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SYNTHESIS OF KUKULKANINS A AND B - METHOXY CHALCONES FROM *MIMOSA TENUFOLIA* L.

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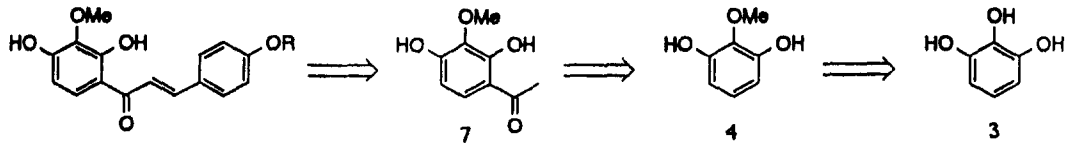
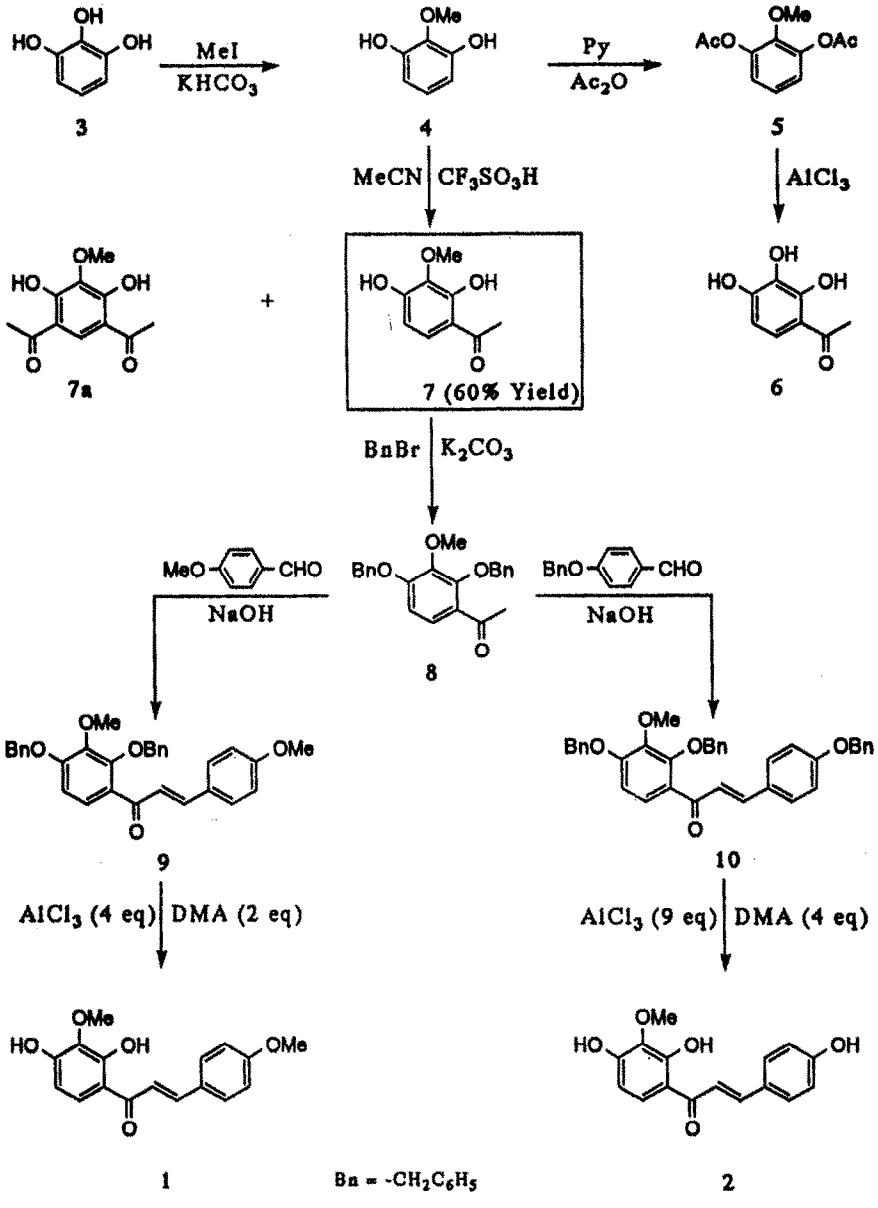
ABSTRACT: *Synthesis of kukulkanins A (1) and B (2) has been achieved starting from pyrogallol.*

Bark of the Mexican plant *Mimosa tenufolia* L. has been traditionally used for the treatment of burns and prevention of inflammation.[2] Recently, two compounds, kukulkanin A (1) and kukulkanin B (2) have been isolated from the extracts of the small branches of this plant and the structure of these compounds determined on the basis of spectroscopic and X-ray diffraction data.[2] To our knowledge the synthesis of these chalcones has not been reported. We describe here a practical synthesis of kukulkanin A and kukulkanin B.

Retrosynthetic analysis of 1 and 2 revealed that pyrogallol (3) is a promising starting material for the synthesis of these natural products. Selective methylation of pyrogallol to pyrogallol-2-methyl ether (4) through the literature procedures[3,4] was found to be unsatisfactory because of the low yield of the product. In our attempts to develop a better method we have tried several alternative reaction conditions and reagents, including the protection of hydroxyls at 1,3 in pyrogallol as pivaloyl or trimethylsilyl derivatives followed by methylation with CH_3I/NaH/DME or dimethyl sulfate/K_2CO_3/DMSO.



1 R=Me
2 R=H
7
4
3


MeI
KHCO3
Py
Ac2O
MeCN CF3SO3H
AlCl3
BnBr K2CO3
NaOH
NaOH
AlCl3 (4 eq) DMA (2 eq)
AlCl3 (9 eq) DMA (4 eq)
3
4
5
6
7a
7 (60% Yield)
8
9
10
1
2
Bn = -CH2C6H5

Direct methylation of pyrogallol with CH_3I in presence of K_2CO_3 in acetone medium gave 4 in 22% yield. The best method, we have found was the use of CH_3I (1.5 eq.) as the methylating agent and $KHCO_3$ (1.25 eq.) as the base. Under these conditions, we were able to obtain 4 in reproducible yields of about 40%.

Pyrogallol-2-methyl ether (4) was acetylated to the diacetate (5) using pyridine-Ac_2O. Fries rearrangement[5] of 5 afforded however, the undesired demethylated compound 6[6] instead of the expected 7.

Recently Booth and Noori[7] have acylated phenols and phenol ethers with nitriles and triflic acid (trifluoromethanesulfonic acid). Under these conditions direct acylation of 4 gave the methyl ketone 7 in 60% yield in addition to the easily separable diacetyl compound 7a as the minor component (20% yield). Benzylation of the two phenolic hydroxy groups in 7 followed by its Claisen-Schmidt condensation with p-anisaldehyde resulted in the fully protected chalcone 9 in 65% yield.

Removal of the benzyl groups in 9 turned out to be more difficult than anticipated because of the presence of the α,β-unsaturated ketone functionality. Recently Akiyama, Hirofuji and Ozaki[8] have reported a method for the cleavage of allyl and benzyl ethers by treating them with aluminum chloride and N,N-dimethylaniline (DMA). Treatment of 9 using their protocol (8 molar equivalents of $AlCl_3$ and 6 molar equivalents of DMA) gave in poor yield a product devoid of one methoxy group [9] which could not be purified for unambiguous characterization. However, when 4 molar equivalents of $AlCl_3$ and 2 molar equivalents of DMA were allowed to react with 9 for 5 min. at 5°C, kukulkanin A (1) was formed in 60% yield.

Condensation of 8 with 4-benzyloxybenzaldehyde[10] in the presence of aqueous NaOH (10%) gave the tribenzyl ether of kukulkanin B (10). Deprotection of the hydroxyl groups in 10 by $AlCl_3$-DMA yielded kukulkanin B (2) in 50% yield.

Thus, a practical synthetic route from readily available starting material has been devised for these natural products. Detailed studies on their physiological activity should now be possible.

EXPERIMENTAL SECTION

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1760 FT-IR spectrometer as Nujol mulls. ^1H and ^{13}C NMR spectra were obtained on a Bruker AF-200 NMR spectrometer, operating at 200.133 MHz and 50.3 MHz respectively, using $CDCl_3$ or d_6-DMSO solutions and TMS as the internal standard. CIMS (Chemical ionization mass spectra) were obtained on a Biospect. mass spectrometer (Scientific Research Instruments Corp., Baltimore, Maryland) using CH_4 as the reagent gas.

Pyrogallol-2-methyl ether (4). A mixture of pyrogallol (3, 25.2 g, 0.2 mol), potassium bicarbonate (25 g, 0.25 mol), methyl iodide (18.7 mL, 0.3 mol) and acetone (300 mL) was refluxed overnight. The reaction mixture was cooled to rt and the precipitated inorganic material was removed by filtration. The filtrate was concentrated and the residue was diluted with ether (200 mL) to precipitate the remaining inorganic impurities, which were removed by a second filtration. The filtrate thus obtained was concentrated and distilled under vacuo. The fraction distilling at 120-130°C (9 mm), was crystallized from carbon tetrachloride to give 4 (11.2 g, 40%) as colorless crystals; mp 82-84°C (lit[4]., mp 84°C); IR (Nujol): 3333, 1592 cm^{-1}; ^1H NMR ($CDCl_3$):δ 3.87 (s,3H), 5.61 (s,two hydroxyls), 6.51 (d,J=8.2 Hz,2H), 6.87 (t,J=7.9 Hz,1H).

2,4-Dihydroxy-3-methoxyacetophenone (7). To acetonitrile (1.5 mL,30 mmol) at room temperature, triflic acid (1.76 mL, 20 mmol) was added dropwise during about 30 min and the reaction mixture was kept at rt for 3h. A solution of pyrogallol-2-methyl ether (2.8 g, 20 mmol) in acetonitrile (5 mL) was then added dropwise. The reaction mixture was stored at rt for 8 days, diluted with water (50 mL) and heated under reflux for 30 min, cooled to rt and extracted with dichloromethane. The organic layer was separated, dried (Na_2S0_4), and the excess acetonitrile removed on a rotary evaporator. The residue was purified by flash chromatography (4:1, Hexane:EtOAc) over silica gel to obtain monoacylated derivative, 7 (2.2 g,60%) and the diacylated compound, 7a (0.9 g, 20%).

2,4-Dihydroxy-3-methoxyacetophenone (7)[11]. Colorless crystals from hexane-dichloromethane, mp 68°C; IR (Nujol): 3404,1620,1590 cm^{-1}; ^1H NMR ($CDCl_3$): δ 12.80 (s, -OH), 7.44 (d,J= 8.9 Hz,1H), 6.52 (d,J=8.9 Hz,1H), 3.99 (s,3H), 2.57 (s,3H); CIMS (CH_4,160°C): m/z 183 $(M+H)^+$; Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.49. Found: C, 59.40; H, 5.08.

2,4-Dihydroxy-5-acetyl-3-methoxyacetophenone (7a). Colorless needles from hexane-dichloromethane, mp 130-132°C; IR (Nujol): 1638, 1588 cm^{-1}; ^1H NMR ($CDCl_3$): δ 13.07 (s,2H), 8.02 (s,1H), 3.92 (s,3H), 2.64 (s,6H); CIMS (CH_4,180°C): m/z 225 $(M+H)^+$. Anal. Calcd for $C_{11}H_{12}O_5$: C, 58.92; H, 5.35. Found C, 58.72; H, 5.10.

2,4-Dibenzyloxy-3-methoxyacetophenone (8). A mixture of 7 (0.41g, 2.2 mmol), potassium carbonate (0.62g, 4.5 mmol), benzyl bromide (0.77g, 4.5 mmol) and glyme (50 mL) was heated under reflux for 12h. The reaction mixture was diluted with water, extracted with dichloromethane and dried (Na_2S0_4). The solvent was removed under reduced pressure and the product was purified by flash chromatography (9:1, Hexane:EtOAc) to give 8 (0.7 g, 82%). mp 65°C; IR (Nujol): 1680, 1588 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.3 - 7.6 (m,11H), 6.78 (d,J=8.9 Hz,1H), 5.15 (s,2H), 5.19 (s,2H), 3.91 (s,3H), 2.51 (s,3H); CIMS (CH_4,175°C); m/z 363 $(M+H)^+$. Anal. Calcd for $C_{23}H_{22}O_4$: C, 76.24; H,6.07. Found C, 76.47; H, 5.93.

2,4,-Dibenzyloxy-3,4-dimethoxychalcone (9). To a solution of 8 (0.8g, 2.2 mmol) in EtOH (10 mL) and 10% NaOH (2 mL), was added p-methoxybenzaldehyde (0.26 mL, 2.2 mmol) at 0^oC. The reaction mixture was kept at 0^oC for 10 days. A solid mass that separated out was filtered and washed with water. After recrystallization from hexane-dichloromethane the residue gave 9 (0.7g,65%) as yellow needles; Mp 98^oC; IR (Nujol): 1645, 1588 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.85 (s,3H), 3.95 (s,3H), 5.08 (s,2H), 5.20 (s,2H), 6.83 (d,J=8.8 Hz,1H), 6.84 (d,J=8.8 Hz,2H), 7.24-7.52 (m,14H), 7.63 (d,J=15.8 Hz,1H). Anal. Calcd for $C_{31}H_{28}O_5$: C, 77.50; H, 5.83. Found C, 77.50; H, 5.65.

Kukulkanin A (2',4',-dihydroxy-3',4-dimethoxychalcone) (1). To a solution of compound 9 (0.15g, 0.31mmol) and N,N-dimethylaniline (0.07g, 0.58 mmol) in dichloromethane (10 mL) at 5^oC, was added anhydrous $AlCl_3$ (0.165g, 1.24mmol) when a dark red solution resulted. The reaction was quenched with 1N HCl (10 mL) after 5 min, and extracted with dichloromethane, dried over Na_2SO_4 and the solvent was evaporated. Flash chromatography (4:1, Hexane:EtOAc) of the residue over silica gel yielded compound 1 (55 mg, 60%); mp 170-75^oC (lit[2]., mp 172^oC). The spectroscopic data of the synthetic 1 were found to be identical with those reported for the natural 1.[2]

2',4',4-Tribenzyloxy-3,-methoxychalcone (10). To a solution of 8(0.2g, 0.55 mmol) in EtOH (5 mL) and 10% NaOH (1 mL) was added p-benzyloxybenzaldehyde[10] (0.12g,0.56 mmol) at 5^oC. The reaction mixture was stirred at 10^oC for 2h, then at rt for 48h. Extraction with dichloromethane, drying over Na_2SO_4 and removal of the solvent followed by flash chromatography (9:1, Hexane:EtOAc) over silica gel gave 10 (160mg, 53%), mp 98-100^oC; IR (Nujol): 1645, 1595 cm^{-1}; ^1H NMR ($CDCl_3$):δ 3.95 (s,3H), 5.07 (s,2H), 5.10 (s,2H), 5.21 (s,2H), 6.83 (d,J=8.9 Hz,1H), 6.91(d,J=8.8 Hz,2H), 7.21-7.50 (m,19H) and 7.63 (d,J=15.8 Hz,1H). Anal. Calcd for $C_{37}H_{32}O_5$: C, 79.85; H, 5.75. Found C, 79.45; H, 5.63.

Kukulkanin B (2',4',4-trihydroxy-3'-methoxychalcone) (2). To a solution of 10 (500 mg, 0.9 mmol) and N,N-dimethylaniline (436 mg, 3.6 mmol) in dichloromethane (50 mL) was added $AlCl_3$ (1.06 g, 8.0 mmol) at 0^oC, and the reaction mixture was stirred at rt for 1h. Work up as described for the preparation of 1 followed by flash chromatography (4:1, Hexane:EtOAc) over silica gel gave 2 (125 mg, 50%); mp 212^oC (lit[2]., mp 215^oC). The spectroscopic data of the synthetic 2 is identical with those reported for the natural 2.[2]

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REFERENCES AND NOTES

1. Visiting Scientist on leave from Sri Venkateswara University, Tirupati, India.
2. Dominguez,X.A.; Garcia,G.S.; Williams,H.J.; Ortiz,C.; Scott,A.I.; Reibenspies,J.H. *J.Nat.Prod.* 1989, 52, 864.
3. Spath,E.; Schmid,H. *Chem.Ber.* 1941, 74, 193.
4. Geissman,T.A.; Moje,W. *J.Am.Chem.Soc.* 1951, 73, 5765.
5. A.I. Vogel "*A text book of practical organic chemistry*", ELBS & Longman, London, 4th ed., 1978, pp 750-751.
6. Price,P.; Israelstam,S.S. *J.Org.Chem.* 1964, 29, 2800.
7. Booth,B.L.; Noori,G.F.M. *J.C.S.Perkin 1.* 1980, 2894.
8. Akiyama,T.; Hirofuji,H.; Ozaki,S. *Tetrahedron Lett.* 1991, 32, 1321.
9. ^{1}H-NMR spectrum of the crude reaction product showed loss of one methoxyl group.
10. Prepared from p-hydroxybenzaldehyde according to the procedure used for the preparation of 8.
11. Different melting points of 7 have been reported in the literature[12]. ^{1}H NMR spectral data of 7 is identical with those reported in ref 12(a).
12. (a) Schreiber,F.G.; Stevenson,R. *J.C.S.Perkin 1.* 1977,90.
    (b) Khanna,R.N.; Seshadri,T.R. *Indian J.Chem.* 1963, 1, 385.
    (c) Baker,W. *J.Chem.Soc.* 1941, 662.
    (d) Perkin,A.G.; Storey,R.C. *J.Chem.Soc.* 1928, 243.
    (e) Perkin,A.G.; Wilson,C.R. *J.Chem.Soc.* 1903, 83, 129.