Pergamon

Tetrahedron 55 (1999) 861–868

TETRAHEDRON

The First Direct Transformation of 2,2′-Dihydroxychalcones into Coumestans

B. Irene Kamara, E. Vincent Brandt,* Daneel Ferreira*

Department of Chemistry, University of the Orange Free State, P.O. Box 339, Bloemfontein 9300, South Africa

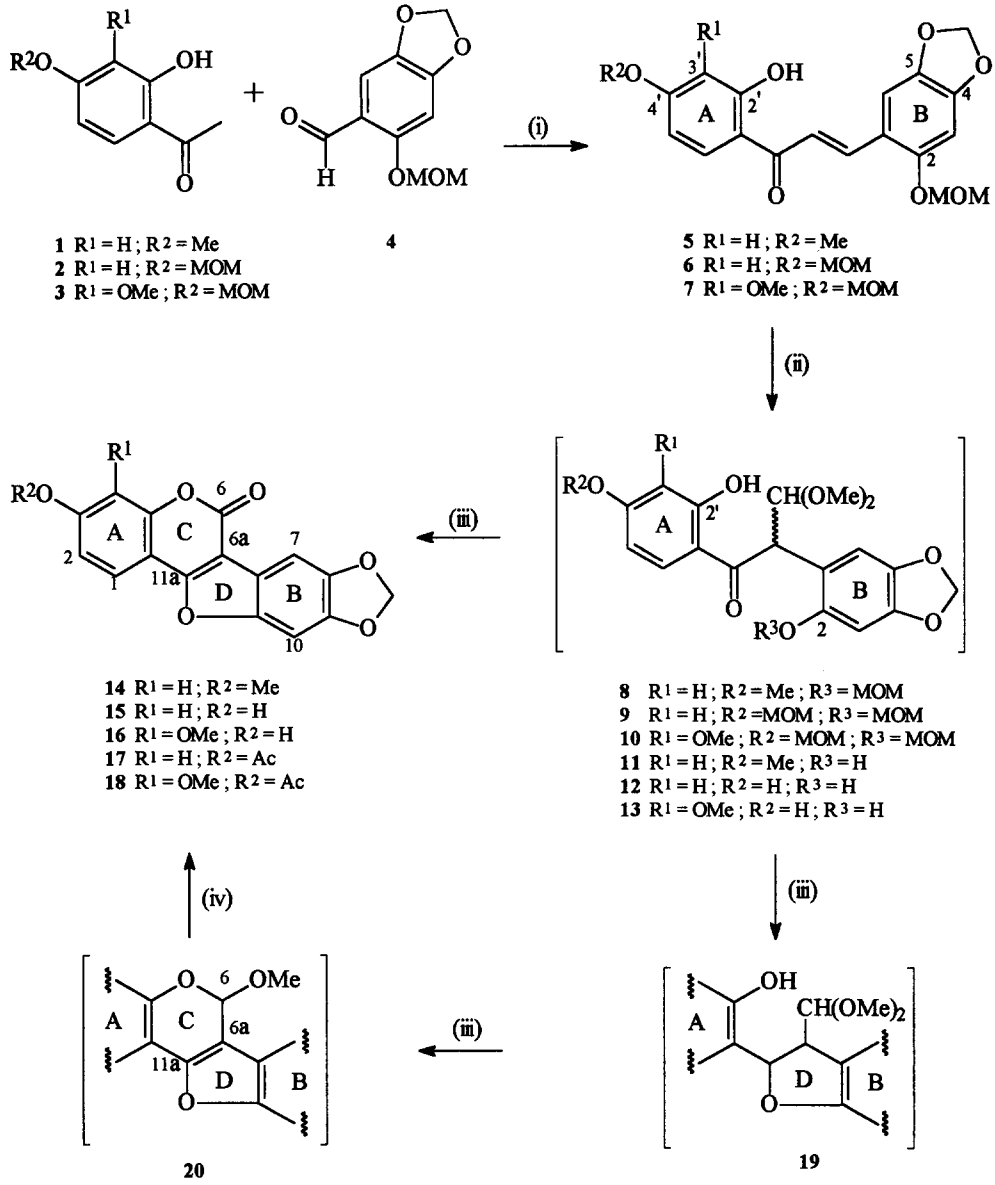
Received 20 August 1998; revised 27 October 1998; accepted 12 November 1998

Abstract - Three coumestans, flemichapparin, medicagol and sophoracoumestan B, are synthesised by direct reaction of the analogous 2,2′-dihydroxychalcones with thallium(III) nitrate in methanol.

Keywords: Chalcones, oxidation, rearrangement, coumestans.

Coumestans, representing the fully oxidized state of the heterocyclic C-ring of isoflavonoids, are widely distributed and possess pronounced physiological activity [1]. Amongst the multitude of synthetic routes to coumestans, the most feasible ones involve the oxidative conversion of pterocarpans [2], 6*a*,11*a*-dehydropterocarpans [2] and 2′-hydroxy-3-arylcoumarins [3], and the tyrosinase-catalyzed coupling of suitably substituted 4-hydroxycoumarins with *o*-quinols [4]. Part of our investigation of the phenolic profile of *Cyclopia intermedia*, one of the primary sources for the health beverage, honeybush tea [2], required the availability of substantial quantities of the coumestans flemichapparin (**14**), medicagol (**15**) and sophoracoumestan (**16**) with a view to unequivocally establish their structures and claimed physiological activity [6-9]. Herein we discuss their syntheses *via* a one-step reaction of the appropriate 2,2′-dihydroxychalcones using the classical thallium(III) nitrate and aqueous acidic medium to effect the two key steps of this transformation.

0040-4020/99/$ - see front matter
PII: S0040-4020(98)01076-X



Scheme 1. Synthesis of coumestans **14-16**. *Reagents and conditions*: (i) 50% aq KOH/MeOH at 20°C; (ii) $Tl(NO_3)_3$/MeOH at 20°C; (iii) reflux in MeOH/10% HCl (10:1); (iv) O_2.

Results and Discussion

Syntheses of the three coumestans (Scheme 1), flemichapparin **14** [10], medicagol **15** [11] and sophoracoumestan B (**16**) [12], were conceived to proceed *via* a procedure commencing with the analogous chalcones (**5**, **6** and **7**). These were prepared by base-catalyzed aldol-type condensation [13] of the appropriate acetophenones (**1-3**) with 2-*O*-methoxymethyl-4,5-methylenedioxybenzaldehyde (**4**), which is common to all three chalcones and accessible by formylation [14] of 3,4-methylenedioxyphenol (sesamol), followed by protection of the 2-OH by methoxymethylation. The acetophenones (**1**) and (**2**) were prepared by selective methylation or methoxymethylation, respectively, of resacetophenone while (**3**) required the selective methylation of pyrogallol [15], Friedel-Crafts acylation of the product with $ZnCl_2$/AcOH [16] and selective protection of the acetophenone at 4-OH by methoxymethylation. The ensuing chalcones (**5**, **6** and **7**) were treated with $Tl(NO_3)_3$/MeOH [17] to yield the intermediate acetal-type 1,2-diaryl-3,3-dimethoxypropanones (**8**, **9**, and **10**), respectively, by oxidative rearrangement.

In the classical approach [18] the masked aldehydes (**8**, **9** and **10**) serve as direct precursors to the isoflavones *via* acid-catalyzed cyclization followed by elimination of MeOH. These are then reduced by $NaBH_4$ in EtOH, deprotected at 2-OH and cyclized (D-ring) [19] to the pterocarpan which is oxidized by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in benzene [20] to the corresponding coumestan. In an attempt, however, to reduce the number of steps, we anticipated that a sequence involving an acetal with free 2-OH, *e.g.* (**11**), should directly give the coumestan (**14**). Consecutive treatment of chalcone (**5**) with $Tl(NO_3)_3$/MeOH and aqueous acid indeed led to a one-step conversion into coumestan (**14**), albeit in modest yield (31 %). An analogous sequence of reactions (**6** → **12** → **15**, 25% yield) and (**7** → **13** → **16**, 21% yield) proceeded similarly. Because yields in the aforementioned multistep approach are often not recorded, we suspect that our isolated yields compare favourably with the overall yield in a typical conversion of chalcone → coumestan [18]. Acetylation of coumestans (**15**) and (**16**) afforded the *O*-acetyl derivatives (**17** and **18**).

The course of the reaction is attributable to the acid lability of the 2-*O*-methoxymethyl protective group on the B-ring. This is hydrolyzed during treatment of the acetals (**8-10**) with

MeOH/10% HCl (10 : 1) to liberate the 2-OH on the B-ring affording intermediate compounds (**11-13**). Under these conditions acid-catalyzed D-ring formation followed by dehydration is presumably the principle step which leads to an intermediate of type (**19**) which could then undergo cyclization *via* transacetalation to a 6-methoxy-6a,11a-dehydropterocarpan (**20**). The latter would be extremely susceptible to allylic autoxidation [2] involving the 6-H to yield the coumestans (**14-16**). An alternative mechanism could involve the reversed order, *i.e.* initial closure of the C-ring followed by D-ring formation, dehydration and autoxidation to give intermediate (**20**), or possibly a combination of the two mechanisms. These mechanistic conclusions are substantiated by the absence of similar conversions in acetals bearing an acid-resistant 2-*O*-benzyl protective group which exclusively give C-ring formation by transacetalation followed by the elimination of MeOH to yield the corresponding isoflavone [2].

We have thus demonstrated a versatile, simplified and generally applicable approach to the synthesis of coumestans.

Experimental

^{1}H NMR spectra were recorded on a Bruker 300 MHz spectrometer at 23 °C for solutions in $CDCl_3$ and TMS as internal standard. IR spectra were recorded on a Hitachi 270-50 instrument in $CHCl_3$, baseline 2200-1300 cm^{-1}. TLC was performed on Merck precoated plastic sheets (silica gel 60 PF_{254}) and the plates sprayed with H_2SO_4-HCHO (40:1) after development. Prep. plates (PLC) (Kieselgel PF_{254}, 1.0 mm) were air-dried and used without prior activation. Flash CC was carried out in a glass column (5 cm. dia.) charged with Merck Kieselgel 60 (230-400 mesh) at a flow rate of 30 ml min^{-1} under N_2 pressure, collecting 10 ml per tube. Methylations were performed in MeOH with a solution of diazomethane in Et_2O and methoxymethylations by addition of chlorodimethyl ether in dry THF at 0 °C, following treatment with NaH, and subsequent stirring at 25 °C for 30 min. Acetylations were carried out with Ac_2O in dry pyridine.

2-O-Methoxymethyl-4,5-methylenedioxybenzaldehyde (**4**). NaOH (15.0 g) in H_2O (20 ml) was added to a stirred solution of sesamol (5.0 g) in EtOH (15 ml). The solution was heated to 80 °C, $CHCl_3$ (10 ml) added dropwise over 10-15 min and refluxed gently with stirring for 6 h.

Excess solvents were evaporated on a water bath and conc. HCl (9 ml) was added dropwise to produce a dark oil. Sufficient H_2O was added to dissolve the precipitated NaCl and the oil was extracted with EtOAc (3x100 ml), dried (Na_2SO_4) and the solvent evaporated. Following purification by flash CC (tubes 28 - 55) with hexane-EtOAc (8 : 2) and methoxymethylation the product (**4**) was obtained as a yellow amorphous solid (1.5 g, 30%). ^{1}H NMR ($CDCl_3$): δ 13.0 (*s*, CHO), 7.28 (*s*, H-6), 6.8 (*s*, H-3), 6.02 (*s*, OCH_2O), 5.25 (*s*, OCH_2OMe), 3.52 (*s*, OCH_2OMe) (Found: M^+, 210.0531. $C_{10}H_{10}O_5$ requires M^+, 210.0528).

2-*Hydroxy*-4-*methoxyacetophenone* (**1**). 2,4-Dihydroxyacetophenone (1.0 g) was methylated to yield the methyl ether (**1**) as white needles (from EtOH), m.p. 51-52 °C, lit. [20] m.p., 52-53 °C (0.96 g, 95%). ^{1}H NMR ($CDCl_3$): δ 7.44 (*d*, *J*=9.0 Hz, H-6), 6.51 (*dd*, *J*=2.5, 9.0 Hz, H-5), 6.54 (*d*, *J*=2.5 Hz, H-3), 3.99 (*s*, OMe), 2.57 (*s*, $COCH_3$).

2-*Hydroxy*-4-*O*-*methoxymethylacetophenone* (**2**). 2,4-Dihydroxyacetophenone (1.0 g) was methoxymethylated to give the product (**2**) as a colourless oil (0.93 g, 91%). ^{1}H NMR ($CDCl_3$): δ 7.53 (*d*, *J*=9.0 Hz, H-6), 6.52 (*d*, *J*=2.5 Hz, H-3), 6.48 (*dd*, *J*=2.5, 9.0 Hz, H-5), 5.12 (*s*, OCH_2OMe), 3.40 (*s*, OCH_2OMe), 2.48 (*s*, $COCH_3$) (Found: M^+, 196.0731. $C_{10}H_{12}O_4$ requires M^+, 196.0736).

2-*O*-*Methylpyrogallol*. To a solution of pyrogallol (8.0 g) in H_2O (12 ml) was added dimethylsulfate (6 ml) and 10% (w/v) *aq* NaOH (28 ml) and the mixture was stirred under N_2 for 10 min. The solution was heated on a waterbath for 2 h., cooled, acidified with 3M HCl, saturated with NaCl, and extracted with EtOAc (5 x 100 ml). Flash CC with hexane-EtOAc (7 : 3) gave a mixture (*ca.* 1 : 1) of 1-*O*- and 2-*O*-methylpyrogallol (tubes 36 - 68, 4.9 g, 30% total) which was not further resolved.

2-*Hydroxy*-3-*methoxy*-4-*O*-*methoxymethylacetophenone* (**3**). To a mixture of anhydrous $ZnCl_2$ (1.65 g) in glacial AcOH (20 ml) at 140 °C was added the mixture of 1-*O*- and 2-*O*-methyl-pyrogallol (1.1 g) with constant stirring. The mixture was refluxed for 6 h., cooled and extracted with EtOAc (4x100 ml). The combined extracts were dried (Na_2SO_4), and the solvent evaporated. Following purification by PLC in C_6H_6-Me_2CO (95 : 5) (R_f 0.42) and methoxymethylation the product **3** was obtained as a colourless oil (0.33 g, 31%). ^{1}H NMR ($CDCl_3$): δ7.46 (*d*, *J*=9.0 Hz, H-6), 6.53 (*d*, *J*=9.0 Hz, H-5), 5.12 (*s*, OCH_2OMe), 4.01 (*s*,

OMe), 3.90 (*s*, OCH_2OMe), 2.59 (*s*, $COCH_3$) (Found: M^+, 226.0838. $C_{11}H_{14}O_5$ requires M^+, 226.0841).

General procedure for the preparation of chalcones. 50% (m/v) *aq* KOH (2.5 ml) was mixed with a solution of the appropriate acetophenone (0.7 g) in EtOH (10 ml), stirred at room temperature for 30 min and an excess of 2-hydroxy-4,5-methylenedioxybenzaldehyde **4** (0.5 g) in EtOH (5 ml) added dropwise. After depletion of the acetophenone (18-24 h.), H_2O (10 ml) was added, the mixture acidified with 10% (v/v) H_2SO_4 and extracted with EtOAc (4x20 ml). Drying of the extract (Na_2SO_4) followed by evaporation of the solvent and flash CC gave the pure chalcone.

2'-Hydroxy-4'-methoxy-2-O-methoxymethyl-4,5-methylenedioxychalcone (**5**). Flash CC of the reaction product with hexane-EtOAc (7 : 3) gave the chalcone (**5**) (tubes 56 - 70) as a yellow amorphous solid (0.60 g, 50%). IR ($CHCl_3$): 1628, 1576, 1506, 1484, 1470, 1380, 1346 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.27 (*d*, *J*=10.5 Hz, H-α), 7.82 (*d*, *J*=9.0 Hz, H-6'), 7.43 (*d*, *J*=10.5 Hz, H-β), 7.15 (*s*, H-6), 6.5 (*d*, *J*=2.5 Hz, H-3'), 6.48 (*dd*, *J*=2.5 and 9.0 Hz, H-5'), 6.80 (*s*, H-3), 6.10 (*s*, OCH_2O), 5.22 (*s*, OCH_2OMe), 3.87 (*s*, OMe), 3.53 (*s*, OCH_2OMe) (Found: M^+, 358.1048. $C_{19}H_{18}O_7$ requires M^+, 358.1053).

2'-Hydroxy-2,4'-di-O-methoxymethyl-4,5-methylenedioxychalcone (**6**). Flash CC of the reaction product with C_6H_6-hexane-EtOAc (5 : 4 : 1) yielded the chalcone (**6**) (tubes 32 - 57) as a yellow amorphous solid (0.72 g, 60%). IR ($CHCl_3$): 1632, 1574, 1506, 1484, 1410, 1370, 1346 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.28 (*d*, *J*=10.5 Hz, H-α), 7.85 (*d*, *J*=9.0 Hz, H-6'), 7.42 (*d*, *J*=10.5 Hz, H-β), 7.16 (*s*, H-6), 6.82 (*d*, *J*=2.5 Hz, H-3'), 6.67 (*dd*, *J*=2.5, 9.0 Hz, H-5'), 6.62 (*s*, H-3), 6.02 (*s*, OCH_2O), 5.25 and 5.23 (2x*s*, OCH_2OMe), 3.54 and 3.51 (2x*s*, OCH_2OMe) (Found: M^+, 388.1319. $C_{20}H_{20}O_8$ requires M^+, 388.1315).

2'-Hydroxy-3'-methoxy-2,4'-di-O-methoxymethyl-4,5-methylenedioxychalcone (**7**). Flash CC of the reaction product with C_6H_6-hexane-EtOAc (5 : 4 : 1) gave the chalcone (**7**) (tubes 45 - 63) as a yellow amorphous solid (0.56 g, 47 %). IR ($CHCl_3$): 1632, 1574, 1506, 1484, 1452, 1338 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.30 (*d*, *J*=10.5 Hz, H-α), 7.66 (*d*, *J*=9.0 Hz, H-6'), 7.44 (*d*, *J*=10.5 Hz, H-β), 7.16 (*s*, H-6), 6.84 (*s*, H-3), 6.75 (*d*, *J*=9.0 Hz, H-5'), 6.02 (*s*, OCH_2O), 5.34 and 5.23 (each *s*, OCH_2OMe), 3.95 (*s*, OMe), 3.55 and 3.535 (each *s*, OCH_2OMe) (Found: M^+,

418.1266. $C_{21}H_{22}O_9$ requires M^+, 418.1264).

General procedure for the preparation of coumestans. $Tl(NO_3)_3.3H_2O$ (38 mg) was added to a vigorously stirred suspension of the chalcone (28 mg) in MeOH (1.0 ml) and the stirring continued for 24 h. The mixture was filtered, satd. *aq* NaCl (0.4 ml) and satd. *aq* $NaHCO_3$ (0.2 ml) were added to the filtrate and the mixture was extracted with EtOAc (3x10 ml). The solvent was evaporated and the residue refluxed with MeOH/10% HCl (10:1, 0.5 ml) for 1 h. Water (30 ml) was added to the mixture and the products were extracted with EtOAc (3x20 ml). Purification by PLC in C_6H_6-Me_2CO (95:5) afforded the coumestan.

3-*Methoxy*-8,9-*methylenedioxycoumestan* (**14**) (flemichapparin). Obtained (R_f 0.81) as white needles (from EtOH), m.p. 178-180 °C, lit. [22] m.p., 179-180 °C (8.4 mg, 31%). IR ($CHCl_3$): 1744, 1634, 1604, 1504, 1430, 1360 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.87 (*d*, *J*=9.0 Hz, H-1), 7.49 (*s*, H-7), 7.14 (*s*, H-10), 7.01 (*d*, *J*=2.5 Hz, H-4), 6.99 (*dd*, *J*=2.5, 9.0 Hz, H-2), 6.1 (*s*, OCH_2O), 3.93 (*s*, OMe).

3-*Hydroxy*-8,9-*methylenedioxycoumestan* (**15**) (medicagol). Obtained (R_f 0.94) as white needles (from MeOH)), m.p. 324-326 °C, lit. [23] m.p. 324-325 °C (7.0 mg, 25%). IR ($CHCl_3$): 1732, 1668, 1626, 1504, 1464, 1360 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.90 (*d*, *J*=9.0 Hz, H-1), 7.50 (*s*, H-7), 6.15 (*s*, H-10), 6.99 (*d*, *J*=2.5 Hz, H-4), 6.86 (*dd*, *J*=2.5, 9.0 Hz, H-2), 6.10 (*s*, OCH_2O).

3-*Hydroxy*-4-*methoxy*-8,9-*methylenedioxycoumestan* (**16**) (sophoracoumestan B). Obtained (R_f 0.79) as white needles (from MeOH), m.p. >300 °C, lit. [12] m.p. >300 °C (5.9 mg, 21%). IR ($CHCl_3$): 1744, 1636, 1604, 1540, 1466, 1426, 1360 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.62 (*d*, *J*=9.0 Hz, H-1), 7.50 (*s*, H-7), 7.15 (*s*, H-10), 7.04 (*d*, *J*=9,0 Hz, H-2), 6.10 (*s*, OCH_2O), 4.21 (*s*, OMe).

3-*O-Acetyl*-8,9-*methylenedioxycoumestan* (**17**). Acetylation of the coumestan (**15**) (5.0 mg) gave the monoacetate (**17**) as white needles (from EtOH), m.p. 260-262 °C, lit. [23] m.p. 262-263 °C (4.9 mg). ^1H NMR ($CDCl_3$): δ 7.98 (*d*, *J*=9.0 Hz, H-1), 7.51 (*s*, H-7), 7.29 (*d*, *J*=2.5 Hz, H-4), 7.20 (*dd*, *J*=2.5, 9.0 Hz, H-2), 7.17 (*s*, H-10), 6.12 (*s*, OCH_2O), 2.38 (*s*, OAc).

3-*O-Acetyl*-4-*methoxy*-8,9-*methylenedioxycoumestan* (**18**). Acetylation of the coumestan (**16**) (4.5 mg) gave the monoacetate (**18**) as a white amorphous solid (4.0 mg). ^1H NMR

($CDCl_3$): δ 7.70 (*d*, *J*=9.0 Hz, H-1), 7.51 (*s*, H-7), 7.16 (*s*, H-10), 7.13 (*d*, *J*=9,0 Hz, H-2), 6.12 (*s*, OCH_2O), 4.13 (*s*, OMe), 2.41 (*s*, OAc) (Found: M^+, 368.0529. $C_{19}H_{12}O_8$ requires M^+, 368.0532).

Acknowledgements - Support by the Foundation for Research Development, Pretoria, the Sentrale Navorsingsfonds of this University and Infruitec, Stellenbosch is gratefully acknowledged.

Reference:

[1] Dewick, P.M. 1988 in The Flavonoids - Advances in Research since 1980, *ed.* J.B. Harborne, Chapman & Hall, London, p. 125; and Dewick, P.M. 1994 in The Flavonoids - Advances in Research since 1986, *ed.* Harborne, Chapman & Hall, London, p. 117.

[2] Ferreira, M.A., Moir, M., Thomson, R.H. J. Chem. Soc., Perkin Trans. 1, 1974, 2429-2435.

[3] Martin, M., Dewick, P.M. Tetrahedron Lett., 1978, 2341-2344.

[4] Bhalerao, U.T., Muralikrishna, C., Pandey, G. Synth. Commun., 1989, 19, 1303-1307; Pandey, G., Muralikhrisna, C. and Bhalerao, U.T. Tetrahedron, 1989, 45, 6867-6874.

[5] Kamara, B.I., Brandt, E.V., Joubert, E., Ferreira, D. J. Agric. and Food Chem., 1998, in the press, paper JF980258X.

[6] Laks, P.E., Pruner, M.S. Phytochemistry, 1988, 28, 87-91.

[7] Adlercreutz, H., Fotsis, T., Bannwart, C., Mäkelä, K., Wähälä, K., Brunow, G., Hase, T. J. of Steroid Biochem., 1986, 25, 791-797.

[8] Martin, P.M., Horowitz, K.B., Ryan, D.S., McGuire, W.L. Endocrinology, 1978, 103, 1860-1867.

[9] Bickoff, E.M., Spencer, R.R., Witt, S.C., Knuckles, B.E. Technical Bull., 1969, no. 1408, U.S.D.A.

[10] Burns, D.T., Dalgrano, B.G., Gargan, P.E., Grimshaw, J. Phytochemistry, 1984, 23, 167-169.

[11] Komatsu, M., Shirataki, Y., Yokoe, I., Manaka, A. Chem. Pharm. Bull., 1981, 29, 532-538.

[12] Komatsu, M., Yokoe, I., Shirataki, Y. Chem. Pharm. Bull., 1981, 29, 2069-2072.

[13] Shimokoriyama, M. in The Chemistry of Flavonoid Compounds, ed. T.A. Geissman Pergamon Press, London, **1962**, p. 308, and references therein.

[14] Wynberg, H. Chem. Rev., 1960, 60, 169-184.

[15] Geissman, T.A., Mojé, W. J. Am. Chem. Soc., 1951, 73, 5765-5768.

[16] Robinson, R., Shah, R.C. J. Chem. Soc., 1934, 1491-1498.

[17] McKillop, A., Swann, B.P., Taylor, E.C. Tetrahedron Lett., 1970, 5281-5284.

[18] Farkas, L., Gotsegen, A., Nógrádi, M., Antus, S. J. Chem. Soc., Perkin Trans. I, 1974, 305-312.

[19] Rappoport, Z., Dyall, L.K., Winstein, S., Young, W.G. Tetrahedron Lett., 1970, 3483-3488.

[20] Gunning, P.J.M., Kavangh, P.J., Meegan, M.J., Donnelly D.M.X. J. Chem. Soc., Perkin Trans. I, 1977, 691-694.

[21] Adams, R. J. Am. Chem. Soc., 1919, 41, 247-270.

[22] Adityachaudhury, N., Gupta, P.K. Phytochemistry, 1973, 12, 425-428.

[23] Livingstone, A.L., Witt, S.C., Lundin, R.E., Bickoff, E.M. J. Org. Chem., 1965, 30, 2353-2355.