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Total Synthesis of (±)-Zoapatanol

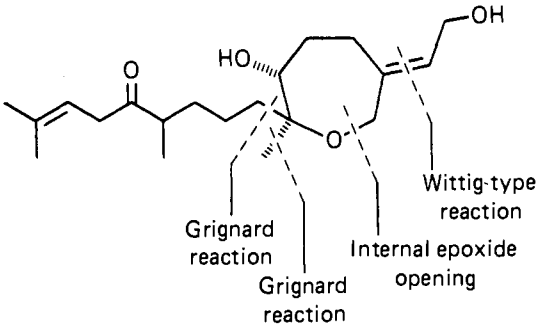
Sir:

In 1979, Levine and his associates[1] reported the isolation and structural elucidation of zoapatanol, one of two novel, oxepane-containing diterpenoids with potent contragestational activity. These biologically active molecules were extracted from the leaves of zoapatle (*Montanoa tomentosa*), a Mexican plant which Mexican women have been using for centuries to prepare "tea", to induce menses and labor, and to terminate early pregnancy. Due to the potential of this new class of compounds for use in human contraception and the novelty of their unique molecular structures, we recently initiated a program directed toward their synthesis. In this communication, we report an efficient and stereocontrolled total synthesis of zoapatanol (Scheme I).

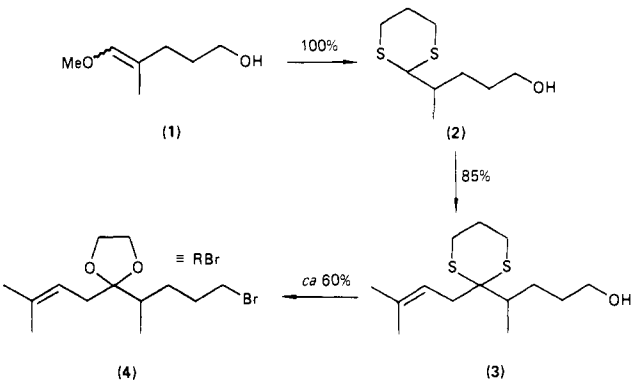
Our synthetic planning was based on the strategic bond analysis of the molecule outlined in Scheme I. Due to the sensitivity of the natural product toward intramolecular-type reactions,[1] our synthesis was designed with the appropriate protections of the three reactive groups and the provision of their liberation under mild conditions at the final stages of the synthesis. Furthermore, our strategy was designed to address the selectivity required to construct (i) the oxepane ring, (ii) the geometrical isomerism of the allylic system, and (iii) the stereochemistry of the two asymmetric centers on the ring system. Since the methyl group adjacent to the carbonyl group in zoapatanol is not defined stereochemically,[1] we were not concerned with its stereochemistry in our initial work.

The long side chain of zoapatanol (as the bromide **4**) was synthesized as illustrated in Scheme II. 5-Hydroxy-2-pentanone on reaction with excess (methoxymethyl)triphenylphosphorane furnished the methoxy enol ether **1**[2] (mixture of geometrical isomers, 75% yield) which was directly converted to the dithiane

Scheme I. Strategic Bond Analysis of Zoapatanol



Scheme II. Synthesis of the Side Chain of Zoapatanol



derivative **2** under standard conditions [$HS(CH_2)_3SH$, HCl gas, $CHCl_3$, 0–25 °C] in quantitative yield. Alkylation of **2** as its dianion (2.2 equiv of *n*-BuLi–THF, −78 → −15 °C) with 1-bromo-3-methyl-2-butene (1.1 equiv, −78 → −15 °C) proceeded smoothly to afford **3** in 85% yield. The conversion of **3** to the required bromide **4** was accomplished in ca. 60% overall yield by the following sequence of reactions: (1) acetylation [1.5 equiv of Ac_2O, 2 equiv of pyridine, 0.05 equiv of 4-(dimethylamino)-pyridine (DMAP), CH_2Cl_2, 0 °C], (2) removal of the dithiane group (2.2 equiv of $HgCl_2$, 2.2 equiv of $CaCO_3$, MeCN–H_2O, reflux), (3) ethylene ketal formation ($HOCH_2CH_2OH$, TsOH, benzene, reflux), (4) deprotection of the hydroxyl group (LAH, ether, 0 °C), and (5) bromide formation (1.3 equiv of CBr_4, 1.35 equiv of PPh_3, CH_2Cl_2, −40 → 0 °C).

Having secured a pathway to the side chain of zoapatanol, we turned our attention to the construction of the natural product itself according to Scheme III. Reaction (−78 → 25 °C, 6 h) of glycidol tetrahydropyranyl (THP) ether **5** (1 equiv) with the dilithio reagent derived from 2-methyl-2-propen-1-ol[4] (1.5 equiv), *n*-BuLi (3 equiv in hexane), and TMEDA[5] (3 equiv) (−78 → 25 °C, 12 h) afforded the diol **6** in 80% yield. Sequential protection of the primary (1.1 equiv of Ph_2-*t*-BuSiCl, 1.5 equiv of Et_3N, 0.04 equiv of DMAP, CH_2Cl_2, 25 °C, 88%)[6] and secondary (3 equiv of $PhCH_2OCH_2Cl$, 6 equiv of *i*-Pr_2EtN, CH_2Cl_2, 25 °C, 85%) alcohols proceeded with high selectivity and efficiency to furnish the triol derivative **7**, in which the three hydroxy groups are distinguished by protection and can be generated individually as they are needed in the synthesis. Thus, mild acid (AcOH–THF–H_2O, 3:2:2, 45 °C, 6 h) treatment of **7** removed only the tetrahydropyranyl ether, leading, after oxidation (9 equiv of SO_3·pyridine complex, 20 equiv of Et_3N, Me_2SO, 25 °C),[7] to the aldehyde **8** (95% overall yield from **7**). Incorporation of the long side chain of zoapatanol was accomplished at this point by coupling the Grignard reagent (RMgBr) derived from bromide **4** (1 equiv) (Mg, THF, 25 °C) with the aldehyde **8** at −78 °C to give a secondary alcohol (mixture of four diastereoisomers, 80% yield)

(1) Levine, S. D.; Adams, R. E.; Chen, R.; Cotter, M. L.; Hirsch, A. F.; Kane, V. V.; Kanojia, R. M.; Shaw, C.; Wachter, M. P.; Chin, E.; Huettemann, R.; Ostrowski, P.; Mateos, J. L.; Noriega, L.; Guzmân, A.; Mijarez, A.; Tovar, L. *J. Am. Chem. Soc.* **1979**, *101*, 3402.

(2) All new compounds exhibited satisfactory infrared, proton magnetic resonance, and mass spectroscopic data. Yields refer to isolated chromatographically homogeneous materials.

(3) ^1H NMR spectral data (250 MHz, $CDCl_3$) **11**: τ 2.63 (m, 5 H, benzenoid), 4.82 (br t, *J* = 7.5 Hz, 1 H, olefinic CH), 4.94, 5.12 (br s, 1 H each, olefinic CH_2), 5.05, 5.22 (d, *J* = 7 Hz, 1 H each, OCH_2O), 5.26, 5.37 (d, *J* = 12 Hz, 1 H each, benzylic), 5.92, 5.95 (s, 1 H each, CH_2OH), 6.06 (m, 4 H, OCH_2CH_2O), 6.65 (dd, *J* = 8, 3 Hz, 1 H, CHO), 6.79, 6.82 (s, 0.5 H each, OH), 7.67 (d, *J* = 7.5 Hz, 2 H, $Me_2C{=}CHCH_2$), 8.29, 8.37 (s, 3 H each, vinyl CH_3), 8.86, 8.89 (s, 1.5 H each, *tert*-CH_3), 9.07, 9.09 (d, *J* = 7 Hz, 1.5 H each), 7.60–9.00 (m, 12 H, CH, CH_2, OH). **14**: τ 2.66 (m, 5 H, benzenoid), 4.84 (br t, *J* = 7 Hz, 1 H, olefinic), 5.15, 5.24 (d, *J* = 7 Hz, 1 H each, OCH_2O), 5.38 (s, 2 H, benzylic), 5.84, 6.02 (d, *J* = 18 Hz, 1 H each, $OCH_2C{=}O$), 6.07 (m, 4 H, OCH_2CH_2O), 6.34 (dd, *J* = 8, 3 Hz, 1 H, CHO), 7.36 (m, 2 H, $CH_2C{=}O$), 7.66 (d, *J* = 7 Hz, allylic), 8.29, 8.38 (s, 3 H each, vinyl CH_3), 8.81 (s, 3 H, *tert*-CH_3), 9.05 (d, *J* = 7 Hz, 3 H, *sec*-CH_3), 7.82–9.00 (m, 9 H, CH, CH_2). **17**: τ 4.53 (t, *J* = 7 Hz, 1 H, $=CHCH_2OH$), 4.69 (t, *J* = 7 Hz, 1 H, $(CH_3)_2C{=}CH$), 5.80 (d, *J* = 7 Hz, 2 H, CH_2OH), 5.87 (s, 2 H, $OCH_2C{=}$), 6.45 (dd, *J* = 8, 4 Hz, 1 H, CHOH), 6.84 (d, *J* = 7 Hz, 2 H, $=CHCH_2$), 7.33–7.85 (m, 3 H, $O{=}CCH$, $CH_2CH_2C{=}$), 8.23, 8.35 (s, 3 H each, vinyl CH_3), 8.83, 8.84 (s, 1.5 H each, *tert*-CH_3), 9.01 (d, *J* = 7 Hz, 3 H, *sec*-CH_3), 8.10–9.00 (m, 10 H, CH, CH_2, OH).

(4) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1979**, *101*, 6429.

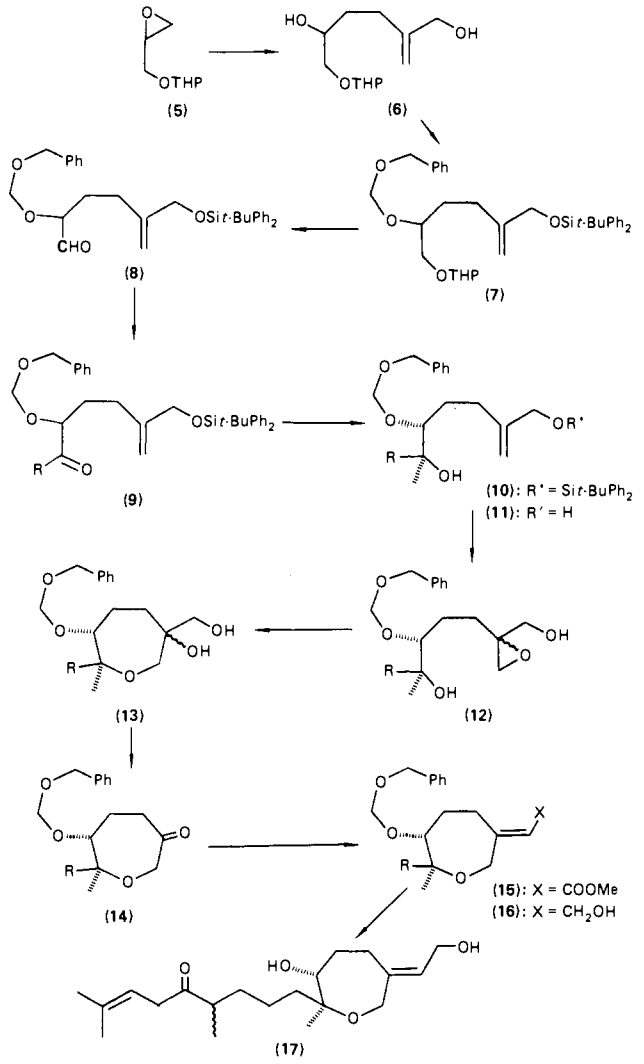
(5) Cardillo, G.; Contento, M.; Sandri, S.; Panunzio, M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1729.

(6) Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, 99.

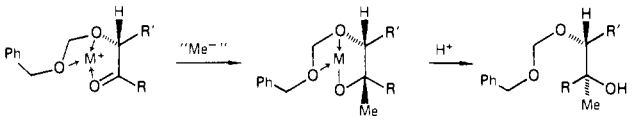
(7) Parikh, J. R.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

0002-7863/80/1502-6611$01.00/0

Scheme III. Total Synthesis of Zoapatanol



Scheme IV



which was oxidized to the ketone **9** (mixture of two diastereoisomers, 85%) with Collins reagent (15 equiv, 0 °C, CH_2Cl_2, Celite). We were now faced with the problem of introducing a methyl group stereoselectively on an acyclic system and in an anti-Cram sense. In this context, a chelation-controlled addition of a Grignard reagent to an α-benzyloxy methyloxy ketone[8] provided a solution. Thus, reaction of MeMgCl (2 equiv, THF, −105 °C) with ketone **9** resulted in the formation of the *erythro* diastereoisomer **10** (epimeric at the secondary methyl) as the only 250-MHz ^{1}H NMR detectable compound (95% yield). The stereochemistry was tentatively assigned as the one predicted by the chelation-controlled mechanism[8] shown in Scheme IV and was verified by the identity of the final synthetic product as natural zoapatanol (**17**). As expected, reversal of the order of addition of the two Grignard reagents to the aldehyde **8** resulted in the exclusive (250-MHz ^{1}H NMR) formation of the other diastereoisomer of **10**.

The next task was to epoxidize the terminal olefin without attack on the trisubstituted double bond. This was selectively achieved by calling upon the allylic hydroxyl group after its quantitative liberation (**10** → **11**[3]) (1.5 equiv of n-Bu_4NF-THF, 0–25 °C) to assist in a $VO(acac)_2$-catalyzed[9] epoxidation (10 equiv of t-BuOOH, 0.05 equiv of $VO(acac)_2$, 0.1 equiv of NaOAc, toluene–CH_2Cl_2 1:1, −25 ± 5 °C), leading to the rather sensitive epoxide diol **12** (mixture of epoxide epimers, 80%).

We then proceeded to construct the oxepane ring by an internal epoxide-opening reaction, a crucial operation in our synthesis. This was successfully realized with a high degree of regioselectivity by exposing epoxide **12** to KCH_2SOCH_3 (4 equiv) in Me_2SO at 25 °C for 4 h, furnishing the desired oxepane system **13** (mixture of diastereomeric diols) in 75% yield accompanied by small amounts of its 6-membered ring isomer.[10] The key intermediate ketone **14**[3] was then generated from diol **13** by cleavage with $NaIO_4$ (2 equiv, EtOH–H_2O phosphate buffer, pH 7.4, 25 °C, 95%).

The oxepane ketone **14** underwent condensation with the lithio salt of trimethyl phosphonoacetate (2 equiv, LDA, THF, −20 °C) to afford selectively the methyl ester **15** as the major product accompanied by its geometrical isomer (ca. 2.5:1 ratio by ^{1}H NMR spectroscopy).[11] The E/Z isomeric mixture was reduced with DIBAL (3 equiv, CH_2Cl_2, −78 °C) to afford the corresponding allylic alcohols as a mixture from which the desired isomer **16** was chromatographically isolated (more polar isomer, R_f = 0.25, silica, ether–petroleum ether 3:1)[12] in 70% overall yield from **14**. Finally, liberation of the secondary alcohol (excess Li in liquid NH_3, −78 °C, 3 min, 89%) followed by acid treatment (AcOH–THF–H_2O, 3:2:2, 38 °C, 18 h, 90%) furnished (±)-zoapatanol (**17**)[3] as a mixture at the secondary methyl center, exhibiting identical spectroscopic properties to those reported for the natural product.[14,15]

With this short and highly stereoselective route to zoapatanol, this plant-derived bioactive substance becomes readily available for widespread investigations.[16]

Supplementary Material Available: A listing of full ^{1}H NMR spectral data of all important intermediates (2 pages). Ordering information is given on any current masthead page.

(8) Still, W. C.; McDonald, J. H., III *Tetrahedron Lett.* **1980**, 1031. Collum, D. B.; McDonald, J. H., III; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2117. See also: Cram, D. J.; Kopecky, K. R. *Ibid.* **1959**, *81*, 2748.

(9) For an excellent review of this reaction, see: Sharpless, K. B.; Verhoeven, J. R. *Aldrichim. Acta* **1979**, *12*, 63, and references cited therein.

(10) Even under mild acidic conditions, the epoxide **12** rearranges to the six-membered ring regioisomer of **13**.

(11) The E configuration of the unsaturated ester was assigned from the relatively high ^{1}H NMR chemical shifts for the OCH_2C= protons (τ 5.75 and 5.84) as compared to the Z isomer (τ 5.13 and 5.23); see ref 1 and Bedoukian, R. H.; Wolinsky, J. *J. Org. Chem.* **1975**, *40*, 2154.

(12) In this chromatographic system, the undesired Z isomer has an R_f value of 0.28. The more polar isomer **16** on oxidation and methylation (1. MnO_2–CH_2Cl_2, 2. NaCN–AcOH–MnO_2–CH_3OH)[13] furnished the E-unsaturated ester **15** whereas its less polar isomer led to the corresponding Z-unsaturated ester on similar treatment. The two esters were clearly differentiated by ^{1}H NMR spectroscopy,[11] but were indistinguishable by TLC.

(13) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616.

(14) We thank Dr. S. D. Levine of Ortho Pharmaceutical Corporation, Raritan, NJ, for providing us with spectra of zoapatanol. We were unable to obtain an authentic sample of the natural product, however.

(15) At the present time, the stereochemistry of the zoapatanol side-chain methyl group is not known with certainty despite the structural work of the Ortho group, including an X-ray crystallographic analysis on a crystalline hydrazone derivative (ref 1 and personal communications with Drs. S. D. Levine, R. Chen, and V. V. Kane). The difficulty apparently arises from the possibility of epimerization at this center during isolation and chemical modification of the natural product as well as the possibility of preferential crystallization of one of the two possible diastereomeric hydrazones. Clearly, further work on the natural product is necessary in order to define its stereochemical nature at the side-chain methyl group. Since racemic compounds were used throughout our synthesis, the synthetic material consists of two racemic diastereoisomers at the side-chain methyl group (presumably 1:1) despite its chromatographic homogeneity.

(16) This work was financially supported by the University of Pennsylvania and Merck Sharp & Dohme.

(17) Fellow of the Alfred P. Sloan Foundation, 1979–1981.

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