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PREPARATION OF *d,l*-MEGAPHONE INTERMEDIATES

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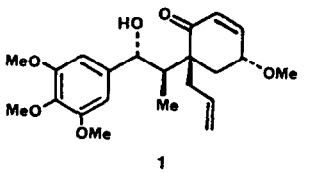
Summary: Chemistry related to the preparation of compounds 2 and 3, demonstrated intermediates in a synthesis of d,l-megaphone, is described.

Megaphone[1] (1) is a cytotoxic neolignan which has now been synthesized by both the Büchi[2] and Zoretic[3] groups. Our efforts in this area[4] were directed very much along the lines of the latter synthesis. Specifically, intermediates 2 and 3 were prepared in both the East Carolina[3] and our laboratories, although by different reaction sequences. It is appropriate to describe some of



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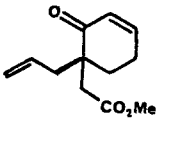

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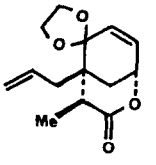

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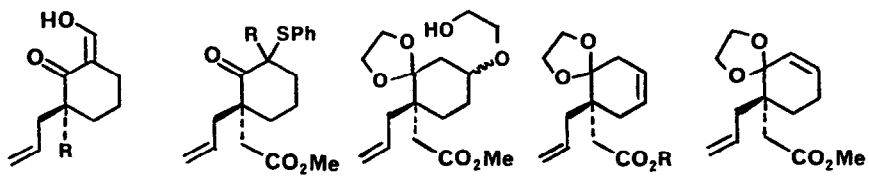
our observations which compliment the chemistry reported here earlier.[3]

2-Allylcyclohexanone[5] was formylated (EtOCHO, NaH, Et_2O, 87%[6]), and the resulting formyl-ketone (4) was converted to its dianion (2eq LDA, HMPA, THF, -78° → -20°C) and alkylated with methyl 2-bromoacetate (-78°C, 30 min) to provide 5. Sulfenylation/deformylation[7] ($PhSSO_2Ph$, KOAc, *p*-dioxane, H_2O) was smoothly achieved (70%[6] from 4 of a 3:2 mixture of diastereomers 6) only after the inclusion of water in the reaction medium. Anhydrous but otherwise identical conditions resulted in the isolation of the intermediate, non-enolizable aldehyde 7 which was

stable in the presence of the soft nucleophiles, acetate and benzenesulfinate. Sulfoxide generation (MCPBA, CH_2Cl_2, -10°C) from 6 and thermolysis ($PhCH_3$ reflux, $CaCO_3$, 15 min) provided the enone 2 (36%[6] from 4).

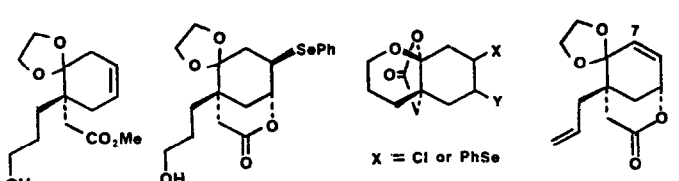
Ketalization of this enone (2) was studied in some detail. Of all the conditions attempted[8] only the standard set (PhH reflux, $HOCH_2CH_2OH$, TsOH) gave detectable quantity of any ketal. The geminally substituted cyclohexenone 2 gave only the "deconjugated" ketal 8 (59%) and the Michael



4 R = H
5 R = CH_2CO_2Me
6 R = H
7 R = CHO
9
8 R = Me
11 R = H
10

adduct/ketal 9 (39%[6]; cf. iv[8]). The latter could be converted back to 2 (10% H_2SO_4, 100°C, 65%[6]). None of the "conjugated" ketal 10 was observed; steric repulsion is minimized when the two completely substituted, vicinal carbons are both homoallylic (rather than allylic and homoallylic) on the cyclohexene ring.

We corroborate the reported preference for iodolactonization of acid 11 to the propenyl double bond[3] and observed the same for phenylselenenyl lactonization.[9] The terminal olefin in ester 8 was therefore selectively hydroborated to generate the primary alcohol 12 (9-BBN, THF, RT; H_2O_2, 10% NaOH; 78%[6]). Saponification and lactonization (PhSeCl, Et_3N, CH_2O_2) gave only the alcohol 13 on a small scale (57%[6] from 4) but could not be controlled so as to avoid the



X = Cl or PhSe
Y = PhSe or Cl

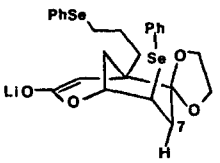
12
13
14
15

acid-catalyzed formation of the unwanted cyclic acylal 14 (32%[6] of a single isomer along with 24% of 13) on a several millimole scale. The Grieco net dehydration[10] of alcohol 13 (*o*-NO_2PhSeCN,

Bu_3P; AcO_2H, CH_2Cl_2; 100°C, 8 min) was accompanied by an expected oxidative elimination of the phenylselenenyl moeity to provide diene 15 in 83% yield.[6]

To establish the methyl-bearing stereocenter of megaphone, the lithium enolate of the bicyclic diene-lactone 15 was methylated at 0°C to generate a 2:1 mixture of 3 and its methyl epimer (3:1 at -78°C).[3] Reasoning that this stereoselection could be substantially improved by alkylation of a bicyclic lactone enolate anion containing an sp^3-hybridized (rather than sp^2 as in 15) C_7,

17



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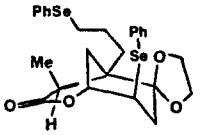

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we prepared 16 by mesylation of alcohol 12, displacement of the primary mesylate with $PhSe^-$ (Ph_2Se_2, $NaBH_4$, EtOH),[11] saponification, and selenenyl lactonization (PhSeCl, py, $CHCl_3$) to give 17. Proton removal by LDA (2 eq, RT, THF)[12] gave the enolate 16 which underwent attack by methyl iodide only from the exo face. The stereochemistry of the product 18 was confirmed by oxidative removal of both phenylselenenyl groups to liberate diene 3, which was identical with the major epimer derived from the methylation of 15. As noted this methylated lactone has subsequently been converted into megaphone.[3]

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References and Notes

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6. This yield refers to distilled or chromatographed (SiO_2) material.

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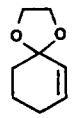
8. The ketalization of cyclohex-2-enone (i) was also examined. Under the usual conditions (PhH, $HOCH_2CH_2OH$, TsOH, Δ) an *equilibrium*, 85:15 mixture of the regioisomeric ketals ii and iii with varying quantities of the Michael adduct ketal iv (see Carney, R. L.; Johnson, W. S. J. Am. Chem. Soc. 1974, 96, 2549) arose. Generation of iv was avoided when i was transketalized with 2-ethyl-2-methyl-1,3-dioxolane. In contrast when i and ethylene glycol were

ii



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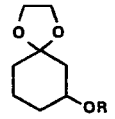

iv R=CH_2CH_2OH
v R=Me

dehydrated by the use of $HC(OCH_3)_3$, v was the only observed product. Substitution of either catechol or 2,2-dimethylpropane-1,3-diol for $HOCH_2CH_2OH$ (TsOH, PhH, Δ) avoided the formation of ethers analogous to iv and v and gave only the ketals analogous to ii and iii (precise equilibrium values were not obtained).

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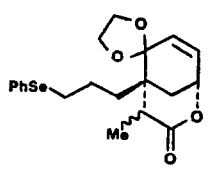
12. Use of just one equivalent of LDA (at -78° or 0°C) led only to recovery of starting material (17). Two equivalents of the base at room temperature (30 min) followed by methylation provided ca. 50% conversion to 18 along with recovered starting material (17). Extending the time for enolate anion formation at RT with two equivalent of LDA led to complete consumption of 17 but compounds vi were isolated (35%)[6] along with 18 (28%).[6] Thus, intramolecular E2 loss of PhSeH at the enolate anion stage had become a viable process. For other reports of



vi

difficulties in generating lactone enolate anions of highly functionalized (oxygenated?) substrates using lithium dialkylamide bases see Ireland, R. E.; Thompson, W. J. J. Org. Chem. 1979, 44, 3041; and Smith, A. B., III; Richmond, R. E. J. Am. Chem. Soc. 1983, 105, 575.

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