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Total Synthesis of (±)-13-Methoxy-15-oxozoapatlin, a Rearranged Kaurane Diterpenoid

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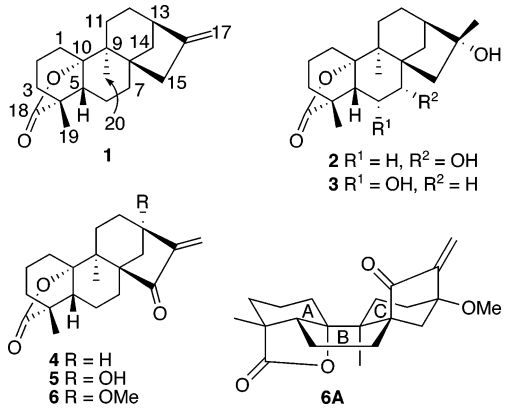
A 21-step linear synthesis of the structurally novel and biologically intriguing diterpenoid (±)-13-methoxy-15-oxozoapatlin (**6**) is described. Of particular note in this work is the development of a new method for the construction of the functionalized bicyclo[3.2.1]octane unit present in the target substance.

Introduction

The natural product (−)-zoapatlin was initially isolated in 1970 from the native Mexican shrub zoapatle (*Montanoa tomentosa*) by Caballero and Wall[1] and was shown to have the constitution and absolute configuration shown in formula **1**[2] (Chart 1). It was recognized that **1** possesses what was at that time a new diterpenoid carbon skeleton. Subsequently, in 1979, a natural product identical with **1** was isolated from *Tetrachyron orizabaensis* var. *websteri* and *Helianthus debilis* ssp. *debilis* but was given the name tetrachyrin.[3] Another report[4] in 1979 disclosed the isolation, from *Eupatorium album* L., of two diterpenoids that were shown to have the constitutions and absolute configurations shown in **2** and **3**. These substances, named eupatalbin and eupatoralbin, respectively, were claimed to be "of a new skeletal type", even though they clearly possess the same skeleton as zoapatlin (**1**). These "errors" (two different names for the same compound and the failure to recognize that **2** and **3** have carbon skeletons identical with that of **1**) were possibly due to the fact that, in 1971, a published statement[5] appeared in which (−)-zoapatlin was erroneously referred to as "a sesquiterpene lactone". Appropriately, a 1984 paper[6] proposed that the name tetrachyrin for **1** "should be abandoned" and that zoapatlin should be recognized as the correct name for this class of diterpenoids. This paper[6] also reported the structural elucidation of (−)-15-oxozoapatlin (**4**), which had been isolated from the aerial parts of *Viguiera maculata*.

CHART 1



In the mid-1990s, Lee et al.[7] and Garo et al.[8] reported, inter alia, the isolation (from *Parinari curatellifolia* and *Parinari capensis*, respectively) of (−)-15-oxozoapatlin (**4**), (−)-13-hydroxy-15-oxozoapatlin (**5**), and (−)-13-methoxy-15-oxozoapatlin (**6**). The absolute configuration of **6** was determined to be as shown by an X-ray crystallographic study.[8]

Substances **4**−**6** exhibit interesting and potentially useful biological activities. It has been shown that compounds **4** and **6** inhibit the growth of the fungus *Cladosporium cucumerinum* within 20 μg mL^{-1}.[8] On the other hand, all three compounds were evaluated against a panel of cultured human cancer cell lines and "were found to be broadly cytotoxic, exhibiting ED_{50} values ranging from 0.3 to 16.5 μM."[7] The cytotoxicity of these substances was reportedly related to their interference with the cell cycle transition from G2 phase to mitosis and mediated by a covalent reaction between a cellular component (such as a sulfhydryl-containing protein) and the α,β-unsaturated ketone function of each of the

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† UBC Structural Chemistry Laboratory.

(1) Caballero, Y.; Walls, F. *Bol. Inst. Quim. Univ. Nac. Auton. Mex.* **1970**, *22*, 79.
(2) Although slightly different numbering systems for the zoapatlin carbon skeleton appear in the literature, we have chosen that shown in formula **1**.
(3) Ohno, N.; Mabry, T. J.; Zabel, V.; Watson, W. H. *Phytochemistry* **1979**, *18*, 1687.
(4) Herz, W.; Govindan, S. V.; Blount, J. F. *J. Org. Chem.* **1979**, *44*, 2999.
(5) *Chem. Abstr.* **1971**, *74* (133), 136398w.
(6) Delgado, G.; Alvarez, L. Romo de Vivar, A. *Phytochemistry* **1984**, *23*, 2674.
(7) Lee, I.-S.; Shamon, L. A.; Chai, H.-B.; Chagwedera, T. E.; Besterman, J. M.; Farnsworth, N. R.; Cordell, G. A.; Pezzuto, J. M.; Kinghorn, A. D. *Chem.-Biol. Interact.* **1996**, *99*, 193.
(8) Garo, E.; Maillard, M.; Hostettmann, K.; Stoeckli-Evans, H.; Mavi, S. *Helv. Chim. Acta* **1997**, *80*, 538.

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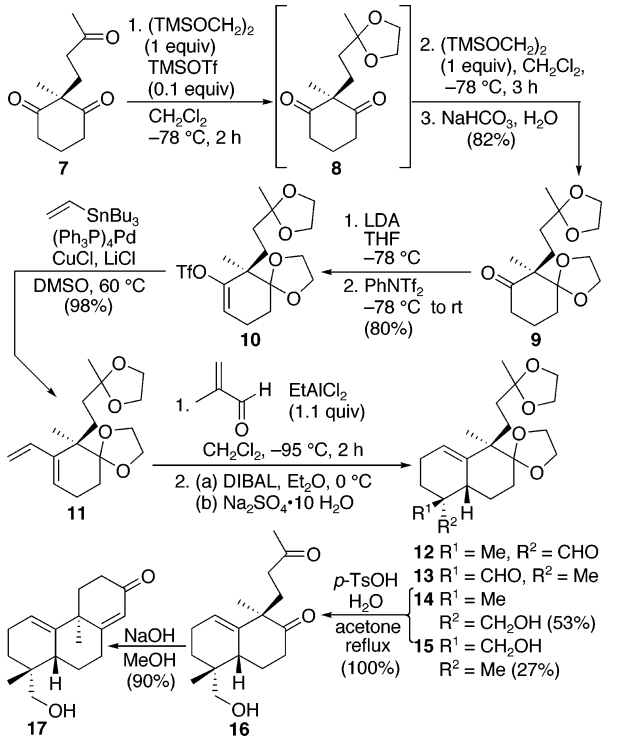
terpenoids. More recently, Roberge and co-workers have demonstrated that 13-hydroxy-15-oxozoapatlin (**5**) is, in fact, both a G2 checkpoint inhibitor and an antimitotic agent.[9] At low micromolar concentrations ($IC_{50} = 10\ \mu M$), **5** causes breast cancer cells, arrested at the G2 checkpoint by ionizing radiation, to be released into mitosis. Additionally, it was discovered that those cells that were able to overcome the G2 checkpoint (approximately 22% of cells) became blocked in mitosis. In a noteworthy recent paper entitled "Evaluation of the Potential Cancer Chemotherapeutic Efficacy of Natural Product Isolates Employing in Vivo Hollow Fiber Tests",[10] Pezzuto and co-workers reported, inter alia, that 13-methoxy-15-oxozoapatlin (**6**) was found to be active and, therefore, has the potential to function as a cancer therapeutic agent. Finally, it has been disclosed that substances **4**−**6** exhibit antimalarial activity, with IC_{50} values of 1.57, 0.54, and 0.67 μg mL^{-1}.[11]

It has been pointed out[3,4,6] that, from the viewpoint of biogenetic origin, zoapatlin (**1**) and its congeners are rearranged *ent*-kauranes. From a structural perspective, it is interesting to note that the *trans-syn-trans* configurational arrangement of the perhydrophenanthrene portion of the zoapatlins dictates that the B-ring of these substances adopt a boat or twist-boat conformation, as shown in formula **6A** (Chart 1). The fact that the natural products **4**−**6** possess novel structures and exhibit potentially fruitful biological properties makes them attractive targets for synthesis. We report herein a total synthesis of (±)-13-methoxy-15-oxozoapatlin (**6**).[12]

Results and Discussion

(a) Preparation of the Functionalized Tricycle 17 (Scheme 1). The pathway retrosynthetically designed for the synthesis of (±)-**6** began with the known[13] triketone **7** (Scheme 1). Direct treatment of **7** with *2* equiv of $(TMSOCH_2)_2$ in the presence of a catalytic amount of TMSOTf[14] gave a mixture of products containing the mono- and diketals **8** and **9**, along with other minor products. However, further experimentation showed that initial reaction of **7** with *1* equiv of $(TMSOCH_2)_2$ in the presence of TMSOTf produced monoketal **8** in good yield.[15] This observation led to development of the protocol summarized in Scheme 1, in which the necessary 2 equiv of $(TMSOCH_2)_2$ was added to the reaction mixture 1 equiv at a time, 2 h apart. In this manner, the required diketal **9** was reproducibly produced in very good yield.

SCHEME 1



Routine conversion[16] of ketone **9** into alkenyl triflate **10**, followed by a CuCl-accelerated Stille coupling[17] of **10** with tributyl(vinyl)stannane, afforded diene **11** in 78% overall yield.

A Diels−Alder reaction was envisaged as a suitable process for construction of the functionalized A-ring of the target compound.[18] It was found that treatment of diene **11** with methacrylic acid or ethyl methacrylate under a variety of conditions provided a complex mixture of products with a poor overall mass balance. On the other hand, when a solution of **11** in methacrolein was stirred at room temperature overnight, a 3:2 mixture of aldehydes **12** and **13**, respectively, was produced in quantitative yield. When this process was carried out in refluxing methacrolein, a 1:1 mixture of the same products was obtained, also quantitatively. Investigations into achieving a more satisfactory product ratio by using Lewis acid catalysts (e.g., $F_3B{\cdot}OEt_2$, $AlCl_3$, $EtAlCl_2$, and $TiCl_4$) led to the reaction shown in Scheme 1. Thus, dropwise treatment of a cold (−95 °C) solution of diene **11** and methacrolein (2 equiv) in dichloromethane with a solution of $EtAlCl_2$ (1.1 equiv) in hexane, followed by a reaction time of 2 h at −95 °C, afforded a 2:1 mixture of **12** and **13** in 90% yield. Use of the other Lewis acids listed above resulted in the formation of complex mixtures, extensive decomposition of starting materials, and-(or) mixtures of **12** and **13** containing proportionately less of the required isomer **12**.

Since separation of aldehydes **12** and **13** by practical chromatographic procedures proved to be very difficult,

(9) Rundle, N. T.; Xu, L.; Andersen, R. J.; Roberge, M. *J. Biol. Chem.* **2001**, *276*, 48231.
(10) Mi, Q.; Lantvit, D.; Reyes-Lim, E.; Chai, H.; Zhao, W.; Lee, I.; Peraza-Sánchez, S.; Ngassapa, O.; Kardono, L. B. S.; Riswan, S.; Hollingshead, M. G.; Mayo, J. G.; Farnsworth, N. R.; Cordell, G. A.; Kinghorn, A. D.; Pezzuto, J. M. *J. Nat. Prod.* **2002**, *65*, 482.
(11) Uys, A. C. U.; Malan, S. F.; van Dyk, S.; van Zyl, R. L. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2167.
(12) For some relevant reviews on diterpenoids, see: (a) Mander, L. N. *Nat. Prod. Rep.* **2003**, *20*, 49. (b) Mander, L. N. *Chem. Rev.* **1992**, *92*, 573. (c) Goldsmith, D. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley-Interscience: New York, 1991; Vol. 8, pp 1−243. (d) Hanson, J. R. *Nat. Prod. Rep.* **2003**, *20*, 70 and previous papers in this series.
(13) Wendler, N. L.; Slates, H. L.; Tishler, M. *J. Am. Chem. Soc.* **1951**, *73*, 3816.
(14) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.
(15) For a related example, see: Ohshima, T.; Kagechika, K.; Adachi, M.; Sodeoka, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1996**, *118*, 7108.
(16) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.
(17) (a) Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359. (b) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905.
(18) Cf. (a) Boukouvalas, J.; Cheng, Y.-X.; Robichaud, J. *J. Org. Chem.* **1998**, *63*, 228. (b) Magnuson, S. R.; Sepp-Lorenzino, L.; Rosen, N.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1998**, *120*, 1615.

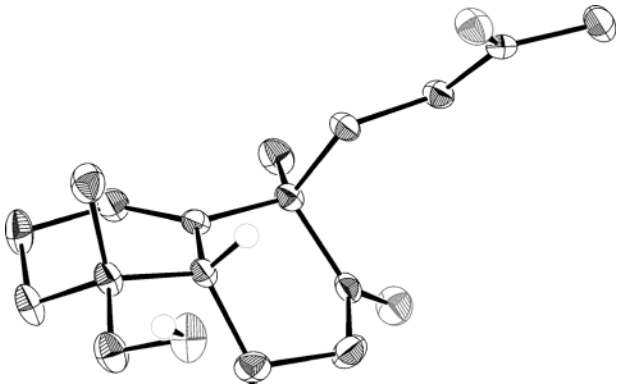
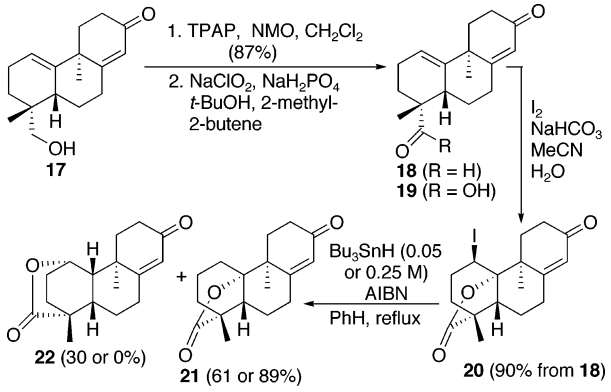


FIGURE 1. X-ray crystal structure of **16**.

SCHEME 2



the mixture was reduced (DIBAL) to the corresponding mixture of alcohols **14** and **15**. The latter materials, which were separable by chromatography on silica gel, were obtained in yields of 53% and 27%, respectively. Acid hydrolysis of the ketal functions in **14** produced diketo alcohol **16** in quantitative yield.

Analysis of the ^{1}H NMR spectral data derived from **14** and **15**, along with NOED experiments, did not provide conclusive evidence for the relative configurations of these substances. Furthermore, although both **14** and **15** were obtained in crystalline form, recrystallization of these materials from a number of solvents or solvent mixtures did not produce crystals suitable for X-ray crystallographic analyses. On the other hand, recrystallization of diketo alcohol **16** from diethyl ether provided crystals that, when subjected to X-ray crystallographic analysis, showed that this material possesses the constitution and relative configuration shown in Scheme 1. An ORTEP depiction of the solid-state structure of **16** is shown in Figure 1. Base-promoted intramolecular condensation of diketone **16** provided the required tricycle **17** in excellent yield.

(b) Preparation of Enone Lactone 21 (Scheme 2). Transformation of **17** into the tetracyclic keto lactone **21** was accomplished as summarized in Scheme 2. Oxidation (TPAP, NMO[19]) of the primary alcohol function of **17** provided aldehyde **18**, which, upon further oxidation,[20] furnished carboxylic acid **19**. Due to its highly polar nature, **19** proved difficult to purify and, therefore, a solution of the crude material in MeCN−H_2O at room temperature was treated sequentially with $NaHCO_3$ and an excess of I_2.[21] Purification of the resultant product gave iodo lactone **20** in 78% yield from alcohol **17**.

Fortuitous dispersions of the NMR signals observed in the ^{1}H and ^{13}C NMR spectra, along with a series of APT, HMBC, HMQC, and COSY experiments, allowed a complete assignment of the proton and carbon resonances derived from **20**. Furthermore, appropriate 1D NOESY experiments produced conclusive evidence for the relative configuration of each of the carbon chirality centers present in this substance.[22] These data are in full accord with those expected from the product of iodolactonization of olefinic acid **19**.

Treatment of **20** with tributylstannane (0.05 M in refluxing benzene) in the presence of a catalytic amount of AIBN produced two products in yields of 61% and 30%. Spectroscopic data derived from these two substances showed that they possess structures represented by formulas **21** and **22**, respectively. The major product **21** exhibited a strong γ-lactone carbonyl absorption at 1770 cm^{-1} (KBr), while its constitutional isomer **22** displayed the corresponding δ-lactone signal at 1746 cm^{-1} (neat). Both IR spectra showed the presence of the cyclohexenone carbonyl function (1667, 1666 cm^{-1}, respectively).

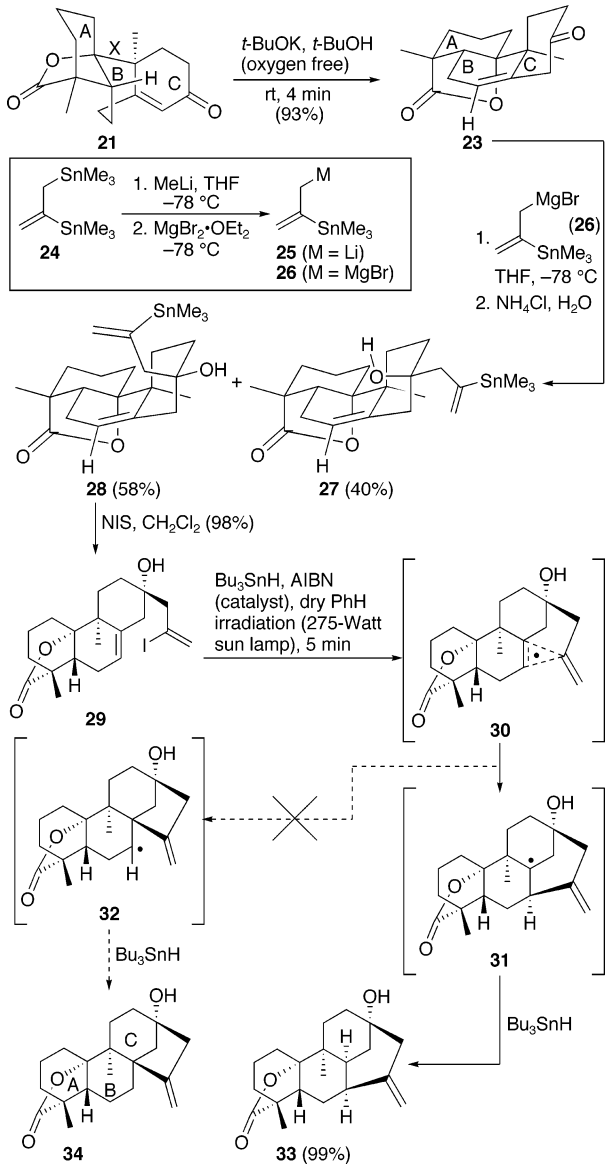
The structure of **22** was confirmed by detailed analyses of its ^{13}C and ^{1}H NMR spectra.[22] Data derived from HMBC, HMQC, COSY, and APT experiments allowed the assignment of all carbon and proton resonances and 1D NOESY experiments established the relative configuration of the two angular protons present in the compound. It should be noted that rearrangements similar to that involved in the conversion of **20** into **22** have been observed previously[23] and the mechanism of such processes has been discussed.[24]

Fortunately, it was found that the required deiodination reaction could be accomplished cleanly by simply increasing the concentration of tributylstannane from 0.05 to 0.25 M. Under these conditions, formation of the rearranged product **22** was completely suppressed and **21** was obtained in excellent yield (89%, Scheme 2).

(c) An Initial Attempt To Construct the Tetracyclic Carbon Skeleton of (±)-13-Methoxy-15-oxozoapatlin (Scheme 3). Molecular models show that the three carbocyclic rings labeled A, B, and C in structural formula **21** (Scheme 3) exist in chair, boat (or boatlike), and half-chair conformations, respectively. Rotation about the carbon−carbon single bond labeled X in **21** leads to three different boatlike conformations for ring B, while rings A and C remain in chair and half-chair conformations, respectively. Molecular modeling[25] predicts that, of these three conformations, that shown in **21** is preferred. More important from the viewpoint of our synthetic work, however, is the prediction[25] that substance **21** is approximately 3.5 kcal mol^{-1} less stable than the

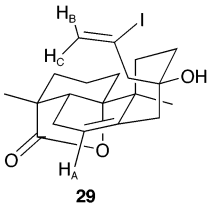
(19) Griffith, W. P.; Ley, S. V. *Aldrichim. Acta* **1990**, *23*, 1.
(20) Kraus, G. A.; Roth, B. *J. Org. Chem.* **1980**, *45*, 4825.
(21) Bartlett, P. A.; Richardson, D. P.; Myerson, J. *Tetrahedron* **1984**, *40*, 2317.
(22) See the Supporting Information for details.
(23) Furber, M.; Kraft-Klaunzer, P.; Mander, L. N.; Pour, M.; Yamaguchi, T.; Murofushi, N.; Yamane, H.; Schraudolf, H. *Aust. J. Chem.* **1995**, *48*, 427.
(24) Crich, D.; Beckwith, A. L. J.; Filzen, G. F.; Longmore, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 7422.
(25) *CambridgeSoft* ChemBats3D Ultra, Version 7.0.0, MOPAC semiemperical PM3 calculations of ΔH_f.

SCHEME 3



β,γ-unsaturated ketone **23**. In the latter substance, the three carbocyclic rings (A, B, C) comfortably adopt chair, half-chair, and chair conformations, respectively. Indeed, it was found that brief treatment of **21** with potassium *tert*-butoxide in dry, *oxygen-free tert*-butyl alcohol[26] produced, in 93% yield, the nonconjugated enone **23**.

It was envisaged that construction of the final ring of the zoapatlin carbon skeleton would involve, as the initial step, addition of a suitably functionalized reagent to the ketonic carbonyl of **23**. The bifunctional reagent 3-lithio-2-trimethylstannylpropene (**25**), which can be prepared readily by transmetalation of 2.3-bis(trimethylstannyl)-propene (**24**) with MeLi in THF (see box, Scheme 3),[27] was initially chosen for this purpose. However, reaction of **23** with **25** produced the carbonyl addition products (**27**, **28**) in mediocre yield (~60% combined) and invariably returned some starting material. Thus, it appeared that the lithio reagent **25**, in addition to serving as a nucleophile, was acting as a base to form an enolate anion from **23**. Protonation of this anion during the required workup step would, of course, produce starting material **23**. Fortunately, the reaction outcome could be improved by using the Grignard reagent **26**, which is easily produced in situ by treatment of the solution of **25** with $Br_2Mg{\cdot}OEt_2$. Reaction of **26** with ketone **23** in THF at low temperature furnished, in nearly quantitative yield, a mixture of tertiary alcohols **27** and **28**. These substances, which were readily separated by flash chromatography on silica gel, were obtained in yields of 40% and 58%, respectively. Treatment of **28** with *N*-iodosuccinimide (NIS) in DCM[28] effected a clean iododestannylation reaction to produce **29** in high yield. Fortunately, the observed dispersion of proton resonances in the ^{1}H NMR spectrum of **29** allowed a series of 1D NOESY experiments that led to an unambiguous assignment of the relative configuration of the tertiary carbinol chirality center in this substance. These NMR experiments, which are summarized in Figure 2, showed that the major product **28** derived from the reaction of **23** with reagent **26** (Scheme 3) possessed the required relative configuration for continuation of our synthetic endeavors.

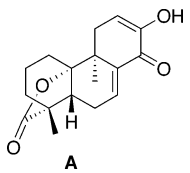


^{1}H NMR data: δ = 2.58, 2.79 (br d, br d, J = 15 Hz in each case, allylic protons of 2-iodoallyl group), 5.40 (br d, J = 6.1 Hz, H_A), 5.98 (br d, J = 1.1 Hz, H_B), 6.13 (br d, J = 1.1 Hz, H_C). In NOESY experiments, irradiation at δ = 2.58 or 2.79 caused enhancement of the signals at δ = 5.40 and 6.13; irradiation at δ = 5.40 or 6.13 caused enhancement of the signals at δ = 2.58 and 2.79.

FIGURE 2. ^{1}H NMR data and NOESY experiments related to compound **29**.

The next projected step of the initially designed synthetic route involved radical cyclization[29] of **29**, (hopefully) via a 5-*exo*-*trig* pathway to afford the required tetracycle **32** (Scheme 3). In the event, subjection of **29** to conditions prescribed by Stork and Baine[30] produced, in essentially quantitative yield, a single product. Although high-resolution mass spectrometry showed that this material had the expected molecular mass, analysis of the ^{13}C NMR spectrum, along with an APT experiment, revealed the presence of a total of five methine and/or methyl carbon atoms. Clearly, these data were inconsistent with the structure of the desired product **34**, which

(26) The *tert*-butyl alcohol was thoroughly purged with a stream of dry argon prior to distillation from calcium hydride under an argon atmosphere. If this precaution was not taken, the base-catalyzed deconjugation reaction was accompanied by oxidation of ring C of **21** to give largely a synthetically unproductive polar compound. On the basis of thorough spectral analyses, this material was shown to possess the structure represented by formula **A**.



(27) (a) Mitchell, T. N.; Kwetkat, K.; Rutschow, D.; Schneider, U. *Tetrahedron* **1989**, *45*, 969. (b) Piers. E.; Kaller, A. M. *Synlett* **1996**, 549.

(28) Piers. E.; Kaller, A. M. *Tetrahedron Lett.* **1996**, *37*, 5857.

(29) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237.

(30) Stork, G.; Baine, N. H. *Tetrahedron Lett.* **1985**, *26*, 5927.

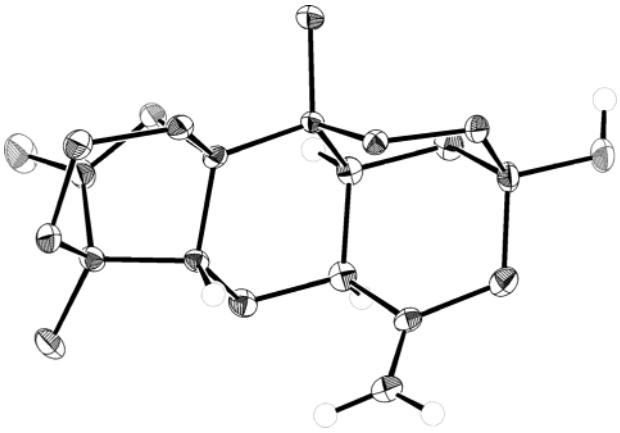


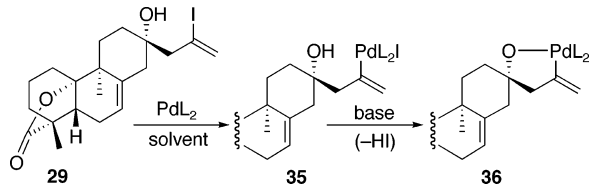
FIGURE 3. X-ray crystal structure of **33**.

contains two methyl groups and one methine carbon. A series of NMR studies, including HMQC, HMBC, COSY, and 1D NOESY experiments,[22] led to the conclusion that the radical cyclization product possessed structure **33**. Furthermore, recrystallization of the material from diethyl ether provided crystals suitable for X-ray crystallographic analysis, which showed conclusively that the product of radical cyclization was indeed **33**. Figure 3 shows an ORTEP depiction of the solid-state structure of this substance. It was thus evident that ring closure of **29** had proceeded via a 6-*endo-trig* alkenyl radical process. Such modes of cyclization have precedent in the chemical literature.[31]

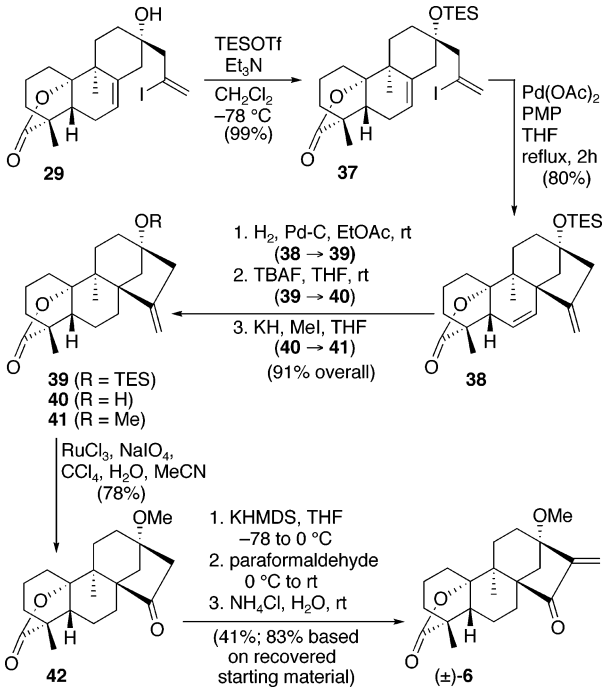
Treatment of alkenyl iodide **29** with tributylstannane and AIBN[30] as shown in Scheme 3 would produce an alkenyl radical that, presumably, would interact with the cyclohexene double bond as shown schematically in formula **30**. In theory, the latter species could produce, via carbon−carbon bond formation(s), one or both of the intermediate radicals **31** or (and) **32**, which, in turn, would abstract a hydrogen atom from tributylstannane to afford **33** or (and) **34**, respectively. Apart from other structural considerations, the tertiary radical **31** would be expected to be more stable than the secondary radical **32**. However, it is evident that other structural factors are also important. Molecular models show that the three six-membered rings labeled A, B, and C in formula **34** adopt chair, boat, and chair conformations, respectively. Consequently, this substance is notably destabilized by torsional and steric strain. On the other hand, all the six-membered carbocycles present in **33** can exist in chair conformations and, accordingly, destabilization as a consequence of torsional strain is essentially absent in this substance. Indeed, calculations[25] predict that substance **33** is about 5.5 kcal mol^{-1} more stable than **34**. Correspondingly, one would predict radical **31** to be appreciably more stable than radical **32** and, on this basis, the exclusive formation of product **33** is understandable.

(d) Completion of the Total Synthesis of (±)-13-Methoxy-15-oxozoapatlin (Scheme 5). In view of the fact that a radical-based cyclization of iodo alkene **29** failed to produce the required intermediate **34** (vide supra), the possibility of effecting the correct mode of ring

SCHEME 4



SCHEME 5



closure via an intramolecular Heck reaction[32] was considered. Initial experiments in this direction, using iodo alcohol **29** as the starting material, were unfruitful. Indeed, use of a variety of conditions, including different solvents (e.g., THF, MeCN, DMA), bases (e.g., Ag_2CO_3, Et_3N), and (or) palladium sources (e.g., $Pd(PPh)_4$, $Pd(dppf)_2$, $Pd_2(dba)_3$) invariably produced complex mixtures that included solid, intractable material.

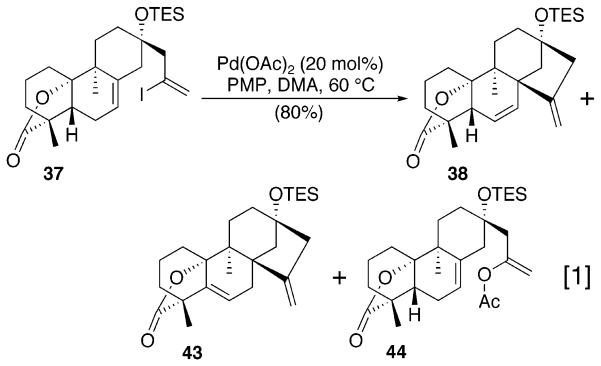
These observations indicated that the hydroxyl function in **29** was interfering with the required Pd(0)-catalyzed process. As shown in Scheme 4, it is possible that initial oxidative addition of the coordinatively unsaturated Pd(0) catalyst to the carbon−iodine bond (**29** → **35**) is followed by loss of HI from **35** to give a Pd(II) species **36**, the (probable) stability of which shuts down the required Pd(0)-based catalytic cycle.

Attempts to emend this predicament began with replacement of the hydroxyl proton of **29** by a bulky trialkylsilyl function. To that end (Scheme 5), alcohol **29** was allowed to react with TESOTf in the presence of Et_3N to produce, in essentially quantitative yield, triethylsilyl ether **37**. Curiously, exposure of **37** to typical Heck

(31) See, for example, Toyota, M.; Yokota, M.; Ihara, M. *J. Am. Chem. Soc.* **2001**, *123*, 1856.

(32) (a) Hegedus, L. S. In *Organometallics in Synthesis*; Schlosser, M., Ed.; John Wiley & Sons: New York, 1994; pp 420−425 (b) Link, T. J.; Overman, L. E. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH Verlag GmbH: Weinheim, Germany, 1998; pp 231−269. (c) Braese, S.; De Meijere, A. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: Hoboken, NJ, 2002; Vol. 1, p 1223. (d) Link, J. T. *Org. React.* **2002**, *60*, 157.

reaction conditions ($Pd(OAc)_2$, Ph_3P, Et_3N, MeCN)[32d] again produced primarily intractable material. On the other hand, subjection of **37** to a Heck reaction in the *absence* of a phosphine ligand [$Pd(OAc)_2$, 1,2,2,6,6-pentamethylpiperidine (PMP), *N*,*N*-dimethylacetamide (DMA)],[32a] as shown in eq 1, produced, in a combined yield of 80%, a mixture (~2:1:1, respectively) of the desired product **38**, the corresponding positional isomer **43**, and a substance that, on the basis of its ^1H and ^{13}C NMR spectra and a determination of its molecular mass by high resolution MS, was tentatively assigned the structure represented by formula **44**. Fortunately, it was found that formation of substances **43** and **44** could be avoided by employing THF as the solvent, rather than DMA. Accordingly (Scheme 5), treatment of substrate **37** with 1 equiv of $Pd(OAc)_2$ in the presence of PMP in refluxing THF consistently furnished the required product **38** in very good yield (~80%).



Chemoselective reduction of diene **38** could be accomplished by stirring a solution (EtOAc) of this material under an atmosphere of hydrogen in the presence of palladium-on-carbon. Although the rate of hydrogenation of the more strained cyclohexenyl double bond was appreciably higher than that of reduction of the exocyclic alkene function, it was necessary to monitor the progress of the reaction and to discontinue the process as soon as possible after complete consumption of the starting material. If this was not done, formation of the product derived from hydrogenation of both alkene functions was observed. The starting material **38**, the required product **39**, and the doubly reduced material were found to be inseparable by TLC on silica gel. Therefore, in initial attempts to effect the required site-selective hydrogenation, the reaction progress was monitored, in each case, by interrupting the process at approximately 15-min intervals. Analyses of the acquired mixtures were accomplished by ^1H NMR spectroscopy. In this manner, experimental conditions that provided high yields of **39** were determined.

Attempts to effect oxidative cleavage of the exocyclic alkenic bond of **39**, using a variety of reagents and experimental conditions, failed to give the corresponding ketone. Since it appeared that the TES ether function present in the substrate was interfering with the required reaction, it was decided to install the required methoxy group first. To that end (Scheme 5), treatment of **39** with TBAF in THF provided alcohol **40**, which was converted into ether **41** via a standard methylation procedure. The overall yield of the three-step conversion of **38** into **41** was excellent (91%).

Treatment of **41** with sodium periodate in the presence of a catalytic amount of ruthenium trichloride in a mixed solvent system (acetonitrile−tetrachloromethane−water)[33] produced, in 78% yield, ketone **42**. Reaction of **42** with KHMDS in THF (−78 → 0 °C), followed by sequential addition of paraformaldehyde and saturated aqueous ammonium chloride, provided, after purification of the derived material by flash chromatography, (±)-13-methoxy-15-oxozoapatlin (**6**) (41%; 84% based on recovered starting material). The ^1H and ^{13}C NMR spectral data derived from our synthetic (±)-**6** are in full accord with those reported for the natural product.[7] Furthermore, the spectra of the former material are in full agreement with those acquired from a sample of natural **6**, which was isolated from the South African tree *P. curatellifolia*.

Although the structure of **6** has been unambiguously established by X-ray crystallography,[8] a complete assignment of the signals in the ^1H and ^{13}C NMR spectra of this substance has not been reported. Analyses of HMQC, HMBC, and COSY experiments performed on synthetic (±)-**6** allowed a full assignment of the proton and carbon resonances for this natural product.[22]

To our knowledge, the work described in this paper represents the first reported total synthesis of a zoapatlin diterpenoid. The synthesis of the racemic version of 13-methoxy-15-oxozoapatlin (**6**), a structurally and biologically interesting substance, was accomplished via a linear 21-step reaction sequence. Of particular note in the synthesis was the development of a new method for the construction of the functionalized bicyclo[3.2.1]octane structural unit present in (±)-**6**. The key steps of this new protocol involved addition of the novel reagent (2-trimethylstannyl)allylmagnesium bromide (**26**) to the β,γ-unsaturated ketone **23** (**23** → **28**, Scheme 3) and an intramolecular Heck reaction to produce the required bicyclo[3.2.1]octane assembly (**37** → **38**, Scheme 5).

Experimental Section

(4a*S,4b*S**,8*R**,8a*R**)-4a,8-Dimethyl-1,2,3,4,4a,4b,5,6,7,8,-8a,9-dodecahydrophenanthren-2-one-8,4b-carbolactone (23).** To a stirred solution of lactone **21** (160 mg, 0.58 mmol) in dry, oxygen-free *t*-BuOH (12 mL, see general experimental methods, Supporting Information) at rt was added *t*-BuOK (390 mg, 3.48 mmol). The mixture was stirred for 4 min and then was treated with saturated aqueous NH_4Cl (10 mL). The resultant mixture was diluted with Et_2O (20 mL), the phases were separated, and the aqueous phase was extracted twice with Et_2O (20 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography (50 g of silica gel, 10:1 CH_2Cl_2−Et_2O). Removal of traces of solvent (vacuum pump) from the acquired solid provided 148 mg (93%) of the β,γ-unsaturated ketone **23**, a colorless solid that exhibited mp 148−152 °C. ^1H NMR (400 MHz): δ 5.42 (m, 1H), 3.31 (ddd, 1H, J = 1.9, 2.2, 15.6 Hz), 2.82 (dd, 1H, J = 2.2, 15.6 Hz), 2.58 (ddd, 1H, J = 7.3, 12.6, 16.4 Hz), 2.40 (dddd, 1H, J = 2.2, 2.2, 5.7, 16.4 Hz), 2.06−2.16 (m, 2H), 1.93 (dd, 1H, J = 7.3, 9.5 Hz), 1.72−1.87 (m, 3H), 1.60−1.69 (m, 2H), 1.44−1.58 (m, 3H), 1.36 (s, 3H), 1.13 (s, 3H). ^{13}C NMR (100.5 MHz): δ 207.3, 179.8, 135.6, 119.9, 86.5, 50.7, 49.2, 44.9, 39.4, 37.6, 34.3, 34.0, 29.8, 24.5, 20.0, 17.4, 15.9. IR (KBr): 2942, 1761, 1717, 1385, 1203, 1115, 936, 912 cm^{-1}. Exact mass calcd for $C_{17}H_{22}O_3$: 274.1569, found 274.1567.

(33) Carlson, H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(2*S,4a*S**,4b*S**,8*R**,8a*R**)-4a,8-Dimethyl-2-(2-(trimethylstannyl)allyl)-1,2,3,4,4a,4b,5,6,7,8,8a,9-dodecahydrophenanthren-2-ol-8,4b-carbolactone (28) and (2*R**,4a*S**,4b*S**,8*R**,8a*R**)-4a,8-Dimethyl-2-(2-(trimethylstannyl)allyl)-1,2,3,4,4a,4b,5,6,7,8,8a,9-dodecahydrophenanthren-2-ol-8,4b-carbolactone (27).** To a cold (−78 °C), stirred solution of freshly distilled 2,3-bis(trimethylstannyl)propene (**24**) (436 mg, 1.18 mmol) in dry THF (8.0 mL) was added a solution of MeLi (1.4 M in Et_2O, 0.68 mL, 0.95 mmol). After the light yellow solution had been stirred for 30 min, solid $MgBr_2{\cdot}OEt_2$ (304 mg, 1.18 mmol) was added, and the resulting milky solution was stirred for a further 30 min at −78 °C. A solution of the β,γ-unsaturated ketone **23** (145 mg, 0.53 mmol) in dry THF (3 mL) was added, and the mixture was stirred for 20 min at −78 °C. The mixture was treated with saturated aqueous NH_4Cl (10 mL), and the resultant mixture was diluted with Et_2O (30 mL). The phases were separated, and the aqueous phase was extracted with Et_2O (2 × 30 mL). The combined organic phases were washed with brine (25 mL), dried ($MgSO_4$), and concentrated. Separation and purification of the crude products by flash chromatography (150 g of silica gel, 3:2 CH_2Cl_2–Et_2O) provided 144 mg (58%) of **28** as a colorless solid (mp 195 °C) and 100 mg (40%) of **27** as a colorless oil.

28. ^{1}H NMR (400 MHz): δ 5.63 (m, 1H, $^3J_{Sn-H}$ = 152 Hz), 5.35 (bd, 1H, J = 6.1 Hz), 5.32 (d, 1H, J = 3.2 Hz, $^3J_{Sn-H}$ = 69 Hz), 2.41 (bd, 1H, J = 13.9 Hz), 2.33 (bd, 1H, J = 13.9 Hz), 2.31 (m, 1H), 2.00−2.15 (m, 3H), 1.92 (dd, 1H, J = 7.0, 9.9 Hz), 1.60−1.85 (m, 6H), 1.40−1.58 (m, 4H), 1.21 (s, 3H), 1.16 (m, 1H), 1.13 (s, 3H), 0.08 (s, 9H). ^{13}C NMR (100.5 MHz): δ 180.2, 152.1, 138.2, 128.6, 119.0, 87.3, 73.1, 50.7, 47.1, 46.9, 45.9, 45.3, 39.5, 34.3, 33.9, 32.7, 29.6, 24.5, 20.1, 17.5, 16.4, −8.0. IR (KBr): 3585, 2932, 1756, 1438, 1381, 1123, 914, 763 cm^{-1}. Exact mass calcd for $C_{23}H_{37}O_3Sn$ (+CI, M + H): 481.1765, found 481.1758.

27. ^{1}H NMR (400 MHz): δ 5.68 (m, 1H, $^3J_{Sn-H}$ = 155 Hz), 5.40 (bd, 1H, J = 6.1 Hz), 5.28 (d, 1H, J = 3.4 Hz, $^3J_{Sn-H}$ = 70 Hz), 2.50 (d, 1H, J = 13.4 Hz), 2.33 (d, 1H, J = 13.4 Hz), 2.33 (m, 1H), 2.15 (ddd, 1H, J = 6.5, 6.5, 17.9 Hz), 2.04 (m, 1H), 1.95 (dd, 1H, J = 7.3, 9.9 Hz), 1.90 (s, 1H), 1.72−1.83 (m, 2H), 1.43−1.70 (m, 8H), 1.32 (ddd, 1H, J = 5.0, 13.4, 13.4 Hz), 1.16 (s, 3H), 1.13 (s, 3H), 0.08 (s, 9H). ^{13}C NMR (100.5 MHz): δ 180.2, 152.0, 139.0, 128.2, 119.6, 87.0, 71.7, 53.1, 50.7, 45.2, 44.5, 39.9, 34.0, 33.8, 32.4, 29.3, 24.5, 20.0, 17.4, 15.3, −8.0. IR (neat): 3606, 2931, 1763, 1437, 1381, 1121, 930 cm^{-1}. Exact mass calcd for $C_{23}H_{37}O_3Sn$ (+CI, M + H): 481.1765, found 481.1758.

(1*S,4*S**,5*S**,9*R**,10*R**,12*S**,16*S**)-4,9-Dimethyl-13-methylidene[10,2,2,0^{4,16},0^{5,10}]tetracyclotetradecan-1-ol-9,5-carbolactone (33).** A stirred solution of alkenyl iodide **29** (47 mg, 0.11 mmol), tributylstannane (57 μL, 0.21 mmol), and a catalytic amount of AIBN in dry benzene (11.0 mL) was irradiated with a 275-W sun lamp for 5 min. The refluxing solution was cooled to rt and concentrated to approximately 1 mL. Flash chromatography (25 g of silica gel, 5:2 CH_2Cl_2−Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the resulting solid provided 33 mg (99%) of the pentacycle **33** as a colorless solid (mp 209 °C). ^{1}H NMR (400 MHz): δ 4.81 (s, 1H), 4.68 (s, 1H), 2.49 (dd, 1H, J = 2.6, 14.0 Hz), 2.34 (ddd, 1H, 2.2, 2.2, 14.0 Hz), 2.31 (m, 1H), 2.15 (ddd, 1H, J = 2.3, 5.7, 14.1 Hz), 2.08 (dd, 1H, J = 5.7, 12.4 Hz), 2.03 (m, 1H), 2.01 (m, 1H), 1.94 (m, 1H), 1.84 (ddd, 1H, J = 5.9, 13.2, 13.2 Hz), 1.76 (m, 1H), 1.75 (m, 1H), 1.66 (m, 1H), 1.63 (m, 1H), 1.50−1.60 (m, 3H), 1.49 (m, 1H), 1.32 (m, 1H), 1.30 (m, 1H), 1.12 (s, 3H), 1.10 (m, 1H), 1.09 (s, 3H). ^{13}C NMR (100.5 MHz): δ 180.6, 147.5, 107.2, 88.6, 69.6, 50.3, 49.2, 44.9, 40.2, 39.5, 38.4, 37.8, 36.1, 34.6, 28.9, 28.6, 26.0, 19.9, 18.9, 17.0. IR (KBr): 3500, 2942, 1752, 1378, 1204, 1136 cm^{-1}. Exact mass calcd for $C_{20}H_{29}O_3$ (+CI, M + H): 317.2117, found 317.2118.

(1*R,4*S**,5*S**,9*R**,10*R**,13*R**)-4,9-Dimethyl-14-methylidene-1-triethylsiloxy[11,2,1,0^{4,13},0^{5,10}]tetracyclopentadec-11-ene-9,5-carbolactone (38).** A stirred solution of alkenyl iodide **37** (17.4 mg, 0.031 mmol), 1,2,2,6,6-pentamethylpiperidine (17 μL, 0.094 mmol), and $Pd(OAc)_2$ (7.0 mg, 0.031 mmol) in dry THF (1.5 mL) was heated to reflux. After the mixture had been stirred for 2 h at reflux, it was cooled to rt and concentrated under reduced pressure. Flash chromatography (25 g of silica gel, 5:1 petroleum ether−Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the resulting solid provided 10.7 mg (80%) of diene **38** as a colorless solid (mp 111−113 °C). ^{1}H NMR (400 MHz): δ 5.91 (dd, 1H, J = 1.7, 9.7 Hz), 5.77 (dd, 1H, J = 3.3, 9.7 Hz), 4.84 (bs, 1H), 4.83 (bs, 1H), 2.53 (m, 1H), 2.50 (dd, 1H, J = 2.1, 16.3 Hz), 2.33 (dd, 1H, J = 1.7, 16.3 Hz), 2.22 (dd, 1H, J = 2.4, 11.3 Hz), 2.06 (dd, 1H, J = 5.8, 13.4 Hz), 1.97 (m, 1H), 1.77 (dd, 1H, J = 4.8, 12.3 Hz), 1.70 (m, 1H), 1.68 (m, 1H), 1.66 (m, 1H), 1.65 (m, 1H), 1.64 (m, 1H), 1.56 (m, 1H), 1.53 (m, 1H), 1.48 (m, 1H), 1.24 (s, 3H), 1.09 (s, 3H), 0.93 (t, 9H, J = 7.9 Hz), 0.57 (q, 6H, J = 7.9 Hz). ^{13}C NMR (100.5 MHz): δ 179.6, 148.2, 138.0, 123.4, 108.7, 89.6, 77.2, 55.4, 54.2, 48.6, 46.5, 45.4, 44.4, 36.8, 36.6, 32.8, 31.1, 19.9, 19.9, 16.9, 7.0, 6.5. IR (KBr) 2957, 1764, 1459, 1143, 1116, 938, 743 cm^{-1}. Exact mass calcd for $C_{26}H_{40}O_3Si$: 428.2747, found 428.2746.

(±)-13-Methoxy-15-oxo-17-norzoapatlin (42). To a cold (0 °C), stirred solution of methyl ether **41** (11.1 mg, 0.033 mmol) and $NaIO_4$ (29 mg, 0.14 mmol) in MeCN (0.5 mL), CCl_4 (0.5 mL), and H_2O (0.75 mL) was added a catalytic amount of $RuCl_3{\cdot}H_2O$. After 40 min, H_2O (5 mL) was added to the dark brown mixture, and the resultant mixture was diluted with CH_2Cl_2 (10 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (15 g of silica gel, 15:1 CH_2Cl_2−Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the resulting solid provided 8.7 mg (78%) of ketone **42** as a colorless solid (mp 156−157 °C). ^{1}H NMR (400 MHz): δ 3.27 (s, 3H), 2.41 (dd, 1H, J = 4.2, 14.5 Hz), 2.33 (m, 2H), 2.24 (dd, 1H, J = 3.1, 11.8 Hz), 1.97 (ddd, 1H, J = 5.7, 12.2, 12.6 Hz), 1.85−1.95 (m, 3H), 1.71−1.82 (m, 2H), 1.54−1.70 (m, 7H), 1.45 (dd, 1H, J = 8.8, 14.9 Hz), 1.23 (m, 1H), 1.22 (s, 3H), 1.07 (s, 3H). ^{13}C NMR (100.5 MHz): δ: 218.8, 180.4, 87.1, 76.6, 56.7, 51.9, 50.8, 47.5, 47.5, 44.7, 42.2, 35.2, 31.4, 31.1, 30.0, 25.2, 20.0, 18.1, 17.9, 17.0. IR (KBr): 2943, 1770, 1733, 1458, 1281, 1141, 1124, 939 cm^{-1}. Exact mass calcd for $C_{20}H_{28}O_4$: 332.1988, found 332.1985.

(±)-13-Methoxy-15-oxozoapatlin (6). To a cold (−78 °C), stirred solution of ketone **42** (6.0 mg, 0.018 mmol) in dry THF (1 mL) was added a solution of KHMDS (0.3 M in toluene, 120 μL, 0.036 mmol). After the mixture had been stirred for 15 min, it warmed to 0 °C and stirred for a further 45 min. Paraformaldehyde (5 mg, 0.17 mmol) was added, and the mixture was stirred for 15 min at 0 °C and for 1 h at rt. After the mixture had been treated with saturated aqueous NH_4Cl (5 mL), it was stirred for 10 min and then was diluted with Et_2O (10 mL). The phases were separated, and the aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (10 g of silica gel, 15:1 CH_2Cl_2−Et_2O) of the remaining material provided 3.0 mg (51%) of recovered starting material as a white solid and 2.5 mg (41%) of (±)-13-methoxy-15-oxozoapatlin (**6**) as a colorless solid (mp 134 °C). ^{1}H NMR (500 MHz): δ 6.12 (s, 1H), 5.35 (s, 1H), 3.24 (s, 3H), 2.49 (dd, 1H, J = 4.3, 14.4 Hz), 2.17 (dd, 1H, J = 7.5, 11.5 Hz), 2.15 (d, 1H, J = 11.8 Hz), 1.82−1.90 (m, 2H), 1.63−1.76 (m, 5H), 1.52−1.62 (m, 2H), 1.44−1.50 (m, 3H), 1.29 (m, 1H), 1.26 (s, 3H), 1.15 (m, 1H), 1.09 (s, 3H). ^{13}C NMR (100.5 MHz): δ 208.2, 180.4, 147.6, 116.5, 87.3, 79.8, 54.4, 51.9, 50.1, 47.5, 43.1, 40.6, 35.3, 34.7, 31.7, 31.2, 25.5, 20.0, 18.6, 18.2, 17.1. IR (KBr): 2938, 1765, 1720, 1644, 1275, 1212, 1140, 1110 cm^{-1}. Exact mass calcd for $C_{21}H_{28}O_4$: 344.1988, found 344.1988.

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Supporting Information Available: Experimental details for the preparation of, and characterization data for, compounds **9**−**11**, **14**−**18**, **20**−**23**, **27**−**29**, **33**, **37**, **38**, **41**, **42**, and (±)-**6**. Details of X-ray crystallographic structure determinations of compounds **16** and **33**. This material is available free of charge via the Internet at http://pubs.acs.org.

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