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 the extracts of this shrub 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...
same conditions, the production of IL-6 or interferon-gamma (IFN-γ) was not altered. 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. 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.

From a structural point of view, acanthoic acid (1) belongs to a large family of tricyclic diterpenes of the pimarane structure (2). 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. 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 entry to acanthoic acid. Herein, we present a full account of our studies toward this goal, culminating in the entry to acanthoic acid.12 These studies confirm the structure and establish accountable for its pharmacological profile. The combination of unusual structural connectivity across the rigid tricyclic core that may be held accountable. 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 stereochirality 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 diione (7) with ester 8. An alternative strategy for the preparation of 5 would involve stereoselective 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).

Results and Discussion

Retrosynthetic Analysis and Bond Disconnection. Close analysis of the structure of acanthoic acid indicated the possibility of constructing the C ring using a Diels–Alder reaction (Figure 1). 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 stereochirality 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.

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Enantioselective Synthesis (−)-Acanthoic Acid


Scheme 1

Reagents and conditions: (a) 1.1 equiv LDA, 1.5 equiv Bu₃SnH, 0.05 equiv AIBN, C₆H₆, reflux, 78 to 0 °C, 40 min; isoprene (excess), 2.0 equiv MeI, 0 °C, 3 h, 71%.

Scheme 2

Reagents and conditions: (a) Bu₃BOTf, 1.5 equiv, CH₂Cl₂, from −78 to 0 °C, 2 h; phosphate buffer, MeOH, 10 equiv H₂O₂, from 0 to 25 °C, 1 h, 57%.

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. Without separation of the diastereomers, this mixture of alcohols 16 was subsequently transformed to ester 17 using the Barton–McCombie radical deoxygenation protocol (60% yield over two steps). 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. Subsequently, this prediction was confirmed on the basis of the alklylation 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 CH₂Cl₂), (S)-camphorsulfonic acid (0.1 and 1.0 equiv in CH₂Cl₂), l-proline (0.1 and 1.0 equiv in MeOH and DMSO), and l-phenylalanine (0.1 and 1.0 equiv in MeOH).


(17) The only chiral derivative of the Nazarov reagent is the (−)-boryl 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.


(20) Barton, D. H. R.; McCombie, S. W. J. Org. Chem. 1984, 59, 4717–4719. However, to the best of our knowledge, there are no reports on enantioselective annulations based on this type of reagent.

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 bicyclic 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 (ZnCl₂, TiCl₄) were attempted but did not yield any annulated products. Among other conditions tried, including THF/Et₃N, MeOH/K₂CO₃, 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 crysalizations (from Et₂O/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 tBuOH, followed by quenching of the resulting enolate with methyl cyanate, 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 substan
dtial 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.

(a) NaH, MOMCl, MeOH, THF, 25 °C, 3 h, 95%; (c) NH₃, 80 °C, 4 h, 90%; (d) Li, 1.0 equiv BuOH, NH₃, 78 °C, from −78 to −45 °C, 30 min, then isopropanol (excess), from −78 to −45 °C; (e) 1.1 equiv NCCO₂Me, Et₂O, from −78 to 0 °C, 2 h, 87%.

Reagents and conditions: (a) 0.1 equiv PTSA, 1.05 equiv (CH₂OH)₂, benzene, 80 °C, 4 h, 90%; (b) 2.2 equiv Li, 1.0 equiv tBuOH, NH₃, from −78 to −45 °C, 30 min, then isopropanol (excess), from −78 to −45 °C; (c) 1.1 equiv NCCO₂Me, Et₂O, from −78 to 0 °C, 2 h, 87%.
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 $\beta$-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 $\beta$-ketooesters. With this concept in mind, ketooester 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-ethylendiamine complex. This sequence afforded alkyne 34 as an 8:1 diastereomeric 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 (H2, Lindlar's catalyst) and dehydrated (BF3·Et2O) to produce diene 35 in 90% yield (over two steps). 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 3:1 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.

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...
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 triphenyl phosphene under free-radical conditions afforded vinyl sulfide 43 in 86% yield (Scheme 6).\(^{31}\) dehydration process gave rise to diene 44 followed by Wittig methylenation, installed the alkene 45 in 91% overall yield (Scheme 6). The structure of these diastereomers was assigned by comparison to the products isolated from the compounds, which were easily separable in silica gel, was afforded aldehyde 45 in 84% yield as a 4:2:1 mixture of diastereomers.\(^{32}\)

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 35 and 36. Treatment of the major diastereomer 46 with Dess–Martin periodinane,\(^{34}\) followed by Wittig methylation, installed the alkene

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\(a\) 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\(_2\)Cl\(_2\)), CH\(_2\)Cl\(_2\), 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\(_2\)Cl\(_2\), 25 °C, 30 min; (g) 2.7 equiv PhPC\(_3\)Br, 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%.

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\(_2\)O, NaOH/THF/H\(_2\)O 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 in 93% yield, presumably via an S\(_\text{4}^\text{2}\)-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).

Enantioselective Synthesis (−)-Acanthoic Acid

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 stereochemistry 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 (Et2O) were distilled from sodium/benzophenone, dichloromethane (CH2Cl2) and toluene were distilled from calcium hydride, and benzene was distilled from potassium. N,N-Diisopropylthethylamine, 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 (1H NMR) homogeneous mixtures; 1H NMR values are reported in cm−1. Optical rotations were recorded on a Jasco P-1010 polarimeter. High-resolution mass spectroscopy was determined on a VG ZAB–ZE spectrometer at the National Research Council Canada (NRC). All spectra were determined in chloroform-d (CDCl3). Mass spectra were determined in Finnigan MAT 711 spectrometers. Chemical shifts were determined in ppm with TMS as the internal standard.

Ethyl-3-hydroxy-4-pentenoate (18). 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 Li (40 mmol, 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 MgSO4, and concentrated under reduced pressure. The residue was purified via a Kugelrohr distillation to afford compound 14 (2.76 g, 19.45 mmol, 56%). 1H NMR (300 MHz, CDCl3) 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).

Ketone 15. A suspension of β-ketone 14 (2.5 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 solution was removed under reduced pressure, and the crude mixture was chromatographed (silica, 20–50% ether in hexanes) to afford ketone 15 (1.54 g, 6.1 mmol, 74%). Light yellow solid; mp = 67–69 °C; Rf = 0.15 (silica, 50% ether in hexanes); 1H NMR (400 MHz, CDCl3) 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). 13C NMR (100 MHz, CDCl3) 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 C14H18O4 (M + Na+) 273.1103, found 273.1102.

Ketone 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 Et3N (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%). Yellow colorless oil; Rf = 0.45 (silica, 50% ether in hexanes); IR (film) νmax 2952, 2928, 2974; 1H NMR (300 MHz, CDCl3) δ 4.23 (q, 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), 1.04–1.01 (m, 2H); 13C NMR (75 MHz, CDCl3) 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 C16H22O5 (M + H+) 295.1545, found 295.1552.

Alcohol 17. To a well stirred solution of ketone 16 (1.87 g, 6.36 mmol) in dry ethanol (30 mL) at 0 °C were added CeCl3 (1.71 g, 6.99 mmol) and NaBH4 (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 MgSO4, and concentrated under reduced pressure. The residue was purified through flash chromatography (10–40% ether in hexanes) to afford alcohol 17 (1.54 g, 5.21 mmol, 82%). Yellow colorless oil; Rf = 0.35 (silica, 50% ether in hexanes); IR (film) νmax 3436, 2943, 1708; 1H NMR (400 MHz, CDCl3) 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); 13C NMR (100 MHz, CDCl3) 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 C16H18O5 (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, Cs2 (231 mg, 3 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 to 0 °C and treated with methyl iodide (7.2 mg, 51 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 MgSO₄, 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 Bu₄SnH (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; Rf = 0.7 (silica, 50% ether in hexanes); IR (film) νmax 2966, 2933, 1794, 1778, 1720, 1252, 1087 cm⁻¹; 1H NMR (400 MHz, CDCl₃) δ 7.40–7.46, 2.05–2.12 (m, 5H, 3H), 1.38–1.45 (m, 3H, 3H), 1.28–1.35 (m, 2H, 2H), 1.16–1.18 (m, 1H, 1H), 0.60 (s, 3H), 2.20 (m, 2H), 1.81 (m, 2H), 1.73–1.78 (m, 3H, 3H), 1.57–1.60 (m, 3H, 3H), 1.45–1.53 (m, 2H, 2H), 1.30–1.35 (m, 1H, 1H), 1.23 (s, 3H, 3H), 0.95 (s, 3H, 3H); 13C NMR (100 MHz, CDCl₃) 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, 24.3, 22.7, 19.0, 15.0, 14.3; HRMS calc'd for C₁₄H₂₂O₄ (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 isopropyl hypophosphite (3.3 mmol) added in four portions over a period of 2 h. After the end of the reaction, the solvent was removed under reduced pressure. 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 (0.34 mL, 5.01 g, 4.0 mmol) was added to the resulting blue solution of lithium (0.72 g, 0.10 mol) in dry benzene (18 mL). The reaction mixture was then poured into a separatory funnel containing water (344 mg, 1.22 mmol, 68%). The mixture was then stirred at 25 °C for 12 h, then concentrated and subjected to chromatography (silica, 5–30% ether in hexanes) to afford ester 20 (371 mg, 1.26 mmol, 71%). 20: colorless oil; Rf = 0.75 (silica, 50% ether in hexanes); IR (film) νmax 1726; 1H NMR (400 MHz, CDCl₃) 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, 3H), 1.57–1.40 (m, 5H, 5H), 1.45–1.32 (m, 3H, 3H), 1.30–1.20 (m, 2H, 2H), 1.23 (s, 3H, 3H), 0.95 (s, 3H, 3H); 13C NMR (100 MHz, CDCl₃) 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, 24.3, 22.7, 19.0, 15.0, 14.3; HRMS calc'd for C₁₄H₂₂O₄ (M + Na⁺) 319.1885, found 319.1899.

Oxazolidinone 21. A solution of oxazolidinone 21 (5.01 g, 22.8 mmol) in dichloromethane (400 mL) was cooled to 0 °C and treated with dibutylboron trifluoride (25.1 mL, 25.1 mmol, 1.0 M in CH₂Cl₂) followed by Et₂N (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 (3 × 50 mL). The combined crude product was purified through chromatography (silica, 5–30% ether in hexanes) to afford oxazolidinone 21 (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 for 1 h. After removal of H₂O, the mixture was diluted with dry benzene (50 mL) and heated to 100 °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 MgSO₄, and subjected to chromatography (silica, 10–40% ether in hexanes) to afford ketone 25 (48 g, 0.22 mol, 90%). 25: yellow oil; Rf = 0.30 (silica, 50% ether in hexanes); [α]D²⁰ −77° (c = 1, CD₃OH); IR (film) νmax 2943, 2790, 1667, 1450, 1325, 1250; 1H NMR (400 MHz, CDCl₃) δ 5.80 (s, 1H), 3.98–3.93 (m, 4H), 2.43–2.35 (m, 3H), 2.34–2.25 (m, 3H), 1.94–1.82 (m, 1H), 1.78–1.60 (m, 3H, 3H), 1.34 (s, 3H, 3H); 13C NMR (100 MHz, CDCl₃) δ 210.7, 198.0, 165.6, 125.7, 50.6, 37.7, 33.7, 31.8, 29.7, 23.4, 23.0.

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 ketone 25 (10 g, 0.045 mol) and tert-butyl alcohol (3.7 mL, 0.045 mol) in ether (40 mL). The resulting reaction mixture was then stirred at 12 °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 MgSO₄, concentrated, and subjected to chromatography (10–40% ether in hexanes) to afford ketone 25 (48 g, 0.22 mol, 90%). 25: yellow oil; Rf = 0.30 (silica, 50% ether in hexanes); [α]D²⁰ −77° (c = 1, CH₃OH); IR (film) νmax 2943, 2790, 1667, 1450, 1325, 1250; 1H NMR (400 MHz, CDCl₃) δ 5.80 (s, 1H), 3.98–3.93 (m, 4H), 2.43–2.35 (m, 3H), 2.34–2.25 (m, 3H), 1.94–1.82 (m, 1H), 1.78–1.60 (m, 3H, 3H), 1.34 (s, 3H, 3H); 13C NMR (100 MHz, CDCl₃) δ 210.7, 198.0, 165.6, 125.7, 50.6, 37.7, 33.7, 31.8, 29.7, 23.4, 23.0.
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 bicarbonate (100 mL). After the organic layer was separated, the aqueous layer was extracted with ether (3 × 50 mL). The combined organic layers were dried over MgSO4, concentrated, and subjected to chromatography (10–20% ether in hexanes) to afford ketoester 28 (11 g, 0.039 mol, 87%).

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; Rf = 0.40 (silica, 20% ether in hexanes); [(a)2]20D +4.1 (c = 1, CH2Cl2); IR (film) νmax 2934, 1746, 1700; 1H NMR (400 MHz, CDCl3) 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); 13C NMR (100 MHz, CDCl3) δ 137.5, 137.0, 102.0, 74.6, 59.9, 52.0, 43.7, 41.6, 37.5, 30.3, 29.8, 26.2, 22.5, 14.0; HRMS calcd for C17H26O6 (M + Na+) 305.1354, found 305.1354.

Ketone 30. This compound was obtained in 81% yield when enolate 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 a solution of sodium bicarbonate (20 mL). The reaction mixture was passed through a silica column (50% ether in hexanes); 1H NMR (400 MHz, CDCl3) δ 4.10 (m, 1H, J = 12.5 Hz), 2.53 (q, 1H, J = 7.8 Hz), 2.46 (m, 1H, J = 12.9 Hz), 2.10 (m, 1H), 1.93 (m, 5H), 1.80–1.84 (m, 3H), 1.76 (m, 1H), 1.57–1.50 (m, 3H). This compound was obtained in 81% yield when enolate 27 (7.40 g, 0.024 mol) in DME (100 mL) was treated with lithium acetylide (0.40 g, 13 mmol). The reaction mixture was allowed to warm and stir at −78 °C for 20 min. The reaction mixture was then quenched with sodium bicarbonate (50 mL) and HMPA (50 mL). The solvent was evaporated under reduced pressure to afford the corresponding aldehyde 30.

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 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 etheral extracts were washed with saturated sodium bicarbonate (30 mL), and subjected to chromatography (silica, 10–20% ether in hexanes) to yield ketoester 31 (7.40 g, 0.024 mol). The resulting white slurry was allowed to stir at reflux (−33 °C) for 1 h, after which the reaction was warmed in a water bath (50 °C) with stirring 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 bicarbonate (100 mL). After the organic layer was separated, the aqueous layer was extracted with ether (3 × 50 mL). The combined etheral extracts were washed with saturated sodium bicarbonate (30 mL), and subjected to chromatography (silica, 10–20% ether in hexanes) to yield ketoester 32 (3.15 g, 0.013 mol, 33%).

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 reaction mixture was quenched with water (100 mL) and ether (100 mL). After the layers were separated, the aqueous layer was extracted with ether (3 × 100 mL). The combined etheral extracts were washed with saturated sodium bicarbonate (30 mL), and subjected to chromatography (silica, 10–20% ether in hexanes) to yield ketone 33 (3.14 g, 0.013 mol, 95%).

Ketone 34. A solution of ketone 33 (2.0 g, 0.033 mol) in ether (50 mL) was treated with lithium acetylide (0.043 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 (75 mL). The reaction mixture was passed through a silica column (50% ether in hexanes); 1H NMR (400 MHz, CDCl3) δ 3.64 (s, 3H), 2.57 (q, 1.9 Hz), 2.43 (m, 1H), 1.50–1.30 (m, 4H), 1.14 (s, 3H), 0.98–0.96 (m, 1H), 0.90 (s, 3H); 13C NMR (100 MHz, CDCl3) 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 C16H24O2 (M + H+) 261.1461, found 261.1482.

Alkyne 35. A solution of ketone 34 (2.0 g, 0.076 mmol) in 1,4-dioxane (50 mL) and pyridine (2 mL) was treated with Lindlar’s catalyst (100 mg). The mixture was hydrogenated under pressure (30 lbs/in2) for 7 min. The reaction mixture was then diluted with ether (10 mL), filtered through a bed of Celite, and washed with water (2 × 50 mL). The solvent was evaporated under reduced pressure to afford the corresponding alkyne (0.48 g, 1.8 mmol, 95%). This alkyne 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 MgSO4, concentrated, and subjected to chromatography (silica, 5% ether in hexanes) to afford diene 35 (0.42 g, 1.7 mmol, 95%).

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 neutral 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 the aldehydes 39 and 40, to afford aldehydes 37 and 38. 37 and 38 were identified by their spectroscopic data: 37: $\delta_{\text{H}}$ (0.3H) = 0.38 (s, 3H), 1.35–1.80 (m, 4H), 2.10–2.12 (m, 1H), 2.15–2.20 (m, 2H), 2.30–2.35 (m, 1H), 2.80–2.85 (m, 1H), 3.40–3.45 (m, 1H), 3.60–3.65 (m, 1H), 3.85–3.90 (m, 1H), 4.00–4.05 (m, 1H), 4.10–4.15 (m, 1H). 38: $\delta_{\text{H}}$ (0.3H) = 0.38 (s, 3H), 1.35–1.80 (m, 4H), 2.10–2.12 (m, 1H), 2.15–2.20 (m, 2H), 2.30–2.35 (m, 1H), 2.80–2.85 (m, 1H), 3.40–3.45 (m, 1H), 3.60–3.65 (m, 1H), 3.85–3.90 (m, 1H), 4.00–4.05 (m, 1H), 4.10–4.15 (m, 1H).

**Alcohols 39 and 40.** A solution of aldehydes 37 and 38 (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 dried (MgSO4), and concentrated, and the residue was chromatographed (silica, 5–5% ether in hexanes) to afford enantiomerically pure alcohols 39 and 40 (0.122 g, 0.38 mmol, 3:1 ratio in favor of 39, 94% overall yield). 39: $\delta_{\text{H}}$ (0.3H) = 0.57 (s, 3H), 1.30–1.85 (m, 4H), 2.10–2.15 (m, 2H), 2.20–2.25 (m, 2H), 2.30–2.35 (m, 1H), 2.80–2.85 (m, 1H), 3.40–3.45 (m, 1H), 3.60–3.65 (m, 1H), 3.85–3.90 (m, 1H), 4.00–4.05 (m, 1H), 4.10–4.15 (m, 1H). 40: $\delta_{\text{H}}$ (0.3H) = 0.57 (s, 3H), 1.30–1.85 (m, 4H), 2.10–2.15 (m, 2H), 2.20–2.25 (m, 2H), 2.30–2.35 (m, 1H), 2.80–2.85 (m, 1H), 3.40–3.45 (m, 1H), 3.60–3.65 (m, 1H), 3.85–3.90 (m, 1H), 4.00–4.05 (m, 1H), 4.10–4.15 (m, 1H).

**Diene 44.** To a solution of sulfide 43 (1.10 g, 2.94 mmol) in hexamethylphosphoramide (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 layers were extracted with ether (3 × 50 mL). The aqueous layer was then dried (MgSO4), and concentrated, and the residue was subjected to chromatography (silica, 2–5% ether in hexanes) to afford diene 44 (0.85 g, 2.38 mmol, 81%); 44: $\delta_{\text{H}}$ (0.3H) = 0.61 (s, 5H, ether in hexanes); $\delta_{\text{C}}$ (0.3H) = 17.3 (C = O, benzene); IR (film) νmax 2234, 1750, 1671, 1602, 1545, 1450, 1380, 1340, 1180, 1080, 1030; MS m/z 223.14, 213.15, 201.15, 190.15, 178.00, 166.10, 145.00, 133.00, 121.00, 109.00, 97.00, 85.00, 73.00, 61.00, 49.00, 37.00, 25.00, 13.00, 9.00, 7.00, 5.00, 3.00, 1.00; HRMS calcd for C22H20SeO3 (M + Na+) 397.1830, found 397.1830.

**Aldehyde 45.** To a stirred solution of diene 44 (0.51 g, 1.43 mmol) and methanol (0.30 g, 4.3 mmol) in dichloromethane (5 mL) at −20 °C was added dropwise tin(iv) chloride (0.29 mmol, 3 mL) solution in dichloromethane (0.25 mmol/mL). 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 ether (3 × 20 mL). The organic layers were then dried (MgSO4), and concentrated, and the residue was subjected to chromatography (silica, 10–15% ether in hexanes) to afford aldehyde 45 (0.51 g, 1.19 mmol, 84%); 45: $\delta_{\text{H}}$ (0.3H) = 0.61 (s, 5H, ether in hexanes); $\delta_{\text{C}}$ (0.3H) = 17.3 (C = O, benzene); IR (film) νmax 2234, 1750, 1671, 1602, 1545, 1450, 1380, 1340, 1180, 1080, 1030; MS m/z 223.14, 213.15, 201.15, 190.15, 178.00, 166.10, 145.00, 133.00, 121.00, 109.00, 97.00, 85.00, 73.00, 61.00, 49.00, 37.00, 25.00, 13.00, 9.00, 7.00, 5.00, 3.00, 1.00; HRMS calcd for C22H20SeO3 (M + Na+) 489.0861, found 489.0882.
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38.1, 31.2, 28.3, 27.8, 26.9, 21.7, 20.2, 19.2, 18.7; HRMS calcd for C_{20}H_{32}O_{3} (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 (MgSO₄), and concentrated. The residue was redis solves 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 (MgSO₄) 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, 42:1 ratio in favor of 46, 91% overall). 46: 0.27 g, 0.86 mmol, 74% colorless liquid; Rₛ = 0.4 (silica, 30% ethyl ether in hexanes); [α]_D^20 = −16.70 (c = 1.0, CH₂Cl₂); IR (film) ν max 2929.5, 2873.4, 1726.8, 1637.7, 1460.7, 1376.8, 1225.1, 1150.4, 997.8, 908.7; 1H NMR (500 MHz, CDCl₃) 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); 13C NMR (125 MHz, CDCl₃) 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, 28.4, 27.8, 22.1, 20.4, 19.0; HRMS calcd for C_{19}H_{32}O₂ (M + Cs') 449.1455, found 449.1471.

**Acanthoic Acid (1).** To a solution of alake 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 H₂O (5 mL), and extracted with ethyl acetate (3 × 10 mL). The organic layer was collected, dried (MgSO₄), 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; Rₛ = 0.20 (silica, 30% ethyl ether in hexanes; [α]_D^20 = −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; 1H NMR (500 MHz, CDCl₃) 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); 13C NMR (125 MHz, CDCl₃) 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_{32}O₂ (M + Cs') 435.1298, found 435.1302.

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**Supporting Information Available:** 1H and 13C 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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