Stereocontrolled Synthesis of *ent*-Grindelic Acid. A Useful Example of Diastereofacial Guidance in an Oxonium Ion-Initiated Pinacolic Ring Expansion

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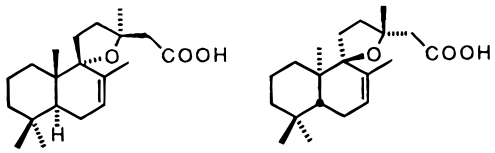
An enantioselective synthesis of (+)-grindelic acid is described, confirming that the dextrorotatory enantiomer is antipodal to the natural diterpenoid. The optically pure bicyclic ketone **5** representing the AB ring system is constructed from the levorotatory Wieland−Miescher ketone and must therefore possess the absolute configuration shown. Coupling of **5** with the 5-lithio derivative of optically active 2,3-dihydrofuran **3** derived from (*R*)-(−)-linalool was effected for the purpose of realizing acid-catalyzed rearrangement with generation of the appropriate spirocyclic framework. This key step is highly stereocontrolled, leading predominantly to **7**. Once the advanced intermediate **15** is available in this fashion, its subsequent exposure to oxidation and dehydration steps led to the target molecule. The synthesis demonstrates unequivocally that natural (−)-grindelic acid is a true labdane diterpenoid.

The grindelane class of bicyclic diterpenoids, encompassing many compounds at the present time, has been the subject of continuous phytochemical investigation for more than 20 years.[1] Grindelic acid (**1**), the most prominent member of this class,[2] is widely considered to be the biogenetic precursor to many structurally interesting, more highly oxygenated metabolites. Despite the central role played by **1**, the assignment of its absolute stereochemistry has been the subject of considerable confusion. Initially, this spirocyclic tetrahydrofuran was formulated to exist in the labdane series, *viz.* **1a**, on the basis of spectroscopic considerations[3] and chemical correlation with sclareol.[4] In 1986, Jakupovic *et al.* succeeded in transforming (−)-**1** into methyl 6-oxo-7,8-



1a **1b**

dihydrogrindelate, which exhibited a positive Cotton effect.[5] Application of the octant rule to this observation led to the alternative conclusion that natural grindelic acid belongs to the *ent*-labdane series and is therefore **1b**. Despite justifiable recorded claims to the contrary,[4b,6,7] the acceptance of **1b** as the correct absolute configuration persists to the present time.[8]

A need to clarify the stereochemical lineage of grindelic acid consequently exists. An opportunity to develop a new method for generating the structural array present in **1** engaged our attention. The successful plan had necessarily to include provision for the elaboration of a spirocyclic carbon with full control over absolute configuration. Ideally, the margins of stereoselectivity would be sufficiently elevated that introduction of the various chirality elements would prove to be strikingly simple.

Experimentally evaluated herein is the adaptation of oxonium ion activated pinacol ring expansion[9,10] to the total synthesis of **1b**. These studies have established the feasibility of incorporating all of the essential structural features of this substance by means of a highly stereocontrolled master reaction. Since **1b** prepared in this manner has proven to be dextrorotatory, it is abundantly clear that natural (−)-grindelic acid is unequivocally the labdane diterpenoid **1a**.[11]

Synthetic Strategy

(*R*)-(−)-Linalool (**2**) had earlier been transformed into dihydrofuran **3**, an intermediate that is amenable to deprotonation at the vinylic center α to the oxygen

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(1) Recent reports of new isolations include: (a) Aphaijitt, S.; Nimgiravath, K.; Suksamrarn, A.; Tooptakong, U. *Aust. J. Chem.* **1995**, *48*, 133. (b) Hayashi, T.; Okamura, K.; Tamada, Y.; Iida, A.; Fujita, T.; Morita, N. *Phytochemistry* **1993**, *32*, 349. (c) Urones, J. G.; Marcos, I. S.; Moro, R. F.; Rodilla, J. M. L.; Mendonca, A. G. *Phytochemistry* **1993**, *32*, 401. (d) Fang, J. M.; Sou, Y. C.; Chiu, Y. H.; Cheng, Y. S. *Phytochemistry* **1993**, *34*, 1581. (e) San Feliciano, A.; Miguel del Corral, J. M.; Lopez, J. L.; de Pascual-Teresa, B. *Phytochemistry* **1993**, *33*, 1165.

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(6) Adinolfi, M.; Della Greca, M.; Mangoni, L. *Phytochemistry* **1988**, *27*, 1878.

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(10) (a) Paquette, L. A.; Lord, M. D.; Negri, J. T. *Tetrahedron Lett.* **1993**, *34*, 5693. (b) Lord, M. D.; Negri, J. T.; Paquette, L. A. *J. Org. Chem.* **1995**, *60*, 191.

(11) Preliminary communication: Paquette, L. A.; Wang, H.-L. *Tetrahedron Lett.* **1995**, *36*, 6005.

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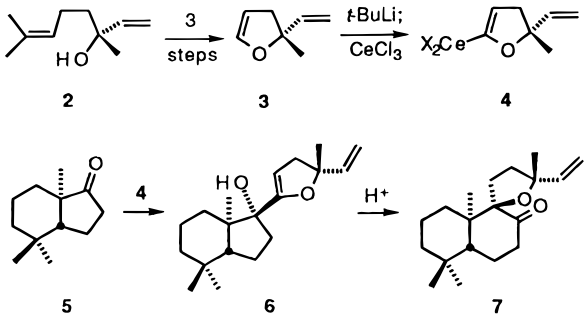
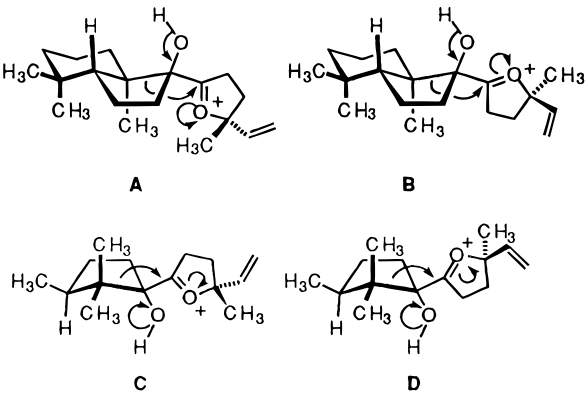
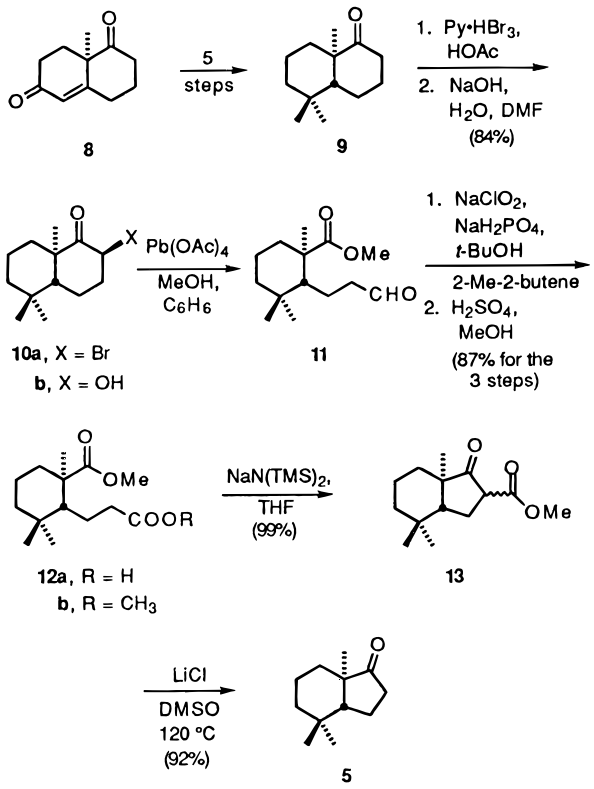
Scheme 1



Scheme 2



Scheme 3



atom.[10] Since the basicity of the resulting organolithium species could be significantly reduced by conversion to the organocerate **4**,[10] the possibility existed that 1,2-addition to bicyclic ketone **5** could be carried out without the serious incursion of competing enolization (Scheme 1). This condensation was expected to proceed from the sterically less congested β face[12] to deliver the tertiary carbinol **6**. It was further conjectured that the protonation of **6** would result in generation of a reactive oxonium ion whose fate it would be to experience a Wagner–Meerwein shift. This migration should involve the more electron-rich tertiary carbon, which should be quite sensitive to prevailing steric factors due to its very substantial space-filling requirements (note the added neopentyl feature). The hope was that the reduced level of nonbonded steric compression present in **A** as compared to **B** (Scheme 2) would be met by kinetically controlled diastereoselection in favor of the first trajectory. The two π surfaces in the oxonium ion acceptor should be equally receptive to bonding, such that differences in reaction exothermicity cannot be distinguished on this basis. However, the migration syn to methyl as encountered in **A** can be expected to be energetically less costly than compression against the vinyl group. The basis for this contention stems from an awareness that the tertiary methyl substituted carbon in oxonium ions **C** and **D** prefers to follow the first of these pathways by a factor of 2:1.[10] The situation in **A** and **B** should be even more imbalanced.

The expected adoption of transition state **A** would lead to **7** and constitute a rather interesting example of diastereofacial guidance. In the end, the challenge of establishing proper absolute configuration in a spirocyclic carbon is met by controlling the ultimate course of a pinacolic-like ring expansion.

(12) For example: Renoud-Grappin, M.; Vanucci, C.; Lhommet, G. *J. Org. Chem.* **1994**, *59*, 3902.

Results and Discussion

Bond disconnection at the carbinol center in **6** leads in turn to the need to prepare the specific enantiomer of bicyclic ketone **5** shown. Our approach to this intermediate was based on ring contraction of the readily available (−)-Wieland–Miescher ketone **8**.[13] Advantage was taken of the known propensity of its monoethylene ketal for incorporation of a (phenylthio)methylene group α to the carbonyl when treated with aqueous formaldehyde, thiophenol, and triethylamine in ethanol.[14] Following Birch reduction, in situ methylation of the resulting desulfurized enolate anion with methyl iodide,[15] Wolff–Kishner reduction,[16] and ketal hydrolysis afforded **9**, $[\alpha]^{24}_D$ +34.5 (*c* 0.055, $CHCl_3$).[17] To set the stage for the cleavage of ring B (Scheme 3), **9** was brominated with pyridinium bromide perbromide in acetic acid[18] and exposed to sodium hydroxide in aqueous DMF.[19] As expected from earlier precedent, the yield in both steps was very good, affording the acyloin **10b** in 84% overall yield.[20]

Subsequent treatment of **10b** with lead tetraacetate in benzene containing methanol at rt[21] afforded aldehydo

(13) (a) Buchschacher, P.; Fürst, A.; Gutzwiller, J. *Organic Syntheses;* Wiley: New York, **1990**, Coll. Vol. *VII*, p 368. (b) Harada, N.; Sugioka, T.; Uda, H.; Kuriki, T. *Synthesis* **1990**, 53.

(14) Kirk, D. N.; Petrow, V. *J. Chem. Soc.* **1962**, 1091.

(15) Smith, A. B., III; Mewshaw, R. *J. Org. Chem.* **1984**, *49*, 3685.

(16) Snitman, D. L.; Tsai, M.-Y.; Watt, D. S.; Edwards, C. L.; Stotter, P. L. *J. Org. Chem.* **1979**, *44*, 2838.

(17) The reported optical rotation for **9** is $[\alpha]^{20}_D$ +30.8 (*c* 0.05, $CHCl_3$): Okamura, W. H.; Peter, R.; Reischl, W. *J. Am. Chem. Soc.* **1985**, *107*, 1034.

(18) Ihara, M.; Toyota, M.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2151.

(19) Numazawa, M.; Nagaoka, M. *J. Org. Chem.* **1982**, *47*, 4024.

(20) The optical rotations recorded for **10a** and **10b** are $[\alpha]^{24}_D$ +17.3 (*c* 0.295, $CHCl_3$) and $[\alpha]^{24}_D$ +32.7 (*c* 0.29, $CHCl_3$), respectively. The results of Ihara *et al.*[18] who worked in the enantiomeric series are $[\alpha]^{17}_D$ −22.0 (*c* 0.30, $CHCl_3$) and $[\alpha]^{17}_D$ −28.9 (*c* 0.28, $CHCl_3$). Their sample of *ent*-**9** was reported to exhibit $[\alpha]^{17}_D$ −39.1 (*c* 0.44, $CHCl_3$).

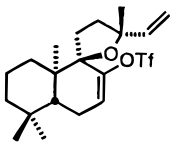
ester **11**, which was directly oxidized to the dicarboxylate level. Two methods for accomplishing this conversion were examined.

In the first, **11** was admixed with iodine and potassium hydroxide in methanol.[22] However, the yield of **12b** produced under these conditions (52% for the two steps) was determined to be less efficient than sequential treatment with sodium chlorite[23] and acidic methanol (87% overall).

Dieckmann cyclization of **12b** was accomplished most efficaciously by making recourse to sodium hexamethyldisilazide in THF at 20 °C.[24] The ability to carry out this ring closure in high yield made possible access to respectable amounts of ketone **5** following decarbomethoxylation by an established protocol.[25]

Preliminary studies involving the condensation of the lithio derivative of **3** with **5** showed the ketone to be easily deprotonated. This is as expected in light of the sterically hindered nature of the carbonyl group and its setting in a five-membered ring. In order to achieve reduced basicity, transmetalation with anhydrous cerium trichloride[26] was implemented to generate **4** as the reactive nucleophile. Under these circumstances, 1,2-addition occurred smoothly to give **6** (Scheme 4). The projected sensitivity of this alcohol prompted us to treat it directly with a catalytic quantity of camphorsulfonic acid in CH_2Cl_2 at rt. Within 10 min, **6** had been completely consumed and replaced by a 10.4:1 mixture (GC analysis) of spirocyclic ketones **7** and **14** (76%). This result occasioned no surprise.

The very similar R_f values of these ring-expanded intermediates prompted introduction of the final requisite carbon atom in advance of chromatographic separation. Although vinyl triflate **20** was easily accessible,[27] coupling with lithium dimethyl cuprate[28] could not be effected under a wide variety of conditions. The steric blockade associated with the neopentyl nature of the reaction center is held responsible for this lack of reactivity. These developments prompted investigation of methyllithium addition. In both instances, the methyl group was introduced from the β-face to provide **15** (87%) and



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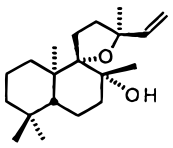

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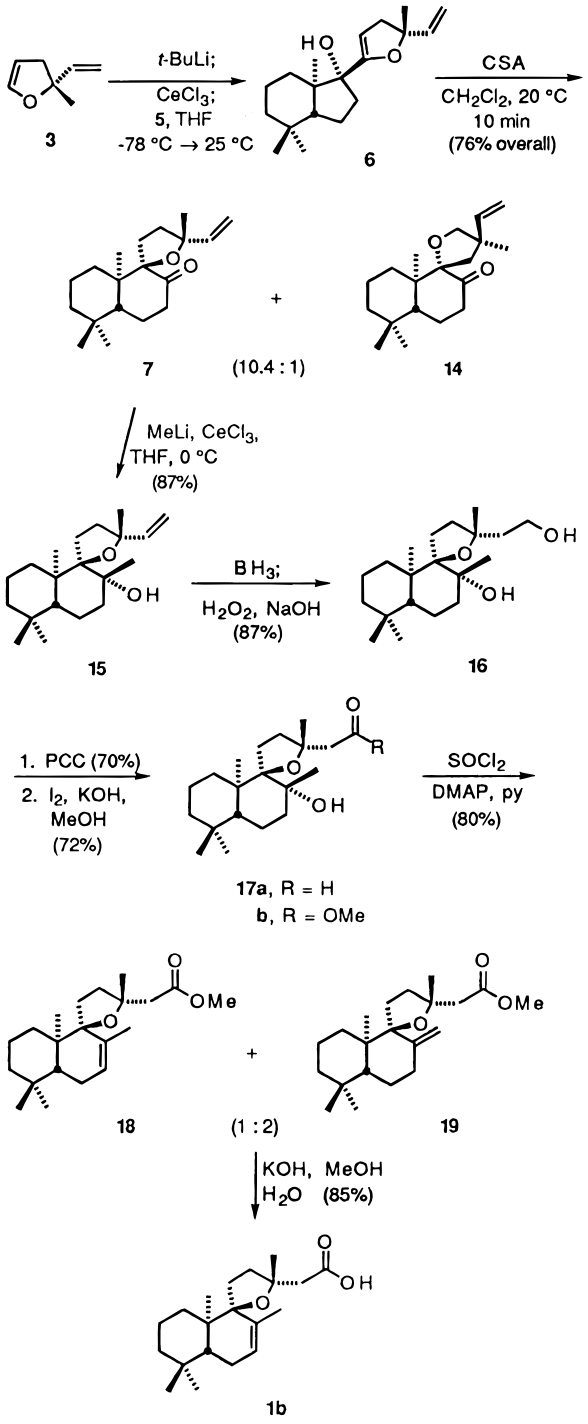
21 (10%) as easily purified diastereomers. The stereochemical assignments to **7**, **15**, and **21** are reliably founded on extensive $^1H-^1H$ COSY and NOE studies performed at 300 MHz. Some of these data are compiled in Table 1.

Following arrival at **15**, attention was given to conversion of the vinyl substituent into the requisite acetic ester

Scheme 4



subunit. To this end, **15** was subjected to standard hydroboration conditions and diol **16** was smoothly oxidized to hydroxy aldehyde **17a** with PCC. Of the methods examined to transform **17a** into **17b**, that involving iodine and potassium hydroxide in methanol[22] proved most serviceable and direct (72%).

Not unexpectedly, the dehydration of **17b** with thionyl chloride in pyridine containing DMAP[28] resulted in preponderant formation of exocyclic olefin **19** relative to the desired endocyclic isomer **18** (ratio 2:1). To our dismay, however, all efforts to achieve internal migration of the double bond in **19** either with iodine in refluxing benzene[29] or with rhodium trichloride in hot ethanol[30]

(21) Hazen, J. R. *J. Org. Chem.* **1970**, *35*, 973.
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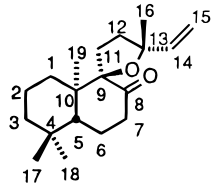
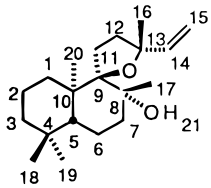
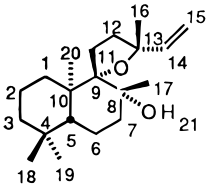
(23) (a) Balkrishna, S. B.; Childers, W. E., Jr.; Pinnick, H. H. *Tetrahedron* **1981**, *37*, 2091. (b) Schwab, J. M.; Klassen, J. B. *J. Am. Chem. Soc.* **1984**, *106*, 7217.
(24) Welch, S. C.; Rao, A. S. C. P.; Gibbs, C. G.; Wong, R. Y. *J. Org. Chem.* **1980**, *45*, 4077.
(25) (a) Krapcho, A. P. *Synthesis* **1982**, 893. (b) Trost, B. M.; Jungheim, L. N. *J. Am. Chem. Soc.* **1980**, *102*, 7910.
(26) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.
(27) Review: Ritter, K. *Synthesis* **1993**, 735.
(28) Posner, G. H.; Schulman-Roskes, E. M. *Tetrahedron* **1992**, *48*, 4677.
(29) Kircher, H. W.; Rosenstein, F. U. *J. Org. Chem.* **1987**, *52*, 2587.

Table 1. Summary of NOE Difference Experiments

Compd	Proton irradiated	Observed integral enhancements
 **7**	5-H	7-H$_{(ax)}$ (3.0%), 17-Me (3.2%)
	7-H$_{(ax)}$	15-H (1.9%), 5-H (3.3%)
	11-H	19-Me (3.5%)
	11-H'	15-H (1.2%)
 **15**	14-H	15-H (2.4%)
	16-Me	14-H (2.7%)
	17-Me	14-H (2.7%), 21-H (5.7%)
	20-Me	19-Me (3.1%), 21-H (3.6%)
 **21**	14-H	15-H (3.6%)
	16-Me	14-H (4.1%), 15-H' (2.0%)
	17-Me	21-H (2.9%), 16-Me (1.1%)
	19-Me	20-Me (4.0%)
	20-Me	16-Me (1.1%), 19-H (2.0%), 21-H (2.0%)

were unsuccessful. The neighboring spirocyclic tetrahydrofuran was not accommodating of more strongly acidic conditions.

Nonetheless, saponification of **18** delivered dextrorotary grindelic acid, $[\alpha]^{24}_D$ +134.3 (*c* 0.035, $CHCl_3$), whose absolute configuration must be expressed as **1b**. Comparable hydrolysis of natural methyl grindelate provided by Dr. Shimizu gave (−)-**1a**, $[\alpha]^{24}_D$ −132.3 (*c* 0.034, $CHCl_3$). The fully synthetic sample exhibited spectral properties showing it decisively to be identical to natural grindelic acid except for the sign of optical rotation. On this basis, it can be confidently asserted that **1** is a member of the labdane family and that the many grindelane diterpenoids derived from **1** are of the same absolute configurational parentage.

Summary

The total synthesis described above demonstrates the capability of oxonium ion-initiated pinacolic ring expansions for constructing oxygen-containing spirocyclic systems in a stereocontrolled manner. Much as in an earlier described application involving preparation of the dactyloxenes,[10] substituent effects operate in the desired direction to set appropriate absolute configuration. A more detailed analysis of migratory aptitudes is under investigation and will be reported shortly.

A number of other concepts were successfully utilized, including the enhancement of effective levels of 1,2-addition to **5** by prior formation of the organocerate. The implementation of other chemoselective reactions was met without setback, such that the saga surrounding the absolute configuration of grindelic acid can now be considered as closed.

Experimental Section

General Procedure. All manipulations were performed under a nitrogen atmosphere. Solvents were dried over 4 Å molecular sieves before distillation. Benzene, ether, tetrahydrofuran, and toluene were distilled from sodium or sodium/benzophenone ketyl. Dichloromethane, diisopropylamine, dimethyl sulfoxide, dimethylformamide, and triethylamine were each distilled from calcium hydride. Melting points are uncorrected. Exact mass measurements were recorded on Kratos MS-30 or VG-70-2505 mass spectrometers at The Ohio State University Chemical Instrumentation Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark. The chromatographic separations were carried out either under flash conditions on Fluka silica gel H or gravimetrically on Woelm silica gel 63-200. The organic extracts were dried over anhydrous sodium sulfate. All reagents were reagent grade and purified where necessary.

(1*R*,2*R*)-2-Carboxy-2,6,6-trimethylcyclohexanepropionic Acid Dimethyl Ester (12b). To a magnetically stirred solution of **10b**, $[\alpha]^{24}_D$ +32.7 (*c* 0.29, $CHCl_3$) (4.0 g, 19.05 mmol), in a mixture of methanol (32 mL) and benzene (96 mL) cooled to 0 °C was added lead tetraacetate (8.91 g, 19.10 mmol). After 30 min at rt, saturated $NaHCO_3$ solution was introduced, the mixture was filtered through a pad of Celite, and the filtrate was extracted with ether. The combined extracts were dried and evaporated to leave the aldehydo ester **11**.

This product was dissolved in *tert*-butyl alcohol (190 mL) containing 2-methyl-2-butene (32 mL), cooled to 0 °C, and treated with a solution of $NaClO_2$ (12.03 g, 133 mmol) and $NaH_2PO_4 \cdot H_2O$ (13.11 g, 95 mmol) in water (91 mL). During 12 h of stirring at rt, the yellow solution became colorless. Most of the *tert*-butyl alcohol was removed on a rotary evaporator, at which point the residue was diluted with water, acidified with 5% HCl to pH 2, and extracted with ethyl acetate. The combined organic phases were washed with brine, dried, and concentrated to leave the crude carboxylic acid **12a**, which was taken up in methanol (380 mL) containing concentrated H_2SO_4 (2.1 mL) and stirred at 0 °C for 1 h. The reaction mixture was concentrated in vacuo, diluted with water, and extracted with ethyl acetate. The combined organic layers were dried and concentrated, and the residue was purified by chromatography on silica gel (elution with 20:1 hexanes/ethyl acetate) to give **12b** as a colorless oil (4.47 g, 87% overall); IR (neat, cm^{-1}) 1782, 1462, 1435, 1244, 1151, 1107, 1062, 980, 874; ^1H NMR (300 MHz, $CDCl_3$) δ 3.65 (s, 6 H), 2.24 (m, 2 H), 1.72 (m, 3 H), 1.55−1.25 (series of m, 6 H), 1.20 (s, 3 H), 0.93 (s, 3 H), 0.90 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 179.4, 174.0, 51.8, 51.4, 48.8, 47.1, 40.8, 37.1, 34.9, 34.2, 32.8, 23.1, 22.6, 18.2, 17.6; MS *m*/*z* (M^+) calcd 270.1831, obsd 270.1834; $[\alpha]^{24}_D$ +4.0 (*c* 0.20, $CHCl_3$). Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.62; H, 9.70. Found: C, 66.68; H, 9.69.

(3a*R*,7a*R*)-Hexahydro-4,4,7a-trimethyl-1-indanone (5). To a cold (0 °C), magnetically stirred solution of sodium hexamethyldisilazide (3.1 mL of 1 M) in dry THF (4.7 mL) was slowly added a solution of **12b** (277 mg, 1.03 mmol) in the same solvent (26 mL). After being stirred at rt for 2 h, the reaction mixture was returned to 0 °C, quenched with cold 1 M HCl (6 mL), and extracted with ethyl acetate. The combined organic phases were dried and evaporated to leave a residue that was chromatographed on silica gel (elution with 20:1 hexanes/ethyl acetate). There was isolated 242 mg (99%) of **13** as a colorless oil.

The above material (258 mg, 1.08 mmol) was dissolved in DMSO (5.0 mL) containing water (23 μL) and lithium chloride (138 mg, 3.24 mmol), and the mixture was heated at 120−140 °C for 2 h, cooled to rt, diluted with water (3 mL), and extracted with ether. The combined ether phases were washed with brine, dried, and concentrated to leave a yellow oil, chromatography of which on silica gel (elution with 20:1 hexanes/ethyl acetate) afforded 176 mg (91%) of **5** as a colorless

(30) (a) Grieco, P. A.; Nishizawa, M.; Marinovic, N.; Ehmann, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 7102. (b) Andrieaux, J.; Barton, D. H. R.; Patin, H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 359.

oil: IR (neat, cm^{-1}) 1739, 1474, 1459, 1369, 1120, 1020; ^1H NMR (300 MHz, $CDCl_3$) δ 2.40 (dd, J = 19.1, 8.8 Hz, 1 H), 2.04 (dt, J = 19.1, 8.8 Hz, 1 H), 1.92−1.83 (m, 1 H), 1.75−1.55 (m, 4 H), 1.51−1.41 (m, 1 H), 1.27 (dd, J = 13.2, 5.6 Hz, 1 H), 1.19−0.97 (m, 2 H), 0.95 (s, 3 H) 0.92 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 221.3, 54.1, 47.9, 41.3, 35.3, 33.9, 32.2, 32.0, 21.4, 19.1, 19.0, 15.6; MS m/z (M^+) calcd 180.1514, obsd 180.1500; $[\alpha]^{24}_D$ −116.7 (c 0.18, $CHCl_3$). The 2,4-dinitrophenylhydrazone of **5** melted at 169−170 °C. Anal. Calcd for $C_{18}H_{24}N_4O_4$: C, 59.97; H, 6.72. Found: C, 59.64; H, 6.72.

(2*R*,4′a*R*,5*R*,8′a*R*)-Decahydro-5,5′,5′,8′a-tetramethyl-5-vinylspiro[furan-2(3*H*),1′(2′*H*)-naphthalen]-2′-one (7) and (2*S*,4′a*R*,5*S*,8′a*R*)-Decahydro-5,5′,5′,8′a-tetramethyl-5-vinylspiro[furan-2(3*H*),1′(2′*H*)-naphthalen]-2′-one (14). Cerium trichloride heptahydrate (3.94 g, 10.57 mmol) was ground to a fine powder and then heated gradually to 100 °C during 12 h and to 135−140° during an additional 12 h while evacuated to 0.5 Torr. While the flask was still hot, dry N_2 was introduced and cooling to rt was allowed to proceed. Freshly distilled anhydrous THF (26 mL) was introduced, and the resulting suspension was well stirred overnight (14 h) at rt.

In another flask, a solution of **3** (986 mg, 8.96 mmol) in dry THF (13 mL) was cooled to −78 °C, treated with *tert*-butyllithium (4.9 mL of 1.7 M in pentane, 8.33 mmol), and stirred for 1 h. The $CeCl_3$ slurry was also cooled to −78 °C, and *tert*-butyllithium was added dropwise until a pink color persisted (0.2 mL). The solution of lithiated dihydrofuran was introduced via cannula to give a yellow-orange mixture and stirring was maintained for 1 h. At this point, a solution of **5** (735 mg, 4.08 mmol) in THF (4.1 mL) cooled to −78 °C was added via cannula. The reaction mixture was agitated at −78 °C for 3 h before being allowed to warm to rt overnight (15 h), treated with saturated $NaHCO_3$ solution (5 mL) at −78 °C, and filtered through Celite. The filter cake was rinsed with ether, and the combined filtrates were dried and concentrated to leave impure **6** as a yellow oil.

This material was directly dissolved in CH_2Cl_2 (41 mL), treated with camphorsulfonic acid (100 mg, 0.43 mmol), and stirred at rt for 10 min. The resulting dark yellow reaction mixture was quenched with saturated $NaHCO_3$ solution (10 mL), and the separated organic layer was washed with brine, dried, and concentrated to leave a yellow oil which was chromatographed on silica gel (elution with 15:1 hexanes/ether). There was isolated 897 mg (76%) of **7** and **14** as a colorless oil. The isomeric ratio was determined to be 10.4:1 by GC analysis.

For **7**: IR (neat, cm^{-1}) 1717, 1464, 1368, 1097, 1060, 1021, 984, 918; ^1H NMR (300 MHz, C_6D_6) δ 5.75 (dd, J = 17.4, 10.7 Hz, 1 H), 5.02 (dd, J = 17.4, 1.2 Hz, 1 H), 4.82 (dd, J = 10.7, 1.2 Hz, 1 H), 3.05 (ddd, J = 12.9, 12.9, 7.1 Hz, 1 H), 2.65−2.58 (m, 1 H), 2.27 (ddd, J = 12.9, 4.5, 2.1 Hz, 1 H), 2.07 (dd, J = 13.0, 3.2 Hz, 1 H), 1.89−1.81 (m, 1 H), 1.73−1.60 (m, 2 H), 1.43−0.85 (series of m, 8 H), 1.19 (s, 3 H), 0.81 (s, 3 H), 0.69 (s, 3 H), 0.62 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 210.3, 144.5, 111.7, 94.3, 84.2, 45.8, 43.9, 42.1, 38.4, 37.6, 33.6, 33.4, 32.2, 26.6, 24.1, 23.5, 22.0, 19.0, 15.9; MS m/z (M^+) calcd 290.2246, obsd 290.2244; $[\alpha]^{24}_D$ +26.6 (c 0.32, $CHCl_3$). Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.56; H, 10.42. Found: C, 78.80; H, 10.40.

(2*R*,2′*R*,4′a*R*,5*R*,8′a*R*)-Decahydro-2′,5,5′,5′,8′a-pentamethyl-5-vinylspiro[furan-2(3*H*),1′(2′*H*)-naphthalen]-2′-ol (15) and (2*S*,2′*R*,4′a*R*, 5*S*,8′a*R*)-Decahydro-2′,5,5′,5′,8′a-pentamethyl-5-vinylspiro[furan-2(3*H*),1′(2′*H*)-naphthalen]-2′-ol (21). Dry THF (5.7 mL) was added to anhydrous $CeCl_3$ (1.7 mmol) and stirred overnight to produce a slurry. A solution of 1.4 M methyllithium in ether (1.2 mL) was added to the cold (0 °C) slurry and stirred for 1.5 h at this temperature. A mixture of **7** and **14** (51 mg, 0.17 mmol) was introduced and, after 40 min, quenching was implemented with saturated NH_4Cl solution (1 mL) and brine (2 mL). The aqueous layer was extracted with ether, and the combined organic phases were washed with brine, dried, and concentrated. Purification of the residue by chromatography on silica gel (elution with 20:1 hexanes/ethyl acetate) furnished 47 mg (87%) of **15** and 5.2 mg (10%) of **21**.

For **15**: colorless oil; IR (neat, cm^{-1}) 3495, 1464, 1366, 1097, 1049, 1014, 913; ^1H NMR (300 MHz, $CDCl_3$) δ 6.08 (dd, J = 17.4, 10.8 Hz, 1 H), 5.08 (dd, J = 17.4, 1.4 Hz, 1 H), 4.94 (dd, J = 10.8, 1.4 Hz, 1 H), 2.13−1.99 (m, 3 H), 1.89−1.73 (m, 2 H), 1.68−1.00 (series of m, 11 H), 1.31 (s, 3 H), 1.12 (s, 3 H), 1.07 (s, 3 H), 0.88 (s, 3 H), 0.83 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 146.2, 110.4, 93.7, 84.8, 75.8, 47.8, 42.3, 41.9, 38.3, 37.6 34.3, 33.6, 33.3, 30.1, 29.3, 26.8, 21.9, 18.5, 18.1, 17.8; MS m/z (M^+) calcd 306.2559, obsd 306.2554; $[\alpha]^{25}_D$ +3.0 (c 0.23, $CHCl_3$). Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.36; H, 11.19. Found: C, 78.29; H, 11.22.

For **21**: colorless oil; IR (neat, cm^{-1}) 3480, 1464, 1367, 1101, 1081, 1048, 1016, 994, 913; ^1H NMR (300 MHz, $CDCl_3$) δ 6.08 (dd, J = 17.5, 10.8 Hz, 1 H), 5.06 (dd, J = 17.5, 1.2 Hz, 1 H), 4.94 (dd, J = 10.8, 1.2 Hz, 1 H), 2.15−0.89 (series of m, 16 H), 1.33 (s, 3 H), 1.24 (s, 3 H), 1.08 (s, 3 H), 0.88 (s, 3 H), 0.81 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 146.1, 109.9, 93.9, 85.0, 75.8, 46.9, 43.0, 41.7, 38.5, 36.9, 34.5, 33.38, 33.35, 29.6, 29.2, 27.2, 21.8, 18.3, 18.2, 17.9; MS m/z (M^+) calcd 306.2559, obsd 306.2556; $[\alpha]^{24}_D$ −4.0 (c 0.05, $CHCl_3$).

(2*R*,2′*R*,4′a*R*,5*R*,8′a*R*)-Decahydro-2′-hydroxy-2′,5,5′,5′,8′a-pentamethylspiro[furan-2(3*H*),1′(2′*H*)-naphthalene]-5-ethanol (16). A solution of **15** (34 mg, 0.11 mmol) in THF (0.1 mL) was added to diborane in THF (0.16 mL of 1.0 M, 0.16 mmol) at −40 °C and stirred for 6 h at 0 °C before being treated with 15% NaOH solution (0.16 mL) and 30% hydrogen peroxide (0.16 mL) at 0 °C. The ice bath was removed, and the mixture was stirred at rt for 30 min and diluted with water and ether. The aqueous phase was extracted with ether and with ethyl acetate. The combined organic layers were washed with brine, dried, and concentrated. The residue was chromatographed on silica gel (elution with 1:1 hexanes/ethyl acetate) to give 31 mg (87%) of **16** as colorless crystals, mp 134−135 °C (from $CHCl_3$); IR (film, cm^{-1}) 3384, 1455, 1388, 1372, 1197, 1171, 1108, 1059, 1003; ^1H NMR (300 MHz, $CDCl_3$) δ 4.03 (ddd, J = 11.2, 11.2, 2.6 Hz, 1 H), 3.75−3.65 (m, 1 H), 3.56 (s, 1 H), 3.53 (s, 1 H), 2.21−0.88 (series of m, 17 H), 1.33 (s, 3 H), 1.25 (s, 3 H), 1.06 (s, 3 H), 0.85 (s, 3 H), 0.81 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 95.3, 86.3, 75.3, 60.2, 48.6, 43.1, 42.3, 41.8, 38.6, 34.5, 33.7, 33.4, 29.4, 27.6, 26.1, 21.9, 18.4, 17.9, 17.1; MS m/z (M^+) calcd 324.2664, obsd 324.2664; $[\alpha]^{24}_D$ −0.5 (c 0.20, $CHCl_3$). Anal. Calcd for $C_{20}H_{36}O_3$: C, 74.01; H, 11.19. Found: C, 74.01; H, 11.17.

(2*R*,2′*R*,4′a*R*,5*R*,8′a*R*)-Decahydro-2′-hydroxy-2′,5,5′,5′,8′a-pentamethylspiro[furan-2(3*H*),1′(2′*H*)-naphthalene]-5-acetaldehyde (17a). Diol **16** (94.4 mg, 0.29 mmol) in CH_2Cl_2 (9 mL) was added to a magnetically stirred mixture of pyridinium chlorochromate (128 mg, 0.59 mmol) and powdered 4 Å molecular sieves (50 mg) in CH_2Cl_2 (7 mL), stirred for 13 h at rt, diluted with ether (2 mL), and filtered through a pad of Florisil. The pad was rinsed with ether and the combined filtrates were evaporated. Flash chromatography of the residue on silica gel (elution with 5:1 hexanes/ethyl acetate) gave **17a** (65.6 mg, 70%) as a white solid: mp 90−91 °C; IR (film, cm^{-1}) 3509 (br), 1721, 1464, 1388, 1108, 1048, 1001; ^1H NMR (300 MHz, $CDCl_3$) δ 9.85 (t, J = 2.8 Hz, 1 H), 2.81 (dd, J = 12.3, 2.8 Hz, 1 H), 2.53 (dd, J = 12.3, 2.8 Hz, 1 H), 2.27−1.01 (series of m, 16 H), 1.41 (s, 3 H), 1.19 (s, 3 H), 1.08 (s, 3 H), 0.87 (s, 3 H), 0.82 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 202.5, 94.7, 82.6, 75.5, 56.5, 47.8, 42.5, 41.9, 40.2, 38.4, 34.6, 33.6, 33.5, 29.7, 29.6, 26.7, 21.9, 18.4, 18.0, 17.8; MS m/z (M^+) calcd 322.2508, obsd 322.2520; $[\alpha]^{24}_D$ −38.5 (c 0.195, $CHCl_3$).

Methyl (2*R*,2′*R*,4′a*R*,5*R*,8′a*R*)-Decahydro-2′-hydroxy-2′,5,5′,5′,8′a-pentamethylspiro[furan-2(3*H*),1′(2′*H*)-naphthalene]-5-acetate (17b). A solution of 4% (w/v) potassium hydroxide in methanol was added dropwise to a mixture of **17a** (11.4 mg, 0.035 mmol) and iodine (17.8 mg, 0.07 mmol) in methanol (0.5 mL) at 45−50 °C until no free iodine remained. The reaction mixture was diluted with water (1 mL) and extracted with chloroform. The combined organic phases were dried and concentrated to leave a residue that was chromatographed on silica gel (elution with 6:1 hexanes/ethyl acetate). There was isolated 9.0 mg (72%) of **17b** as a colorless oil; IR (neat, cm^{-1}) 3542, 1738, 1463, 1364, 1201, 1094, 1048, 1022, 990; ^1H NMR (300 MHz, $CDCl_3$) δ 3.66 (s, 3 H), 2.70 (d, J = 13.9 Hz, 1 H), 2.64 (d, J = 13.9 Hz, 1 H), 2.12−

1.09 (series of m, 16 H), 1.38 (s, 3 H), 1.19 (s, 3 H), 1.07 (s, 3 H), 0.87 (s, 3 H), 0.81 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 171.8, 94.1, 83.0, 75.6, 51.4, 47.7, 47.5, 42.5, 41.8, 39.0, 38.3, 34.5, 33.6, 33.4, 29.4, 28.3, 27.0, 21.9, 18.4, 18.0, 17.8; MS *m*/*z* (M^+) calcd 352.2613, obsd 352.2613; $[\alpha]^{24}_D$ −19.8 (*c* 0.205, $CHCl_3$).

Methyl (2*S*,4′a*R*,5*R*,8′a*R*)-4,4′a,5,5′,6′,7′,8′,8′a-Octahydro-2′,5,5′,5′,8′a-pentamethylspiro[furan-2(3*H*),1′(4′*H*)-naphthalene]-5-acetate (18) and Methyl (2*S*,4′a*R*,5*R*,8′a*R*)-Decahydro-5,5′,5′,8′a-tetramethylspiro[furan-2(3*H*),1′(2′*H*)-naphthalene]-5-acetate (19). Thionyl chloride (6.0 μL, 0.08 mmol) was added to a soution of **17b** (9.0 mg, 0.025 mmol) and DMAP (3.1 mg, 0.025 mmol) in pyridine (0.1 mL, 1.23 mmol) at 0 °C. The reaction mixture was stirred under N_2 for 30 min, quenched by pouring into ice−water (1 mL), and extracted with ethyl acetate. The combined organic layers were dried and evaporated to leave an oil which was chromatographed on silica gel (elution with 20:1 hexanes/ethyl acetate) to give 2.2 mg (26%) of **18** and 4.6 mg (54%) of **19**.

For **18**: white solid, mp 67−68 °C (from $CHCl_3$); IR (neat, cm^{-1}) 1740, 1455, 1436, 1224, 1093, 1022, 992; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.50 (m, 1 H), 3.65 (s, 3 H), 2.74 (d, J = 14.2 Hz, 1 H), 2.61 (d, J = 14.2 Hz, 1 H), 2.27−2.17 (series of m, 13 H), 1.76 (s, 3 H), 1.55 (s, 3 H), 1.33 (s, 3 H), 0.89 (s, 3 H), 0.81 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 171.9, 134.9, 126.6, 90.6, 81.6, 51.4, 48.0, 42.7, 42.0, 40.7, 38.2, 33.2, 32.9, 32.8, 28.5, 27.4, 24.2, 22.4, 21.3, 18.8; MS *m*/*z* (M^+) calcd 334.2501, obsd 334.2508; $[\alpha]^{24}_D$ +125.9 (*c* 0.085, $CHCl_3$). Natural methyl grindelate exhibits $[\alpha]^{24}_D$ −127.1 (*c* 0.085, $CHCl_3$).

For **19**: colorless oil; IR (neat, cm^{-1}) 1740, 1456, 1436, 1094, 1043, 895; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.78 (s, 1 H), 4.67 (s, 1 H), 3.63 (s, 3 H), 2.58−2.46 (m, 3 H), 2.17−2.02 (m, 3 H), 1.96−1.88 (m, 1 H), 1.74−1.48 (series of m, 6 H), 1.39−1.18 (m, 4 H), 1.29 (s, 3 H), 0.88 (s, 3 H), 0.79 (s, 3 H), 0.76 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 171.9, 150.9, 106.7, 91.2, 81.2, 51.2, 46.9, 46.7, 41.8 (2 C), 36.8, 33.6, 33.42, 33.36, 32.0, 27.2, 25.4, 23.7, 22.0, 19.2, 17.1; MS *m*/*z* (M^+) calcd 334.2508, obsd 334.2509; $[\alpha]^{24}_D$ −17.9 (*c* 0.28, $CHCl_3$).

(+)-Grindelic Acid (1b). A solution of **18** (2.2 mg, 0.006 mmol) in methanol (1 mL) and water (0.1 mL) was treated with potassium hydroxide (4.8 mg, 0.085 mmol), stirred at rt for 48 h, quenched with 5% HCl (0.1 mL), and extracted with ethyl acetate. The combined organic phases were dried and concentrated to leave an oil, chromatography of which on silica gel (elution with 10:1:0.2 hexanes/ethyl acetate/acetic acid) afforded **1b** as a colorless solid: mp 98−99 °C (from $CHCl_3$); IR (film, cm^{-1}) 3500−3000, 1707, 1456, 1378, 1094, 1018, 993; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.61 (br s, 1 H), 2.68 (d, J = 15.3 Hz, 1 H), 2.56 (d, J = 15.3 Hz, 1 H), 2.17−1.12 (series of m, 13 H), 1.76 (s, 3 H), 1.38 (s, 3 H), 0.90 (s, 3 H), 0.87 (s, 3 H), 0.82 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 172.0, 133.1, 128.9, 92.6, 81.1, 47.4, 42.6, 41.8, 40.8, 39.5, 33.2, 32.9, 32.7, 27.5, 26.8, 24.2, 22.0, 21.2, 18.6, 16.7; MS *m*/*z* (M^+) calcd 320.2351, obsd 320.2353; $[\alpha]^{24}_D$ +134.3 (*c* 0.035, $CHCl_3$). Natural grindelic acid exhibits $[\alpha]^{24}_D$ −132.3 (*c* 0.034, $CHCl_3$).

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Supporting Information Available: 300-MHz ^{1}H NMR and 75-MHz ^{13}C NMR spectra of those compounds lacking combustion data (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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