Enantioselective Synthesis of the Antiinflammatory Agent (−)-Acanthoic Acid

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An enantioselective synthesis of the potent antiinflammatory agent (−)-acanthoic acid (**1**) is described. The successful strategy departs from (−)-Wieland−Miescher ketone (**10**), which is readily available in both enantiomeric forms and constitutes the starting point toward a fully functionalized AB ring system of **1**. Conditions were developed for a regioselective double alkylation at the C4 center of the A ring, which produced compound **32** as a single stereoisomer. Construction of the C ring of **1** was accomplished via a Diels−Alder reaction between sulfur-containing diene **43** and methacrolein (**36**), which after desulfurization and further functionalization yielded synthetic acanthoic acid. The described synthesis confirms the proposed stereochemistry of the natural product and represents a fully stereocontrolled entry into an underexplored class of biologically active diterpenes.

Introduction and Background

For thousands of years, mankind has known about the benefit of drugs from nature. Among them, plants and extracts thereof have formed the basis for numerous traditional medicines, which even today continue to play an important role in health care worldwide.[1,2] Although the medical use of folkloric recipes and rituals is still ongoing in some parts of the world, it has become increasingly essential to develop drugs in a form of purified, single compounds, that are well understood in terms of biology, pharmacology, and overall medical value. With this concept in mind, traditional medicines are constantly being examined in an effort to isolate and structurally characterize the active ingredients that provide starting points for further biological and medicinal studies. In fact, it has been estimated that 77% of all currently used drugs were discovered as a result of chemical studies and structural modifications of active substances used in folkloric medicines.[3] Notable examples of such successful endeavors are the plant-derived metabolites camptothecin, podophyllotoxin, and Taxol.[4]

Another more recent example of a traditional medicinal plant is *Acanthopanax koreanum* Nakai, a deciduous shrub that grows indigenously in Cheju Island of The Republic of Korea.[5] It has been reported that wine made from the root bark of this bush has been used traditionally by local populations for treatment of neuralgia, hypertension, rheumatism, and diabetes. Although the beneficial analgesic and tonic effects of this plant were known since ancient times, it was only recently that a systematic study of its extracts was undertaken. Notably, in 1988 Chung and co-workers isolated and structurally characterized from these extracts a novel diterpene, which was subsequently named acanthoic acid (**1**).[6] Following its isolation, the biological mode of action of this natural product was more methodically examined.[7] To this end, in vitro studies with activated human monocytes and macrophages revealed that acanthoic acid inhibits up to 90% of the production of the pro-inflammatory cytokines, tumor necrosis factor-alpha (TNF-α), and interleukin-1 (IL-1).[8] This inhibition was concentration dependent and cytokine specific since, under the

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(1) For selected monographs on this subject, see: Kinghorn, A. D., Balandrin, M. F., Eds. *Human Medicinal Agents from Plants*; ACS Symposium Series 534: American Chemical Society, Washington, DC, 1993. Gullo, V. P., Ed. *The Discovery of Natural Products with Therapeutic Potential*; Butterworth-Heinemann: Boston, 1994. Kaufman, P. B., Cseke, L. J., Warber, S., Duke, J. A., Brielmann, H. L., Eds. *Natural Products from Plants*; CRC Press: Boca Raton, FL and Boston, 1999. Grabley, S., Thiericke, R., Eds. *Drug Discovery from Nature;* Springer: Berlin, 2000.

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(4) Cragg, G. M. *Med. Res. Rev.* **1998**, *18*, 315−331. Suffness, M. *Ann. Rep. Med. Chem.* **1993**, *28*, 305−314. Joel, S. P. *Chem. Ind.* **1994**, 172−175. Lee, K.-H. *Med. Res. Rev.* **1999**, *19*, 569−596. Lee, K.-H. *J. Biomed. Sci.* **1999**, *6*, 236−250. Wall, M. E. *Med. Res. Rev.* **1998**, *18*, 299−314.

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(6) Kim, Y.-H.; Chung, B. S.; Sankawa, U. *J. Nat. Prod.* **1988**, *51*, 1080−1083. More recently, acanthoic acid was also isolated from root extracts of *Coleonema pulchellum* Williams, a shrub found in South Africa: Brader, G.; Bacher, M.; Hofer, O.; Greger, H. *Phytochemistry* **1997**, *45*, 1207−1212.

(7) (a) Kang, H.-S.; Kim, Y.-H.; Lee, C.-S.; Lee, J.-J.; Choi, I.; Pyun, K.-H. *Cellular Immunol.* **1996**, *170*, 212−221. (b) Kang, H.-S.; Song, H. K.; Lee, J.-J.; Pyun, K.-H.; Choi, I. *Mediators Inflamm.* **1998**, *7*, 257−259.

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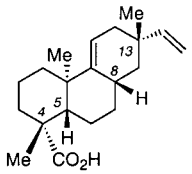
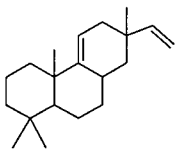
same conditions, the production of IL-6 or interferon-gamma (IFN-γ) was not altered.[7a] Moreover, experiments performed in mice treated with silica to induce silicosis (chronic lung inflammation) and carbon tetrachloride to induce cirrhosis (liver inflammation) demonstrated that treatment with **1** led to a substantial reduction of fibrotic granulomas in the lungs and a remarkable reduction of hepatic liver enzyme elevations, respectively.[7b] In addition, acanthoic acid was found to be active upon oral administration and showed minimal toxicity in experiments performed in rats. Taken together, these data support the folkloric reports surrounding the parent plant and demonstrate clearly the medicinal potential of acanthoic acid as an antiinflammatory agent.



1: acanthoic acid



2: generic structure of pimarane diterpenes

From a structural point of view, acanthoic acid (**1**) belongs to a large family of tricyclic diterpenes of the pimarane structure (**2**).[9] Interestingly, however, the structure of **1** is distinguished by an uncommon connectivity across the rigid tricyclic core that may be held accountable for its pharmacological profile. The combination of unusual structural constitution and promising pharmacological activity of **1** prompted us to initiate a synthetic program toward this family of biologically important metabolites.[10,11] Our major objective was to develop a concise and fully stereocontrolled synthetic entry to acanthoic acid. Herein, we present a full account of our studies toward this goal, culminating in the expedient and stereoselective synthesis of (−)-acanthoic acid.[12] These studies confirm the structure and establish the absolute stereochemistry of this natural product and pave the way for a more precise study of its structure−activity relationship.[13]

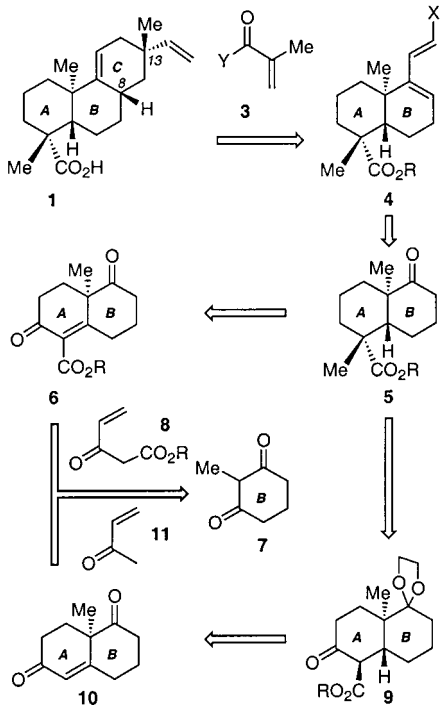


Figure 1. Retrosynthetic analysis of acanthoic acid (**1**).

Results and Discussion

Retrosynthetic Analysis and Bond Disconnections. Close analysis of the structure of acanthoic acid indicated the possibility of constructing the C ring using a Diels−Alder reaction (Figure 1).[14] In the forward sense, this could be accomplished by reacting dienophile **3** with diene **4**, thereby forming the C9−C11 double bond and introducing simultaneously stereochemistry at the C8 and C13 carbon centers. At the onset of our studies, we had concerns regarding the stereofacial accessibility of diene **4**, which could be responsible for the stereochemical outcome at centers C8 and C13. Nonetheless, we felt that a wrong outcome could be influenced in favor of the desired stereoisomer with the use of chiral auxiliaries or by performing the cycloaddition in the presence of chiral catalysts.

Diene **4** was envisioned to be produced by manipulation of ketone **5**, which represents a fully functionalized AB ring system of acanthoic acid. Compound **5** was projected to be derived by functional group manipulation of ketoester **6**, which in turn could be made by annealing 2-methyl-1,3-cyclohexane dione (**7**) with ester **8**.[15] An alternative strategy for the preparation of **5** would invoke stereocontrolled alkylation of β-ketoester **9**, suggesting the use of (−)-Wieland−Miescher ketone **10** as a putative starting material. As in the previous strategy, this approach also converges to use diketone **7** during an annulation reaction with methylvinyl ketone (**11**) (Figure 1).

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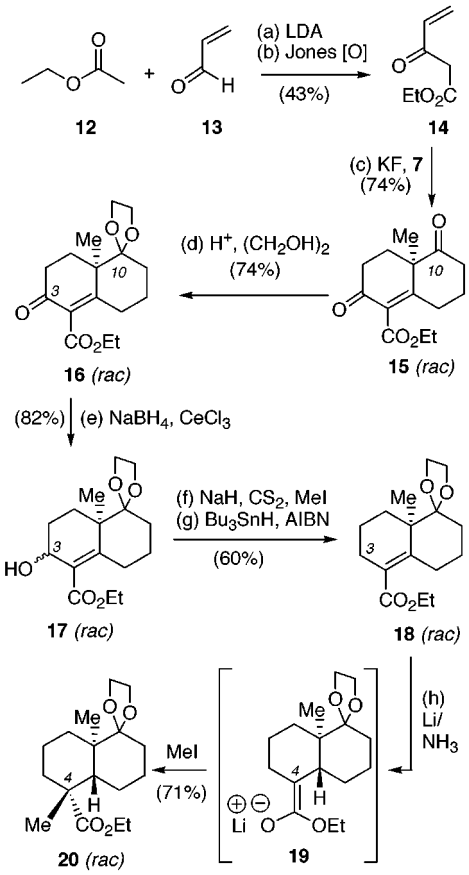
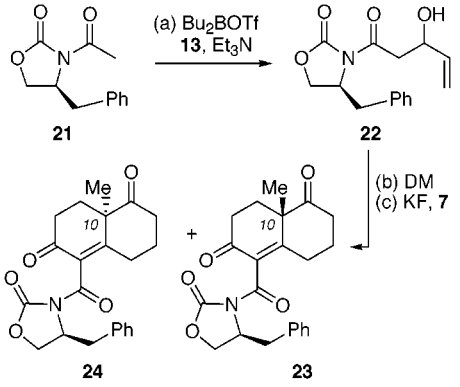
Scheme 1[a]



[a] Reagents and conditions: (a) 1.1 equiv LDA, 1.5 equiv **13**, −78 °C, 1 h, 76%; (b) Jones [O], from 0 to 25 °C, 6 h, 56%; (c) 1.4 equiv **14**, 1.0 equiv **7**, 2.2 equiv KF, MeOH, 25 °C, 16 h, 74%; (d) 0.1 equiv PTSA, 1.15 equiv $(CH_2OH)_2$, C_6H_6, reflux, 4 h, 74%; (e) 1.1 equiv $NaBH_4$, 1.1 equiv $CeCl_3$, EtOH, from 0 to 25 °C, 2 h, 82%; (f) 1.3 equiv NaH, 1.5 equiv CS_2, 2.5 equiv MeI, THF, from 0 to 25 °C, 4 h, 89%; (g) 1.5 equiv $n$$Bu_3SnH$, 0.05 equiv AIBN, C_6H_6, reflux, 2 h, 68%; (h) 2.5 equiv Li, liquid NH_3, 1.0 equiv tBuOH, from −45 to −50 °C, 40 min; isoprene (excess), 2.0 equiv MeI, 0 °C, 3 h, 71%.

Initial Approach to the AB Ring System of 1. Our initial synthetic plan benefited from published reports related to the synthesis of ketoester **14**, which is also known as Nazarov reagent (Scheme 1).[16] Compound **14** was formed by reaction of ethyl acetate (**12**) with LDA and quenching of the anion with acrolein (**13**). The resulting alcohol was subsequently oxidized to ketone **14** using Jones oxidation (two steps, 43% yield).[17] Condensation of Nazarov reagent (**14**) with diketone **7** proceeded smoothly in methanol or ethyl acetate using KF or triethylamine, respectively, to produce compound **15** in 74% yield as a racemate. Despite the rather conspicuous absence from the literature of an enantioselective variant of this reaction,[18] we decided to look initially at the feasibility of using **15** as a precursor of a fully functionalized AB ring system of acanthoic acid and defer until later the task of an enantioselective strategy. To this end, the more basic C9 carbonyl group of **15** underwent

Scheme 2[a]



[a] Reagents and conditions: (a) 1.2 equiv Et_3N, 1.1 equiv Bu_2BOTf, 1.5 equiv **13**, CH_2Cl_2, from −78 to 0 °C, 2 h; phosphate buffer, MeOH, 10 equiv H_2O_2, from 0 to 25 °C, 1 h, 57%; (b) 1.2 equiv Dess−Martin periodinane, CH_2Cl_2, 25 °C, 1.5 h, 81%; (c) 1.2 equiv **7**, 2.2 equiv KF, MeOH, 25 °C, 12 h, 53%.

selective ketalization upon treatment with ethylene glycol and catalytic acid to afford ketoester **16** in 74% yield. The C3 carbonyl group of **16** was then reduced with sodium borohydride and cerium chloride to produce alcohol **17** as a mixture of diastereomers at the C3 center.[19] Without separation of the diastereomers, this mixture of alcohols **16** was subsequently transformed to ester **18** using the Barton−McCombie radical deoxygenation protocol (60% yield over two steps).[20] Treatment of α,β-unsaturated ester **18** with lithium in ammonia afforded enolate **19**, which upon alkylation with methyl iodide gave rise to compound **20**, as a single stereoisomer at the C4 center. The stereochemistry of **20** was initially assigned on the basis of previously published studies, indicating that alkylation of the exocyclic enolate **19** proceeds from the more accessible β-face of the bicyclic system.[21] Subsequently, this prediction was confirmed on the basis of the alkylation results of the similar enolate **31** (see Scheme 4).

Having achieved the construction of a fully functionalized AB ring of acanthoic acid as a racemic mixture, we focused our attention on developing an enantioselective entry into this structure. In principle, this could be accomplished by constructing enone **15** as a single enantiomer. To this end, the condensation of **14** with **7** was attempted in the presence of D-proline methyl ester (0.1 and 1.0 equiv in CH_2Cl_2), (*S*)-camphorsulfonic acid (0.1 and 1.0 equiv in CH_2Cl_2), L-proline (0.1 and 1.0 equiv in MeOH and DMSO), and L-phenylalanine (0.1 and 1.0

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(17) The only chiral derivative of the Nazarov reagent is the (−)-bornyl 3-hydroxy-4-pentenoate. See: Zibuck, R.; Streiber, J. M. *J. Org. Chem.* **1989**, *54*, 4717−4719. However, to the best of our knowledge, there are no reports on enantioselective annulations based on this type of reagent.

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equiv in MeOH and DMSO). The best results were obtained when the annulation was performed in the presence of 1.0 equiv of L-proline in MeOH at 25 °C for 24 h. Nonetheless, under these conditions, the bicycle **15** was isolated in 40% yield and with 60% enantiomeric excess (ee) (analyzed by chiral HPLC).[22]

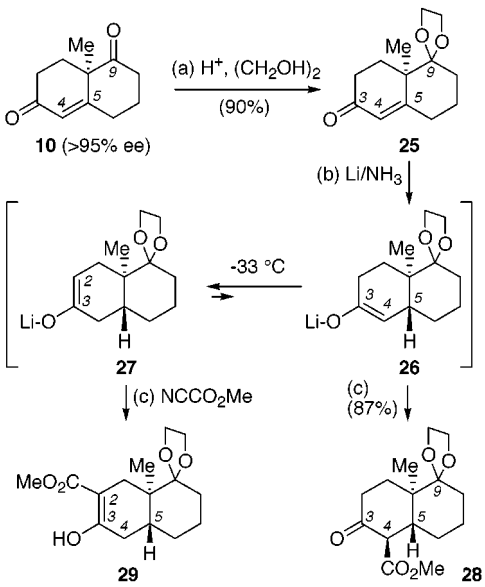
The disappointing results above prompted us to consider construction of the desired AB ring system of acanthoic acid in an enantioselective way by embedding chirality on the ester part of the bicyclic system. In principle, this could be achieved by using a modified Nazarov reagent covalently attached to an Evans chiral oxazolidinone.[23] The construction of the AB ring system along these lines is shown in Scheme 2.

The modified Nazarov reagent was prepared by reacting oxazolidinone **21** with acrolein (**13**) in the presence of dibutyl boron triflate to afford alcohol **22**. Treatment of **22** with Dess−Martin periodinane produced the desired α,β-unsaturated ketone, which was subjected to several annulation conditions in the presence of diketone **7**. A variety of Lewis acid conditions ($ZnCl_2$, $TiCl_4$) were attempted but did not yield any annulated products. Among other conditions tried, including THF/Et_3N, MeOH/KOH (cat), MeOH/K_2CO_3, and MeOH/MeONa at 25 and 60 °C, the best yields of annulated product were obtained with KF/MeOH at 25 °C. In this case, we isolated a 1:1 mixture of bicyclic products **23** and **24** in 53% overall yield. Gratifyingly, the less polar spot, corresponding to compound **23**, was crystalline and its structure was unambiguously assigned on the basis of X-ray studies (Supporting Information). By analogy, the more polar stereoisomer was assigned to structure **24**, containing the desired (R) absolute configuration at the C10 quaternary center.

Second Approach to the AB Ring System of 1. In light of the problems associated with the construction of the AB system of acanthoic acid as a single enantiomer using Nazarov reagent (or modifications thereof), we decided to pursue its synthesis from the less-functionalized Wieland−Miescher enone **10** (Scheme 3).

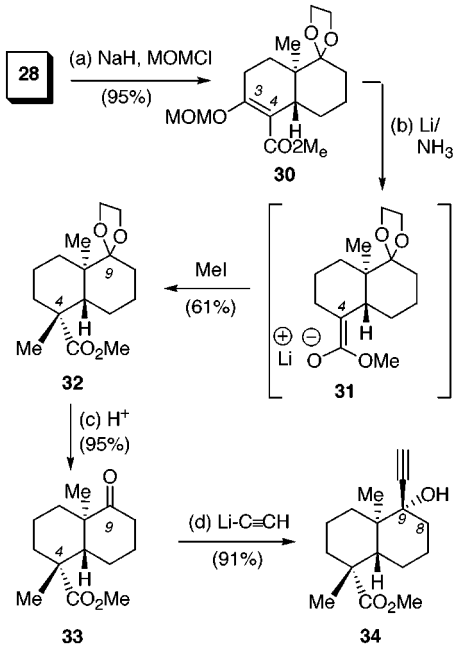
Enone **10** was readily available through a D-proline-mediated asymmetric Robinson annulation, followed by two successive crystallizations (from Et_2O/hexane) (70−75% yield, >95% ee).[24] After selective protection of the C9 carbonyl group (90% yield), ketal **25** was subjected to reductive alkylation across the enone functionality. To this end, treatment of **25** with lithium in ammonia containing *t*BuOH, followed by quenching of the resulting enolate with methyl cyanoformate, afforded the desired compound **28** together with variable amounts of **29**.[25] We found that the ratio of products **28** and **29** depends on the temperature at which enolate **26** is allowed to be warmed during the necessary evaporation of the excess ammonia. For example, if the entire reductive alkylation sequence is performed at −78 °C, the adduct **28** is formed in low yield (ca. 30%) and is accompanied with substantial amounts of recovered enone (**25**). Alternatively, allowing enolate **26** to be warmed at temperatures higher than −40 °C resulted in substantial formation of compound **27**. The desired compound **28** is obtained in the best yield (87%) if enolate **26** is formed at temperatures between −50 and −45 °C, the excess ammonia is evaporated under vacuum at −45 °C, and the resulting enolate is subsequently alkylated at −78 °C. Under these conditions, formation of compound **29** was not observed.

Scheme 3[a]



[a] Reagents and conditions: (a) 0.1 equiv PTSA, 1.05 equiv $(CH_2OH)_2$, benzene, 80 °C, 4 h, 90%; (b) 2.2 equiv Li, 1.0 equiv *t*BuOH, NH_3, from −78 to −45 °C, 30 min, then isoprene (excess), from −78 to −45 °C; (c) 1.1 equiv $NCCO_2Me$, Et_2O, from −78 to 0 °C, 2 h, 87%.

Scheme 4[a]



[a] Reagents and conditions: (a) 1.1 equiv NaH, 25 °C, 3 h; 1.1 equiv MOMCl, 25 °C, 2h, 95%; (b) 7.0 equiv Li, NH_3, from −78 to −30 °C, 20 min; CH_3I (excess), from −78 to −30 °C, 1 h, 61%; (c) 1 N HCl, THF, 25 °C, 15 min, 95%; (d) 1.6 equiv Li acetylide, Et_2O, 25 °C, 1 h, 91%.

(22) The HPLC analysis was performed in a CHIRALPAK AD column (No. 19025) with a 4.6 nm diameter and a 250 nm length that was purchased from Chiral Techn. Inc., Exton, PA. The compounds were eluted with 100% hexanes (HPLC grade).

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(25) Crabtree, S. R.; Mander, L. N.; Sethi, P. S. *Org. Synth.* **1992**, *70*, 256−263. Stork, G.; Rosen, P.; Goldman, N.; Coombs, R. V.; Tsuji, J. *J. Am. Chem. Soc.* **1965**, *87*, 275−286.

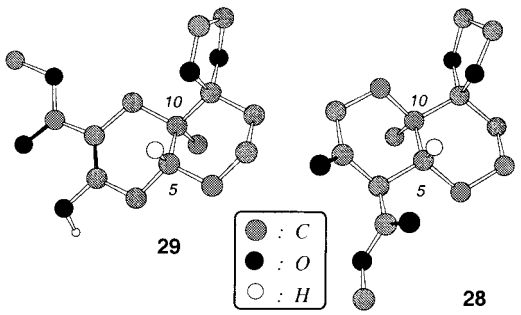


Figure 2. Chem3D representations of ORTEP drawings of **28** and **29** (for clarity, only selected hydrogens are shown).

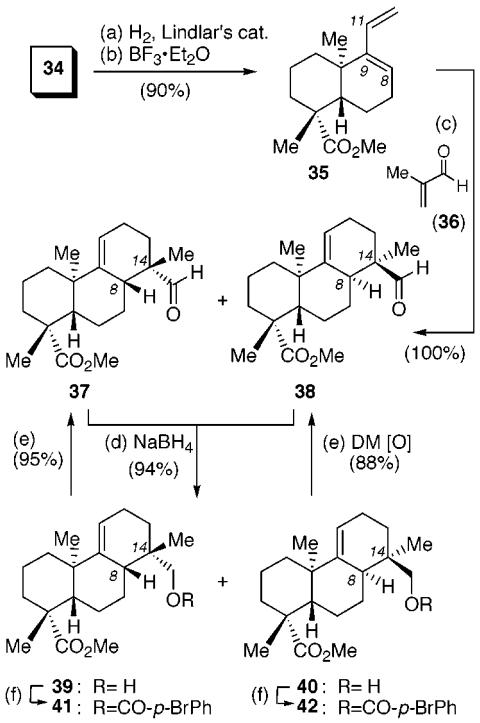
Formation of compound **29** can be explained mechanistically if we consider epimerization of the kinetically formed enolate **26** to the thermodynamically more stable enolate **27**, in which the double bond is located between the C2 and C3 carbon centers. Interestingly, the enolate character of **29** is also shown in the crystal structure of this compound, while in comparison, the X-ray structure of compound **28** suggests its preference to exist in the β-ketocarbonyl form (Figure 2).

Further functionalization of the AB ring of acanthoic acid is accomplished as shown in Scheme 4 and is based on a Coates and Shaw "double reduction" of β-ketoesters.[26] With this concept in mind, ketoester **28** was selectively O-alkylated with methoxymethyl chloride and sodium hydride to afford MOM ether **30** in 95% yield. Treatment of **30** with lithium in liquid ammonia resulted in deoxygenation at the C3 center and formation of enolate **31**, which upon reaction with iodomethane produced ester **32** in 61% yield. Similar to the conversion of **18** to **20** (shown in Scheme 1), it was expected that the stereoselectivity of this addition will arise from the strong preference of the presumed intermediate enolate **31** to undergo alkylation at the less-hindered equatorial side. Nonetheless, unambiguous confirmation of this structure was deferred until assembly of the entire backbone of acanthoic acid was achieved.

Synthetic Studies Toward the C Ring of 1. Having completed the synthesis of the AB ring system of acanthoic acid, we sought to attach the C ring across centers C8 and C9. To this end, ketal **32** was subjected to acid-catalyzed deprotection (1 N HCl, 95% yield) and the resulting ketone **33** was alkylated with lithium acetylide·ethylenediamine complex.[27] This sequence afforded alkyne **34** as an 8:1 diasteromeric mixture at C9 (in favor of the isomer shown) and in 86% overall yield (Scheme 4).

Attachment of the alkyne part at C9 of compound **34** was strategically planned to allow flexibility in introducing a heteroatom at the terminal position (corresponding to the C12 center), thereby influencing the outcome of the Diels−Alder reaction. Nonetheless, at this point, it was deemed important to examine the diastereofacial selectivity of the Diels−Alder cycloaddition and evaluate the overall feasibility of our plan using a nonfunctionalized diene such as **35** (Scheme 5). With this concept in mind, the diastereomeric mixture of propargyl alcohols **34** was partially reduced (H_2, Lindlar's catalyst) and dehydrated (BF_3·Et_2O) to produce diene **35** in 90% yield (over two steps).[28] The Diels−Alder cycloaddition between **35** and methacrolein (**36**) proceeded smoothly under neat conditions at 25 °C and afforded in quantitative yield a mixture of two diastereomeric aldehydes **37** and **38** in a 3.4:1 ratio and 100% overall yield. Since the obtained mixture of aldehydes could not be separated via silica gel chromatography, it was subjected to reduction with sodium borohydride to afford alcohols **39** and **40** in 94% yield. The resulting alcohols **39** and **40** were separable via flash chromatography and, upon treatment with Dess−Martin periodinane, afforded aldehydes **37** and **38** in 95 and 88% yields, respectively, thereby allowing adequate spectroscopic characterization of the Diels−Alder adducts.

Scheme 5[a]



[a] Reagents and conditions: (a) Lindlar's catalyst (20% per weight), H_2, 10:1 dioxane/pyridine, 25 °C, 10 min, 95%; (b) 4.4 equiv BF_3·Et_2O, 4:1 benzene/THF, 80 °C, 5 h, 95%; (c) 13 equiv **36**, neat, 8 h, 25 °C, 100%; (d) 1.4 equiv $NaBH_4$, 10:1 THF/MeOH, 30 min, 25 °C, 94%; (e) 1.6 equiv Dess−Martin [O], CH_2Cl_2, 0 °C, 3 h, 95% for **39**, 88% for **40**; (f) 1.1 equiv *p*Br−C_6H_4−COCl, 1.5 equiv pyridine, 0.1 equiv DMAP, CH_2Cl_2, 25 °C, 2 h, 95% for **41**, 97% for **42**.

Unambiguous proof of structures for compounds **39** and **40** was obtained after derivatization to the corresponding *p*-bromobenzoate esters (**41** and **42**, respectively), which upon recrystallization with dichloromethane/ethanol yielded crystals suitable for X-ray analysis (Supporting Information). The results of the X-ray studies clarified several key issues related to the overall strategy toward acanthoic acid. First, they demonstrated that the C4 carbon center had the desired configuration, thereby confirming the predictions of the alkylation outcome of the C4 enolates **19** and **31** (shown in Schemes 1 and 4, respectively). More importantly, they revealed that the Diels−Alder cycloaddition of **35** with **36** proceeded with

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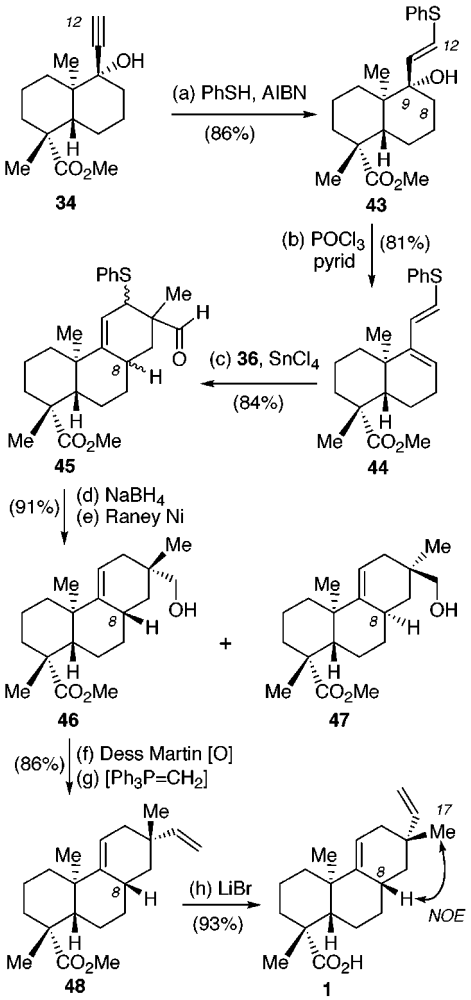
exclusive *endo* orientation[29] and good stereofacial preference (from the α-face of diene **35**, as shown in Supporting Information).[30] In addition, these data indicated that synthesis of acanthoic acid would require an inversion in the orientation of the incoming dienophile **36**. In principle, this could be accomplished by inverting the atomic orbital coefficients at the termini of diene **35**, supporting the notion to attach strong electron-donating groups at its C12 center. The synthesis of acanthoic acid based on this strategy is shown in Scheme 6.

Total Synthesis of Acanthoic Acid. Treatment of alkyne **34** with thiophenol under free-radical conditions afforded vinyl sulfide **43** in 86% yield (Scheme 6).[31] Dehydration of allylic alcohol **43** was found to be more difficult and unsuccessful under the previously employed $BF_3{\cdot}Et_2O$ treatment. Nonetheless, a stonger $POCl_3$-mediated dehydration process gave rise to diene **44** in 81% yield, presumably through an unstable allyl chloride intermediate.[32] With a substantial amount of **44** on hand, we investigated the Diels−Alder reaction using **36** as the dienophile. Several thermal- (from −78 to 80 °C) and Lewis acid- ($BF_3{\cdot}Et_2O$, $TiCl_4$, $AlCl_3$, and $SnCl_4$) catalyzed Diels−Alder conditions were tested. The best results were obtained with $SnCl_4$ in methylene chloride at −20 °C and afforded aldehyde **45** in 84% yield as a 4.2:1 mixture of diastereomers.[33]

To simplify the product characterization and allow adequate separation, the unseparable mixture of aldehydes **45** was reduced with $NaBH_4$ and reductively desulfurized using Raney Ni to produce alcohols **46** and **47** in 91% overall yield (Scheme 6). The structure of these compounds, which were easily separable in silica gel, was assigned by comparison to the products isolated from the reaction between **35** and **36**. Treatment of the major diastereomer **46** with Dess−Martin periodinane,[34] followed by Wittig methylenation, installed the alkene functionality at the C13 center and produced **48** in two steps and in 86% overall yield. The final step of our synthesis was the deprotection of the C19 carboxylic acid. The initially examined saponification methods (LiOH/THF/H_2O, $NaOH/THF/H_2O$ at 25−100 °C) failed, presumably due to the steric hindrance created by the methyl group attached at the C10 center and the axial orientation of the acid function. Gratifyingly, exposure of **48** to LiBr in refluxing DMF gave rise to acanthoic acid **1** in 93% yield, presumably via an S_N2-type displacement of the acyloxyl functionality.[35]

Synthetic acanthoic acid had spectroscopic and analytical data identical to those reported for the natural product. Additional evidence for the desired relative stereochemistry of the C ring of **1** was obtained by NOE difference experiments, which showed that the H17 and H8 protons are at the same face of the tricyclic scaffold (Scheme 6).

Scheme 6[a]



[a] Reagents and conditions: (a) 3.0 equiv PhSH, 0.05 equiv AIBN, xylenes, 120 °C, 18 h, 86%; (b) 1.1 equiv $POCl_3$, HMPA, 25 °C, 1 h; 1.1 equiv pyridine, 150 °C, 18 h, 81%; (c) 3.0 equiv **36**, 0.2 equiv $SnCl_4$ (1 M in CH_2Cl_2), CH_2Cl_2, from −20 to 0 °C, 20 h, 84%; (d) 1.4 equiv $NaBH_4$, EtOH, 25 °C, 30 min; (e) Raney Ni (excess), THF, 65 °C, 10 min, 91% (over two steps); (f) 1.3 equiv Dess−Martin periodinane, CH_2Cl_2, 25 °C, 30 min; (g) 2.7 equiv Ph_3PCH_3Br, 2.2 equiv NaHMDS (1.0 M in THF), THF, 25 °C, 18 h, 86% (over two steps); (h) 3.0 equiv LiBr, DMF, 160 °C, 3 h, 93%.

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(30) The Diels−Alder reaction has been utilized toward the syntheses of polycyclic terpenes and steroids. In these studies, its facial selectivity was found to be critically dependent on the structures of both the diene and the dienophile. For selected references on this topic, see: Das, J.; Kubela, R.; MacAlpine, G. A.; Stojanac, Z.; Valenta, Z. *Can. J. Chem.* **1979**, *57*, 3308−3319. Kakushima, M.; Allain, L.; Dickinson, R.; White, P. S.; Valenta, Z. *Can. J. Chem.* **1979**, *57*, 3354−3356. Kakushima, M.; Das, J.; Reid, G. R.; White, P. S.; Valenta, Z. *Can. J. Chem.* **1979**, *57*, 3356−3358. Das, J.; Dickinson, R. A.; Kakushima, M.; Kingston, G. M.; Reid, G. R.; Sato, Y.; Valenta, Z. *Can. J. Chem.* **1984**, *62*, 1103−1111. Schuster, T.; Bauch, M.; Durner, G.; Goebel, M. W. *Org. Lett.* **2000**, *2*, 179−181. Minuti, L.; Selvaggi, R.; Taticchi, A. *Synth. Comm.* **1992**, *22*, 1535−1542. Lee, J.; Li, J.; Oya, S.; Snyder, J. *J. Org. Chem.* **1992**, *57*, 5301. Antonaroli, S.; Berettoni, M.; Cifarelli, G.; Lupi, A.; Bettolo, R. M.; Romeo, S. *Gazz. Chim. Ital.* **1992**, *122*, 55−57. Kolaczkowski, L.; Reusch, W. *J. Org. Chem.* **1985**, *50*, 4766−4768.

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In conclusion, we present herein a concise, enantioselective synthesis of acanthoic acid (**1**). The synthetic strategy departs from the Wieland−Miescher enone **10**, in which the desired stereochemistry at the C10 center was introduced via an enantioselective Robinson annulation. The relative stereochemistry at the C4 and C5 centers was subsequently introduced via a sequence of substrate-controlled reductive alkylations. Finally, the sterochemistry at C8 and C13 centers was introduced via a Diels−Alder reaction between the sulfur-containing diene **44** and methacrolein (**36**). The described synthesis of **1** requires 14 steps (starting with enone **10**) and proceeds in 9% overall yield. Moreover, the overall efficiency and versatility of our strategy sets the foundation for the preparation of designed analogues with improved pharmacological profiles.

Experimental Section

General Techniques. All reagents were commercially obtained (Aldrich, Acros) at the highest commercial quality and used without further purification except where noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 45 °C at about 20 mmHg. All nonaqueous reactions were carried out using flame-dried glassware under an argon atmosphere in dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone, dichloromethane (CH_2Cl_2) and toluene were distilled from calcium hydride, and benzene was distilled from potassium. *N*,*N*-Diisopropylethylamine, diisopropylamine, pyridine, triethylamine, and boron trifluoride etherate were distilled from calcium hydride prior to use. Dimethyl sulfoxide and dimethylformamide were distilled from calcium hydride under reduced pressure (20 mmHg) and stored over 4 Å molecular sieves. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as a visualizing agent and 7% ethanolic phosphomolybdic acid or *p*-anisaldehyde solution and heat as developing agents. E. Merck silica gel (60, particle size = 0.040−0.063 mm) was used for flash chromatography. Preparative thin-layer chromatography separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Varian Mercury 300, 400, and/or Unity 500 MHz instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. IR spectra were recorded on a Nicolet 320 Avatar FT-IR spectrometer, and values are reported in cm^{-1} units. Optical rotations were recorded on a Jasco P-1010 polarimeter. High-resolution mass spectra (HRMS) were recorded on a VG 7070 HS mass spectrometer under chemical ionization (CI) conditions or on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions.

Ethyl-3-hydroxy-4-pentenoate.[17] To a stirred solution of THF (200 mL) and diisopropylamine (7.7 mL, 55 mmol) at −78 °C was added *n*-BuLi (22 mL, 55 mmol, 2.5 M in hexane). The reaction mixture was stirred at −78 °C for 15 min, treated with ethyl acetate (50 mmol) added slowly, and then stirred for another 45 min. Distilled acrolein (3.35 mL, 50 mmol) in 10 mL THF was added dropwise, and the whole reaction mixture was allowed to stir at −78 °C for another 10 min. The reaction was then quenched by saturated ammonium chloride solution (10 mL), and the mixture was extracted with ether (3 × 150 mL). Evaporation of solvent and purification over silica gel chromatography afforded the desired allylic alcohol (5.47 g, 38 mmol, 76% yield).

Ethyl-3-oxo-4-pentenoate (**14**).[17] To a well stirred solution of ethyl-3-hydroxy-4-pentenoate (5 g, 34.74 mmol) in acetone (60 mL) at 0 °C was added Jones reagent (40 mL, 40 mmol) in four portions over a period of 2 h. After complete addition of the reagent, the reaction mixture was allowed to stir for another 4 h at 25 °C. The reaction mixture was extracted with ethyl ether (3 × 80 mL) and washed with water (80 mL) and brine (80 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified via a Kugelrohr distillation to afford compound **14** (2.76 g, 19.45 mmol, 56%). **14**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.80 (s, enol OH), 6.48−5.95 (m, 2H), 5.58 (m, 1H), 5.06 (s, 1H), 4.22−4.17 (m, 2H), 3.63 (s, 2H), 1.31−1.25 (m, 3H).

Ketoester 15. A suspension of β-ketoester **14** (1.65 g, 11.6 mmol), diketone **7** (1.05 g, 8.3 mmol), and KF (1.06 g, 18.3 mmol) in methanol (10 mL) was stirred at 25 °C for 16 h. The solvent was removed under reduced pressure, and the crude mixture was chromatographed (silica, 20−50% ether in hexanes) to afford ketoester **15** (1.54 g, 6.1 mmol, 74%). **15**: light yellow solid; mp = 67−69 °C; R_f = 0.15 (silica, 50% ether in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.25 (m, 2H), 2.72−2.50 (m, 3H), 2.49−2.40 (m, 3H), 2.15−2.05 (m, 3H), 1.77−1.64 (m, 1H), 1.43 (s, 3H), 1.29 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.6, 293.6, 166.1, 161.7, 132.1, 61.4, 50.2, 37.2, 33.2, 29.0, 28.6, 23.3, 21.8, 14.2; HRMS calcd for $C_{14}H_{18}O_4$ ($M + Na^+$) 273.1103, found 273.1121.

Ketoester 16. A solution of enone **15** (5.95 g, 23.8 mmol), *p*-TsOH (0.41 g, 2.38 mmol), and ethylene glycol (1.7 g, 27.4 mmol) in benzene (100 mL) was heated in a Dean−Stark apparatus under reflux for 4 h with azeotropic removal of water. After the end of the reaction, the solution was treated with Et_3N (5 mL) and the solvent was evaporated under reduced pressure. The crude mixture was purified through flash chromatography (silica, 5−40% ether in hexanes) to afford the protected ketone **16** (5.18 g, 17.6 mmol, 74%). **16**: colorless oil; R_f = 0.45 (silica, 50% ether in hexanes); IR (film) ν_{max} 2952, 1728, 1674; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.23 (q, 2H, J = 6.9 Hz), 3.98−3.89 (m, 4H), 2.46−2.41 (m, 2H), 2.33−2.25 (m, 3H), 1.9−1.61 (m, 5H), 1.34 (s, 3H), 1.25 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.9, 166.2, 164.0, 132.1, 112.1, 65.4, 65.1, 61.2, 44.9, 33.6, 29.8, 28.4, 26.3, 21.4, 20.9, 14.3; HRMS calcd for $C_{16}H_{22}O_5$ ($M + H^+$) 295.1545, found 295.1552.

Alcohol 17. To a well stirred solution of ketoester **16** (1.87 g, 6.36 mmol) in dry ethanol (30 mL) at 0 °C were added $CeCl_3$ (1.71 g, 6.99 mmol) and $NaBH_4$ (265 mg, 6.99 mmol). The reaction mixture was allowed to warm to 25 °C and stirred for 2 h. The reaction was then quenched with aqueous saturated ammonium chloride (10 mL), and the mixture was extracted with ethyl ether (3 × 30 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was subjected to chromatography (10−40% ether in hexanes) to afford alcohol **17** (1.54 g, 5.21 mmol, 82%). **17**: colorless oil; R_f = 0.35 (silica, 50% ether in hexanes); IR (film) ν_{max} 3436, 2943, 1708; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.35 (bs, 1H), 4.23−4.21 (q, J = 8 Hz, 2H), 4.15−3.90 (m, 4H), 3.04−3.01 (m, 1H), 2.19−2.09 (m, 3H), 1.89−1.83 (m, 2H), 1.73−1.55 (m, 5H), 1.31 (t, J = 8 Hz, 3H), 1.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 149.6, 129.9, 113.1, 67.3, 65.2, 65.0, 60.6, 45.0, 30.2, 27.8, 26.6, 25.8, 23.7, 22.5, 14.4; HRMS calcd for $C_{16}H_{24}O_5$ ($M + Na^+$) 319.1522, found 319.1541.

Ester 18. NaH (104 mg, 2.6 mmol, 60% suspension in mineral oil) was washed twice with hexanes and added slowly to a well-stirred and precooled (0 °C) solution of alcohol **17** (601 mg, 2 mmol) in THF (10 mL). Immediately thereafter, CS_2 (231 mg, 3.0 mmol) was added and the red-orange solution was allowed to warm at 25 °C at which temperature it was stirred over a period of 3 h. The reaction mixture was then re-cooled at 0 °C and treated with methyl iodide (720 mg, 5.1 mmol). After being stirred at 25 °C for an additional 30 min, the colorless solution was quenched with ice−water (50 mL) and extracted with ethyl ether (3 × 30 mL). The combined ethereal layers were washed with aqueous saturated sodium bicarbonate (50 mL) and brine (50 mL). The organic layers

were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was subjected to chromatography (0−20% ether in hexanes) to afford the corresponding xanthate (697 mg, 1.8 mmol, 89%) as a light yellow liquid. This liquid was dissolved in dry benzene (50 mL) and treated with Bu_3SnH (787 mg, 2.7 mmol). The reaction mixture was preheated at 80 °C and treated with AIBN (15 mg, 0.09 mmol) added in four portions over a period of 2 h. After the end of the reaction, the solvent was removed under reduced pressure and the crude residue was purified through flash chromatography (silica, 5−30% ether in hexanes) to produce ester **18** (344 mg, 1.22 mmol, 68%). **18**: colorless oil; $R_f = 0.7$ (silica, 50% ether in hexanes); IR (film) ν_{max} 2933, 1717; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15 (q, $J = 8$ Hz, 2H), 3.98−3.88 (m, 4H), 2.89−2.70 (m, 1H), 2.40−2.20 (m, 4H), 2.03−1.49 (m, 7H), 1.38−1.25 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 147.2, 126.2, 113.4, 65.3, 60.1, 51.3, 44.9, 37.8, 30.5, 28.9, 27.7, 26.3, 23.7, 22.7, 14.4; HRMS calcd for $C_{16}H_{24}O_4$ ($M + H^+$) 281.1747, found 281.1754.

Ester 20. To a solution of lithium (31 mg, 4.4 mmol) in liquid ammonia (50 mL) at −78 °C was added dropwise a solution of ester **18** (495 mg, 1.76 mmol) and *tert*-butyl alcohol (132 mg, 1.76 mmol) in THF (5 mL). The resulting blue mixture was allowed to warm to −50 °C and stirred for 40 min. The reaction was then cooled to −78 °C and treated with isoprene (3 mL). The mixture was then warmed to −45 °C, and the excess ammonia was evaporated under reduced pressure. After an additional 5 min under high vacuum, the argon atmosphere was restored and the white residue was diluted with 20 mL of dry THF. The reaction mixture was cooled to 0 °C and treated with methyl iodide (502 mg, 3.51 mmol) added dropwise. After being stirred for 2 h, the reaction was quenched with water (30 mL), warmed to 25 °C, and extracted with ether (2 × 50 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated. The crude product was purified through chromatography (silica, 5−30% ether in hexanes) to afford ester **20** (371 mg, 1.26 mmol, 71%). **20**: colorless oil; $R_f = 0.75$ (silica, 50% ether in hexanes); IR (film) ν_{max} 1726; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 (q, $J = 8$ Hz, 2H), 3.94−3.84 (m, 4H), 2.18−2.03 (m, 2H), 1.81−1.60 (m, 3H), 1.57−1.40 (m, 5H), 1.45−1.32 (m, 3H), 1.30−1.20 (m, 3H), 1.23 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 112.9, 65.2, 64.9, 60.0, 50.9, 43.8, 38.1, 30.8, 30.3, 29.8, 28.9, 23.4, 22.7, 19.0, 15.0, 14.3; HRMS calcd for $C_{17}H_{28}O_4$ ($M + Na^+$) 319.1885, found 319.1899.

Oxazolidinone 22. A solution of oxazolidinone **21** (5.01 g, 22.8 mmol) in dichloromethane (40 mL) was cooled to 0 °C and treated with dibutylboron triflate (25.1 mL, 25.1 mmol, 1.0 M in CH_2Cl_2) followed by Et_3N (3.86 mL, 27.5 mmol). The reaction mixture was stirred at 0 °C for 1 h, cooled at −78 °C, and treated with a solution of acrolein (**13**) (2.2 mL, 34.25 mmol) in dichloromethane (5 mL). The mixture was stirred at −78 °C for 30 min and then warmed to 0 °C at which temperature it was stirred for another 1 h. The reaction was quenched by the addition of 25 mL of aqueous phosphate buffer (pH = 7.2) and 75 mL of methanol. To this cloudy mixture was added another 75 mL of a 2:1 solution of methanol:30% aqueous H_2O_2, and the mixture was allowed stir for another 1 h. The organic phase was washed with aqueous saturated sodium bicarbonate (20 mL) and brine (20 mL) and extracted with dichloromethane (3 × 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by chromatography (silica, 20−50% ether in hexanes) to afford the alcohol **22** (3.58 g, 13.0 mmol, 57%). **22**: colorless oil; $R_f =$ 0.5 (silica, 50% ether in hexanes); IR (neat) 3464, 2932, 1778, 1693; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51−7.20 (m, 5H), 5.96−5.91 (m, 1H), 5.36 (d, $J = 17.2$ Hz, 1H), 5.19 (d, $J = 10$ Hz, 1H), 4.71−4.65 (m, 2H), 4.25−4.18 (m, 1H), 3.31−3.14 (m, 3H), 2.80 (t, $J = 12$ Hz, 1H), 1.24 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 153.2, 138.5, 134.9, 129.3, 128.9, 128.4, 127.3, 115.4, 68.7, 66.4, 55.1, 42.34, 38.0; HRMS calcd for $C_{15}H_{17}NO_4$ ($M +$ Na^+) 298.1050, found 298.1058.

Enones 23 and 24. Allylic alcohol **22** (1.1 g, 4.0 mmol) was dissolved in dichloromethane (8 mL) and treated with Dess−Martin periodinane (2.03 g, 4.8 mmol), which was added portionwise at 25 °C. After the disappearance of the starting material (TLC, 1.5 h), the reaction was quenched with aqueous saturated sodium bicarbonate (10 mL) and aqueous saturated sodium thiosulfate (10 mL). The organic phase was extracted with ether (3 × 10 mL), and the combined ethereal layers were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting ketone (884 mg, 3.24 mmol, 81%) was used in the following step without any further purification. The resulting ketone (450 mg, 1.65 mmol) was added dropwise to a well-stirred solution of 2-methyl-1,3-cyclohexanone (**7**) (270 mg, 2.10 mmol) and potassium fluoride (210 mg, 3.57 mmol) in methanol (8 mL). After the mixture was stirred at 25 °C for 12 h, the methanol was removed under reduced pressure and the residue was diluted with brine (10 mL) and extracted with dichloromethane (3 × 10 mL). The organic phases were combined, dried over $MgSO_4$, and concentrated. The residue was purified through chromatography (silica, 5−30% AcOEt in hexanes) to afford compounds **23** and **24** in a 1:1 ratio and 53% overall yield. **23**: top diastereomer, white solid (crystallized from ethyl ether); $R_f = 0.62$ (silica, 50% ether in hexanes); mp = 159−161 °C; $[\alpha]^{25}_D$ +127.9 ($c = 1$, CH_2Cl_2); IR (neat) 2955, 1786, 1689, 1669, 1619; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.24 (m, 5H), 4.81−4.76 (m, 1H), 4.29−4.15 (m, 2H), 3.57−3.46 (m, 1H), 2.84−2.47 (m, 7H), 2.18−2.08 (m, 3H), 1.85−1.82 (m, 1H), 1.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major rotamer) 209.9, 194.5, 165.8, 161.1, 155.1, 134.8, 129.3, 128.9, 127.1, 66.7, 55.1, 50.4, 38.4, 37.4, 33.1, 29.1, 28.1, 23.5, 21.9; HRMS calcd for $C_{22}H_{23}NO_5$ ($M + H^+$) 382.1649, found 382.1637. **24**: bottom diastereomer, colorless oil; $R_f = 0.60$ (silica, 50% ether in hexanes); $[\alpha]^{25}_D$ +1.9 ($c = 1$, CH_2Cl_2); IR (neat) 2959, 1778, 1693, 1619; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.17 (m, 5H), 4.80−4.73 (m, 1H), 4.32−4.07 (m, 2H), 3.55−3.4 (m, 1H), 2.89−2.34 (m, 7H), 2.18−2.08 (m, 2H), 1.85−1.66 (m, 2H), 1.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.1, 194.7, 166.0, 161.5, 152.7, 135.2, 129.4, 128.8, 127.1, 69.7, 66.4, 53.9, 50.4, 41.5, 37.4, 29.7, 29.0, 28.2, 22.0, 21.2; HRMS calcd for $C_{22}H_{23}NO_5$ ($M + H^+$) 382.1649, found 382.1629.

Wieland−Miescher Enone (10). This compound was synthesized on the basis of the procedure reported in ref 24 using D-proline as the chiral reagent. After chromatography purification (silica 10−40% ether in hexanes), the resulting liquid was crystallized twice using ether/hexanes at −30 °C. **10**: $R_f = 0.25$ (silica, 50% ether in hexanes); $[\alpha]^{25}_D$ −96.0 ($c =$ 1, C_6H_6); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (s, 1H), 2.72−2.66 (m, 2H), 2.51−2.42 (m, 4H), 2.14−2.10 (m, 3H), 1.71−1.68 (m, 1H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.7, 198.0, 165.6, 125.7, 50.6, 37.7, 33.7, 31.8, 29.7, 23.4, 23.0.

Ketal 25. A solution of ketone **10** (43 g, 0.24 mol) in benzene (700 mL) was treated with *p*-toluenesulfonic acid (4.6 g, 0.024 mol) and ethylene glycol (15 mL, 0.27 mol). The reaction was refluxed with a Dean−Stark apparatus and condenser at 120 °C. Once water stopped collecting in the Dean−Stark apparatus, the reaction was complete (approximately 4 h). Leaving the reaction for longer periods of time tended to darken the reaction mixture and lower the overall yield. The reaction mixture was cooled to 25 °C, and the reaction was quenched with triethylamine (5 mL, 0.036 mol); the mixture was then poured into a separatory funnel containing water (300 mL) and saturated sodium bicarbonate (200 mL). The resulting mixture was then extracted with ether (3 × 800 mL). The organic layers were combined, dried over $MgSO_4$, concentrated, and subjected to chromatography (10−40% ether in hexanes) to afford ketal **25** (48 g, 0.22 mol, 90%). **25**: yellow oil; $R_f = 0.30$ (silica, 50% ether in hexanes); $[\alpha]^{25}_D$ −77 ($c = 1$, C_6H_6); IR (film) ν_{max} 2943, 2790, 1667, 1450, 1325, 1250; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (s, 1H), 3.98−3.93 (m, 4H), 2.43−2.35 (m, 3H), 2.34−2.20 (m, 3H), 1.94−1.82 (m, 1H), 1.78−1.60 (m, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 167.5, 125.5, 112.2, 65.4, 65.1, 45.1, 34.0, 31.5, 30.1, 26.9, 21.8, 20.6.

Ketoester 28. A solution of lithium (0.72 g, 0.10 mol) in liquid ammonia (400 mL) at −78 °C was treated dropwise with a solution of the ketal **25** (10 g, 0.045 mol) and *tert*-butyl alcohol (3.7 mL, 0.045 mol) in ether (40 mL). The resulting

blue mixture was allowed to warm to −45 °C over a period of 30 min and then cooled to −78 °C again. Sufficient isoprene (approximately 8 mL) was added dropwise to discharge the residual blue color of the reaction mixture. The reaction was then warmed at −45 °C at which temperature the excess ammonia was quickly evaporated under vacuum. The remaining ether was removed under reduced pressure to leave a white foam. After an additional 5 min under high vacuum, the nitrogen atmosphere was restored, and the lithium enolate was suspended in dry ether (150 mL) and cooled to −78 °C. Methyl cyanoformate (4.0 mL, 0.050 mol) was then added and the reaction stirred for 40 min at −78 °C. The reaction was warmed to 0 °C and stirred for an additional 1 h. Water (300 mL) and ether (200 mL) were added, and the mixture was poured into a separatory funnel containing saturated sodium chloride (100 mL). After the organic layer was separated, the aqueous phase was extracted with ether (2 × 400 mL). The combined organic layers were dried over $MgSO_4$, concentrated, and subjected to chromatography (10−40% ether in hexanes) to afford ketoester **28** (11 g, 0.039 mol, 87%). **28**: white crystals; $R_f = 0.40$ (silica, 50% ether in hexanes); $[\alpha]^{25}_D$ −4.1 (c = 1, C_6H_6); IR (film) ν_{max} 2943, 1746, 1700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.00−3.96 (m, 2H), 3.95−3.86 (m, 2H), 3.74 (s, 3H), 3.23 (d, 1H, J = 13.2 Hz), 2.50−2.42 (m, 3H), 2.05−1.92 (m, 1H), 1.79−1.50 (m, 5H), 1.32−1.28 (m, 2H), 1.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.4, 170.0, 111.9, 65.2, 65.1, 59.9, 52.0, 43.7, 41.6, 37.5, 30.3, 29.8, 26.2, 22.5, 14.0; HRMS calcd for $C_{15}H_{22}O_5$ (M + Na^+) 305.1365, found 305.1354.

Ketoester 29. This compound was obtained in 81% yield when enolate **26**, formed as indicated above, was allowed to equilibrate to enolate **27** at −33 °C for 1 h before and after the reaction with isoprene. **29**: white crystals; R_f = 0.40 (silica, 20% ether in hexanes); $[\alpha]^{25}_D$ +41.1 (c = 1.6, C_6H_6); IR (film) ν_{max} 2932.2, 1654.6, 1615.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.1 (s, 1H), 3.95 (s, 4H), 3.74 (s, 3H), 2.35−2.18 (m, 2H), 2.15−1.2 (m, 9H), 0.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 170.1, 112.1, 96.2, 65.0, 64.7, 51.2, 40.7, 36.0, 32.9, 31.5, 30.1, 27.9, 27.2, 22.5, 13.6; HRMS calcd for $C_{15}H_{22}O_5$ (M + Na^+) 305.1365, found 305.1387.

Ester 30. A solution of ketoester **28** (7.0 g, 0.025 mol) in HMPA (50 mL) (or DME 50 mL) was treated with sodium hydride (0.71 g, 0.030 mol). After being stirred for 3 h at 25 °C, the resulting yellow-brown reaction mixture was quenched with chloromethyl methyl ether (2.3 mL, 0.030 mol) and the reaction allowed to stir an additional 2 h at 25 °C. The resulting white-yellow mixture was then poured into a separatory funnel containing ice−water (100 mL), saturated sodium bicarbonate (50 mL), and ether (200 mL). After the layers were separated, the aqueous layer was extracted with ether (3 × 200 mL). The combined ethereal extracts were dried over $MgSO_4$, concentrated, and subjected to chromatography (silica, 10−40% ether in hexanes) to yield ester **30** (7.7 g, 0.024 mol, 95%). **30**: yellow oil; R_f = 0.45 (silica, 50% ether in hexanes); $[\alpha]^{25}_D$ +26.3 (c = 1, C_6H_6); IR (film) ν_{max} 2951, 1728, 1690, 1430, 1170; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.89 (dd, 2H, J = 22.8, 6.4 Hz), 3.93−3.91 (m, 2H), 3.90−3.84 (m, 2H), 3.69 (s, 3H), 3.40 (s, 3H), 2.72−2.68 (m, 1H), 2.24 (bs, 2H), 1.80−1.42 (m, 4H), 1.37−1.15 (m, 2H), 0.96 (s, 3H), 0.95−0.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 150.5, 115.8, 112.1, 93.0, 65.2, 65.1, 56.3, 51.3, 40.7, 40.3, 30.3, 26.4, 23.6, 22.9, 22.3, 13.9; HRMS calcd for $C_{17}H_{26}O_6$ (M + Na^+) 349.1622, found 349.1621.

Acetal 32. A solution of lithium (1.1 g, 0.17 mol) in liquid ammonia (400 mL) at −78 °C was treated dropwise with a solution of ester **30** (7.7 g, 0.024 mol) in 1,2-DME (30 mL). The blue reaction mixture was allowed to warm and stir at reflux (−33 °C) for 20 min. The reaction mixture was then cooled to −78 °C again and the reaction rapidly quenched with excess iodomethane (15 mL, 0.24 mol). The resulting white slurry was allowed to stir at reflux (−33 °C) for 1 h, after which time the reaction was warmed in a water bath (50 °C) with stirring for 1 h, allowing the ammonia to evaporate. The reaction was quenched with water (100 mL), sodium bicarbonate (100 mL), and ether (200 mL) and the mixture poured into a separatory funnel. After the layers were separated, the aqueous layer was extracted with ether (3 × 200 mL). The combined ethereal extracts were dried over $MgSO_4$, concentrated, and subjected to chromatography (silica, 10−30% ether in hexanes) to yield acetal **32** (4.1 g, 0.014 mol, 61%). **32**: white solid; R_f = 0.80 (silica, 50% ether in hexanes); $[\alpha]^{25}_D$ +16.9 (c =10, C_6H_6); IR (film) ν_{max} 2934, 1728, 1466, 1379, 1283, 1125, 942; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95−3.80 (m, 4H), 3.64 (s, 3H), 2.17−2.15 (m, 1H), 1.84−1.37 (m, 11H), 1.16 (s, 3H), 1.05−1.00 (m, 1H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 112.9, 65.2, 64.9, 51.2, 44.0, 43.7, 38.1, 30.7, 30.3, 28.8, 23.4, 19.1, 14.7; HRMS calcd for $C_{16}H_{26}O_4$ (M + H^+) 283.1904, found 283.1904.

Ketone 33. A solution of ester **32** (4.1 g, 0.014 mol) in THF (50 mL) was treated with 1 M HCl dropwise (approximately 15 mL) at 25 °C with stirring. The reaction was monitored by thin-layer chromatography and neutralized with sodium bicarbonate (30 mL) once the starting material disappeared. The resulting mixture was poured into a separatory funnel containing water (100 mL) and ether (100 mL). After the layers were separated, the aqueous layer was extracted with ether (3 × 100 mL). The combined ethereal extracts were dried over $MgSO_4$, concentrated, and subjected to chromatography (silica, 10−20% ether in hexanes) to yield ketone **33** (3.14 g, 0.013 mol, 95%). **33**: white solid; R_f = 0.70 (silica, 50% ether in hexanes); $[\alpha]^{25}_D$ +3.5 (c = 1.0, C_6H_6); IR (film) ν_{max} 2943, 1728, 1449, 1239, 1143, 1095, 985; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (s, 3H), 2.55−2.45 (m, 1H), 2.92−1.95 (m, 5H), 1.8−1.6 (m, 2H), 1.50−1.30 (m, 4H), 1.14 (s, 3H), 0.98−0.96 (m, 1H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.8, 177.0, 54.4, 51.3, 49.3, 44.2, 37.9, 37.7, 33.1, 28.6, 26.4, 22.8, 18.8, 17.0; HRMS calcd for $C_{14}H_{22}O_3$ (M + Na^+) 261.1461, found 261.1482.

Alkyne 34. A solution of ketone **33** (2.0 g, 8.3 mmol) in ether (50 mL) was treated with lithium acetylide (0.40 g, 13 mmol). The reaction mixture was stirred at 25 °C for 1 h, and then the reaction was quenched with sodium bicarbonate (20 mL) and water (30 mL). The mixture was poured into a separatory funnel, and the layers were separated. The aqueous layer was extracted with ether (3 × 50 mL). The organic layers were combined, dried with $MgSO_4$, concentrated, and subjected to chromatography (silica, 10−30% ether in hexanes) to afford alkyne **34** (2.0 g, 7.6 mmol, 91%). **34**: white solid; R_f = 0.65 (silica, 50% ether in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (s, 3H), 2.56 (s, 1H), 2.18−2.10 (m, 1H), 1.92−1.40 (m, 12H), 1.18 (s, 3H), 1.17−1.01 (m, 1H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 177.6, 86.8, 76.5, 75.0, 51.2, 50.5, 43.9, 42.5, 37.9, 35.3, 33.4, 28.8, 23.5, 22.5, 19.1, 11.5; HRMS calcd for $C_{16}H_{24}O_3$ (M + H^+− H_2O) 247.1693, found 247.1697.

Alkene 35. A solution of alkyne **34** (0.50 g, 1.9 mmol) in 1,4-dioxane (20 mL) and pyridine (2 mL) was treated with Lindlar's catalyst (100 mg). The mixture was hydrogenated under pressure (30 lbs/in^2) for 7 min. The reaction mixture was then diluted with ether (10 mL), filtered through a pad of Celite, and washed with ether (2 × 50 mL). The solvent was evaporated under reduced pressure to afford the corresponding alkene (0.48 g, 1.8 mmol, 95%). This alkene was redissolved in benzene (80 mL) and THF (20 mL) and treated with boron trifluoride etherate (1 mL, 7.9 mmol), and the reaction mixture was refluxed at 80 °C for 5 h. After the mixture was cooled, the reaction was quenched with 1 N NaOH (1 mL, 26 mmol); the mixture was then poured into a separatory funnel containing water (100 mL) and ether (100 mL). After the layers were separated, the aqueous layer was extracted with ether (3 × 100 mL). The organic layers were combined, dried with $MgSO_4$, concentrated, and subjected to chromatography (silica, 5% ether in hexanes) to afford diene **35** (0.42 g, 1.7 mmol, 95%). **35**: colorless oil; R_f = 0.95 (silica, 50% ether in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.26−6.23 (dd, 1H), 5.70 (s, 1H), 5.253 (d, 1H, J = 19.2 Hz), 4.91 (d, 1H, J = 12.8 Hz), 3.64 (s, 3H), 2.22−2.12 (m, 2H), 2.10−1.94 (m, 2H) 1.92−1.67 (m, 3H), 1.60−1.44 (m, 3H), 1.378 (d, 1H, J = 13.6), 1.21 (s, 1H), 1.19−1.00 (m, 2H), 0.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 146.7, 136.1, 121.9, 113.3, 53.0, 51.2, 43.9, 38.0, 37.9, 37.4, 28.5, 27.8, 20.5, 19.5, 18.3; HRMS calcd for $C_{16}H_{24}O_2$ (M + H^+) 249.1854, found 249.1871.

Aldehydes 37 and 38. A solution of methacrolein (**36**, 0.5 mL, 5.2 mmol) and diene **35** (0.1 g, 0.40 mmol) was stirred for

8 h at 25 °C under neat conditions. The excess methacrolein (**36**) was then removed under reduced pressure. The crude product was subjected to chromatography (silica, 10−20% ether in hexanes) to afford aldehydes **37** and **38** (0.13 g, 0.40 mmol, 100%) as a mixture of diastereomers at C8 and C14 (3:1−4:1 ratio). Spectroscopic characterization of **37** and **38** was achieved by reduction with sodium borohydride, followed by reoxidation of alcohols **39** and **40**, to aldehydes **37** and **38**. **37**: colorless oil; $R_f = 0.55$ (silica, 25% ether in hexanes); $[\alpha]^{25}_D$ −58.8 ($c = 1$, C_6H_6); IR (film) ν_{max} 3441, 2936, 1726, 1451, 1233, 1152; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (s, 1H), 5.58 (m, 1H), 3.62 (s, 3H), 2.38−2.25 (m, 1H), 2.21−2.18 (m, 1H), 2.17−1.98 (m, 4H), 1.96−1.62 (m, 6H), 1.61−1.58 (m, 1H), 1.57−1.43 (m, 2H),1.40−1.23 (m, 1H), 1.17 (s, 3H), 1.04 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.6, 177.7, 148.3, 188.6, 51.3, 47.8, 47.0, 44.2, 41.2, 39.3, 38.8, 38.1, 29.5, 28.4, 22.9, 22.5, 21.8, 20.6, 20.5, 19.7; HRMS calcd for $C_{20}H_{30}O_3$ (M + H^+) 319.2273, found 319.2261. **38**: colorless oil; $R_f = 0.55$ (silica, 25% ether in hexanes); $[\alpha]^{25}_D$ +36.8 ($c = 0.7$, C_6H_6); IR (film) ν_{max} 3441, 2936, 1726, 1451, 1233, 1152; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 1H), 5.42 (m, 1H), 3.66 (s, 3H), 2.29−2.10 (m, 4H), 2.09−1.84 (m, 4H), 1.81−1.77 (m, 2H), 1.75−1.63 (m, 2H), 1.62−1.58 (m, 2H), 1.57−1.45 (m, 1H), 1.43 (s, 1H), 1.13 (s, 3H), 1.03 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.3, 177.5, 147.4, 114.6, 55.8, 51.3, 47.3, 44.5, 40.7, 40.4, 38.4, 37.5, 31.5, 28.6, 25.0, 24.2, 21.9, 19.9, 19.6, 18.7; HRMS calcd for $C_{20}H_{30}O_3$ (M + H^+) 319.2273, found 319.2288.

Alcohols 39 and 40. A solution of adehydes **37** and **38** (mixture of diastereomers) (0.13 g, 0.40 mmol) in THF (30 mL) and methanol (2 mL) was treated with sodium borohydride (22 mg, 0.56 mmol). The reaction mixture was stirred for 30 min at 25 °C, and then the reaction was quenched with sodium bicarbonate (20 mL) and water (30 mL). The mixture was poured into a separatory funnel containing ether (30 mL). After the layers were separated, the aqueous layer was extracted with ether (3 × 50 mL). The organic layers were combined, dried with $MgSO_4$, and concentrated, and the residue was subjected to chromatography (silica, 0−5% ether in hexanes) to afford enantiomerically pure alcohols **39** and **40** (0.122 g, 0.38 mmol, 3.3:1 ratio in favor of **39**, 94% overall yield). **39**: 94.1 mg, 0.29 mmol, 72%; colorless oil; $R_f = 0.12$ (silica, 25% ether in hexanes); $[\alpha]^{25}_D$ −64.5 ($c = 0.5$, C_6H_6); IR (film) ν_{max} 3446, 2933, 1725, 1459, 1375, 1228; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.51 (m, 1H), 3.63 (s, 3H), 3.42 (m, 2H, $J = 10.4$ Hz), 2.22−2.14 (m, 1H), 2.13−2.04 (m, 1H), 2.03−1.92 (m, 3H), 1.91−1.72 (m, 4H), 1.64−1.57 (m, 2H), 1.53−1.40 (m, 5H), 1.33−1.18 (m, 1H), 1.17 (s, 3H), 0.96 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 149.0, 118.1, 67.3, 51.2, 47.7, 44.2, 41.0, 39.3, 39.2, 38.1, 35.8, 28.8, 28.4, 22.9, 22.6, 22.3, 21.4, 20.5, 19.9; HRMS calcd for $C_{20}H_{32}O_3$ (M + Cs^+) 453.1404, found 453.1421. **40**: 28.2 mg, 0.085 mmol, 22%; colorless oil; $R_f = 0.10$ (silica, 25% ether in hexanes); $[\alpha]^{25}_D$ +29.6 ($c = 0.7$, C_6H_6); IR (film) ν_{max} 3446, 2934, 1725, 1456, 1375, 1230, 1157, 1030; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (m, 1H), 3.65 (s, 3H), 3.48 (d, 1H, $J = 10.8$ Hz), 3.35 (d, 1H, $J = 10.8$ Hz), 2.18−2.14 (m, 1H), 2.07−1.88 (m, 6H), 1.61−1.40 (m, 5H), 1.38−1.18 (m, 4H), 1.13 (s, 3H), 1.12−0.95 (m, 1H), 0.90 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 149.0, 114.1, 70.1, 56.1, 51.3, 44.6, 41.2, 40.3, 38.5, 37.6, 36.0, 30.4, 28.6, 26.9, 24.5, 22.3, 21.6, 20.0, 18.6; HRMS calcd for $C_{20}H_{32}O_3$ (M + Cs^+) 453.1404, found 453.1428.

Benzoyl Derivatives 41 and 42. A solution of alcohol **39** (or **40**) (30 mg, 0.094 mmol) in dichloromethane (20 mL) was treated with *p*-bromobenzoyl chloride (23 mg, 0.10 mmol) and DMAP (2.3 mg, 0.019 mmol). The reaction mixture was stirred at 25 °C for 2 h, and then the reaction was quenched with sodium bicarbonate (5 mL) and water (20 mL). The reaction mixture was poured into a separatory funnel, and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 30 mL), and the organic layers were combined, dried with $MgSO_4$, concentrated, and subjected to chromatography (silica, 10−30% ether in hexanes) to afford benzoyl ester **41** (or **42**). **41**: 45 mg, 95%; colorless crystals (from ether/hexanes); $R_f = 0.40$ (silica, 25% ether in hexanes); $[\alpha]^{25}_D$ +68.6 ($c = 1.0$, C_6H_6); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, 2H, $J =$ 8.4 Hz), 7.60 (d, 2H, $J = 8.4$ Hz), 5.54 (m, 1H), 4.15 (m, 2H), 3.64 (s, 3H), 2.21−1.78 (m, 7H), 1.77−1.41 (m, 6H), 1.39−1.20 (m, 3H), 1.18 (s, 3H), 1.07 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 166.2, 149.0, 131.7, 131.0, 129.5, 127.9, 118.2, 68.8, 51.1, 47.3, 44.2, 41.2, 40.3, 38.9, 38.0, 34.7, 30.2, 28.2, 23.7, 22.3, 21.9, 20.3, 19.7; HRMS calcd for $C_{27}H_{35}BrO_4$ (M + H^+) 503.1796, found 503.1781. **42**: 47 mg, 97%; colorless crystals (from ether/hexanes); $R_f = 0.40$ (silica, 25% ether in hexanes); $[\alpha]^{25}_D$ +42 ($c = 1.0$, C_6H_6); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, 2H, $J = 8.8$ Hz), 7.61 (d, 2H, $J = 8.4$ Hz), 4.40 (m, 1H), 4.11 (s, 2H), 3.66 (s, 3H), 2.2−1.85 (m, 8H), 1.61−1.40 (m, 6H), 1.30−1.20 (m, 2H), 1.14 (s, 3H), 1.00 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 166.1, 148.7, 131.8, 131.1, 129.5, 128.0, 114.5, 71.6, 55.9, 51.2, 44.4, 41.9, 40.1, 38.2, 37.5, 34.9, 30.2, 28.6, 27.4, 24.2, 22.4, 22.0, 19.8, 18.7; HRMS calcd for $C_{27}H_{35}BrO_4$ (M + H^+) 503.1796, found 503.1790.

Sulfide 43. A solution of alkyne **34** (1.1 g, 4.2 mmol), thiophenol (1.37 g, 12.4 mmol), and AIBN (34.5 mg, 0.21 mmol) in xylenes (25 mL) was stirred at 120 °C under argon for 18 h. The reaction mixture was cooled to 25 °C, diluted with aqueous saturated sodium bicarbonate, and extracted with ethyl ether (3 × 50 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated, and the residue was chromatographed (silica, 2−5% ethyl ether in hexane) to afford sulfide **43** (1.35 g, 3.6 mmol, 86%). **43**: colorless liquid; $R_f =$ 0.5 (silica, 5% ethyl ether in hexanes); $[\alpha]^{25}_D$ +24.2 ($c = 1.0$, benzene); IR (film) ν_{max} 2946, 1724, 1472, 1438; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.5 (m, 2H), 7.3−7.2 (m, 3H), 5.24 (d, 1H, $J =$ 8.4 Hz), 5.11 (d, 1H, $J = 8.4$ Hz), 3.6 (s, 3H), 2.2−2.1 (m, 2H), 1.9−1.1 (m, 9 H), 1.10 (s, 3H), 0.9 (m, 3 H), 0.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 151.7, 133.9, 128.7, 127.9, 118.2, 54.9, 53.5, 51.1, 44.3, 40.4, 38.0, 37.2, 28.7, 27.7, 25.4, 23.4, 19.5, 18.5; HRMS calcd for $C_{22}H_{30}O_3S$ (M + Na^+) 397.1814, found 397.1830.

Diene 44. To a solution of sulfide **43** (1.10 g, 2.94 mmol) in hexamethyl phosphoramide (HMPA, 10 mL) was added dropwise phosphorus oxychloride (0.50 g, 3.3 mmol), and the mixture was stirred at 25 °C until it became clear. Pyridine (0.26 mL, 3.23 mmol) was then added, and the mixture was stirred at 150 °C (under argon) for 18 h. The reaction mixture was cooled to 25 °C, and the reaction was quenched with aqueous saturated sodium bicarbonate (50 mL). The organic layer was extracted with ethyl ether (3 × 60 mL), collected, dried ($MgSO_4$), and concentrated, and the residue was chromatographed (silica, 2−5% ethyl ether in hexane) to afford diene **44** (0.85 g, 2.38 mmol, 81%); **44**: colorless liquid; $R_f =$ 0.60 (silica, 5% ethyl ether in hexanes); $[\alpha]^{25}_D$ −17.3 ($c = 1.08$, benzene); IR (film) ν_{max} 2957.0, 1726.6, 1581.6, 1478.3, 1439.0, 1234.7, 1190.8, 1094.8, 1024.4, 739.1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20−7.60 (m, 5H), 6.43 (d, 1H, $J = 15.0$ Hz), 6.36 (d, 1H, $J = 14.5$ Hz), 5.72 (m, 1H), 3.64 (s, 3H), 1.48−2.32 (m, 10H), 1.21 (s, 3H), 1.05 (m, 1H), 0.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.9, 133.7, 129.1, 128.9, 128.6, 127.5, 126.2, 123.4, 120.9, 52.8, 51.1, 43.7, 37.7, 37.3, 30.2, 28.3, 27.7, 20.1, 19.3, 18.3; HRMS calcd for $C_{22}H_{28}O_2S$ (M + Cs^+) 489.0861, found 489.0882.

Aldehyde 45. To a stirred solution of diene **44** (0.51 g, 1.43 mmol) and methacrolein (0.30 g, 4.3 mmol) in dichloromethane (5 mL) at −20 °C was added dropwise tin(IV) chloride (0.29 mL of 1 M solution in dichloromethane, 0.29 mmol). The mixture was allowed to warm slowly to 0 °C and stirred at that temperature for 18 h. The reaction was quenched with aqueous sodium bicarbonate (15 mL) and the mixture extracted with ethyl ether (3 × 20 mL). The organic layers were collected, dried ($MgSO_4$), and concentrated, and the residue was chromatographed (silica, 10−15% ether in hexanes) to afford aldehyde **45** (0.51 g, 1.19 mmol, 84%). **45**: colorless liquid; $R_f = 0.5$ (silica, 10% ethyl ether in hexanes); $[\alpha]^{25}_D$ +30.0 ($c = 1.13$, benzene); IR (film) ν_{max} 2930, 2871, 1724, 1458, 1226; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.5 (s, 1H), 7.4 (m, 2H), 7.25 (m, 3H), 5.58 (d, 1H, $J = 4.4$ Hz), 3.64 (s, 3H), 2.3−2.0 (m, 4H), 1.9−1.1 (m, 11H), 1.16 (s, 3H), 1.05 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.6, 178.0, 153.7, 133.6, 133.5, 129.0, 128.9, 127.7, 117.1, 51.3, 51.2, 49.1, 47.7, 44.2, 41.6, 38.7,

38.1, 31.2, 28.3, 27.8, 26.9, 21.7, 20.2, 19.2, 18.7; HRMS calcd for $C_{26}H_{34}O_3S$ (M + H^+) 427.2306, found 427.2320.

Alcohols 46 and 47. To a solution of aldehyde **45** (mixture of diastereomers) (0.50 g, 1.17 mmol) in anhydrous ethanol (5 mL) was added portionwise sodium borohydride (62 mg, 1.63 mmol), and the mixture was stirred for 30 min. Aqueous saturated sodium bicarbonate (10 mL) was then added, and the mixture was extracted with ethyl ether (3 × 20 mL). The organic layer was collected, dried ($MgSO_4$), and concentrated. The residue was redissolved in tetrahydrofuran (5 mL) and treated with an excess of Raney Nickel under argon at 65 °C for 10 min. The reaction mixture was filtered, and the filtrate was dried ($MgSO_4$) and concentrated; the residue was chromatographed (silica, 2−5% ethyl ether in hexane) to afford alcohols **46** and **47** (0.34 g, 1.07 mmol, 4.2:1 ratio in favor of **46**, 91% overall). **46**: 0.27 g, 0.86 mmol, 74%; colorless liquid; R_f = 0.4 (silica, 30% ethyl ether in hexanes); $[\alpha]^{25}_D$ −16.70 (*c* = 1.0, C_6H_6); IR (film) ν_{max} 3436.8, 2929.0, 2872.2, 1728.1, 1433.9, 1260.6, 1029.7, 801.6; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.37 (m, 1H), 3.62 (s, 3H), 3.30 (m, 2H), 2.28 (bs, 1H), 2.06−2.20 (m, 2H), 1.20−2.00 (m, 13H), 1.16 (s, 3H), 0.99 (m, 1H), 0.86 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.2, 150.4, 116.4, 73.6, 51.2, 47.9, 44.2, 41.9, 38.8, 38.23, 38.20, 34.3, 33.9, 28.3, 28.2, 27.8, 22.1, 20.3, 20.1, 18.9; HRMS calcd for $C_{20}H_{32}O_3$ (M + Cs^+) 453.1404, found 453.1419. **47**: 63.6 mg, 0.2 mmol, 17%; colorless liquid; R_f = 0.35 (silica, 30% ethyl ether in hexanes); $[\alpha]^{25}_D$ −40.7 (*c* = 1.0, C_6H_6); IR (film) ν_{max} 3436.8, 2929.0, 2872.2, 1728.1, 1433.9, 1260.6, 1029.7, 801.6; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.39 (m, 1H), 3.65 (s, 3H), 3.30 (m, 2H), 2.26−2.20 (m, 3H), 1.20−2.00 (m, 14H), 1.17 (s, 3H), 0.88 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.2, 150.5, 116.4, 73.7, 51.2, 47.9, 44.2, 41.9, 38.9, 38.29, 38.26, 34.3, 33.9, 29.6, 28.4, 27.8, 22.1, 20.3, 20.1, 19.0; HRMS calcd for $C_{20}H_{32}O_3$ (M + Cs^+) 453.1404, found 453.1400.

Alkene 48. To a solution of alcohol **46** (20.0 mg, 0.062 mmol) in dichloromethane (2 mL) was added Dess−Martin periodinane (35 mg, 0.08 mmol) in portions, and the mixture was stirred at 25 °C for 30 min. The reaction was quenched with aqueous saturated sodium bicarbonate (5 mL) and the mixture extracted with ethyl ether (3 × 10 mL). The organic layer was collected, dried ($MgSO_4$), and concentrated. The residue was redissolved in tetrahydrofuran (0.5 mL) and added under argon to a yellow suspension of (methyl) triphenyl-phosphonium bromide (60 mg, 0.17 mmol) and sodium bis(trimethylsilyl) amide (0.14 mL of 1.0 M in THF) in THF (1.5 mL). After being stirred at 25 °C for 18 h, the mixture was diluted with aqueous saturated sodium bicarbonate (5 mL) and extracted with ethyl ether (3 × 10 mL). The organic layer was collected, dried ($MgSO_4$), and concentrated, and the residue was chromatographed (silica, 2−5% ethyl ether in hexane) to afford alkene **48** (16.8 mg, 0.05 mmol, the overall yield for the two-step reaction is 86%); **48**: colorless liquid; R_f = 0.74 (silica, 5% ethyl ether in hexanes); $[\alpha]^{25}_D$ −29.40 (*c* = 0.50, benzene); IR (film) ν_{max} 2929.5, 2873.4, 1726.8, 1637.7, 1460.7, 1376.8, 1225.1, 1150.4, 997.8, 908.7; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (dd, 1H, *J* = 10.5, 17.5 Hz), 5.39 (m, 1H), 4.93 (d, 1H, *J* = 17.5 Hz), 4.86 (d, 1H, *J* = 10.5 Hz), 3.64 (s, 3H), 2.3−1.4 (m, 14 H), 1.18 (s, 3H), 0.96−1.08 (m, 2H), 0.95 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.3, 150.4, 125.6, 116.6, 109.2, 51.2, 47.9, 44.3, 41.9, 41.8, 38.3, 37.4, 34.8, 30.2, 29.6, 28.6, 28.4, 27.8, 22.1, 20.4, 19.0; HRMS calcd for $C_{21}H_{32}O_2$ (M + Cs^+) 449.1455, found 449.1471.

Acanthoic Acid (1). To a solution of alkene **48** (16.8 mg, 0.05 mmol) in *N*,*N*-dimethylformamide (2 mL) was added lithium bromide (13.0 mg, 0.15 mmol), and the mixture was refluxed at 160 °C for 3 h. The reaction mixture was then cooled to 25 °C, diluted with H_2O (5 mL), and extracted with ethyl acetate (3 × 10 mL). The organic layer was collected, dried ($MgSO_4$), and concentrated, and the residue was chromatographed (silica, 15−20% ethyl ether in hexane) to afford acanthoic acid (**1**) (14.9 mg, 0.05 mmol, 93%). **1**: white solid; R_f = 0.20 (silica, 30% ethyl ether in hexanes); $[\alpha]^{25}_D$ −26.0 (*c* = 0.33, benzene); IR (film) ν_{max} 3080.6, 2928.9, 2857.6, 1693.6, 1638.2, 1464.7, 1413.8, 1376.4, 1263.1, 1179.3, 1095.9, 1027.5, 999.2, 909.2, 801.7; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (dd, 1H, *J* = 10.5, 17.5 Hz), 5.40 (m, 1H), 4.92 (d, 1H, *J* = 17.5 Hz), 4.86 (d, 1H, *J* = 10.5 Hz), 2.30 (bs, 1H), 2.16−1.2 (m, 14H), 1.24 (s, 3H), 1.00−1.10 (m, 2H), 0.99 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.0, 150.3, 149.9, 116.7, 109.2, 47.9, 41.8, 41.7, 38.3, 38.2, 37.4, 34.8, 31.8, 28.6, 28.5, 27.7, 22.4, 22.1, 20.3, 18.9; HRMS calcd for $C_{20}H_{30}O_2$ (M + Cs^+) 435.1298, found 435.1302.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **10**, **15**−**18**, **20**, **22**−**25**, **28**−**30**, **32**−**48**, and **1**; X-ray data for compounds **23**, **28**, **29**, **41**, and **42**; Chem3D representations of ORTEP drawings of compounds **23**, **41**, and **42**; and Chem3D representations of reaction between compounds **35** and **36**. This material is available free of charge via the Internet at http://pubs.acs.org.

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