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TOTAL SYNTHESIS OF (±) ZOAPATANOL

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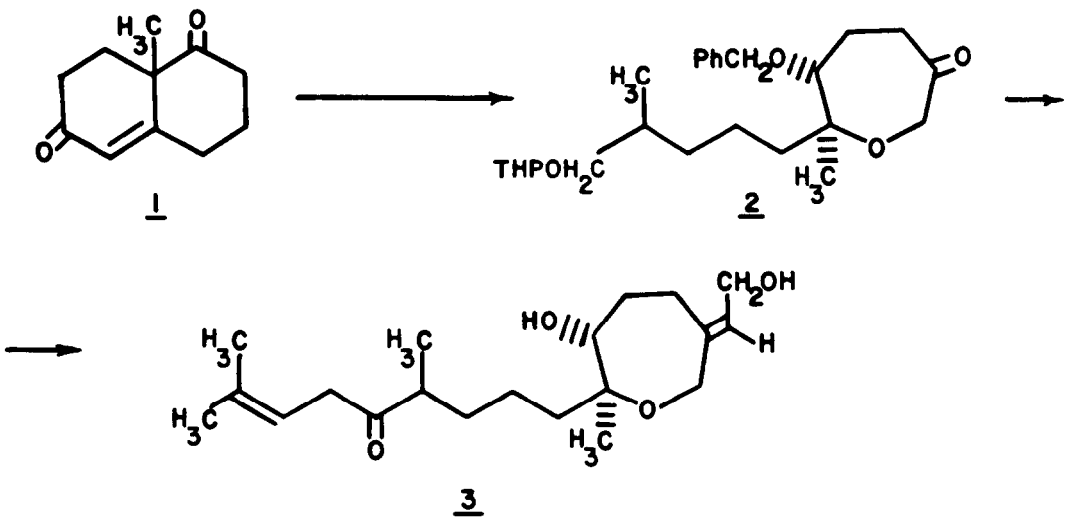
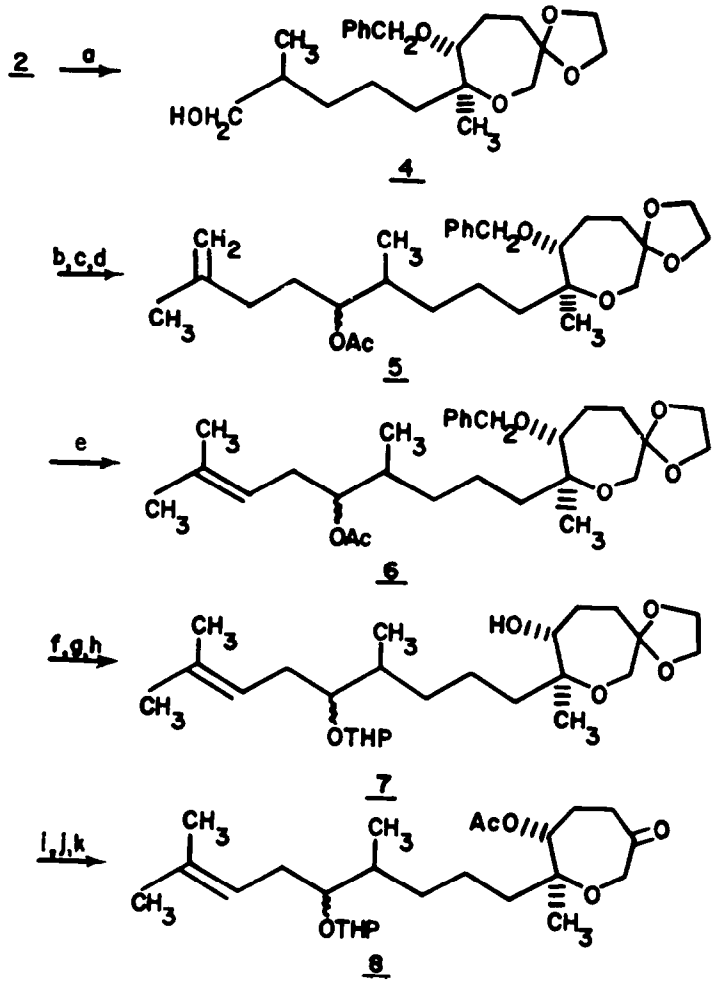
ABSTRACT: A stereoselective synthesis of (±) zoapatanol is described.

In the previous communication,[2] we described a method of converting bicyclic diketone 1[3] (commonly known as the Wieland-Miescher ketone) to β-keto ether 2, which has the desired stereochemistry and all the requisite functionalities for further elaboration to zoapatanol (3) Zoapatanol (3) is one of the novel biologically active diterpenoids isolated from the zoapatle plant, Montanoa tomentosa.[4]



The next stage of our synthesis centered on elaboration of the side chain (Scheme 1). Ketalization of 2 gave the ketal alcohol 4 (87%)[5,6] which was oxidized with Collins reagent to an aldehyde (83%). Several methods are available[8] for addition of a dimethylallyl side chain (5-carbon chain) to an aldehyde, and after examining several of these we selected the reaction sequence described below. Reaction of this aldehyde with the Grignard reagent generated from 4-bromo-2-methyl-1-butene[9] gave an alcohol (96%) which was acetylated to give acetate 5 (97%). Isomerization of the double bond of 5 with TsOH-C_6H_6 at reflux for 24 hr gave 6[9] (95%). Basic hydrolysis (94%), THP ether formation (86%) and reductive cleavage of the benzyl ether with Na in a mixture of NH_3/t-BuOH/THF gave the alcohol 7 (86%). Acetylation (86%) and selective hydrolysis (75%) followed by reprotection of the secondary alcohol afforded the THP ether 8 (98%).



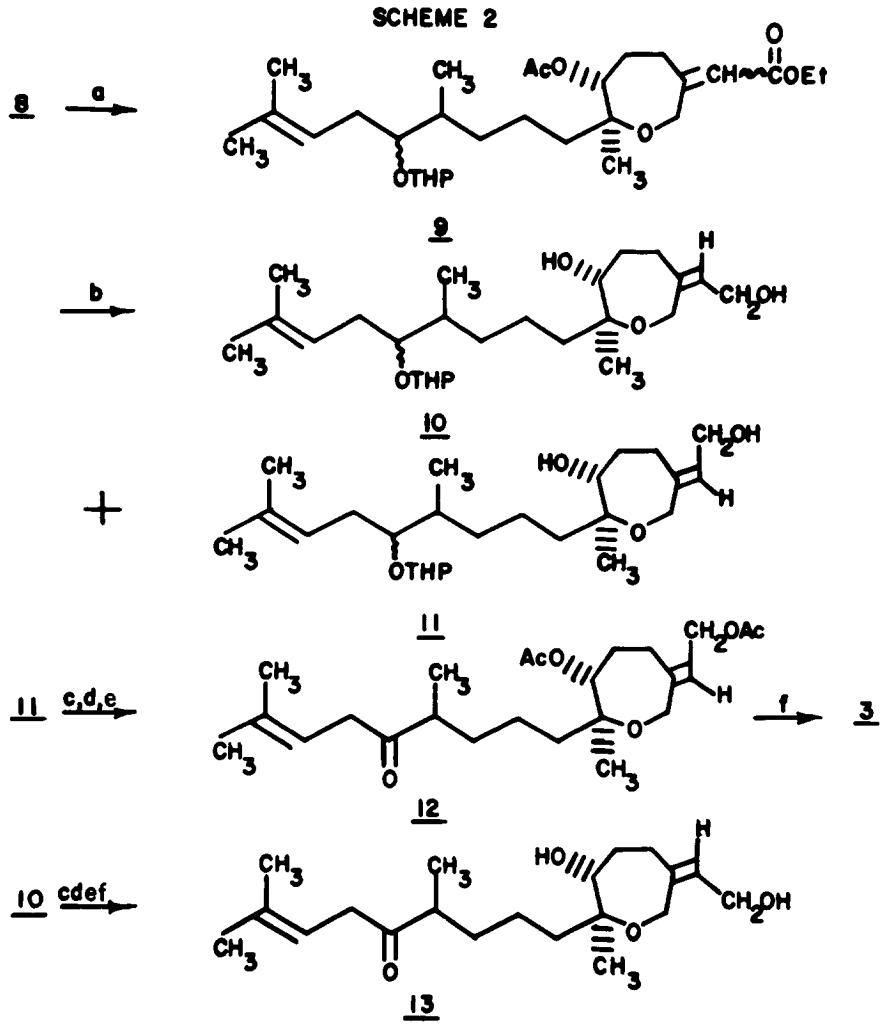
SCHEME I

a, $\left[\begin{smallmatrix}OH\\OH\end{smallmatrix}\right]$/TsOH/$C_6H_6$; b, CrO_3/Pyr/CH_2Cl_2; c, $H_3C\text{-}\overset{CH_2}{\overset{\|}{C}}\text{-}CH_2\text{-}CH_2MgBr$/THF, D, $(CH_3CO)_2O$/Pyr; e, TsOH/C_6H_6/Δ; f, K_2CO_3/MeOH/H_2O; g, DHP/TsOH/Et_2O; h, liq NH_3/Na/t-BuOH/THF; i, $(CH_3CO)_2O$/Pyr; j, $(CH_3)_2CO/H_2O$/0.002N H_2SO_4; k, DHP/TsOH/Et_2O.

Completion of the synthesis of 3 now required transformation of the 6-ketone to the (E)-2 hydroxyethylidene group and conversion of the side chain oxygen function to a ketone (Scheme 2) Condensation of 8 with triethylphosphonoacetate-NaH[10] in C_6H_6 followed by acidic work-up[11] afforded unsaturated ester 9 as an inseparable mixture of E and Z-isomers (98%). Reduction of

9 with LAH in Et_2O at 0° gave the alcohols 10 (Z-isomer) and 11 (E-isomer) in the ratio of 3:2 (70%) which were separable by column chromatography. The diol 11 was diacetylated (96%), the THP protecting group removed (84%) and the alcohol was oxidized with Collins reagent[7] to give ketone 12 (88%). Treatment of 12 with excess tetrabutylammonium hydroxide (40% solution in CH_3OH) in THF-H_2O (1:1) resulted in complete saponification of the acetate groups to give (±)-zoapatanol 3. The isomeric diol 10 was converted to (±) 6-(Z)-zoapatanol 13 using the same reaction sequence. Synthetic 3 and 12[12] were identical with natural zoapatanol and its diacetate by comparison of their chromatographic (TLC, GC) and spectral properties (NMR, IR, mass spec.), thus providing a confirmation of the structure for the natural product.[13,14]

SCHEME 2



a, $(EtO)_2\overset{O}{\overset{\|}{P}}-CH_2COOEt/NaH/C_6H_6$; b, LAH/Et_2O; c, $(CH_3CO)_2O/Pyr$;
d, $CH_3COOH/H_2O/THF$; e, $CrO_3/Pyr/CH_2Cl_2$; f, $[CH_3(CH_2)_3]_4NOH/THF/H_2O$.

Thus, a preparatively useful route to a wide variety of zoapatanol analogs has become available from bicyclic enones. Since the Wieland-Miescher ketone is now available in large quantities in optically active form.[15] The synthesis of optically pure zoapatanol without involving a resolution step is now in hand.

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6. All intermediates were purified using silica gel column chromatography and yields mentioned are of pure products.
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11. Neutral (pH 7) and basic work-up gives predominantly the undesired vinyl ether.
12. Both zoapatanol (3) and its diacetate are noncrystalline as are the racemic counterparts.
13. For two different approaches, see R. Chen and D. A. Rowand, J. Am. Chem. Soc., 102, 6609 (1980); K. C. Nicolaou, D. A. Claremon, and W. E. Barnette, ibid, 102, 6611 (1980).
14. At the present time, the stereochemistry of the methyl group α to the ketone has not been determined in the natural product.[4] X-ray crystallographic determination of a crystalline hydrazone derivative indicates that it posses R configuration. The synthetic material is a mixture of R and S at this center giving a pair of diastereomers.
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