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A SYNTHESIS OF ZOAPATANOL

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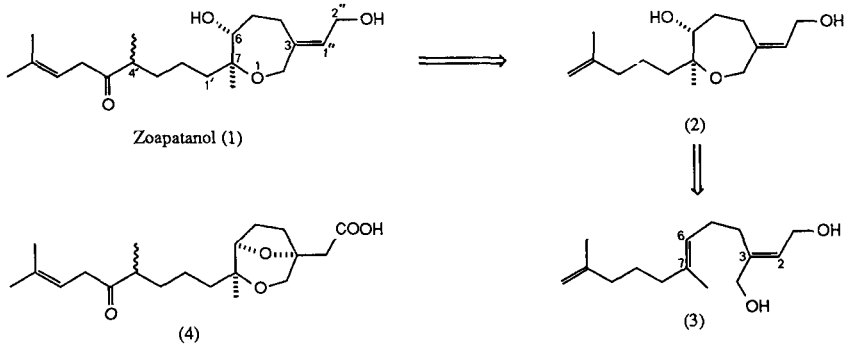
Abstract: Organomagnesium chemistry plays a crucial role in the stereoselective construction of the two tri-substituted alkenes in the diol (**3**)-a key intermediate in a synthesis of the spasmogenic diterpenoid zoapatanol (**1**). A Ni(0)-catalysed coupling of MeMgBr with a dihydrofuran gives the C(6)-C(7) alkene; carbomagnesiation or hydromagnesiation of acetylene intermediates gives the C(2)-C(3) alkene.

Zoapatanol (**1**) is one of several diterpenoid oxepanes isolated from the leaves of the Mexican zoapatle plant *Montanoa tomentosa* which has been traditionally used in folk medicine as an antifertility agent[1]. Recent studies suggest that zoapatanol has significant spasmogenic activity in isolated cat coronary artery[2] and it inhibits spontaneous contraction of guinea pig uterine strips *in vitro*[3]. Although the abortifacient properties of the aqueous zoapatle extract have been confirmed[4], there is some question as to whether zoapatanol is the active agent since it is highly insoluble in water and is unstable[5]. In fact the 3,8-dioxabicyclo[3.2.1]octane-1-acetic acid derivative (**4**) is one of a number of analogues which is more active than zoapatanol itself[6,7] and it has been suggested that *in vivo* transformations of the monocyclic oxepane to the bicyclic system, an easy transformation *in vitro*, is a prerequisite for biological activity[6].

We now report a 3-stage synthesis of (±)-zoapatanol as outlined in Scheme 1 in which the intermediates (**2**) and (**3**) are important milestones. In the first stage highly stereoselective organomagnesium-based reactions were used to construct the C(6)-C(7) and C(2)-C(3) trisubstituted alkenes of the diol (**3**) which, in the second stage, was converted with high stereoselectivity to the oxepane (**2**). In the final stage of the synthesis , the side chain of oxepane (**2**) was elaborated to give (±)-zoapatanol as a 1:1 mixture of C-(4') diastereoisomers. In common with previous syntheses of zoapatanol[8-11], we did not attempt to control the relative stereochemistry at C(4') because it has never been proven unambiguously and there is no firm evidence that the natural product is a single isomer. Consequently, the synthetic plan in Scheme 1 was adopted so that the purification and spectroscopic analysis of intermediates was unhampered by the complications of diastereoisomers until very late in the synthesis.



Scheme 1

Synthesis of Diol (3). In the first phase of the synthesis (Scheme 2) diol (**3**) was prepared in 5 steps (40% overall yield) from the iodide (**5**). There were two crucial steps in this sequence both of which proceeded with very high stereoselectivity. The homoallylic alcohol (**7**) was prepared using a modification of the Wenkert reaction[12] which incorporates some improvements which make it experimentally easier to do on a large scale. Thus the requisite Ni(0) catalyst was prepared by adding 2 eq of ethereal MeMgBr to a suspension of 2 mol % of $[Ph_3P]_2NiCl_2$ in benzene. After 15 min at room temperature, the remaining MeMgBr (3 eq in total) was added to the dark red solution of the Ni(0) catalyst followed by 1 eq of the dihydrofuran (**6**) and the mixture refluxed for 3h whereupon standard aqueous workup gave (**7**) in 89% yield (60 mmol scale, ≥97% E). The Wenkert reaction is slower in co-ordinating solvents and in the past the ether was removed *in vacuo* before addition of the dihydrofuran[13]. However, the dihydrofurans are highly reactive substrates in the coupling and the presence of ether depressed the rate only slightly. The reduced amount of catalyst also made the workup easier.

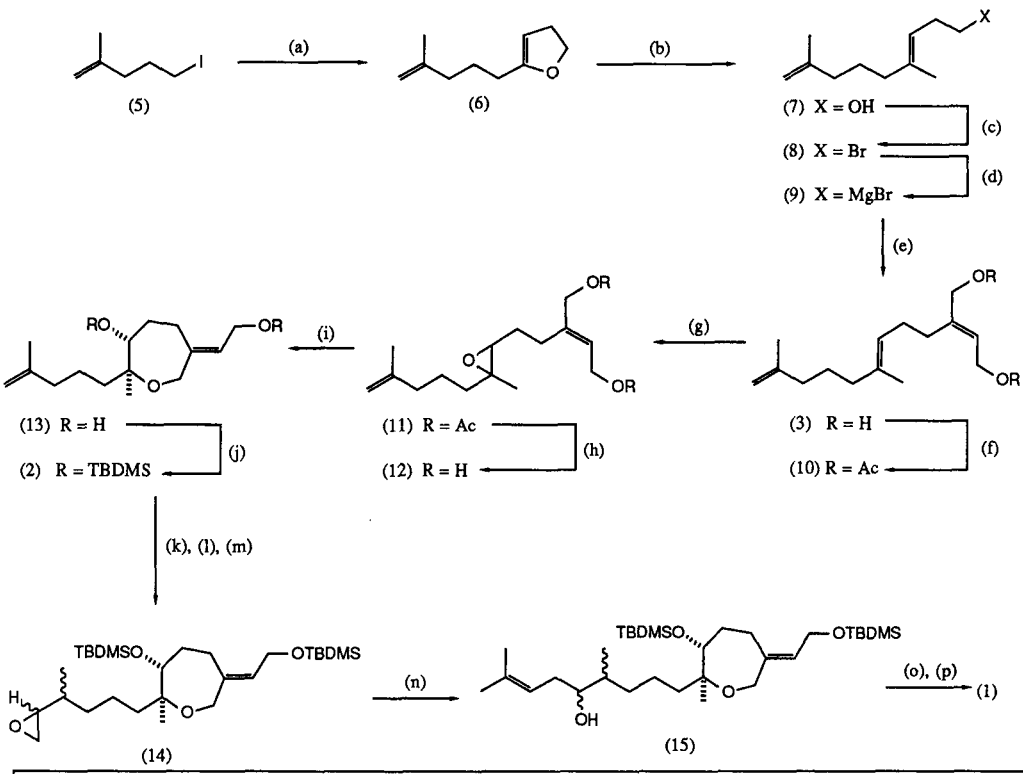
The second crucial step in in the sequence involved a highly stereoselective carbomagnesiation of butyne-1,4-diol[14] with the Grignard reagent (**9**) [prepared by standard methods in two steps from (**7**)]. Consistent yields of 55% based on the bromide (**8**) were obtained for this reaction only when ether was used as the solvent[15]. This was unfortunate because the di-magnesium bromide salt of butyn-1,4-diol was best prepared in THF by adding MeMgBr in ether to a THF solution of the diol. The resultant flocculent precipitate was allowed to settle and the supernatent removed *via* cannula. The solid was then suspended in ether, allowed to settle, and again the supernatent withdrawn. This procedure was repeated 3 times. Then the Grignard reagent (**9**) was added and the heterogeneous mixture refluxed for 16h whereupon aqueous workup gave the desired diol (**3**) as a single isomer.

In an attempt to improve the overall yield in the conversion of the alcohol (**3**) to the diol (**7**) an alternative procedure was examined (Scheme 3) in which the key step was a Ti-catalysed hydromagnesiation[16] of the alkyne (**18**) followed by reaction with CO_2. The desired diol (**3**) was again obtained with high stereoselectivity after esterification and reduction but the overall yield (44% from **18**) was lower. The organomagnesium derivative (**19**) reacted with formaldehyde to give the diol (**3**) directly but the yields were only slightly better and separation of by-products more cumbersome The easy esterification of the acid (**20**) using tetramethylguanidine and MeI by the procedure of Wlostowski and Jaworski[17] is noteworthy.

Conversion of Diol (3) to Oxepane (2). Clean and regioselective epoxidation of the diol (**3**) could only be achieved after protection of the hydroxyl functions as the acetates which were then easily removed by methanolysis. In order to achieve regio- and stereoselective intramolecular cleavage of the epoxide it was necessary to use conditions which favored intramolecular backside attack on the epoxide at the more hindered C(7) position by the C(3) hydroxymethyl. The best results were obtained using stannic chloride[18] in THF at 0-20°C. Under these conditions, the oxepane (**2**)(m.p. 71.5-72.5°C) was obtained in 64% yield along with several minor products which were not identified.

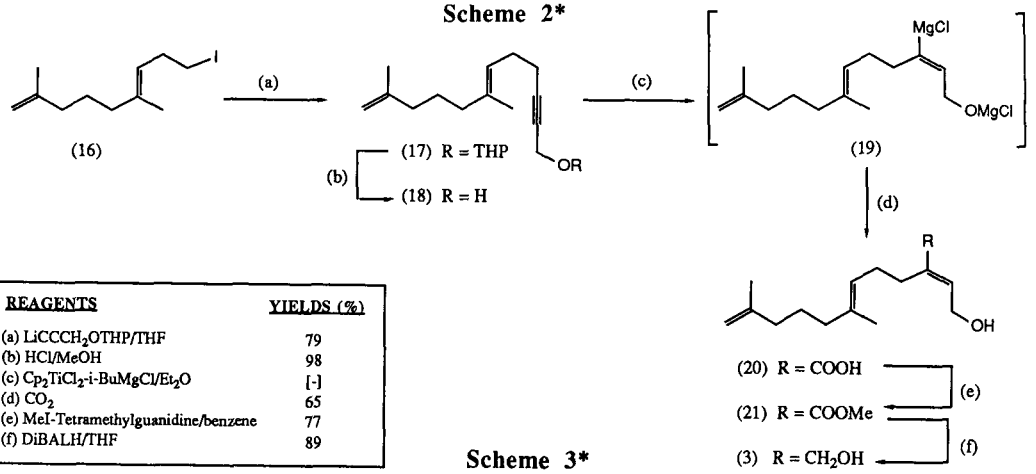
Elaboration of the Side Chain. In the final phase of the synthesis, the oxepane (**2**) was converted in 7 steps (36% overall) to zoapatanol using the standard reactions outlined in Scheme 2. The nucleophilic cleavage of the epoxide (**14**) was best achieved with the homocuprate derived from 1,1-dimethylvinyl-lithium and CuI. This gave the desired alcohol (**15**) in 64% yield along with 30% of the alkene derived from reductive deoxygenation of the epoxide.

The zoapatanol obtained by the route described herein was comparable with Cookson's[11] and Nicolaou's[9] by high field nmr spectroscopy and was a 1:1 mixture of diastereoisomers at C(4') as indicated by the doubling of the C(4') and C(7) Me signals in the proton nmr spectra and the doubling of 10 of the 20 signals in the carbon nmr spectra: ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.43 [1H, t, J = 6.8 Hz, C(2")H], 5.26 [1H, t with fine splitting, J = 7.1 Hz, C(7')H], 4.20 [2H, d, J = 6.8 Hz, C(1")H_2], 4.12 [2H, apparent br s (AB system), C(2)H_2], 3.52 [1H, dd with fine splitting, J = 8, 3Hz, C(6)H], 3.12 [2H, br d, J = 7.1 Hz, C(6')H_2], 2.56 [1H, m, C(4')H], 2.45 [1H, m, C(4)H], 2.3-2.1 [3H, m, C(4)H and 2 x OH], 1.73 [3H, d, J = 1.5 Hz, C(9')Me], 1.88-1.69 [2H, m, C(5)H_2], 1.60 [3H, br s, C(8')Me], 1.68-1.46 [4H, m, C(3')H_2 and C(1')H_2], 1.38-1.20 [2H, m, C(2')H_2], 1.12 and 1.11 [1.5H each, s, C(7)Me], 1.07 and 1.04 [1.5H each, d, J = 7.0 Hz, C(4')Me]. In the ^{13}C NMR (67.5 MHz, $CDCl_3$)the average position for the doubled peaks is given along with the difference in chemical shift (Δδ) : 213.6 (s), 143.2 (2s, Δδ = 0.04), 135.6 (s), 123.5 (2d, Δδ = 0.02), 116.1 (d), 80.0 (s), 76.5 (2d, Δδ = 0.20), 69.3 (2t, Δδ = 0.01), 58.7 (t), 45.9 (2t, Δδ = 0.01), 41.0 (2t, Δδ = 0.14), 38.3 (2t, Δδ = 0.12), 33.6 (t), 31.7 (t), 25.9 (q), 23.6 (2t, Δδ = 0.07), 21.1 (2t, Δδ = 0.05), 18.6 (q), 18.2 (2q, Δδ = 0.04), 16.8 (q).



REAGENTS	YIELDS (%)	REAGENTS	YIELDS (%)
(a) 5-Lithio-2,3-dihydrofuran/THF	89	(i) $SnCl_4$/THF, 20°C	64
(b) MeMgBr, $[Ph_3P]_2NiCl_2/Et_2O$-Benzene (1:1); 60°C	92	(j) TBDMSOTf, 2,6-lutidine/CH_2Cl_2	100
(c) MsCl, Et_3N/CH_2Cl_2, -10°C; LiBr/acetone, reflux	92	(k) 9-BBN/THF; NaOH, H_2O_2	96
(d) Mg/Et_2O	[-]	(l) Swern Oxidation	88
(e) $BrMgO\text{-}CH_2\text{-}C{\equiv}C\text{-}CH_2\text{-}OMgBr/Et_2O$, reflux, 16h	55	(m) 2 eq $Me_2S{=}CH_2$/DMSO-THF, 0°C	92
(f) AcCl, Et_3N/CH_2Cl_2	90	(n) $[Me_2C{=}CH]_2CuLi/Et_2O$, -10°C	64
(g) mcpba/CH_2Cl_2	76	(o) Swern Oxidation	93
(h) K_2CO_3/MeOH	100	(p) HF/MeCN	79

Scheme 2*



REAGENTS	YIELDS (%)
(a) $LiCCCH_2OTHP$/THF	79
(b) HCl/MeOH	98
(c) Cp_2TiCl_2-i-BuMgCl/Et_2O	[-]
(d) CO_2	65
(e) MeI-Tetramethylguanidine/benzene	77
(f) DiBALH/THF	89

Scheme 3*

*With the exception of iodide and mesylate intermediates, all compounds in this study gave satisfactory high resolution mass spectra on compounds judged to be ≥95% pure by tlc or hplc and nmr analysis.

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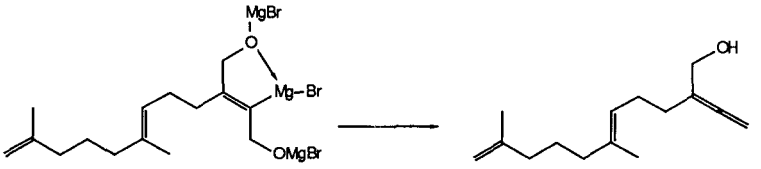
15. The carbomagnesiated intermediate (i) appeared to be stable in ether but in THF elimination occurred to give allene (ii):



(i) (ii)

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18. For an independent study of the Lewis acid catalysed opening of similar epoxides see reference 11. In three analogous cases examined so far the tetrahydropyran resulting from nucleophilic attack at C(6) represents ca 5-10% of the cyclised products. No evidence for nucleophilic attack by the C(1) hydroxyl to form an 8-membered ring has been obtained.

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