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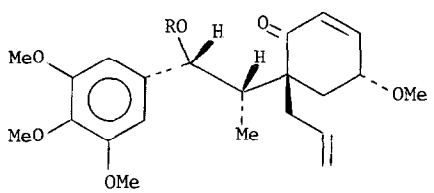
TOTAL SYNTHESIS OF d,l-MEGAPHONE

P.A. Zoretic*, C. Bhakta and R.H. Khan

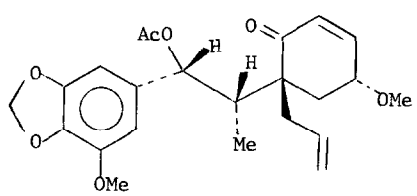
Department of Chemistry
East Carolina University
Greenville, North Carolina 27834

Summary: The Synthesis of racemic megaphone 1, a cytotoxic neolignan, is described.

Three new cytotoxic neolignans, megaphone 1, megaphone acetate 2 and megaphyllone acetate 3 have recently been isolated from Aniba megaphylla Mex. (Laureaceae)[1] by Kupchan and co-workers. These new neolignans were found to demonstrate "inhibitor activity, in vitro, against cells derived from human carcinoma of the nasopharynx (KB)."[2] Recently a total synthesis of megaphone 1 and its acetate 2 has been reported by Büchi and Chu.[3] Herein we describe an alternate approach to these cytotoxic neolignans utilizing the bicyclic lactone 15, as a key synthon, in the synthesis of racemic megaphone 1.



1: R=H
2: R=Ac



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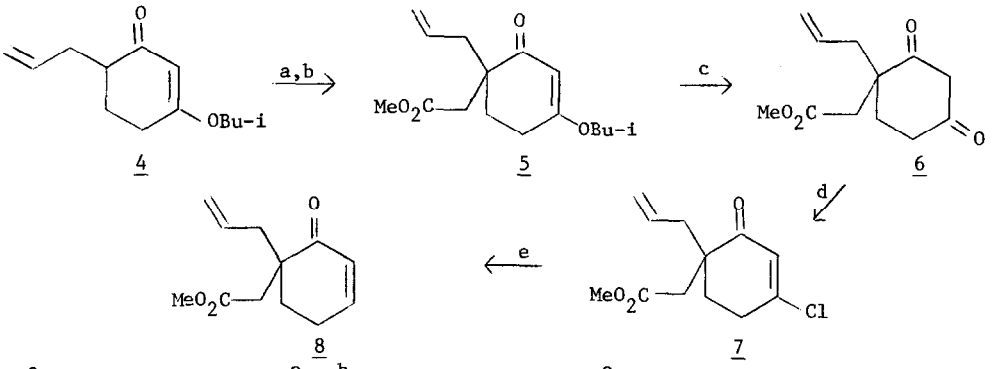
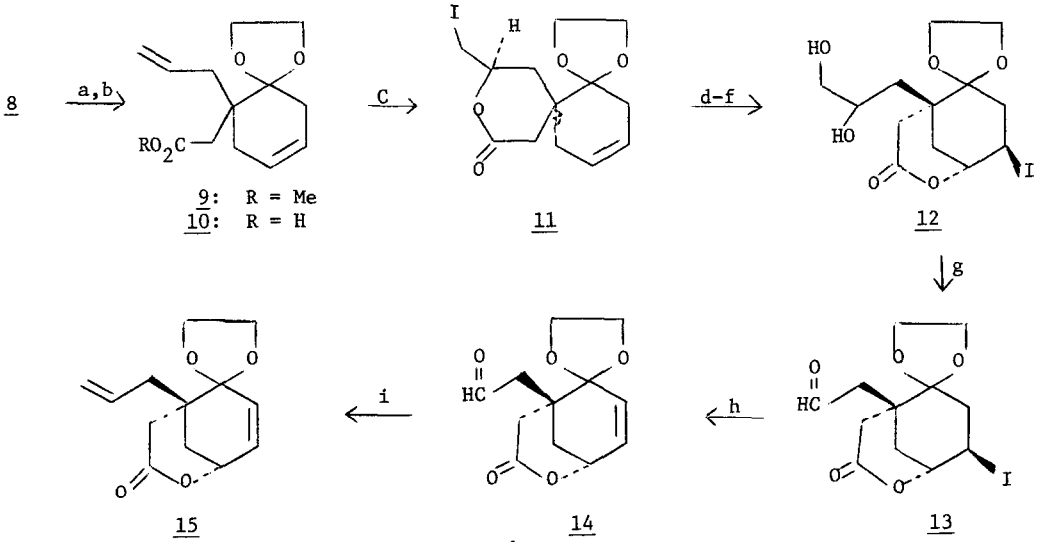
Kinetic alkylation of the lithium enolate of 3-alkoxycyclohexenone 4[4] with methyl bromoacetate in THF at -78°C afforded ester 5 (70%). Acid hydrolysis of the enol ether moiety in (5) gave dione 6 (97%, mp 81-81.5°C). Reaction of (6) with oxalyl chloride[5] yielded the vinyl chloride 7 (84%). Dehalogenation [5] of the vinyl chloride was effected smoothly by reaction of (7) with a zinc-silver couple to afford the desired enone 8 (80%).

Ketalization of enone 8 (ethylene glycol in the presence of p-TsOH in PhH) with concomitant isomerization of the enone double bond gave ketal 9 (53%) and 27% of unreacted (8), after chromatography. Saponification of (9) in the presence of one equivalent of 4-dimethylaminopyridine followed by acidification (3.5% oxalic acid) afforded 10 (98%; mp 74-74.8°C). Although there are two possible modes of lactonization in (10), experimentally it was deter-

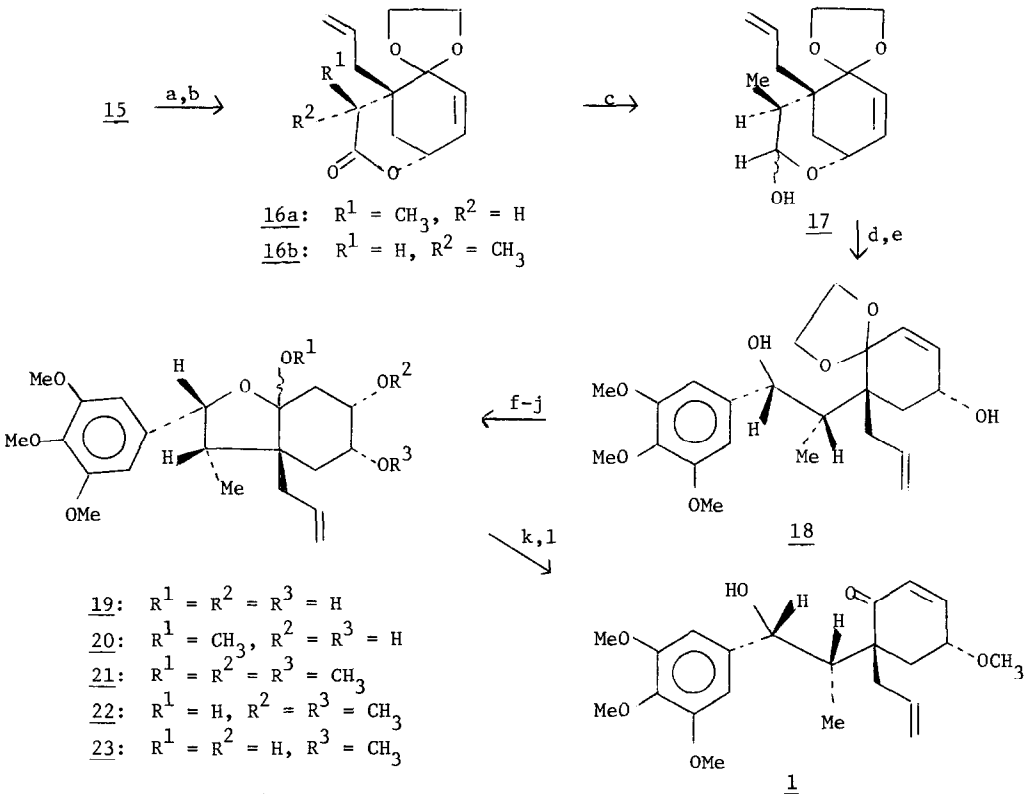


[a] 1.2 eq LDA, THF, -78°C; [b] $BrCH_2CO_2Me$, THF, -78°C → rt; [c] 2N HCl, THF, rt, 1h; [d] oxalyl chloride, $CHCl_3$, rt, 30-min; then reflux 40-min; [e] Zn-Ag, MeOH, rt, 35-min.

mined that only the spiro lactone is formed during the iodolactonization reaction. Therefore a diiodolactonization approach to synthon 15 was pursued. Thus, reaction of acid 10 with KI_3 in a 0.5 N $NaHCO_3$ solution gave a diastereoisomeric mixture of the spiro lactones 11. Separation of the diastereomers by column chromatography afforded a less polar diastereomer (33%; mp 97.5-98°C) and a more polar diastereomer (54%; mp 112°C). Reaction of the more polar diastereomer with an aqueous NaOH solution followed by neutralization of excess NaOH with CO_2 and subsequent treatment of the resulting carboxylate with KI_3 gave lactone 12



[a] $HOCH_2CH_2OH$, p-TsOH, PhH, reflux 30h; [b] aq MeOH, NaOH, 4-DMAP, rt, 45h; then 3.5% HO_2CCO_2H; [c] 0.5N $NaHCO_3$, aq KI_3, dark, 3h; [d] aq NaOH, 65°C, 4h; then rt, 24h; [e] CO_2 [f] aq KI_3, dark, 6h; [g] aq $NaIO_4$, p-dioxane, rt, 2.25h; [h] DBU, PhH, rt, 1h; then 65°C for 3.5h; [i] $Ph_3P{=}CH_2$, THF, 0°C, 2h.



16a: $R^1 = CH_3$, $R^2 = H$
16b: $R^1 = H$, $R^2 = CH_3$

19: $R^1 = R^2 = R^3 = H$
20: $R^1 = CH_3$, $R^2 = R^3 = H$
21: $R^1 = R^2 = R^3 = CH_3$
22: $R^1 = H$, $R^2 = R^3 = CH_3$
23: $R^1 = R^2 = H$, $R^3 = CH_3$

[a] LDA, THF, -78°C; [b] CH_3I, THF, 1 eq HMPA, -78°C, 2h; then rt, 20h; [c] DIBAH, $PhCH_3$, -78°C, 1.5h; [d] 3,4,5-trimethoxyphenyl lithium (10 eq), TMEDA (20 eq), THF, -98°C, 45-min; then 20-min, 0°C; [e] aq NH_4Cl; [f] aq HCl-THF, rt, 3h; [g] $BF_3 \cdot Et_2O$, MeOH, -20°C, 1.5h; then 0°C, 1h; [h] NaH, THF, CH_3I, 45°C, 1h; [i] conc HCl:H_2O:THF (1:3:5), rt, 25-min; [j] i, 6h; [k] MsCl, Et_3N, CH_2Cl_2, -15 → 5°C, 1h; [l] DBU, PhH, rt, 3h; then 60°C, 2h.

(86%; mp 93-94°C). Oxidation of (12) with $NaIO_4$ in aqueous dioxane yielded aldehyde 13[6] (82%; 88-88.5°C). Treatment of (13) with DBU in PhH gave olefin 14 (72%; mp 124-125.5°C) and subsequent reaction of (14) with methylenetriphenylphosphorane in THF at 0°C afforded the bicyclic lactone 15[7] (45%; mp 110.5-111°C), after chromatography.

Alkylation of the lithium enolate of (15) with CH_3I in THF at -78°C in the presence of one equiv. of HMPA afforded the exo and endo methylated lactones 16a and 16b in a 75:25 ratio as determined by ^1H 250 MHz NMR analysis. Reduction of (16) with DIBAH at -78°C in toluene and subsequent cyrstallization gave acetal 17 (63%; mp 106-107.5°C). Reaction of (17) with 3,4,5-trimethoxyphenyl lithium (10 equiv) in the presence TMEDA (20 equiv) in THF and subsequent chromatograph afforded ketal 18[8] (68%; mp 61.5-62°C) as the major product.[9] Hydrolysis of (18) with an aqueous HCl-THF solution gave the hemiketal 19 (51%; mp 170-71°C). Treatment of (19) with $BF_3 \cdot Et_2O$ in MeOH afforded ketal 20 (85%; mp 160-160.5°C). Alkylation of the disodium

salt of (20) with MeI in THF yielded the diether 21 (75%; mp 115-116°C). Subsequent treatment of (21) with an aqueous HCl-THF solution (HCl:H_2O:THF; 1:3:5) for 25 min gave the intermediate hemiketal (22); and continued hydrolysis afforded the ether 23 (64%; mp 159-160°C). Reaction of (23) with methanesulfonyl chloride in the presence of triethylamine in THF and subsequent treatment of the resulting mesylate with DBU in PhH followed by aqueous work-up and chromatography afforded a 71% yield of racemic megaphone 1. The spectra of synthetic (1) were identical to those of natural megaphone.[10,11]

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References and Notes

1. S.M. Kupchan, K.L. Stevens, E.A. Rohlfing, B.R. Sikles, A.T. Sneden, R.W. Miller and R.F. Bryan, J. Org. Chem., 43, 586 (1978).
2. The KB activity was assayed at the National Cancer Institute.
3. G. Büchi and P.-S. Chu, J. Am. Chem. Soc., 103 2719 (1981).
4. G. Stork and R.L. Danheiser, J. Org. Chem., 38 1775 (1973).
5. R.D. Clark and C.H. Heathcock, J. Org. Chem., 41 636 (1973).
6. The less polar diastereomer and the diastereomeric mixture 11 also afforded aldehyde 13 via the same reaction sequence.
7. For synthetic progress towards megaphone see: M.J. Kurth, Chem. Abstr., 75, 204173e (1981); also see: T.R. Hoye and M.J. Kurth, Abstract ORGN 113, 178th National Meeting of the American Chemical Society, Las Vegas, August, 1980.
8. All new compounds displayed satisfactory spectral and analytical data.
9. D.J. Cram and F.A. Abd Elkfez; J. Am. Chem. Soc., 74 5851 (1952).
10. We are indebted to Prof. S. Hecht for making available to us the spectra of megaphone from the late S.M. Kupchan's collection.
11. The 250 and 400 MHz ^1H NMR date ($CDCl_3$, δ) for several of the compounds in this work are: 8 6.88 (m,1H), 5.97 (ddd,1H,J=10.0,2.2,1.5); 11 (less polar) 2.69 (d,1H,J=15,CH_eCO_2), 2.25 (d,1H,J=15,CH_aCO_2); 11 (more polar) 2.70 (d,1H,J=16,CH_eCO_2), 2.11 (d,1H,J=16); 14 9.70 (t,1H,J=3), 6.09 (m,1H), 5.77 (d,1H,J=10); 15 5.81 (d,J=10) and 5.79 (m) [2H], 5.15 (m,2H); 16a 3.21 (q,J=7.3), 1.35 (d,J=7.3); 16b 2.76 (q,J=7.3), 1.31 (d,J=7.3); 17 2.41 (dq,1H, J=7.4,3.2), 1.04 (d,3H,J=7.3); 18 6.63 (s,2H), 3.86 (s,6H), 3.83 (s,3H), 0.94 (d,3H,J=7.5); 19 (DMSO-d_6) 5.89 (s,1H,OCOH), 5.08 (d,1H,J=9.6), 4.75 (d,1H,J=3.9,OH), 4.63 (d,1H,J=3.9, OH), 0.48 (d,3H,J=7.3); 20 5.04 (d,J=9.8), 3.31 (s,3H), 0.57 (d,3H,J=7.5); 21 3.51 (s,3H), 3.40 (s,3H), 3.32 (s,3H); 23 5.27 (d,1H,J=9.7,ArCHO), 3.36 (s,3H).

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