990

SYNTHESIS OF MINOR XANTHONES FROM *GARCINIA MANGOSTANA*

GRAHAM J. BENNETT, HIOK-HUANG LEE,* and LIAK-PHONG LEE

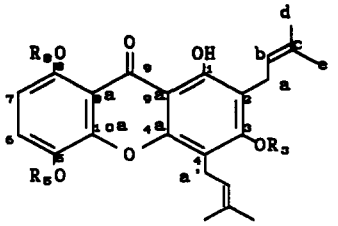
Department of Chemistry, National University of Singapore, 10 Kent Ridge Crescent, Singapore 0511

ABSTRACT.—Reaction of 2,3,6-trimethoxybenzoic acid and phloroglucinol in the presence of P_2O_5 and $MeSO_3H$ afforded 1,3-dihydroxy-5,8-dimethoxyxanthone [**8**] which, on 3-methylbut-2-enylation followed by methylation, gave a mixture of the mono- and di-(3-methylbut-2-enyl)xanthones **2**, **5**, **6**, and **12**. Whereas demethylation of xanthone **2** with hot aqueous morpholine yielded gartanin [**1**] and its 5-*O*-methylether **3**, similar reaction of xanthone **5** gave, in addition to the expected products **14** and **15**, two 1,3,7,8-tetraoxygenated xanthones **16** and **17**. Selective methylation of **14** gave the natural xanthone **4**.

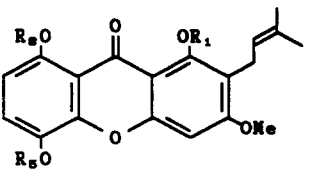
Various parts of the fruit tree *Garcinia mangostana* L. (Guttiferae) have been utilized in folk medicine (1), notably in the treatment of wounds and skin infections, and mangostin (2), the major metabolite, has been shown to possess significant antimicrobial properties (1,3). A large number of other prenylated xanthones have been found in the plant (4,5), including two unique 1,3,5,8-tetraoxygenated xanthones, gartanin [**1**] (6) and the recently isolated xanthone **4** (7). 3-Methylbut-2-enylated xanthones containing 1,3,5- (8), 1,3,7- (9) and 1,3,6,7-oxygenation (10) have been synthesized previously. In this paper we describe the synthesis of **1** and **4**, as well as a Wessely-Moser-type rearrangement observed in the course of this work. A preliminary communication has been published (11).

A direct approach to the synthesis of **1** and **4** would be the 3-methylbut-2-enylation of 1,3,5,8-tetrahydroxyxanthone. However, this xanthone has been obtained in poor yield by a circuitous method (12). A more viable starting material appeared to be isobellidifolin [**7**], available from the condensation of 2,3,6-trimethoxybenzoic acid with phloroglucinol by the Grover, Shah, and Shah (GSS) procedure (13). 3-Methylbut-2-enylation of **7** followed by demethylation (5) of the products should yield gartanin [**1**] as well as the desired tetrahydroxy precursor to **4**.

In our hands however, the GSS reaction gave as the major product 1,3,8-trihydroxy-7-methoxyxanthone [**10**], identified by its mp and spectroscopic data (14,15) and by conversion to 1,3,7,8-tetramethoxyxanthone [**11**] (13). The minor product, mp 293–295°, was assigned as 1,3-dihydroxy-5,8-dimethoxyxanthone [**8**] based on the following evidence. Its uv spectrum was indicative of 1,3,5,8-tetraoxygenation (14), and this was confirmed when methylation gave the known 1,3,5,8-tetramethoxyxanthone [**9**] (13). The methoxyl groups were located by comparing the ^{1}H-nmr spectra of **8** and its diacetate. The neighboring acetoxy groups caused strong deshield-



1 $R_3=R_5=R_8=H$
2 $R_3=R_5=R_8=Me$
3 $R_3=R_8=H$, $R_5=Me$



4 $R_1=R_5=R_8=H$
5 $R_1=H$, $R_5=R_8=Me$
6 $R_1=R_5=R_8=Me$

ing (16) of H-2 and H-4, while H-6 and H-7 remained unchanged. It is of interest to note that the mp and ^{1}H-nmr spectrum of our synthetic xanthone are significantly different from those of a compound isolated from *Swertia petiolata* and also assigned structure **8** (17).

The poor yield of this equally useful xanthone **8** from the GSS reaction prompted us to attempt the condensation of 2,3,6-trimethoxybenzoic acid and phloroglucinol by a more recent method using P_2O_5 and $MeSO_3H$ (18). The reaction gave less resinous material, and the crude product, after recrystallizations from EtOH, afforded pure **8** in 33% yield.

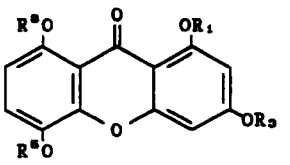
Isoprenylation of **8** with 1-bromo-3-methylbut-2-ene in the presence of NaOMe (8) resulted in a mixture which was found to be unstable to chromatography over Si gel. The crude product was therefore methylated with Me_2SO_4 and separated by flash chromatography. Three compounds were eluted, and based on analytical and spectroscopic data, they were assigned structures **2**, **5**, and **6**. ^{1}H-nmr spectroscopy showed compounds **5** and **6** to be mono-3-methylbut-2-enylated and to contain three and four methoxyls, respectively. Methylation of **5** gave **6**. The site of the alkenyl group was established as C-2 from the ^{13}C-nmr spectrum of **6** (Table 1), which displayed one di-ortho-substituted methoxyl carbon (δ>60) (19). The ^{1}H-nmr spectrum of the third product exhibited signals for two 3-methylbut-2-enyl groups, three methoxyls, and a chelated hydroxyl. The ^{13}C-nmr chemical shifts of the methoxyl groups (Table 1) are in accord with this compound having structure **2**. From the recrystallization mother liquor of xanthone **5**, a fourth product, isomeric with **5**, was obtained in trace quantity by plc. This xanthone was assigned the 4-(3-methylbut-2-enyl) structure **12**, as the aromatic singlet (H-2) appears upfield at δ 6.35 (20).

As it is often difficult to distinguish between 2- and 4-(3-methylbut-2-enyl)-1,3-dioxygenated xanthones, it is worth mentioning that the separation of the two ^{1}H-nmr

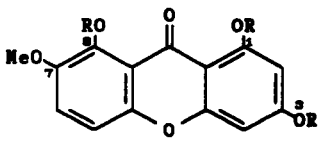
TABLE 1. ^{13}C-nmr Spectra of Synthetic Xanthones.

Carbon	Compound					
	8 (DMSO-d_6)	**9** ($CDCl_3$)	**1**[a] ($CDCl_3$)	**2**[b] ($CDCl_3$)	**3**[c] ($CDCl_3$)	**4** (DMSO-d_6)
1	163.0	161.4	158.2	159.1	157.9	157.9
2	98.1	95.6	107.2	112.7	107.8	111.0
3	165.0	164.4	161.6	163.4	161.7	164.7
4	93.2	92.4	109.5	117.3	109.7	90.6
5	141.3	141.9	136.1	142.5	140.1	137.3
6	117.7	115.5	121.0	117.5	120.5	123.5
7	105.4	105.4	109.6	104.2	108.7	109.2
8	152.8	153.8	153.9[d]	153.8[d]	154.2[d]	151.7
9	180.8	175.2	184.6	182.2	184.8	184.0
4a	156.1	158.6	152.5[d]	151.9[d]	152.6[d]	155.8
8a	110.7	108.5	105.8	111.7	105.9	107.5
9a	102.6	102.7	102.2	106.6	102.3	101.8
10a	146.4	146.8	142.9	148.2	145.7	143.4
a	—	—	21.6	22.6	21.9	20.7
b	—	—	121.9	122.9	121.4	121.8
c	—	—	133.9	131.6	134.4	130.9
d	—	—	25.8	25.7	25.8	25.5
e	—	—	17.9	17.8	17.9	17.6
OMe	56.1 56.4	55.7 56.2 56.8 56.9	—	56.5 57.1 61.8	57.4	56.4

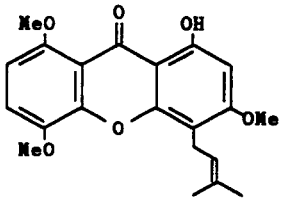
[a]Additional signals from second 3-methylbut-2-enyl group (a'–e'): 22.0, 122.9, 135.8, 25.7, 17.9.
[b]Additional signals from second 3-methylbut-2-enyl group (a'–e'): 22.7, 122.5, 132.0, 25.7, 17.9.
[c]Additional signals from second 3-methylbut-2-enyl group (a'–e'): 21.6, 121.5, 135.1, 25.8, 17.8.
[d]Assignments in the same column may be interchanged.
[e]Not observed.



7 $R_1=R_3=R_8=H$, $R_5=Me$
8 $R_1=R_3=H$, $R_5=R_8=Me$
9 $R_1=R_3=R_5=R_8=Me$



10 R=H
11 R=Me



12

singlets due to the side-chain methyl groups appears to be of diagnostic value. In the spectra of all the 2-(3-methylbut-2-enyl)-xanthones reported herein the separation is 0.11–0.14 ppm, whereas the spectrum of 4-(3-methylbut-2-enyl)xanthone **12** shows a greater separation (0.18 ppm). A similar separation (0.18–0.20 ppm) is also apparent in the spectra of other 4-(3-methylbut-2-enyl)xanthones (21–23).

Although a variety of reagents have been used in the selective demethylation of polymethoxyxanthones (24,25), only aqueous piperidine or aqueous morpholine (5) is eminently suited to effect such reaction involving 3-methylbut-2-enylated poly-

TABLE 1. (Continued).

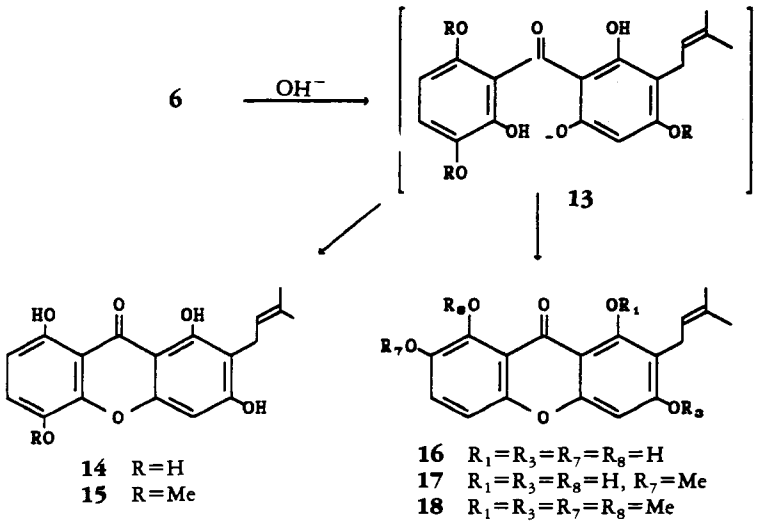
Compound								
5 ($CDCl_3$)	**6** ($CDCl_3$)	**14** (Me_2CO-d_6)	**15** (DMSO-d_6)	**10** (DMSO-d_6)	**11** ($CDCl_3$)	**16** (Me_2CO-d_6)	**17** (Me_2CO-d_6)	**18** ($CDCl_3$)
159.5	158.6	160.8	158.9	162.1	161.7	160.7	160.8	158.7
111.6	121.2	111.9	110.6	98.2	95.6	111.5	111.7	120.6
163.7	162.5	164.7	164.3	166.6	164.4	164.9	165.0	162.7
89.2	95.0	94.5	93.6	94.1	92.4	94.3	94.4	94.4
141.7	141.9	137.5	139.5	105.5	112.0	106.8	106.2	112.1
116.1	115.4	124.2	120.8	121.2	118.8	124.2	123.0	119.3
104.1	104.9	110.1	108.7	142.5	150.2[d]	141.1	143.8	150.4[d]
153.3[d]	153.8	154.1	152.7	149.1[d]	149.4[d]	149.6[d]	150.4[d]	149.1[d]
180.9	174.9	185.4	183.4	183.8	175.2	185.5	185.7	174.8
154.7[d]	156.4	156.5	155.0	157.7	159.1	157.1	156.9	156.8
n.o.[e]	114.5	108.3	107.2	106.9	118.5	108.2	108.4	118.5
104.0	111.5	102.6	100.9	100.7	107.8	102.1	102.1	110.6
147.1	147.0	144.4	144.4	148.7[d]	149.0[d]	147.9[d]	151.4[d]	n.o.
21.4	22.4	21.9	20.8	—	—	21.8	21.9	22.3
122.2	122.8	123.0	121.9	—	—	123.0	122.5	122.7
131.7	131.4	131.7	130.7	—	—	131.6	131.8	131.4
25.8	25.7	25.8	25.4	—	—	25.8	25.8	25.7
17.8	17.8	17.9	17.6	—	—	17.9	17.9	17.8
56.0	56.0	—	56.6	56.6	55.6	—	57.4	55.8
56.6	56.8				56.3			57.3
56.9	56.8				57.0			61.1
	62.3				61.7			62.1

methoxyxanthones. Treatment of xanthone **2** with aqueous morpholine at 145° for 7 days gave, in addition to the expected gartanin [**1**], a trihydroxymethoxyxanthone which showed two chelated hydroxyl protons in its ^{1}H-nmr spectrum. The third hydroxyl was placed in the 3 position because the uv spectrum showed a bathochromic shift of the long-wavelength band on addition of NaOAc. Thus, the second product was 5-*O*-methylgartanin [**3**].

Similar demethylation of the 2-(3-methylbut-2-enyl)xanthone **5** yielded a mixture which was separated by normal and centrifugal plc into four products. Analytical and ^{1}H-nmr data indicated that two of the compounds were fully demethylated, monoprenylated xanthones. Only one of these contained a quinol moiety as indicated by a positive gosseypetone test (26). This compound was therefore 1,3,5,8-tetrahydroxy-2-(3-methylbut-2-enyl)xanthone [**14**]. Selective methylation of **14** gave the natural product **4**, identified by comparison of its diacetate with an authentic sample. The uv spectrum of the second tetrahydroxyxanthone indicated a 1,3,7,8-oxygenation pattern (14), suggesting structure **16**. This was confirmed by total methylation to give a tetra-*O*-methyl derivative **18** that displayed two di-ortho-substituted methoxyl carbons in its ^{13}C-nmr spectrum. Based on their ^{1}H-nmr and uv spectra, the remaining two products were assigned as the 5- and 7-*O*-methyl derivatives **15** and **17**. Total methylation of **17** also yielded **18**.

The isolation of xanthones **16** and **17** from the reaction of **5** with hot aqueous morpholine could only be explained if ring-opening to an intermediate benzophenone **13** had occurred. Re-cyclization of **13** could then result in a mixture of 1,3,5,8- and 1,3,7,8-tetraoxygenated xanthones as shown in Scheme 1. This is not unlike the mechanism proposed for the Wessely-Moser rearrangement of 1,4-dihydroxy-7-methoxyxanthone to 1,2,7-trihydroxyxanthone in the course of demethylation with HI (27).

To explore this rearrangement, both 1,3,5,8- and 1,3,7,8-tetramethoxyxanthones **9** and **11** were separately subjected to similar treatment with aqueous morpholine. Both reactions yielded complex mixtures which appeared almost identical on tlc. The mixtures were simplified by methylation with excess Me_2SO_4. The products of each reaction were found to contain low yields of both 1,3,7,8- and 1,3,5,8-tetramethoxyxanthones in approximately the same ratio (7:1 by ^{1}H nmr).



14 R=H
15 R=Me

16 $R_1=R_3=R_7=R_8=H$
17 $R_1=R_3=R_8=H$, $R_7=Me$
18 $R_1=R_3=R_7=R_8=Me$

SCHEME 1

Because cyclization of 2,2′-dioxygenated benzophenones to xanthones is well-known to be catalyzed by hot aqueous organic bases (24), our observations imply that this reaction is reversible under these conditions. Consequently, 1,2(or 7,8)- or 1,4(or 5,8)-dioxygenated xanthones may undergo rearrangement in hot alkaline media.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Unless otherwise stated, uv-visible spectra were measured in EtOH with a Shimadzu UV-240 spectrophotometer, and ^{1}H- and ^{13}C-nmr spectra were determined in $CDCl_3$ solutions with a JEOL FX-90Q FT spectrometer. Mass spectra were recorded at 70 eV with a VG Micromass 7035 instrument. Plc was conducted using Merck Kieselgel 60 glass-backed plates (0.5 mm layer) and on a Chromatotron (Harrison Research, California) (2 mm layer). Hexane refers to the fraction of bp 64–68°. Elemental analyses were carried out by the Microanalytical Laboratory, National University of Singapore.

REACTION OF 2,3,6-TRIMETHOXYBENZOIC ACID WITH PHLOROGLUCINOL.—*Grover, Shah and Shah conditions* (13,28).—A mixture of 2,3,6-trimethoxybenzoic acid (29) (6.4 g, 30 mmol), phloroglucinol (6.3 g, 50 mmol), freshly fused $ZnCl_2$ (13 g), and $POCl_3$ (30 ml) was heated at 75° for 2.5 h and then poured into ice-H_2O. The product, after drying, was extracted with hot EtOAc to yield a red-brown solid which was separated by flash chromatography. Elution with hexane-EtOAc (1:1) gave 1,3,8-trihydroxy-7-methoxyxanthone [**10**] (1.1 g): mp 298–300° (EtOH) [lit. (13) 300°]; uv λ max (log ε) 370 (sh), 332 (4.12), 315 (sh), 262 (4.34), 236 (4.33); +NaOAc 360 (4.29), 268 (4.26), 262 (4.24), 235 nm (4.42); ^{1}H nmr ($CDCl_3$/DMSO-d_6) δ 3.91 (3H, s, OMe), 6.21, 6.32 (1H each, d, J = 1.9 Hz, H-2, H-4), 6.83, 7.30 (1H each, d, J = 9.1 Hz, H-5, H-6), 11.83, 12.10 (1H each, s, 8-OH, 1-OH). Tri-*O*-methyl derivative **11**: mp 168° [lit. (13) 166–167°]. Further elution gave 1,3-dihydroxy-5,8-dimethoxyxanthone [**8**] (0.3 g): mp 292–295° (EtOH) [lit. (17) 192.5–194.5°]; uv λ max (log ε) 365 (sh), 330 (4.11), 273 (4.11), 248 (4.43), 240 (sh); +NaOAc 354 (4.21), 272 (4.18), 249 (4.46), 240 nm (sh); ^{1}H nmr ($CDCl_3$/DMSO-d_6) δ 3.96, 3.97 (3H each, s, 2 × OMe), 6.27, 6.43 (1H each, d, J = 2.0 Hz, H-2, H-4), 6.71, 7.20 (1H each, d, J = 9.2 Hz, H-7, H-6), 10.15 (1H, s, 3-OH), 13.22 (1H, s, 1-OH); ms *m/z* 288 (100%), 273 (32), 271 (13), 259 (69), 257 (36), 245 (18), 244 (26), 242 (12), 229 (11). *Anal.* calcd for $C_{15}H_{12}O_6$, C 62.50, H 4.20; found C 62.46, H 4.16. Di-*O*-methyl derivative **9**: mp 210–212° [lit. (13) 210°]; diacetate, mp 196°; ^{1}H nmr δ 2.33, 2.48 (3H each, s, 2 × MeCO), 3.93, 3.94 (2 × OMe), 6.69, 7.16 (1H each, d, J = 9.1 Hz, H-7, H-6), 6.78, 7.31 (1H each, d, J = 2.3 Hz, H-2, H-4); ms *m/z* $[M]^+$ 372.0846 (calcd for $C_{19}H_{16}O_8$, 372.0845) (14%), 330 (92), 270 (100), 259 (52).

In the presence of P_2O_5/$MeSO_3H$ (18).—A mixture of P_2O_5 (5 g) and $MeSO_3H$ (35 ml) was heated for 45 min on a steam bath, and to this was added phloroglucinol (2.5 g, 20 mmol) and 2,3,6-trimethoxybenzoic acid (2.1 g, 10 mmol). Heating was continued for a further 25 min, and the viscous residue was poured into ice-H_2O. The product, after drying, was extracted repeatedly with hot EtOAc (9 × 100 ml). The extract, on concentrating to a small volume (100 ml), deposited a yellow solid which was filtered and washed with cold EtOAc (30 ml). Three recrystallizations of the solid from aqueous EtOH afforded pure 1,3-dihydroxy-5,8-dimethoxyxanthone [**8**] (0.95 g), mp and mmp 293–295°. A further quantity of this xanthone (0.3 g) was obtained from the filtrate by flash chromatography using hexane-EtOAc (1:1) as eluent.

3-METHYLBUT-2-ENYLATION OF XANTHONE **8**.—Following the published method (8), xanthone **8** (8.35 g, 29 mmol) in dry MeOH (120 ml) was treated with a solution of NaOMe (100 ml, from 10.5 g Na) and 1-bromo-3-methylbut-2-ene (14 ml, 121 mmol) under N_2. The solution was heated at reflux for 3 h, then concentrated to dryness in vacuo and the residue acidified with 50% HCl (90 ml). The precipitate was filtered off, washed thoroughly with H_2O, and dried under vacuum over P_2O_5. To the dried solid (12.8 g) in Me_2CO (150 ml) was added anhydrous K_2CO_3 (18 g) and Me_2SO_4 (11 ml), and the mixture was stirred and heated at reflux for 20 h. After filtration and evaporation of the solvent, the red gum (10.5 g) that remained was divided into two portions and subjected to flash chromatography. Elution with hexane-EtOAc (3:1 to 1:1) gave the following three compounds.

1-Hydroxy-3,5,8-trimethoxy-2-(3-methylbut-2-enyl)xanthone [**5**].—Pale yellow plates (wt 1.05 g): mp 167–169° (aqueous EtOH); uv λ max (log ε) 370 (sh), 325 (4.08), 277 (4.33), 250 (sh), 244 nm (4.44); ^{1}H nmr δ 1.67, 1.79 (3H each, s, Me_2C), 3.34 (2H, br d, CH_2), 3.90 (3H), 3.96 (6H) (each s, 3 × OMe), 5.24 (1H, br t, CH), 6.49 (1H, s, 4-H), 6.67, 7.14 (1H each, d, J = 8.9 Hz, H-7, H-6), 13.22 (1H, s, 1-OH). *Anal.* calcd for $C_{21}H_{22}O_6$, C 68.09, H 5.99; found C 68.22, H 5.88.

1-Hydroxy-3,5,8-trimethoxy-2,4-di-(3-methylbut-2-enyl)-xanthone [**2**].—Light yellow needles (wt 0.84 g): mp 108–110° (aqueous MeOH); uv λ max (log ε) 342 (4.08), 276 (4.34), 255 (4.50), 238 nm (4.43); ^{1}H nmr δ 1.69 (6H), 1.80 (3H), 1.85 (3H) (each s, 2 × Me_2C), 3.41, 3.54 (2H each, br d,

$2\times CH_2$), 3.81, 3.92, 3.97 (3H each, s, $3\times OMe$), 5.30 (2H, br t, $2\times CH$), 6.67, 7.17 (1H each, d, $J=9.2$ Hz, H-7, H-6), 13.25 (1H, s, 1-OH); ms *m/z* 438 (61%), 396 (22), 395 (100), 383 (70), 369 (14), 367 (14), 313 (23), 51 (23). *Anal.* calcd for $C_{26}H_{30}O_6$, C 71.21, H 6.90; found C 71.29, H 6.88. Methylation gave tetra-*O*-methylgartanin, mp 87–89° (hexane) [lit. (6) 85°], with ^{1}H-nmr data comparable to that reported (6).

1,3,5,8-Tetramethoxy-2-(3-methylbut-2-enyl)xanthone [**6**].—Colorless needles (wt 0.3 g): mp 162–164° (aqueous EtOH); ^{1}H nmr δ 1.67, 1.79 (3H each, s, $2\times Me_2C$), 3.38 (2H, br d, CH_2), 3.91, 3.93, 3.94, 3.97 (each s, $4\times OMe$), 5.17 (1H, br t, CH), 6.73 (1H, s, 4-H), 6.68, 7.10 (1H each, d, $J=9.0$ Hz, H-7, H-6). *Anal.* calcd for $C_{22}H_{24}O_6$, C 68.74, H 6.29; found C 68.62, H 6.21.

From the mother liquor from the recrystallizations of xanthone **5** a minor product was obtained by plc [hexane-EtOAc, (2:1)]. *1-Hydroxy-3,5,8-trimethoxy-4-(3-methylbut-2-enyl)xanthone* [**12**] crystallized from aqueous EtOH as fine yellow needles: mp 167–169°; uv λ max (log ε) 340 (4.13), 315 (sh), 274 (4.17), 252 (4.43), 238 nm (4.34); ^{1}H nmr δ 1.67, 1.85 (3H each, s, Me_2C), 3.51 (2H, br d, CH_2), 3.90, 3.92, 3.97 (3H each, s, $3\times OMe$), 5.27 (1H, br t, CH), 6.35 (1H, s, H-2), 6.67, 7.16 (1H each, d, $J=9.0$ Hz, H-7, H-6), 13.3 (1H, s, 1-OH); ms *m/z* 370 (79%), 3.55 (100), 337 (15), 315 (18). *Anal.* calcd for $C_{21}H_{22}O_6$, C 68.09, H 5.99; found C 68.23, H 5.72.

DEMETHYLATION OF XANTHONE **2** WITH AQUEOUS MORPHOLINE (5).—Xanthone **2** (543 mg), morpholine (12 ml), and H_2O (3 ml) sealed under N_2 in a glass tube were heated at 140–145° for 7 days. The cooled solution was poured into ice-cold 2 M HCl (50 ml), and the precipitate was filtered, washed with H_2O, and dried. Separation of the products on plc developed with hexane-EtOAc (3:1) yielded 1,3,8-trihydroxy-5-methoxy-2,4-di-(3-methylbut-2-enyl)xanthone [**3**] (135 mg) as yellow needles (hexane/CH_2Cl_2): mp 137–139°; uv λ max (log ε) 357 (4.19), 318 (sh), 283 (4.43), 238 (sh); +NaOAc 379 (4.35), 284 (4.40), 240 nm (sh); ^{1}H nmr δ 1.76 (6H), 1.86 (3H), 1.88 (3H) (each s, $2\times Me_2C$), 3.12, 3.19 (2H each, br d, $2\times CH_2$), 3.92 (3H, s, 5-OMe), 5.26 (2H, br t, $2\times CH$), 6.57 (1H, s, 3-OH), 6.68, 7.21 (1H each, d, $J=9.0$ Hz, H-7, H-6), 11.50, 12.32 (1H each, s, 8-OH, 1-OH) (*Anal.* calcd for $C_{24}H_{26}O_6$, C 70.23, H 6.38; found C 70.25, H 6.25); and gartanin [**1**] (128 mg), mp and mmp 167–169°, with uv and ^{1}H-nmr spectra in agreement with published data (5); tetra-*O*-methyl derivative, mp 87–89° [*lit.* (5) 85°].

DEMETHYLATION OF XANTHONE **5**.—Xanthone **5** (655 mg) was similarly treated with morpholine (18 ml) and H_2O (2 ml) and worked up as described above. Analytical tlc [hexane-EtOAc (1:1)] of the crude product showed a spot at R_f 0.18 and two unresolved spots at R_f 0.37. The mixture was separated by plc to yield pure 1,3,5,8-tetrahydroxy-2-(3-methylbut-2-enyl)xanthone [**14**] (136 mg) as yellow-brown rods: mp 260–262° (aqueous MeOH); uv λ max (log ε) 346 (4.18), 317 (sh), 282 (4.39), 255 (sh), 239 nm (sh); ^{1}H nmr [$(CD_3)_2CO$] δ 1.66, 1.79 (3H each, s, Me_2C), 3.36 (2H, br d, CH_2), 5.27 (1H, br t, CH), 6.56 (1H, 2, H-4), 6.61, 7.28 (1H each, d, $J=8.9$ Hz, H-7, H-6), 11.23, 12.27 (1H each, s, 8-OH, 1-OH); ms *m/z* 328 (76%), 313 (38), 285 (66), 273 (100), 260 (12), 149 (13). *Anal.* calcd for $C_{18}H_{16}O_6$, C 65.85, H 4.91; found C 65.57, H 4.78. The less polar band (235 mg) at R_f 0.37 was separated on a Chromatotron using gradient elution with hexane-CH_2Cl_2 (1:1) to 100% CH_2Cl_2 to give the following three compounds.

1,3,8-Trihydroxy-5-methoxy-2-(3-methylbut-2-enyl)xanthone [**15**].—Yellow prisms (55 mg): mp 246–249° (MeOH); uv λ max (log ε) 375 (sh), 343 (4.03), 330 (sh), 279 (4.21), 250 (sh), 240 (4.30); +NaOAc 372 (4.10), 278 (4.20), 238 nm (4.36); ^{1}H nmr [$(CD_3)_2CO$] δ 1.65, 1.66 (3H each, s, Me_2C), 3.37 (2H, br d, CH_2), 3.94 (3H, s, 5-OMe), 5.28 (1H, br t, CH), 6.58 (1H, s, 4-H), 6.68, 7.42 (1H each, d, $J=9.2$ Hz, H-7, H-6), 11.36, 12.23 (1H each, s, 8-OH, 1-OH); ms *m/z* 342 (92%), 327 (47), 299 (72), 287 (100), 271 (63). *Anal.* calcd for $C_{19}H_{18}O_6$, C 66.66, H 5.30; found C 66.48, H 5.19.

1,3,8-Trihydroxy-7-methoxy-2-(3-methylbut-2-enyl)xanthone [**17**].—Yellow needles (85 mg): mp 195–197° (aqueous MeOH); uv λ max (log ε) 385 (3.60), 327 (4.20), 271 (4.41), 264 (4.39), 240 (4.41); +NaOAc 372 (4.25), 271 (4.44), 263 (4.41), 239 nm (4.46); ^{1}H nmr ($CDCl_3$/DMSO-d_6) δ 1.68, 1.80 (3H each, s, Me_2C), 3.36 (2H, br d, CH_2), 3.92 (3H, s, 7-OMe), 5.27 (1H, br t, CH), 6.42 (1H, s, H-4), 6.79, 7.23 (1H, each, d, $J=9.1$ Hz, H-5, H-6), 9.94 (1H, br s, 3-OH), 12.12, 12.29 (1H each, s, 8-OH, 1-OH); ms *m/z* 342 (84%), 327 (25), 299 (94), 287 (100). *Anal.* calcd for $C_{19}H_{18}O_6$, C 66.66, H 5.30; found C 66.48, H 5.07. Triacetate, pale yellow needles (aqueous MeOH): mp 187–189°; ^{1}H nmr δ 1.67 (3H), 1.74 (3H), 2.34 (3H), 2.45 (6H), 3.25 (2H), 3.88 (3H), 7.15 (1H, s, H-4), 7.33 (2H, s, H-5, H-6); ms *m/z* $[M]^+$ 468.1422 (calcd for $C_{25}H_{24}O_9$, 468.1420) (4%), 426 (100), 384 (66), 341 (64), 329 (28), 299 (51), 287 (67). Tri-*O*-methyl derivative **18**: mp 151–152°; uv λ max 354, 305 (sh), 286, 246 nm; ^{1}H nmr δ 1.67, 1.80 (3H each, s, Me_2C), 3.39 (2H, br d, CH_2), 3.90 (9H, s, $3\times OMe$), 4.00 (3H, s, OMe), 5.18 (1H, br t, CH), 6.57 (1H, s, H-4), 7.07, 7.25 (1H each, d, $J=9.3$ Hz, H-5, H-6). *Anal.* calcd for $C_{22}H_{24}O_6$, C 68.73, H 6.29; found C 68.70, H 6.33.

1,3,7,8-Tetrahydroxy-2-(3-methylbut-2-enyl)xanthone [**16**].—Yellow needles (80 mg): mp 202–204° (C_6H_6/hexane); uv λ max (log ε) 392 (3.73), 324 (4.25), 271 (4.45), 266 (4.43), 240 nm (4.43); ^{1}H nmr [$(CD_3)_2CO$] δ 1.66, 1.79 (3H each, s, Me_2C), 3.33 (2H, br d, CH_2), 5.26 (1H, br t, CH), 6.44 (1H, s, H-4), 6.81, 7.27 (1H each, d, J = 8.9 Hz, H-5, H-6), 7.95, 9.99 (1H each, br s, 3-OH, 7-OH), 11.83, 12.16 (1H each, s, 8-OH, 1-OH); ms *m/z* 328 (73%), 313 (32), 285 (59), 273 (100), 272 (41). *Anal.* calcd for $C_{18}H_{16}O_6$, C 65.85, H 4.91; found C 65.93, H 4.84. Methylation with Me_2SO_4/K_2CO_3 gave a product identical (uv, mmp, ^{1}H nmr) with xanthone **18**.

SELECTIVE METHYLATION OF XANTHONE **14**.—A mixture of **14** (90 mg, 0.28 mmol), Me_2SO_4 (55 mg, 0.43 mmol), and anhydrous K_2CO_3 (0.2 g) in Me_2CO (8 ml) was heated at reflux for 12 h. The products were separated by plc (hexane-EtOAc, 3:1) to give the following two compounds.

1,5,8-Trihydroxy-3-methoxy-2-(3-methylbut-2-enyl)xanthone [**4**].—Yellow-orange needles (aqueous EtOH): mp 205–207° (softens at 190°) [lit. (7) 193–195°]; uv λ max (log ε) 398 (3.60), 336 (4.00), 314 (3.95), 282 (4.37), 256 (4.31), 242 nm (4.27), unchanged on addition of NaOAc; ^{1}H nmr (DMSO-d_6) δ 1.62, 1.71 (3H each, s, Me_2C), 3.17 (2H, br d, CH_2), 3.91 (3H, s, 3-OMe), 5.11 (1H, br t, CH), 6.62 (1H, s, H-4), 6.70, 7.24 (1H each, d, J = 8.8 Hz, H-7, H-6), 9.66 (1H, s, 5-OH), 11.06, 12.01 (1H, s, 8-OH, 1-OH); ms *m/z* 342 (79%), 327 (50), 299 (81), 287 (100), 274 (16). *Anal.* calcd for $C_{19}H_{18}O_6$, C 66.66, H 5.30; found C 66.49, H 5.47. Diacetate (prepared using two equivalents of Ac_2O and stirring overnight at 30°), pale yellow needles (aqueous EtOH): mp 206–208° [lit. (7) 172–175°]; uv λ max (log ε) 365 (sh), 324 (4.23), 266 (4.11), 255 (sh), 241 nm (4.45); ^{1}H nmr δ 1.68, 1.78 (3H each, s, Me_2C), 2.28, 2.29 (3H each, s, 5- and 8-MeCO), 3.23 (2H, br d, CH_2), 3.92 (3H, s, 3-OMe), 5.19 (1H, br t, CH), 6.34 (1H, s, H-4), 6.94, 7.43 (1H each, d, J = 8.7 Hz, H-7, H-6), 12.79 (1H, s, 1-OH); ms *m/z* 426 (46%), 384 (38), 371 (34), 342 (54), 329 (34), 327 (41), 299 (76), 287 (100). *Anal.* calcd for $C_{23}H_{22}O_8$, C 64.78, H 5.20; found C 64.49, H 4.99. This compound was identical (uv, tlc, ^{1}H nmr) to an authentic sample.

1,8-Dihydroxy-3,5-dimethoxy-2-(3-methylbut-2-enyl)xanthone.—Yellow needles: mp 182–184° (MeOH); uv λ max (log ε) 390 (3.64), 335 (4.03), 315 (4.00), 282 (4.38), 255 (4.34), 242 nm (4.32); ^{1}H nmr δ 1.69, 1.80 (3H each, s, Me_2C), 3.34 (2H, br t, CH_2), 5.21 (1H, br t, CH), 6.53 (1H, s, H-4), 6.67, 7.19 (1H each, d, J = 8.9 Hz, H-7, H-6), 11.47, 12.04 (1H each, s, 8-OH, 1-OH); ms *m/z* $[M]^+$ 356.1268 (calcd for $C_{20}H_{20}O_6$, 356.1260) (80%), 341 (53), 313 (92), 301 (100), 285 (31). This compound was identical (mmp, uv, ^{1}H nmr) to a xanthone isolated from the methylated extract of *G. mangostana* leaves (30).

DEMETHYLATION OF 1,3,5,8-TETRAMETHOXYXANTHONE [**9**].—Xanthone **9** (110 mg) was similarly heated with morpholine (4 ml) and H_2O (1 ml) at 150° for 7 days and worked up as described for xanthone **2**. The dried precipitate was treated with excess Me_2SO_4 in refluxing Me_2CO for 15 h in the presence of anhydrous K_2CO_3, and the products were separated by plc, using EtOAc-hexane (1.5:1) (two developments). The major band at R_f 0.28 gave 1,3,7,8-tetramethoxyxanthone [**11**] (7 mg), identified by its ^{1}H-nmr and uv spectra, tlc, mmp 167–168°. A band at R_f 0.11 gave unreacted starting material **9** (1 mg), identified by uv and ^{1}H nmr.

DEMETHYLATION OF 1,3,7,8-TETRAMETHOXYXANTHONE [**11**].—Xanthone **11** (110 mg) was reacted with aqueous morpholine as described above. The methylated products were similarly separated by plc and gave chiefly the starting xanthone **11** (5 mg), with 1,3,5,8-tetramethoxyxanthone [**9**] in trace amount, both identified by tlc, uv, and ^{1}H nmr.

ACKNOWLEDGMENTS

We are grateful to Dr. N.U. Khan for providing an authentic sample of the diacetate of **4**.

LITERATURE CITED

1. W. Mahabusarakam, P. Wiriyachitra, and S. Phongpaichit, *J. Sci. Soc. Thailand*, **12**, 239 (1986).
2. P. Yates and G.H. Stout, *J. Am. Chem. Soc.*, **80**, 1961 (1958).
3. B.M. Sundaram, C. Gopalakrishnan, S. Subramanian, D. Shankaranarayanan, and L. Kameswaran, *Planta Med.*, **49**, 59 (1983).
4. G.J. Bennett and H.H. Lee, *Phytochemistry*, **28**, 967 (1989).
5. A. Jefferson, A.J. Quillinan, F. Scheinmann, and K.Y. Sim, *Aust. J. Chem.*, **23**, 2539 (1970).
6. T.R. Govindachari, P.S. Kalyamaraman, N. Muthukumaraswarmy, and B.P. Pai, *Tetrahedron*, **27**, 3919 (1971).
7. M. Parveen and N.U. Khan, *Phytochemistry*, **27**, 3694 (1988).
8. S.M. Anand and A.C. Jain, *Aust. J. Chem.*, **27**, 1515 (1974).
9. S.M. Anand and A.C. Jain, *Indian J. Chem.*, **11**, 1233 (1973).

10. H.H. Lee, *J. Chem. Soc., Perkin Trans. 1,* 3205 (1981).
11. G.J. Bennett and H.H. Lee, *Tetrahedron Lett.,* **30**, 7265 (1989).
12. K.R. Markham, *Tetrahedron,* **21**, 1449 (1965).
13. S.R. Dalal and R.C. Shah, *Chem. Ind. (London),* 140 (1957).
14. K.R. Markham, *Tetrahedron,* **21**, 3687 (1965).
15. R.K. Chaudhuri and S. Ghosal, *Phytochemistry,* **10**, 2425 (1971).
16. G. Delle Monache, F. Delle Monache, P.G. Waterman, E.G. Crichton, and R. Alves De Lima, *Phytochemistry,* **23**, 1757 (1984).
17. P. Kulanthaivel, S.W. Pelletier, K. Khetwal, and D.L. Verma, *J. Nat. Prod.,* **51**, 379 (1988).
18. R.K.M. Pillai, P. Naiksatam, F. Johnson, R. Rajogopalan, P.C. Watts, R. Cricchio, and S. Borras, *J. Org. Chem.,* **51**, 717 (1986).
19. K.S. Dhami and J.B. Stothers, *Can. J. Chem.,* **44**, 2855 (1966).
20. D. Barraclough, H.D. Locksley, F. Scheinmann, M. Taveira Magalhaes, and O.R. Gottlieb, *J. Chem. Soc. B,* 603 (1970).
21. H.D. Locksley, I. Moore, and F. Scheinmann, *J. Chem. Soc. C,* 2265 (1966).
22. E.D. Burling, A. Jefferson, and F. Scheinmann, *Tetrahedron,* **21**, 2653 (1965).
23. P.J. Owen and F. Scheinmann, *J. Chem. Soc., Perkin Trans. 1,* 1018 (1974).
24. A.J. Quillinan and F. Scheinmann, *J. Chem. Soc. C,* 1329 (1973).
25. R.K. Chaudhuri, F. Zymalkowski, and S. Ghosal, *J. Pharm. Sci.,* **67**, 1321 (1978).
26. A.G. Perkin, *J. Chem. Soc.,* **103**, 657 (1913).
27. E.M. Philbin, J. Swirski, and T.S. Wheeler, *J. Chem. Soc.,* 4455 (1956).
28. P.K. Grover, G.D. Shah, and R.C. Shah, *J. Chem. Soc. C,* 3982 (1955).
29. H. Gilman and J.R. Thirtle, *J. Am. Chem. Soc.,* **66**, 858 (1945).
30. G.J. Bennett, "The Biosynthesis and Biomimetic Synthesis of Natural Products," Ph.D. Thesis, National University of Singapore, 1990, p. 153.

Received 26 March 1990