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REGIOSELECTIVITY IN LITHIATION OF t-BUTYLDIMETHYLSILOXY-3,5-DIMETHOXYBENZENE. A SYNTHESIS OF THE TRIMETHYL ETHER OF SOPHORAFLAVANONE A

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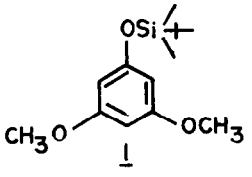
Summary. Selective metallation by inhibiting the directive effect of an oxygen substituent leads to selective substitution of a trioxygenated benzene and a five step synthesis of the titled potentially anti-fungal natural product.

In connection with the synthesis of rocaglamide,[1] we required a differentiated 3,5-dialkoxy 4-substituted phenol, a type of aromatic that is widely distributed among natural products.[2] The failure of classic approaches is illustrated by the preference for Friedel-Crafts acylation to substitute at the 2-position of 3,5-dimethoxyphenol.[3] For a lithiation reaction,[4] the general approach of using specific activators such as MOM or THP ethers[5,6,7] would also result in the wrong substitution pattern. An alternative strategy envisions specific deactivation of the phenolic oxygen as might occur with the t-butyldimethylsilyl ether as in 1 which is available in 98% yield from the corresponding phenol under standard silylation conditions [t-$C_4H_9(CH_3)_2SiCl$, imidazole, 2:1 THF:DMF, 25°, 24 h]. Treating a 0.2-0.3 M solution of 1 in toluene with 1.1-1.2 eq. of



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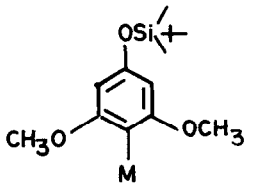
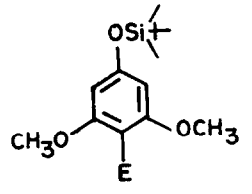


2 M=Li
3 M=ZnBr
4 M=MgBr



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t-butyllithium in pentane (-78°, 1 h; 25°, 5-6 h) selectively generated the 4-lithio species 2 as demonstrated by deuterium quenching. Transmetallation to the zinc and magnesium species occurs upon addition of anhydrous zinc or magnesium bromide at room temperature. The Table summarizes the ability to 1) brominate 2, 2) allylate 2, and 3) condense 2, 3 or 4 with aldehydes and ketones. With an easily enolizeable ketone, the zinc reagent proves most effective. Allylations are best accomplished using copper catalysis.

The facility of this methodology offers a very simple method for elaboration of flavanoids. The Scheme outlines the complete synthesis of the methyl ether 6 of sophoraflavanone A (7).[8,9] Geranylation of 2 to give 5c[10] followed by quantitative cleavage of the silyl group produces phenol 8 in 72% yield. A major obstacle arose in the failure of Friedel-Crafts and

Table I. Reaction of 2, 3, and 4 with Electrophiles in $PhCH_3$.

Entry	M	Electrophile	Product 5[a]	Isolated[b,c] Yield	Mp
1	Li	$Br_2CHCHBr_2$	E = Br (5a)	77%	68-70°C
2	Li[e]	allyl bromide	E = allyl (5b)	70%	oil
3	Li[e]	geranyl bromide	E = geranyl (5c)	72%	crystalline at -10°
4	Li[f]	acetaldehyde	$CH(OH)CH_3$ (5d)	55%	74.5-6°C
5	Li	benzaldehyde	CH(OH)Ph (5e)	61%(84%)	86-8°C
6	ZnBr	acetone	$C(OH)(CH_3)_2$ (5f)	40%(63%)	47-8°C
7 a.	Li	p-anisylacetone	$C(OH)(CH_3)CH_2C_6H_4OCH_3$-p (5g)	35%(55%)	crystalline at -10°
b.	$MgBr$[d]	same	same	39%(64%)	
c.	ZnBr	same	same	56%(93%)	

a. All products gave satisfactory 200 or 270 MHz ^1H NMR spectra, 50.1 MHz ^{13}C NMR spectra, and high resolution mass spectra and/or combustion analyses. b. Yields are of flash chromatographed product which was pure by nmr and homogeneous by TLC. c. Values in parentheses are based on recovered 1. d. Prepared by cannulation of 2 into a flask containing anhydrous $MgBr_2$ (CA 1.5 equiv.) which was generated *in situ* from magnesium and 1,2-dibromoethane in Et_2O followed by solvent evaporation to leave a white solid. e. 3-5 mol% $CuBr-Me_2S$ was used for the coupling reaction. f. THF was used in place of $PhCH_3$ for this example. Lithiation of 1 at -78°C (40 min) then -20->-10°C (1 h).

Fries types of reactions for acylation of 8 due, in part, to the sensitivity of the geranyl side chain. To selectively activate acylation of the aromatic ring by forming an ammonium salt of the phenol and to serve as a scavenger for HCl, a complex of aluminum chloride and N,N-diisopropylethyl amine in ether is first reacted with the phenol. Portionwise addition of acetyl chloride to the resultant hetereogeneous reaction mixture at 0° in a sonicator gives a 56% yield of 9[11] at 48% conversion. Aldol condensation[12] forms the open chain aldol adduct 10[13,14] which refused to close under standard acid or base cyclization methods to form flavanones[15]. Smooth cyclization (88%) to the desired flavanone 6[16] contaminated only by a small amount (10%) of the simple elimination product occurs under Mitsunobu conditions.[17]

The spectral data fully documents the correctness of the structural assignment. Most interesting is the observation that at 270 MHz the benzylic methylene protons of the geranyl side chain of 6 appear as an AB portion of an ABX pattern;[16] whereas, in the precursor 10 this methylene group appears as a simple doublet.[13] The conformational restriction of the side chain due to the flanking methoxy groups combined with the anisotropy associated with the flavanone ring system account for this dramatic long range effect. Overall, this methodology translates into a 31% yield of 6 from 1 in five steps.

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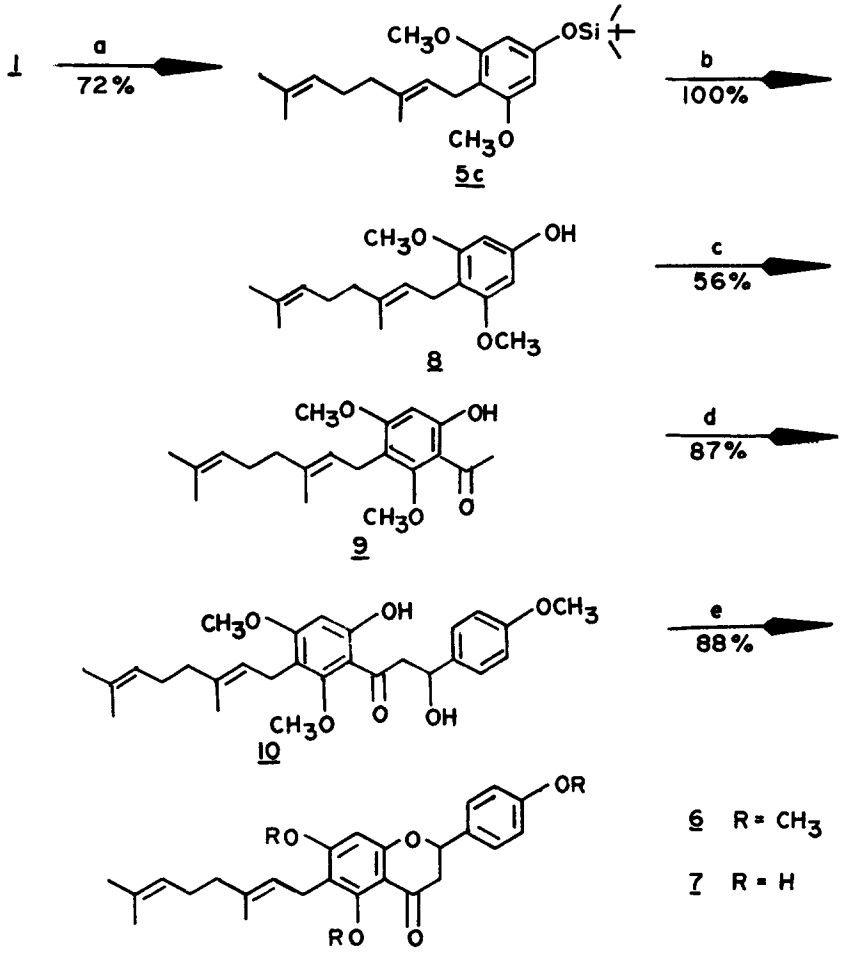
Scheme. **Synthesis of Trimethyl Ether of Sophoraflavanone A**



6 R = CH_3

7 R = H

a) t-C_4H_9Li, $PhCH_3$, -78°, 1 h, 25°, 5-6 h; geranyl bromide, 3% CuBr·DMS, -78°, 1h, -15°, 15 h.
b) 1.25 eq. $(C_4H_9)_4NF$, 5% aq. THF, 0°.
c) 4 eq. $AlCl_3$, 4 eq. N,N-diisopropylethylamine, ether, 0°, CH_3COCl, sonicator.
d) 2.5 eq. LDA, -78°, 0.5 h, -22°, 2.5 h; p-anisaldehyde, -78°, 1 h, -22°, 2 h.
e) 2 eq. Ph_3P, 2 eq. DEADCAT, THF, rt.

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9. Shirataki, Y.; Endo, M.; Yokoe, I.; Komatsu, M. Chem. Pharm. Bull., 1983, 31, 2859.
10. 5c: ^{1}H NMR ($CDCl_3$) δ 6.03 (s, 2 H), 5.18-4.97 (m, 2H), 3.74 (s, 6 H), 3.24 (d, 2H, J = 7 Hz), 2.12-1.87 (m, 4H), 1.73 (s, 3H), 1.63 (s, 3H), 1.55 (s, 3H), 0.97 (s, 9H), 0.19 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 158.5 (s), 154.9 (s), 133.8 (s), 130.8 (s), 124.7 (d), 123.7 (d), 111.8 (s), 96.7 (d), 55.6 (q), 39.9 (t), 26.8, 25.8, 25.7, 21.8, 18.2 (s), 17.6 (q), 15.9 (q), -4.3 (q); mass spectrum, m/e, M^+, 404.2745. $C_{24}H_{40}O_3Si$ requires, M^+, 404.2744.
11. Data for 9: IR ($CDCl_3$) 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.23 (s, 1H), 5.17-4.97 (m, 2H), 3.82 (s, 3H), 3.70 (s, 3H), 3.24 (d, 2H, J = 6.6 Hz), 2.66 (s, 3H), 2.12-1.91 (m, 4H), 1.73 (s, 3H), 1.62 (s, 3H), 1.56 (s, 3H); mass spectrum, m/e, M^+, 332.1989. $C_{20}H_{28}O_4$ requires, M^+, 332.1986.
12. For o-hydroxyacetophenone enolate generation see, Banerji, A.; Goomer, N.C. Tetrahedron Lett., 1979, 3685.
13. 10: IR ($CDCl_3$) 1619 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.32 (d, 2H, J = 8.7 Hz), 6.88 (d, 2H, J = 8.7 Hz), 6.24 (s, 1H), 5.29-5.17 (m, 1H), 5.15-4.95 (m, 2H), 3.83 (s, 3H), 3.79 (s, 3H), 3.64 (s, 3H), 3.60-3.30 (m, 3H), 3.21 (d, 2H, J = 6.8 Hz), 2.12-1.86 (m, 4H), 1.70 (s, 3H), 1.61 (s, 3H), 1.55 (s, 3H); ^{13}C NMR ($CDCl_3$) δ204.4 (s), 164.9 (s), 164.6 (s), 160.4 (s), 158.9 (s), 135.6 (s), 134.9 (s), 131.0 (s) 126.9 (d), 124.2 (d), 122.9 (d), 115.8 (s), 113.8 (d), 108.9 (s), 96.0 (d), 70.0 (d), 62.5 (q), 55.6 (q), 55.1 (q), 50.9 (t), 39.5 (t), 26.5, 25.5 22.3, 17.5 (q), 15.9 (q).
14. In addition a small amount (9%) of the chalcone forms also.
15. Poonia, N.S.; Chhabra, K.; Kumar, C.; Bhagwat, V.W. J. Org. Chem., 1977, 42, 3311.
16. Data for 6: IR ($CDCl_3$) 1674, 1517, 1257, 1102, 830 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ7.37 (d, 2H, J = 8.8 Hz), 6.93 (d, 2H, J = 8.8 Hz), 6.30 (s, 1H), 5.34 (d of d, 1H, J = 2.7 and 13.4 Hz), 5.16-4.99 (m, 2H), 3.81 (s, 9H), 3.31 (d of d, 1H, J = 13.8 and 7.7 Hz), 3.25 (d of d, 1H, J = 13.8 and 6.5 Hz), 3.02 (d of d, 1H, J = 17 and 13.4 Hz), 2.73 (d of d, 1H, J = 17 and 2.7 Hz), 2.09-1.87 (m, 4H), 1.74 (s, 3H), 1.62 (s, 3H), 1.55 (s, 3H); partial ^{1}H NMR (d6-benzene) 5.50 (m, 1H), 5.16 (m, 1H), 4.98 (d of d, 1H, J = 13 and 2.7 Hz), 3.96 (s, 3H), 3.28 (s, 3H), 3.18 (s, 3H); ^{13}C NMR ($CDCl_3$) δ189.0, 164.2, 163.0, 159.9, 159.6, 134.8, 131.1, 130.9, 127.7, 124.4, 122.9, 118.4, 114.2, 108.8, 95.6, 78.9, 61.8, 55.8, 55.3, 45.4, 39.7, 26.7, 25.6, 22.0, 17.6, 16.1; mass spectrum, m/e 450 (M^+, 48%), 381 (27%), 327 (100%) (calcd for $C_{28}H_{34}O_5$, 450.2404; Found, 450.2407).
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