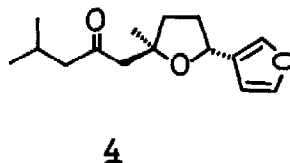
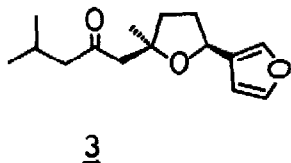
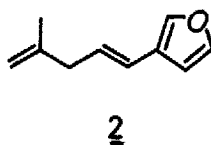
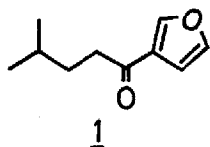


SYNTHESES OF FURANOTERPENES: PERILLAKETONE, α -CLAUSENANE,
(\pm)-IPOMEAMARONE, AND (\pm)-EPIIPOMEAMARONE

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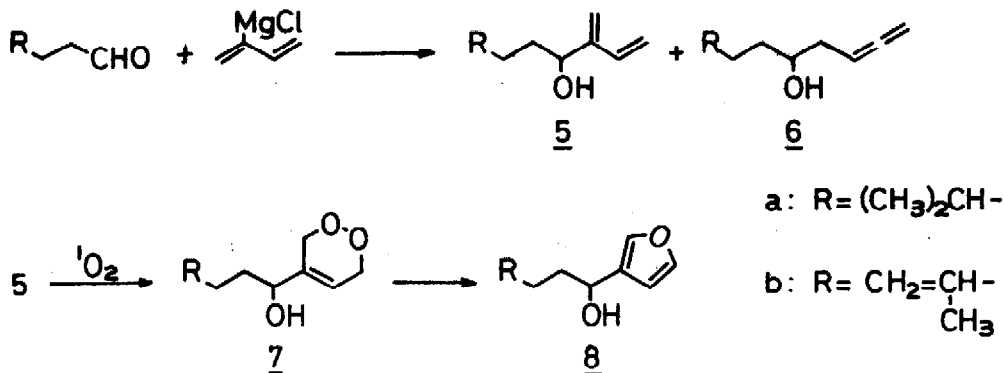
It has recently been shown that sensitized photooxygenation of terpenes bearing 1,3-diene moiety can be utilized as a key step in the syntheses of certain furanoterpenes.^{1,2} In order to prove the generality and powerfulness of this new method, we have now applied the reaction sequence to the syntheses of more complex naturally-occurring furanoterpenes. The target compounds selected are perillaketone (1) which was originally isolated from Perilla frutescens Brit.,³ α -clausenane (2) found in Clausena willdenovii,⁴ and ipomeamarone (3). The last compound is well-known as a phytoalexin existing in mold-damaged sweet potatoes⁵ and both 3 and its epimer 4 were also isolated from Myoporium deserti.^{6,7}



Our method of synthesizing (\pm)-3 and (\pm)-4 would be characterized by the preparation of the furan 8b from the monoterpene alcohol 5b. Before being engaged in this goal, we have examined the possibility of the synthesis of furan 8a from alcohol 5a as a preliminary experiment. Treatment of 4-methylpentanal with 2-(1,3-butadienyl)magnesium chloride which was easily prepared from 2-chloro-1,3-butadiene (chloroprene) and magnesium in tetrahydrofuran (THF),⁸ followed by usual work-up and distillation, afforded a mixture of alcohols 5a and 6a (5a/6a = 4/1) (89%). As we knew that the presence of 6a did not disturb the next operation, the mixture of 5a and 6a (5.4 g) was directly photooxygenated in dichloromethane (250 ml) containing 5% of methanol in the presence

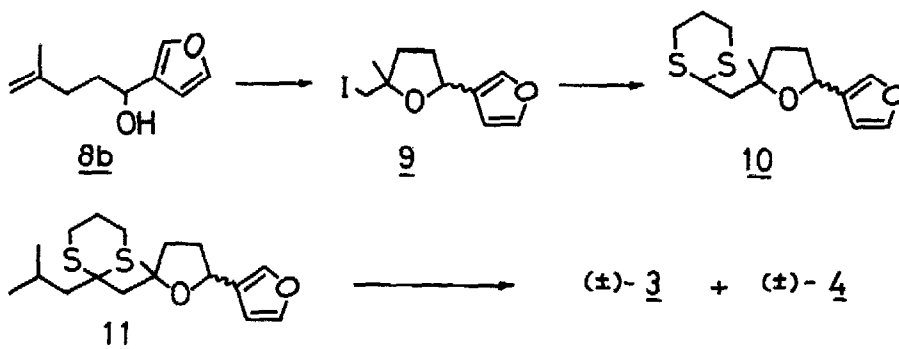
of rose bengal (0.2 g) under an oxygen atmosphere using halogen lamp (Toshiba JD100V 500W). The crude photolysate was chromatographed on silica gel to afford 1.4 g of starting material (almost 6a) and 3.4 g of cyclic peroxide 7a⁹ (70%). The dehydration of 7a was achieved by treatment with lithium *t*-butoxide followed by acidification with H₂SO₄ in THF to give the furan 8a¹⁰ in 88% yield. Oxidation of the alcohol 8a with active MnO₂ in *n*-hexane at ambient temperature for 3 days produced perillaketone (1)¹¹ in 89% yield.

Based on the above information, the furan 8b was now prepared as follows: The sensitized photooxygenation of 5b, which was obtained together with the isomeric alcohol 6b from 4-methyl-4-pentenal and chloroprene (85%) (bp 67°/2mm), was carried out for 13 hrs, thus affording the peroxide 7b¹² in 84% yield. The cyclic peroxide was converted to 8b¹³ in 83% yield by successive treatment with *t*-butoxide and H₂SO₄. Dehydration of the furan 8b with KHSO₄ at 140° (bath temperature) under 30 mm. afforded α -clausenane (2)¹⁴ in 80% yield. The NMR spectrum of the product revealed that 2 was contaminated with a small amount of its *cis*-isomer.



When the alcohol 8b was stirred with an equimolar *N*-iodosuccinimide and NaHCO₃ in dioxane at room temperature for 1.5 hr in the dark, oxidative cyclization proceeded to give the iodide 9¹⁵ as a mixture of stereoisomers in 94% yield. Condensation of 9 with the carbanion¹⁶ derived from 2-isobutyl-1,3-dithian would produce the basic skeleton of ipomeamarone. However, all attempts of the reaction under various conditions were fruitless. On the other hand, the condensation of 1,3-dithian itself with 9 was successful. Thus the carbanion prepared from 1,3-dithian and *n*-butyl lithium was treated with the iodide 9 in a mixed solvent system composed of hexamethylphosphoric triamide (HMPA), diglyme, and THF (2:3:3) at -78° for 2 hrs, and then at -20° overnight, to afford the adduct 10¹⁷ as a mixture of stereoisomers in 54% yield.¹⁸ The adduct 10 was then further lithiated with *n*-butyl lithium and treated with isobutyl chloride in HMPA-THF (3:20) at -78° for 4hr to afford the desired product 11¹⁹ in 86% yield. Treatment of the 1,3-dithian derivative 11 with 4 equivalents of AgNO₃ and *N*-chlorosuccinimide in aq. acetonitrile¹⁶ at room temperature for 5 min furnished finally a mixture of (\pm)-ipomeamarone (3) and (\pm)-epiipomeamarone (4) (2:3) (98%).

When the product was refluxed with a catalytic amount of sodium methoxide in methanol for 30 min,^{7c} an equilibrium mixture of racemic 3 and 4 (1:1) was obtained and its NMR and ir spectra were exactly identical with those of the equilibrium mixture obtained from natural ipomeamarone under the same condition. The mixture of 3 and 4 is known to be separable from each other by glpc^{7c} or by high-pressure liquid chromatography.^{5e} In conclusion, the works of this series have attested that the 1,4-cycloaddition of singlet oxygen to acyclic dienes is synthetically useful and especially powerful in the preparation of 3-substituted furans.



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- (9) A colorless oil, NMR (CCl_4); δ 5.74 (m, 1H, olefinic CH), 4.46 (m, 4H, two ring CH_2), 3.99 (t, $J = 6.0$ Hz, 1H, CHOH), 2.05 (broad s, 1H, OH), 1.22 - 1.70 (m, 5H), and 0.93 (d, $J = 6.0$ Hz, 6H, CH_3) ppm.
- (10) A colorless oil, NMR (CCl_4); δ 7.22 (m, 2H, furyl), 6.23 (m, 1H, furyl), 4.41 (t, $J = 6.0$ Hz, 1H, CHOH), 2.35 (broad s, 1H, OH), 1.10 - 1.74 (m, 5H), and 0.90 (d, $J = 6.5$ Hz, 6H, CH_3) ppm.
- (11) A colorless oil, NMR (CCl_4); δ 7.92, 7.34, and 6.25 (three m, 3H, furyl), 2.63 (t, $J = 7.0$ Hz, 2H, $\text{CH}_2\text{C}=\text{O}$), 1.40 - 1.70 (m, 3H) and 0.94 (d, $J = 6.0$ Hz, 6H, CH_3) ppm.
- (12) A colorless oil, NMR (CCl_4); δ 5.76 (m, 1H, olefinic CH), 4.63 (broad s, 2H, olefinic CH_2), 3.88 - 4.15 (m, 1H, CHOH), 2.64 (broad s, 1H, OH), 1.90 - 2.20 (m, 2H, allylic CH_2), 1.48 - 1.80 (m, 2H), and 1.71 (s, 3H, CH_3) ppm.
- (13) A colorless oil, NMR (CCl_4); δ 7.24 (m, 2H, furyl), 6.25 (m, 1H, furyl), 4.33 - 4.74 (m, 3H, olefinic CH_2 and CHOH), 1.53 - 2.22 (m, 4H, CH_2CH_2), and 1.72 (s, 3H, CH_3) ppm.
- (14) A colorless oil, NMR (CCl_4); δ 7.23 (m, 2H, furyl), 6.35 (m, 1H, furyl), 5.94 (q_{AB} , $J_{\text{AB}}=15.0$ Hz, the high-field pair was composed of two t ($J = 6.5$ Hz), 2H, $\text{CH}=\text{CH}$), 4.67 (m, 2H, olefinic CH_2), 2.77 (d, $J = 6.5$ Hz, 2H, CH_2), 1.72 (s, 3H, CH_3) ppm.
- (15) A colorless oil, NMR (CCl_4); δ 7.24 (m, 2H, furyl), 6.23 and 6.19 (two m, 1H (2:3), furyl), 4.89 (m, 1H, $-\text{CHO}-$), 3.20 (m, 2H, CH_2I), 1.75 - 2.31 (m, 4H, CH_2CH_2), and 1.46 (s, 3H, CH_3) ppm.
- (16) For a review, see D. Seebach, Synthesis, 17 (1969).
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- (18) Condensation of the corresponding bromide, prepared from 8b and N-bromo-succinimide (94%) [a colorless oil, NMR (CCl_4); δ 7.23 (m, 2H, furyl), 6.21 (m, 1H, furyl), 4.87 (t, $J = 6.0$ Hz, 1H, CHO), 3.29 and 3.24 (two s, 2H (1:4), CH_2Br), 1.68 - 2.32 (m, 4H, CH_2CH_2), 1.39 (s, 3H, CH_3) ppm], with 1,3-dithian under the similar conditions afforded 10 in 42% yield.
- (19) A colorless oil; NMR (CCl_4); δ 7.22 (m, 2H, furyl), 6.24 and 6.19 (two m, 1H (2:3), furyl), 4.82 (m, 1H, CHO), 2.75 (m, 4H, two CH_2S), 1.75 - 2.30 (m, 11H, five CH_2 and CH), 1.41 (s, 3H, CH_3), and 1.00 (m, 6H, two CH_3) ppm.