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TOTAL SYNTHESIS OF (±) ZOAPATANOL: A STEREOSPECIFIC SYNTHESIS OF A KEY INTERMEDIATE

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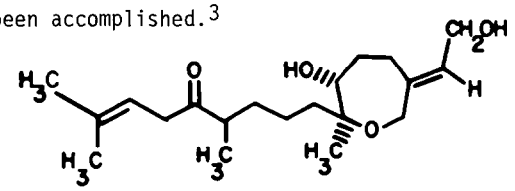
ABSTRACT: The development of a stereospecific synthesis of a key intermediate in the synthesis of (±)-zoapatanol from the Weiland-Miescher ketone is described.

Zoapatanol (1) and montanol (2) are two novel biologically active diterpenoids which have been isolated from the zoapatle plant, Montanoa tomentosa.[2] The plant has been used for centuries in the form of a tea to induce menses and labor and terminate early pregancy. In this and the following communication, we wish to report the total synthesis of (±)-zoapatanol, which also constitutes the synthesis of a diterpenoid containing an oxepane ring. Prior to this work, two other syntheses of (±) zoapatanol detailing totally different approaches had been accomplished.[3]



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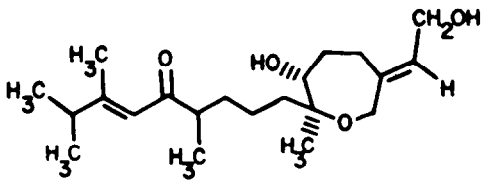
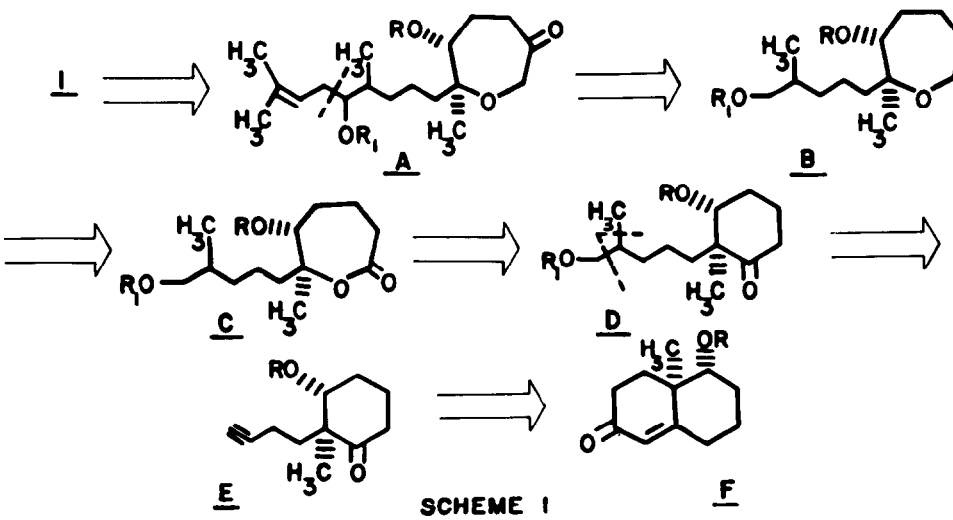


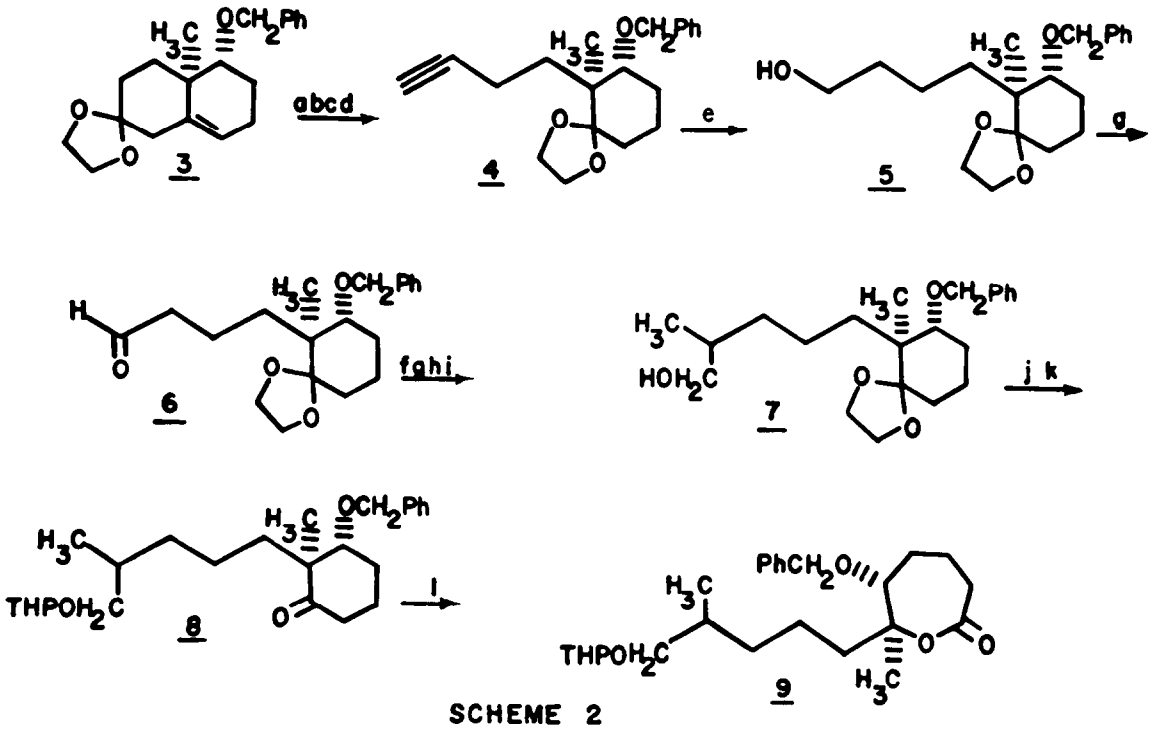
2

The overall synthetic plan is depicted in the antithetic sequence outlined in Scheme 1. The basic plan entailed the use of bicyclic intermediate F to establish and control the stereorelationship required for the ring geminal alkyl and hydroxyl groups. A key requirement in the synthesis involved conversion of lactone C to the β-keto ether B. The successful synthesis of a suitable form of B is described herein.



SCHEME 1

The requisite starting material, ketal 3[4] was readily available on a large scale in five steps from the Wieland-Miescher ketone[5] (Scheme 2). Ketal 3 on acid hydrolysis gave an α,β-unsaturated ketone[6] (90%),[7] which upon epoxidation yielded a mixture of keto epoxides (74%). Eschenmoser fragmentation[8] with p-toluenesulfonylhydrazide gave an acetylenic ketone (83%) which was ketalized to give 4 (95%). Hydroboration with 9-BBN[9,10] (2.1 equivalents) afforded a mixture (85:15 after chromatography) of alcohol 5 and aldehyde 6 (85%). Collins oxidation[11] of 5 gave the aldehyde 6 (90%). Treatment of this aldehyde with CH_3Li in Et_2O gave an alcohol (97%), which was oxidized (85%) with Collins reagent.[11] The resulting methyl ketone upon treatment with methyltriphenylphosphonium iodide-NaH in DMSO[12] gave the terminal alkene (92%), which was converted to alcohol 7 upon hydroboration[9,13] with 9-BBN (91%). Hydrolysis of the ketal (99%), followed by protection of the alcohol as its THP derivative (90%) yielded ketone 8 which underwent Baeyer-Villiger oxidation to the desired lactone 9 (70%).

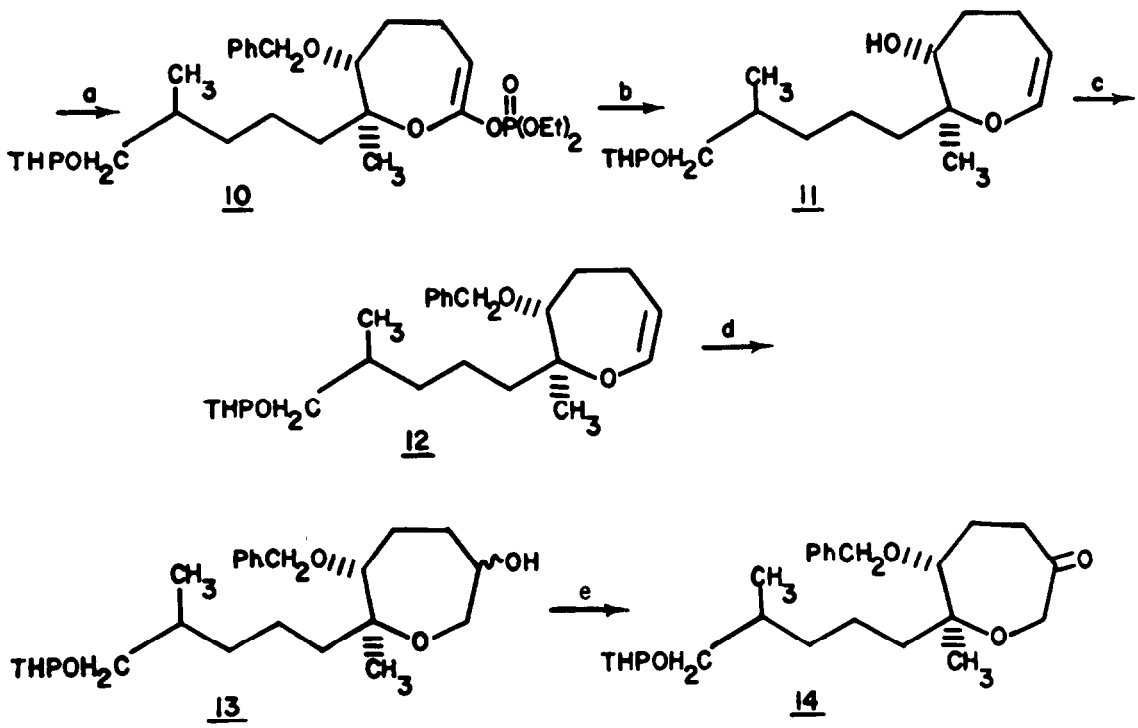


SCHEME 2

a, CH_3COOH/MeOH (1:1); b, H_2O_2/NaOH/CH_3OH; c, p-$TsNHNH_2$/CH_3COOH/CH_2Cl_2;
d, $\begin{bmatrix}OH\\OH\end{bmatrix}$/TsOH/$C_6H_6$; e, 9-BBN/THF; H_2O_2/NaOH; f, CH_3Li/Et_2O; g, CrO_3/C_5H_5N/CH_2Cl_2;
h, ϕ_3PCH_3I/NaH/DMSO; i, 9-BBN/NaOH/H_2O_2; j, CH_3COCH_3/H_2O/0.002N H_2SO_4;
k, DHP/TsOH/Et_2O; l, MCPBA/NaOAc/CH_2Cl_2,Δ.

With lactone 9 in hand, we focused our attention on its conversion to the β-keto ether 14 (Scheme 3). After considerable experimentation, an effective, new scheme was developed.[14] Reaction of lactone 9 in THF with LDA at -78°C and treatment of the resulting solution with diethyl chlorophosphate gave the enol phosphate 10 (85%). Reduction of the enol phosphate[15] with Na in a mixture of NH_3/t-BuOH/THF led to the desired tetrahydrooxepane 11 (57%), which was benzylated to give the benzyloxy tetrahydrooxepane 12 (98%). Hydroboration of vinyl ether 12 with BH_3,[9,16] afforded a mixture of epiperic alcohols 13 (75%), which upon Collins oxidation[11] gave the desired β-keto ether 14 (90%). Elaboration of this β-keto ether 14 to (±) zoapatanol is described in the subsequent communication.

SCHEME 3



a, LDA/$(EtO)_2\overset{O}{\overset{\|}{P}}Cl$/THF/TMEDA/HMPA; b, liq NH_3/Na/t-BuOH; c, $PhCH_2Br$/NaH/C_6H_6; d, BH_3/THF; H_2O_2/NaOH; e, CrO_3/C_5H_5N/CH_2Cl_2.

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References and Notes

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