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THE TOTAL SYNTHESIS OF (±)-MEGAPHONE, A CYTOTOXIC NEOLIGNAN

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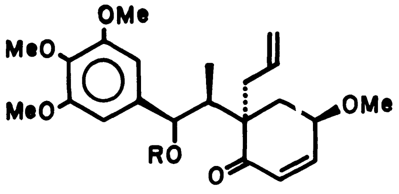
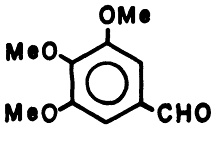
The racemic megaphone, a cytotoxic neolignan, has been synthesized from 3,4,5-trimethoxybenzaldehyde via an intermediate, 2-methoxycarbonyl-3-methyl-4-(3,4,5-trimethoxyphenyl)-γ-butyrolactone.

Megaphone (1) and megaphone acetate (2), new cytotoxic neolignans, have been isolated from the root of *Aniba megaphylla* Mez. (Lauraceae) by Kupchan and his coworkers.[1] The total synthesis of (±)-megaphone has recently been reported by two groups, Büchi and Chu[2] and Zoretic et al.[3] However, since these neolignans exhibit an vitro inhibitory activity against cells derived from human carcinoma of the nasopharynx (KB), we also have designed a new synthetic route and herein wish to report the successful total synthesis[4] of (±)-megaphone starting from 3,4,5-trimethoxybenzaldehyde (3).



1 R=H
2 R=Ac

Condensation of 3 in tetrahydrofuran with 2-methyl-1,3-dithiane (4) using butyllithium at room temperature under a stream of nitrogen afforded 2-methyl-2-(3,4,5-trimethoxyphenylhydroxymethyl)-1,3-dithiane (5) (84% yield, mp 115-116 °C). This was converted into 1-acetoxy-1-(3,4,5-trimethoxyphenyl)propanone (7) (70% from 5; IR: 1740, 1727 cm^{-1}) by acetylation with acetic anhydride in pyridine, followed by hydrolysis of the resulting acetate (6) (mp 115-116 °C) with N-chlorosuccinimide[5] in aqueous acetone at 10-16 °C. Condensation of 7 in tetrahydrofuran with dimethyl malonate in the presence of titanium tetrachloride and pyridine at room temperature under a stream of nitrogen produced methyl 4-acetoxy-2-methoxycarbonyl-3-methyl-4-(3,4,5-trimethoxyphenyl)-2-butenoate (8)[6] (90%). The diester 8 was treated with concentrated hydrochloric acid in refluxing methanol to give a butenolide ester (9).[7] The crude 9, without purification,[8] was submitted to reduction using sodium borohydride in methanol at 5 °C to give a saturated compound (10)[9] (64% from 8, mp 123.5-124.5 °C) along with a small amount of its stereoisomer (11)[10] (4% from 8, mp 106.5-107.5 °C). Decarbomethoxylation[12] of 10 and 11 with sodium chloride in wet dimethyl sulfoxide at 140 °C afforded the corresponding butanolides 12 and 13, respectively. The ^{1}H NMR spectra of 10 and 12 showed doublet signals due to the C-3 methyl at δ 0.79 and 0.70, while those of 11 and 13 showed the corresponding signals at δ 1.15 and 1.14. The appearance of the C-3 methyl signals in 10 and 12 in very high field must be attributable to the shielding effect of the C-4 aromatic ring. Thus, the relative configurations of the methyl and aryl groups in 10 and 11 were assigned to be cis and trans dispositions respectively. However, the stereochemistry of the C-2 methoxycarbonyl group in 10 remained unsettled. Michael reaction of 10 with methyl vinyl ketone in the presence of triethylamine in methanol at 5 °C afforded a C-2 epimeric mixture of keto lactone esters (14)[13] (92%) in a ratio of 90:2. Alkaline hydrolysis of 14 in refluxing methanol, followed by decarboxylation, produced a C-2 epimeric mixture of keto lactones (15) (85%; IR: 1769, 1712 cm^{-1}). This was then converted into a mixture of the corresponding acetals (16) (87%, IR: 1769 cm^{-1}) by treatment with 1,2-ethanediol, boron trifluoride etherate, and tetramethyl orthocarbonate in dichloromethane at room temperature. To introduce an allyl group the acetal 16 was treated with allyl bromide and lithium diisopropylamide in tetrahydrofuran under a stream of nitrogen. The resulting single product 17 (76%, mp 117.5-118.5 °C) was hydrolyzed with dilute hydrochloric acid in methanol to give a keto lactone (18)[14] (68%; IR: 1764, 1717, 1639 cm^{-1}). The relative configuration of the C-2 allyl and C-3 methyl groups in 17 was assigned to be trans by assuming the introduction of the allyl group from the less hindered side of the molecule. The keto lactone 18 was submitted to the intramolecular aldol condensation using potassium t-butoxide in refluxing tetrahydrofuran. The crude product was immediately refluxed with p-toluenesulfonic acid in benzene to give an α,β-unsaturated ketone (19) (71%,[15] IR: 1629 cm^{-1}). Introduction of a hydroxyl group at the C-5 position of 19 was carried out as follows.[16,17] The compound 19 in dimethoxyethane was treated with chlorotrimethylsilane and lithium



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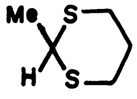

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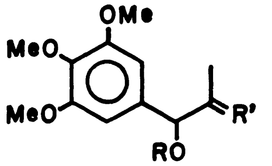
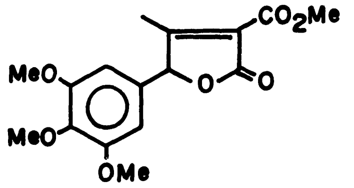


5 R=H, R'=$S(CH_2)_3S$

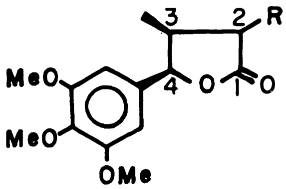
6 R=Ac, R'=$S(CH_2)_3S$

7 R=Ac, R'=O

8 R=Ac, R'=$C(CO_2Me)_2$

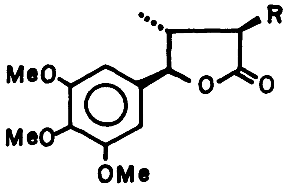


9



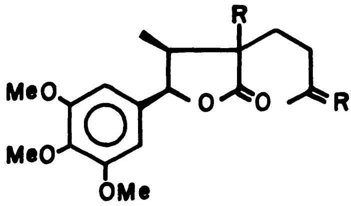
10 R=CO_2Me

12 R=H



11 R=CO_2Me

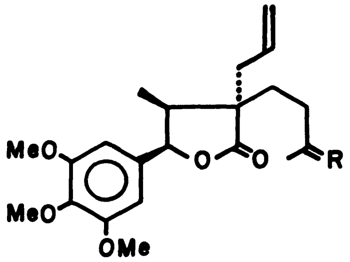
13 R=H



14 R=CO_2Me, R'=O

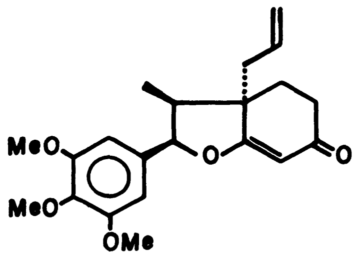
15 R=H, R'=O

16 R=H, R'=$O(CH_2)_2O$



17 R=$O(CH_2)_2O$

18 R=O



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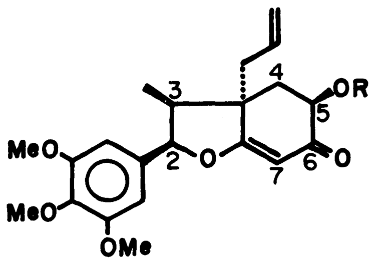

20 R=H

21 R=Me

diisopropylamide under a stream of nitrogen to give an enol silyl ether which was converted into a hydroxyenone (20) (30%,[15] IR: 3470 cm^{-1}) by oxidation with m-chloroperbenzoic acid in the presence of sodium hydrogencarbonate in dichloromethane and subsequent treatment with triethylammonium fluoride. Methylation of 20 with diazomethane in ether in the presence of silica gel afforded the desired methoxyenone (21) (49%, mp 139-141 °C; IR: 1654, 1632 cm^{-1}); ^1H NMR (90 MHz, $CDCl_3$) δ 0.54 (3H, d, J=7.5 Hz, C_3-CH_3), 3.60 (3H, s, C_5-OCH_3), 3.84 (3H, s) and 3.86 (6H, s) ($-OCH_3 \times 3$), 3.98 (1H, dd, J=12 and 5 Hz, C_5-H), 5.20-5.45 (2H, m) and 5.71-6.22 (1H, m) ($-CH_2\underline{CH}=\underline{CH_2}$), 5.58 (1H, s, C_7-H), 5.84 (1H, d, J=5 Hz, C_2-H), 6.42 (2H, s, aromatic protons). The physical and spectral data of 21 were identical with those of the known rel-(2R,3S,3aR,5R)-3,3a,4,5-tetrahydro-5-methoxy-3-methyl-3a-

(2-propenyl)-2-(3,4,5-trimethoxyphenyl)-6(2H)-benzofuranone.$^{2)}$ Since conversion of 21 into (±)-megaphone (1) and (±)-megaphone acetate (2) had already been achieved by Büchi and Chu,$^{2)}$ the present work also constitutes another synthesis of these natural products.

References

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2) G. Büchi and P-S. Chu, J. Am. Chem. Soc., 103, 2718 (1981).
3) P. A. Zoretic, C. Bhakta, and R. H. Khan, Tetrahedron Lett., 24, 1125 (1983).
4) Although the nomenclature and formulas represent only one enantiomer, they should be taken to indicate racemates. The IR spectra were measured in chloroform and the ^{1}H NMR spectra in carbon tetrachloride at 60 MHz, with tetramethylsilane as an internal standard, unless otherwise stated.
5) E. J. Corey and B. W. Erickson, J. Org. Chem., 36, 3553 (1971).
6) ^{1}H NMR of 8: δ 1.94 (3H, s) and 2.11 (3H, s) ($=\overset{|}{C}CH_3$ and $-OCOCH_3$), 3.72 (3H, s), 3.75 (3H, s), and 3.86 (9H, s) ($-CO_2CH_3$x2 and $-OCH_3$x3), 6.66 (3H, s, $-\overset{|}{C}HOAc$ and two aromatic protons).
7) ^{1}H NMR of 9: δ 2.15 (3H, s, C_3-CH_3), 3.70 (3H, s) and 3.78 (9H, s) ($-CO_2CH_3$ and $-OCH_3$x3), 5.62 (1H, s, C_4-H), 6.41 (2H, s, aromatic protons).
8) Purification of 9 by column chromatography on silica gel afforded the corresponding 3-buten-4-olide.
9) ^{1}H NMR of 10 (90 MHz): δ 0.79 (3H, d, J=7 Hz, C_3-CH_3), 2.87-3.24 (2H, m, C_2-H and C_3-H), 3.72 (3H, s), 3.80 (3H, s), and 3.82 (6H, s) ($-CO_2CH_3$ and $-OCH_3$x3), 5.56 (1H, d, J=6 Hz, C_4-H), 6.33 (2H, s, aromatic protons).
10) ^{1}H NMR of 11 (90 MHz): δ 1.15 (3H, d, J=6.5 Hz, C_3-CH_3), 2.5-3.0 (1H, m, C_3-H), 3.24 (1H, d, J=12 Hz, C_2-H), 3.73 (3H, s), 3.80 (3H, s), and 3.83 (6H, s) ($-CO_2CH_3$ and $-OCH_3$x3), 4.67 (1H, d, J=9.5 Hz, C_4-H), 6.50 (2H, s, aromatic protons). The coupling constant of C_2-H suggested that the relative configuration of the C-2 methoxycarbonyl and C-3 methyl groups was trans.$^{11)}$
11) D. Savostlanoff and M. Pfau, Bull. Soc. Chim. Fr., 1967, 4162.
12) A. P. Krapcho and A. J. Lovey, Tetrahedron Lett., 1973, 957.
13) The column chromatography of the mixture 14 on silica gel afforded 14a (90%, mp 119.5-120.5 °C; IR: 1777, 1730sh, 1715 cm^{-1}) and 14b (2%; IR: 1779, 1733sh, 1725 cm^{-1}).
14) ^{1}H NMR of 18: δ 0.65 (3H, d, J=7.5 Hz, C_3-CH_3), 2.11 (3H, s, $-COCH_3$), 3.72 (3H, s) and 3.83 (6H, s) ($-OCH_3$x3), 4.90-5.28 (2H, m) and 5.35-6.15 (1H, m) ($-CH_2\underline{CH}=\underline{CH_2}$), 5.39 (1H, d, J=7 Hz, C_4-H), 6.38 (2H, s, aromatic protons).
15) Yield was based on the starting material consumed.
16) L. Blanco, P. Amice, and J. M. Conia, Synthesis, 1976, 195.
17) G. M. Rubottom and J. M. Gruber, J. Org. Chem., 43, 1599 (1978).

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