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Total Synthesis of Natural (+)-(2′*S*,3′*R*)-Zoapatanol

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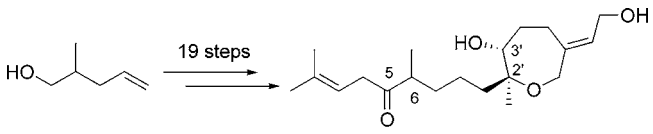
ABSTRACT



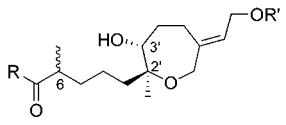
(+)-(2′*S*,3′*R*)-zoapatanol **1**

(+)-Zoapatanol was synthesized by using four key-steps: a Suzuki cross-coupling to prepare a (*Z*)-α,*β*-unsaturated ester followed by an enantioselective dihydroxylation to control the C2′ and C3′ stereocenters, an intramolecular Horner–Wadsworth–Emmons olefination to construct the oxepane ring, and a chemoselective nucleophilic addition/Birch reduction process of a Weinreb amide to introduce simultaneously the *β*,*γ*-unsaturated ketone on the side-chain and regenerate alcohols from benzyl ethers.

(+)-Zoapatanol **1** (Figure 1) is one of several natural diterpenoid oxepanes **1**−**4** isolated from leaves of the Mexican zoapatle plant *Montanoa tomentosa*.[1] "Tea" prepared from extracts of the leaves has long been used as a contraceptive in local folk medicine[2] and follow-up studies now support the belief that zoapatanol metabolites might be responsible for the observed antifertility activity.[3]

Due to its biological profile and its challenging structure, several groups have reported total syntheses of zoapatanol,[4] but only one of these was enantioselective.[5] A number of groups have also described synthetic approaches to the natural product.[6] Key issues for a successful synthesis of **1** are the stereocontrolled preparation of the oxepane core, the introduction of the (*E*)-exocyclic double bond, and the installation of the nonenyl side-chain. Since (+)-zoapatanol **1** is isolated as a 1/1 mixture of epimers at C6, control of this stereocenter is not required.[7]

In this letter, we now report an enantioselective total synthesis of (+)-zoapatanol **1** where the strategy relied upon the successful preparation of the oxepinone intermediate **5**. Retrosynthetic analysis of **5** revealed that the oxepane ring with the required stereochemistry could potentially be constructed through application of an intramolecular Horner−



1	R = $(CH_3)_2C{=}CHCH_2$-	R' = H	Zoapatanol
2	R = $(CH_3)_2CHC(CH_3){=}CH$-	R' = H	Montanol
3	R = $(CH_3)_2C(OH)CH{=}CH$-	R' = Ac	Tomentol
4	R = $H_2C{=}C(CH_3)CH(CH_3)CH_2$-	R' = H	Tomentanol

Figure 1.

(1) Levine, S. D.; Adams, R. E.; Chen, R.; Cotter, M. L.; Hirsch, A. F.; Kane, V. V.; Kanijoa, R. M.; Shaw, C. J.; Wachter, M. P.; Chin, E.; Huetteman, R.; Ostrowski, P.; Mateos, J. L.; Noriega, L.; Guzmán, A.; Mijarez, A.; Tovar, L. *J. Am. Chem. Soc.* **1979**, *101*, 3404−3405.

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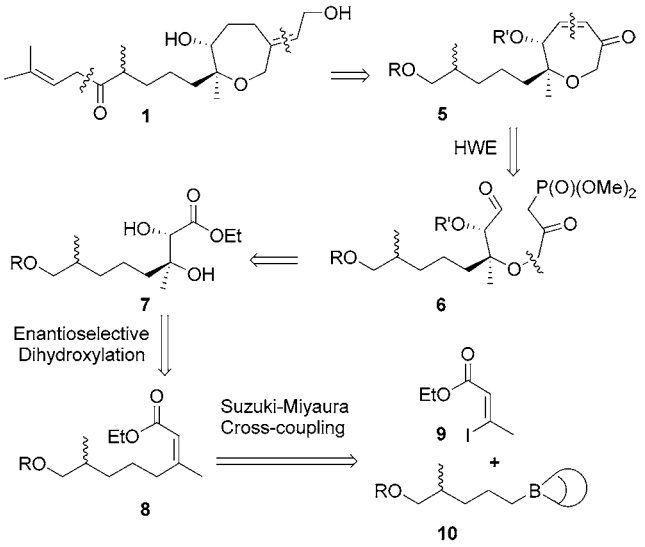
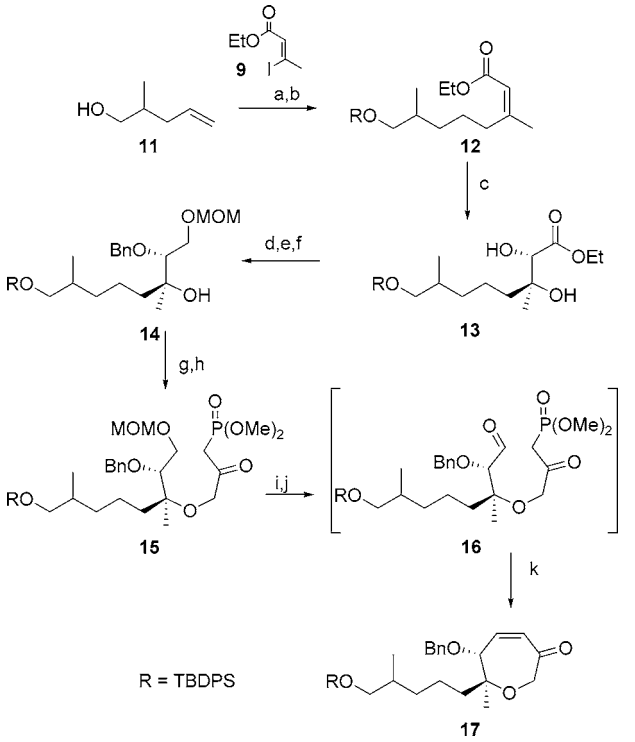
Scheme 1. Retrosynthetic Analysis



Wadsworth−Emmons reaction to the phosphono-aldehyde **6** derived from the *anti*-diol **7**. Control of the two contiguous stereocenters of **7** could possibly come through application of the Sharpless asymmetric dihydroxylation reaction to the (*Z*)-trisubstituted olefin **8**, which could be elaborated by a Suzuki−Miyaura coupling between vinyl iodide **9** and organoborane **10** (Scheme 1).

Our preparation of (+)-zoapatanol started with the synthesis of the phosphono-aldehyde **16** from 2-methylpent-4-en-1-ol **11** (Scheme 2).[8] The unsaturated alcohol **11** was protected as a *tert*-butyldiphenylsilyl ether under classical conditions, and the resulting product was then treated with 9-BBN-H (9-BBN dimer, THF, rt). The organoborane product was then subjected to a Suzuki cross-coupling with (*Z*)-vinyl iodide **9**[9] in the presence of $Pd(PPh_3)_4$ and K_3PO_4 (dioxane, 85 °C) to afford the α,β-unsaturated ester **12** in 74% yield.[10,11] Enantioselective Sharpless dihydroxylation (AD-mix-β, H_2NSO_2Me, *t*-BuOH/H_2O (1/1), 0 °C) next afforded the diol **13** in 65% yield and 92% ee as determined by ^{1}H NMR spectroscopy of the (*R*)- and (*S*)-methoxyphenylacetic esters.[12] Construction of the phosphono-aldehyde **16** was now investigated from **13**. The selective protection of the secondary alcohol in **13** as a benzyl ether turned out to be a difficult task. Among the reagents tested, benzyl bromide in the presence of silver oxide and tetrabutylammonium iodide was the most effective in this capacity, affording the desired product in 74% yield.[13] After reduction of the carboxylic ester with $LiAlH_4$ in diethyl ether, the resulting primary hydroxyl group was protected as a methoxymethyl ether (MOMCl, NaH, THF, 0 °C to rt) to provide **14** (89%, two steps). Rhodium-catalyzed insertion of ethyl diazoacetate (excess N_2CHCO_2Et, 10 mol % $[Rh(OAc)_2]_2$, toluene, 110 °C)[14] followed by the condensation of an excess of the lithium salt of methyldimethylphosphonate (10 equiv) with the resulting ester led to the β-keto phosphonate **15** in

Scheme 2. Synthesis of the Oxepinone **17**[a]



[a] Reagents and conditions: (a) TBDPSCl, imidazole, DMF, rt, 91%. (b) (i) 9-BBN dimer, THF, rt; (ii) **9**, $Pd(PPh_3)_4$, K_3PO_4, dioxane, 85 °C, 74%. (c) AD-mix-β, H_2NSO_2Me, *t*-BuOH/H_2O (1/1), 0 °C, 65%, ee = 92%. (d) BnBr, Ag_2O, *n*-Bu_4NI, CH_2Cl_2, rt, 74%. (e) $LiAlH_4$, Et_2O, 0 °C to rt. (f) MOMCl, NaH, THF, 0 °C to rt, 89% (two steps). (g) N_2CHCO_2Et (10 equiv), $[Rh(OAc)_2]_2$ (10 mol %), toluene, 110 °C. (h) $MeP(O)(OMe)_2$ (10 equiv), *n*-BuLi (10 equiv), THF, −78 °C, 60% (two steps). (i) TMSBr, CH_2Cl_2, −40 °C, 84%. (j) PDC, 4 Å MS, CH_2Cl_2, 20 °C. (k) NaH, THF, 0 °C to rt, 53% (two steps).

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(7) Either the epimerization occurred during isolation or purification of the natural product, or the natural zoapatanol itself is a mixture of epimers at C6. Kanijoa, R. M.; Wachter, M. P.; Levine, S. D.; Adams, R. E.; Chen, R.; Chin, E.; Cotter, M. L.; Hirsch, A. F.; Huetteman, R.; Kane, V. V.; Ostrowski, P.; Shaw, C. J. *J. Org. Chem.* **1982**, *47*, 1310−1319.

(8) 2-Methylpent-4-en-1-ol **11** was prepared by a two-step sequence: allylation of the dianion derived from propionic acid followed by reduction of the carboxylic acid with $LiAlH_4$.

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(11) (*Z*)-Configuration of the enoate **12** was confirmed by ^{1}H NMR−NOE analysis.

(12) (2*S*,3*S*) absolute configurations of **13** were confirmed by the ^{1}H NMR spectra of the two corresponding mandelates following the practical procedure described by: Seco, J. M.; Quiñoa, E.; Riguera, R. *Tetrahedron: Asymmetry* **2001**, *12*, 2915−2925.

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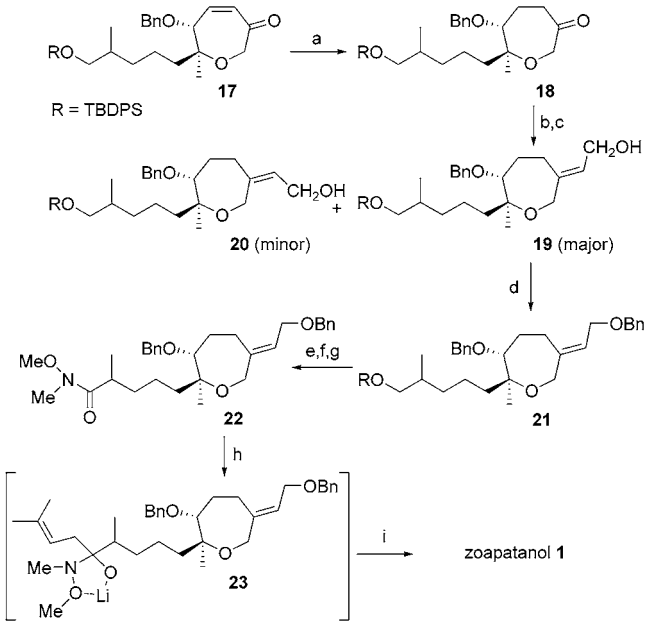
60% overall yield (two steps).[15] As an intramolecular Horner−Wadsworth−Emmons reaction was envisaged to construct the oxepane ring of zoapatanol, the methoxymethyl ether group had to be transformed into an aldehyde. Thus, after removal of the methoxymethyl ether protecting group with TMSBr, the corresponding hydroxy phosphonate was obtained (84%),[16] and oxidation of the primary alcohol was conveniently accomplished with PDC. The resulting crude aldehyde, which turned out to be unstable was subjected directly to treatment with NaH in THF to afford oxepinone **17** in 53% overall yield, via intramolecular Horner−Wadsworth−Emmons cyclization (Scheme 2).[17]

To convert the oxepinone **17** to (+)-zoapatanol, several functional group transformations were required. First of all, a catalytic hydrogenation of oxepinone **17** (10% Pd/C, EtOH, 5 min) was effected to afford ketone **18** chemoselectively. The benzyl protecting group was not affected under these conditions.[18] The resulting oxepanone **18** was then treated with the lithium salt of triethylphosphonoacetate ($EtO_2C-CH_2-P(O)(OEt)_2$, LiHMDS, THF, rt) to generate the corresponding α,β-unsaturated esters (97%) as an inseparable mixture of *E*/*Z* isomers (*E*/*Z* = 70/30 ratio by ^{1}H NMR spectroscopy).[17a,19] After reduction with $LiAlH_4$, the corresponding stereomeric allylic alcohols **19** and **20** were separated by SiO_2 flash chromatography, and the desired (*E*)-isomer **19**[20] was obtained in 63% overall yield from **18**. The allylic alcohol **19** was then protected as a benzyl ether (BnBr, Ag_2O, *n*-Bu_4NI, CH_2Cl_2) in 98% yield. Elaboration of the nonenyl side-chain present in (+)-zoapatanol first required conversion of **21** to the corresponding Weinreb amide **22** since it was assumed that a stable tetrahedral intermediate resulting from the addition of prenyllithium to the Weinreb amide could serve as a latent carbonyl protecting group during the debenzylation of the hydroxy groups by a Birch reduction.[21]

After removal of the silyl protecting group in **21**, the resulting primary hydroxy group was oxidized to the corresponding carboxylic acid (Jones reagent, acetone, 0 °C) and the latter was directly converted to the Weinreb amide **22** (HN(OMe)Me·HCl, EDCI, *i*-Pr_2NEt, DMAP cat, CH_2Cl_2, rt) with an overall yield of 60% (three steps).[22] Treatment of amide **22** with prenyllithium[23] (Et_2O, THF, −78 °C) led to the stable intermediate **23**, which was directly subjected to the Birch reduction conditions[24] (Li, NH_3(l), *t*-BuOH/THF, −78 °C) to afford the desired (+)-zoapatanol, in 66% yield. The analytical and spectral data were in agreement with those previously reported in the literature for (+)-zoapatanol (Scheme 3).[1,4]

Scheme 3. Synthesis of (+)-(2′*S*,3′*R*)-Zoapatanol[a]



[a] Reagents and conditions: (a) H_2, Pd/C (10%), EtOH, 5 min, 98%; (b) $EtO_2CCH_2P(O)(OEt)_2$ (10 equiv), LiHMDS, THF, rt, 97%, *E*/*Z* = 70/30; (c) $LiAlH_4$, Et_2O, 0 °C to rt; flash chromatography, *E* isomer: 63%, *Z* isomer: 27% from **18** (two steps); (d) BnBr, Ag_2O, *n*-Bu_4NI, CH_2Cl_2, rt, 98%; (e) *n*-Bu_4NF, THF, rt, (f) CrO_3/H_2SO_4, acetone, 0 °C; (g) HN(OMe)Me·HCl, EDCI, *i*-Pr_2NEt, DMAP cat, CH_2Cl_2, 0 °C to rt, 60% (three steps); (h) prenyllithium, Et_2O/THF (1:1), −78 °C; (i) Li, NH_3(l), *t*-BuOH (20 equiv), THF, −78 °C, 66%.

In conclusion, we have achieved an enantioselective total synthesis of natural (+)-(2′*S*,3′*R*)-zoapatanol **1** using Suzuki cross-coupling and Sharpless asymmetric dihydroxylation chemistry as key steps. An intramolecular Horner−Wadsworth−Emmons cyclization was employed to construct the oxepane core, and an organolithium addition/Birch reduction tactic was applied on a Weinreb amide at the end of the synthesis to access (+)-zoapatanol. The latter process could provide the opportunity to synthesize structurally related analogues.

Acknowledgment. C.T. thanks the MRES for a grant.

Supporting Information Available: Experimental procedure and characterization data of the key derivatives **12**, **13**, **15**, **17**, **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) (*E*)-Configuration of the major stereoisomer **19** was confirmed by ^{1}H NMR−NOE analysis.
(21) See preceding paper: Taillier, C.; Bellosta, V.; Meyer, C.; Cossy, J. *Org. Lett.* **2004**, *6*, 2145−2148.
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