Enantiospecific Synthesis of the Phospholipase A_2 Inhibitor (−)-Cinatrin B

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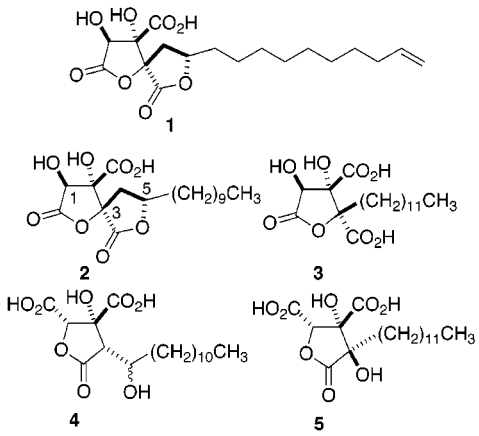
The first enantiospecific synthesis of phospholipase A_2 (PLA_2) inhibitor (−)-cinatrin B (**2**) from the D-arabinose derivative **9** is described. The spirolactone system was formed by an Ireland−Claisen rearrangement of the allyl ester **8** followed by hydrolysis and stereoselective iodolactonization. The stereoselectivity of the rearrangement was controlled by the asymmetry in the allylic alcohol fragment. Ester (*S*)-**8** gave the desired rearrangement product **7** and the epimer **13** in high yield as a 73:27 ratio, respectively. The final stereocenter at C2 was introduced via a chelation-controlled addition of the Grignard reagent derived from trimethylsilylacetylene to α-hydroxy ketone **6**. Transformation of the terminal alkyne into the methyl ester **21** followed by acetal hydrolysis and selective lactol oxidation afforded cinatrin B methyl ester (**22**). Base hydrolysis and acid-induced relactonization then gave (−)-cinatrin B (**2**).

Introduction

The rate-limiting step in the biosynthesis of eicosanoids is the hydrolytic cleavage of arachidonic acid from the ester linkage to the phospholipid backbone.[1] This is achieved via the action of the lipolytic enzyme, phospholipase A_2 (PLA_2), which specifically hydrolyses the 2-acyl position of a glycerophospholipid.[2] PLA_2 also mediates the formation of the precursor of platelet-activating factor (PAF). PAF is released from many inflammatory cells when activated and is responsible for producing most phenomena of inflammation.[3]

While screening for microbial products that possess pharmacological activity, Itazaki and co-workers isolated a family of PLA_2 inhibitors, cinatrins A (**1**), B (**2**), C_1 (**3**), C_2 (**4**), and C_3 (**5**), from the fermentation broth of the microorganism *Circinotrichum falcatisporum* RF-641.[4] The cinatrins are potent inhibitors of rat platelet PLA_2 with maximal inhibition shown by cinatrin C_3 (**5**) (IC_{50} 70 μM) and B (**2**) (IC_{50} 120 μM).[5] As several eicosanoids are potent mediators of disease, inhibition of the enzymatic activity of PLA_2 would be therapeutically beneficial; therefore, the cinatrins are potential antiinflammatory agents.

The structures of all the members of the cinatrin family were determined by elemental analysis, SI-mass spectrometry, various NMR techniques, and analysis of the respective methyl esters, which also serve to confirm the number of carboxylic acid residues present.[4] A single-crystal X-ray structure of cinatrin C_3 (**5**) was determined, and this revealed the relative configuration while CD spectroscopy was used to assign the absolute stereochemistry. In 1997, Evans and co-workers reported the first total synthesis of (−)-cinatrin C_1 (**3**) and (+)-cinatrin C_3 (**5**)[6] using a tartrate aldol methodology.[7] This work established the structures of the cinatrins were in fact enantiomeric to that originally proposed.[4] The revised stereochemical assignment of cinatrin C_3 (**5**) and cinatrin C_1 (**3**) reveals that these compounds are stereochemically related to the zaragozic acids.[8] The novel structure and biological activity of the cinatrins makes them interesting targets, and we have embarked on a synthetic program toward these compounds. We now report the first total synthesis of spirolactone (−)-cinatrin B (**2**), which is in agreement with the absolute stereochemical assignment for this family of compounds as reported by Evans.[6]



Retrosynthetic Analysis

A retrosynthetic analysis of (−)-cinatrin B (**2**) is shown in Scheme 1. A chelation-controlled[9] carbanion addition

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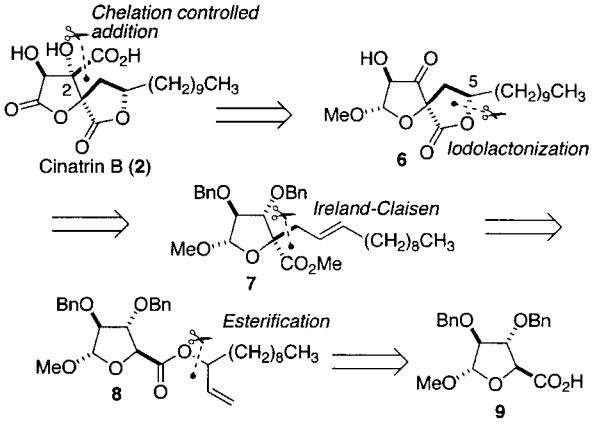
Scheme 1



to α-hydroxy ketone **6** should provide a method for the introduction of C2 acid functionality. In this step, the free hydroxyl group delivers an appropriate nucleophile to the ketone from the *β*-face. Stereoselective iodolactonization of the acid derived from ester **7** and reduction would form the spirolactone system. Intermediate **7** is available via an Ireland−Claisen rearrangement[10] of the allylic ester **8** derived from acid **9**, which in turn could be obtained from the chiral pool starting material D-arabinose.

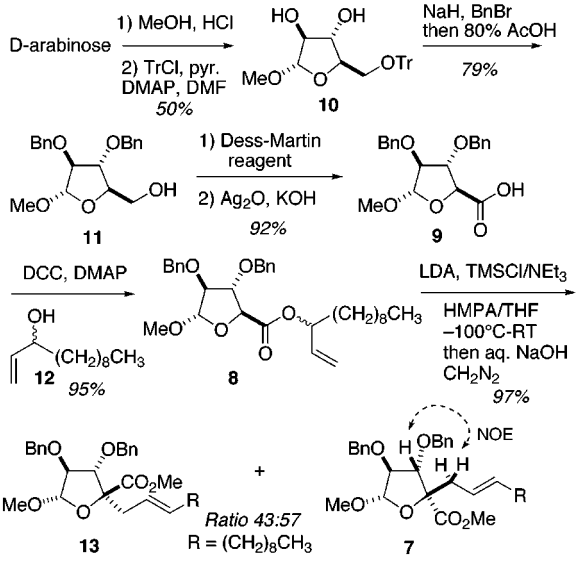
We have utilized the Ireland−Claisen rearrangement in the presence of a *β*-leaving group[11] for the synthesis of 2,2-disubstituted furanoid natural products such as sphydrofuran[12] and the core of the zaragozic acids.[13,14] This approach involves enolization and silylation of an allylic ester **I**, derived from a furansiduronic acid, and subsequent stereoselective [3,3]-rearrangement of the resulting silyl ketene acetal to give tetrahydrofuran **II** (Figure 1). Critical to the success of this approach is the mode of addition in which a solution of the ester is added to a solution of the base/silylating mixture ($TMSCl/NEt_3$) in THF at −100 °C in the presence of HMPA as cosolvent.[12,13b,15] Under such conditions, *β*-elimination does not occur and rearrangement can proceed via the less hindered face opposite to the *β*-OP group in high yield as shown in Figure 1.

Results and Discussion

The route to cinatrin B (**2**) began with the synthesis of the enantiopure acid **9** (Scheme 2). Treatment of D-arabinose with HCl in dry methanol followed by tritylation of the crude product gave diol **10**[16] (50%) and the corresponding *β*-anomer (16%), which were easily separated by flash chromatography. The major product α-anomer **10** was utilized for the rest of the synthesis. Thus, compound **10** was perbenzylated and subsequent removal of the trityl protecting group gave alcohol **11**. Two-step oxidation[12] provided acid **9** in excellent yield,

Figure 1.

Scheme 2



and esterification with racemic alcohol **12**[17] afforded the rearrangement substrate **8**.

Addition of ester **8** to a solution of LDA and the centrifugate from a 1:1 v/v mixture of $TMSCl/NEt_3$[11,12,18] in THF/HMPA at −100 °C followed by warming to room temperature afforded, after hydrolysis and esterification, esters **13** and **7** in excellent yield but as a 43:57 mixture. The stereochemistry of major ester **7** was assigned on the basis of a strong NOE observed between the allylic protons and H2 in the NOESY spectrum of **7**. We attributed the low stereoselectivity to the fact that facial selectivity of the rearrangement is mainly governed by the allyl ester stereocenter marked (Scheme 3), which overrides the influence of the *β*-stereocenter on the THF ring observed previously.[12−14] Enolization and silylation should provide a (*Z*)-*O*-silyl ketene acetal **14** as the major isomer,[19] and this intermediate then rearranges via the two chairlike transition states[20] in which the alkyl chain is in a pseudoequatorial orientation in each.[21] Therefore, the *R*-epimer would then provide ester **13** while the desired ester **7** would form from the *S*-epimer as shown.

To test this proposal, diasteroisomerically pure (*S*)-**8**, synthesized from acid **9** and optically pure (*S*)-**12**,[22] was subjected to the rearrangement conditions (Scheme 3). A higher selectivity was observed, favoring the desired

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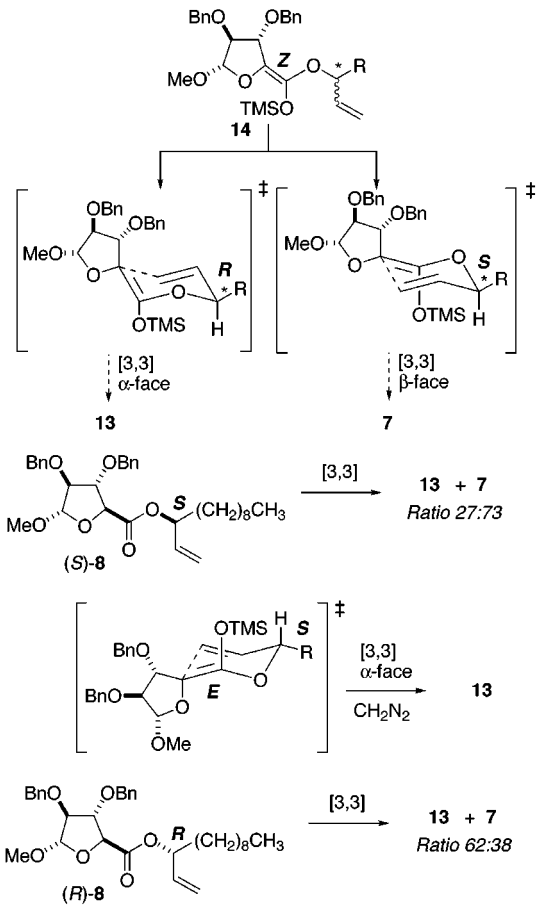
Scheme 3



isomer **7**; however, some of the undesired ester **13** was also obtained. In this case, it appears that the ratio of **13**/**7** (27:73) corresponds to the original *E*/*Z* ratio obtained since the (*E*)-*O*-ketene acetal would give **13** upon rearrangement via the transition state shown in Scheme 3. This is in close agreement with the observation that enolization of ethyl 2-tetrahydrofuroate with LDA in THF/23% HMPA followed by silylation gives a 63:37 ratio of (*Z*)- and (*E*)-*O*-ketene acetals, respectively.[19] As expected, exposure of the corresponding diastereoisomer (*R*)-**8** to the rearrangement conditions gave ester **13** as the major product but with lower selectivity (Scheme 3). This suggests that the *β*-stereocenter in the THF ring may have some effect on the stereochemical outcome as was observed when the mixture of esters **8** was rearranged.

With ester **7** in hand, we proceeded to investigate the formation of the spirolactone (Scheme 4). Hydrolysis of **7** provided the corresponding acid, which upon treatment with I_2 in ether[23] gave the predicted iodolactone **15** in high yield as the major isomer (88% ds by ^{1}H NMR). Radical deiodination[24] was effected by Bu_3SnH/AIBN in toluene at 60 °C to give spirolactone **16**, which was debenzylated by exposure to 60 psi H_2 gas and $Pd(OH)_2$.

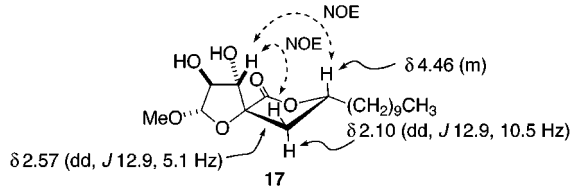


Figure 2.

The stereochemistry of resultant diol **17** was assigned on the basis of the NMR data shown in Figure 2. In particular, the strong NOE observed between H2 and H5 indicated that the desired stereochemistry had been installed at C5. A similar NOE enhancement was detected between the 2-OH group and H5 in cinatrin B (**2**) itself.[4]

Protection of the less hindered alcohol by treatment with TBSCl and imidazole provided monoether **18**, and Dess−Martin oxidation[25] followed by careful HF-induced desilylation gave labile α-hydroxy ketone **6**, which was utilized in the addition reaction immediately. Prolonged reaction times (>4 h) for the desilylation resulted in a large amount of decomposition. After some experimentation, the chelation-controlled addition[26] to the α-hydroxy ketone[27] **6** was achieved using 3 equiv of the Grignard reagent derived from TMS acetylene[28] in THF at −78 °C (Scheme 4). This gave the desired C2 isomer **19** and the corresponding epimer as a 3.3:1 mixture, respectively, in acceptable yield for three steps from alcohol **18**. Multiple addition products and starting ketone accounted for the remaining material. Attempts to drive the reaction to completion led only to the production of multiple addition products. Removal of the TMS group enabled separation of the C2 epimers to give pure alkyne **20** and partial reduction followed by ozonolysis, oxidation, and esterification yielded methyl ester **21**. One-step oxidation to form the lactone[29] failed, so a two-step sequence was employed that involved acid hydrolysis of the methyl ketal followed by selective lactol oxidation[30] to provide (−)-cinatrin B methyl ester (**22**). The data obtained for synthetic **22** compared well to that reported for naturally derived material.[4] Base hydrolysis of **22** followed by relactonization and purification by reversed-phase HPLC afforded (−)-cinatrin B (**2**) [synthetic: $[\alpha]_D$ −10.4 (*c* 0.17, MeOH); natural sample: $[\alpha]_D$ −14.5 (*c* 0.17, MeOH)], which was identical with the natural product[4,31] in all respects.

In conclusion, we have completed the first total synthesis of (−)-cinatrin B (**2**), which utilized a high-yielding

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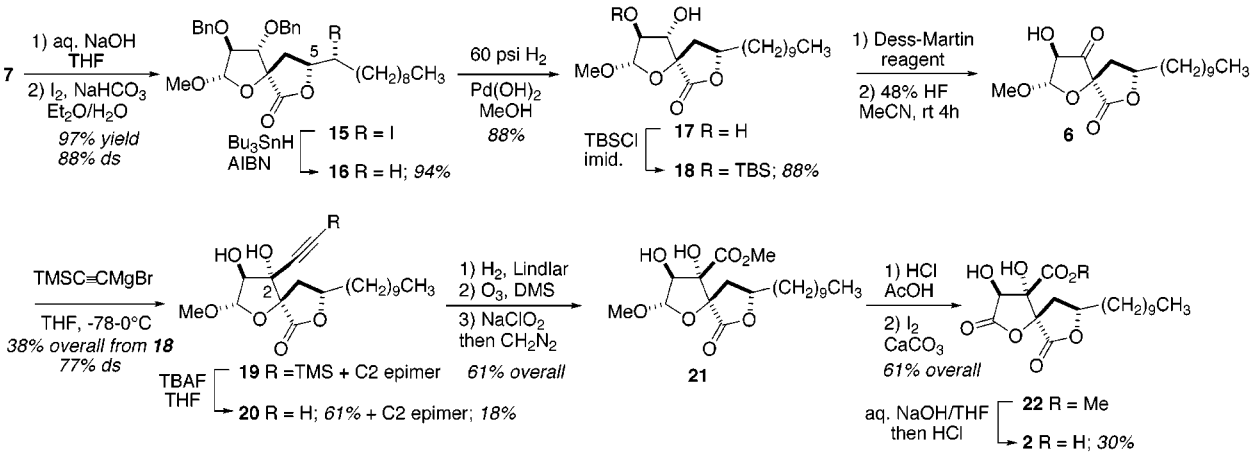
(31) The specific rotation reported[4] for **2** was −24.4 (*c* 0.308, MeOH). A natural sample provided by Dr. Toshiyuki Kamigauchi originally had a specific rotation of −23.0 (*c* 0.16, MeOH); however, when this sample was treated with acid, a value of −14.5 (*c* 0.17, MeOH) was obtained. We believe the authentic sample was originally ionized and this was also evident by slight changes observed in the ^{1}H NMR spectrum of the natural sample upon acidification.

Scheme 4



Ireland−Claisen rearrangement in the presence of a β-leaving group. Other highlights of the synthesis included a stereoselective iodolactonization to form the C5 stereocenter and a chelation-controlled addition to an α-hydroxy ketone to introduce the C2 substituent. The synthesis of other members of this family of compounds will be reported in due course.

Experimental Section

General Methods. Unless otherwise stated, ^{1}H NMR and proton-decoupled ^{13}C NMR spectra were recorded for deuteriochloroform solutions with residual chloroform as internal standard. Optical rotations were recorded in a 10 cm microcell. HRMS [electrospray ionization (ESI) or electron impact (EI)] mass spectra were run at Monash University, Clayton, Victoria. Microanalyses were carried out at the University of Otago, Dunedin, New Zealand. Flash chromatography was carried out on Merck silica gel 60. Anhydrous THF was distilled from sodium metal/benzophenone under a nitrogen atmosphere. All other anhydrous solvents were purified according to standard methods. Petrol refers to the fraction boiling between 40 and 60 °C.

Methyl Ketal 10. This method is a modification of the literature procedure:[16b] To a suspension of D-arabinose (10.0 g, 66.5 mmol) in dry methanol (384 mL) was added acetyl chloride (2.0 mL, 28.1 mmol), and the mixture was allowed to stir at rt overnight, after which time a clear solution resulted. The reaction mixture was neutralized with Amberlite resin IRA-400 (OH) (60.0 g) and then filtered, and the resin was washed with methanol (3 × 500 mL). The combined methanol washings and the filtrate were concentrated and pumped under high vacuum (0.05 mmHg) overnight. The crude product was dissolved in dry DMF (100 mL) and dry pyridine (13.7 mL, 166.3 mmol), DMAP (794 mg, 6.50 mmol) and triphenylmethyl chloride (43.5 g, 156 mmol) were added, and the reaction was stirred at 65 °C for 4 h. Saturated aqueous $NaHCO_3$ was added, and the aqueous phase was extracted with ether. The combined extracts were washed with saturated aqueous $CuSO_4$, water, and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography with 60% EtOAc/petrol as eluent to give the methyl ketal **10** (13.1 g, 50%) as a yellow solid: mp 113−114 °C (lit.[16a] 112−113 °C); $[\alpha]^{24}_D$ +85.9 (*c* 1.06, $CHCl_3$) [lit.[2] $[\alpha]^{20}_D$ +62.4 (*c* 1.56, EtOAc)]; IR (Nujol) 3399, 2927, 1487, 1445, 1074, 633 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.59 (s, 1H), 2.79 (d, J = 11.1 Hz, 1H), 3.25 (dd, J = 10.5, 2.1 Hz, 1H), 3.41 (s, 3H), 3.66 (dd, J = 10.5, 3.0 Hz, 1H), 3.84 (d, J = 11.1 Hz, 1H), 3.98 (d, J = 11.1 Hz, 1H), 4.11 (m, 1H), 5.01 (s, 1H), 7.33 (m, 15H); ^{13}C NMR (75.5 MHz) δ 54.9, 63.5, 78.3, 78.9, 86.4, 88.4, 109.3, 127.4, 128.0, 128.8, 142.8; Anal. Calcd for $C_{25}H_{26}O_6$: C, 73.87; H, 6.44. Found: C, 73.90; H, 6.37.

Further elution using 60% EtOAc/petrol as eluent gave the β-anomer (4.45 g, 16%) as a gum: $[\alpha]^{24}_D$ −31.7 (*c* 0.89, $CHCl_3$); IR (thin film) 3400, 2923, 1487, 1445, 1045, 1001, 765, 701, 632 cm^{-1}; ^{1}H NMR (300 MHz) δ 2.37 (br s, 1H), 2.50 (d, J = 9.3 Hz, 1H), 3.26 (d, J = 4.8 Hz, 2H), 3.40 (s, 3H), 3.95 (m, 1H), 4.07 (m, 2H), 4.83 (d, J = 4.0 Hz, 1H), 7.32 (m, 15H); ^{13}C NMR (75.5 MHz) δ 55.4, 64.8, 78.0, 80.8, 86.5, 101.8, 127.0, 127.8, 128.7, 143.9; HRMS (ESI) calcd for $C_{25}H_{26}O_5Na$ [M + Na]$^+$ 429.1678, found 429.1677.

Alcohol 11. To a mixture of NaH (3.05 g) (60% w/w dispersion in mineral oil, washed with dry pentane) and benzyl bromide (9.16 mL, 76.41 mmol) in dry DMF (71 mL) was added a solution of the diol **10** (11.53 g, 28.37 mmol) in dry DMF (85 mL) via cannula. The reaction mixture was allowed to stir at rt for 3 h and then quenched by the slow addition of water, and the aqueous phase was extracted with ether. The combined extracts were washed with water and brine and dried ($MgSO_4$), and the solvent was removed under reduced pressure. To the crude product was added 80% aqueous acetic acid (145 mL), and the mixture was heated at 70 °C for 1.5 h. Water was added, and the aqueous phase was extracted with ether. The combined extracts were washed with water, saturated aqueous $NaHCO_3$, and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography with 30% EtOAc/petrol as the eluent to give the alcohol **11** (7.70 g, 79%) as a yellow oil: $[\alpha]^{24}_D$ +83.2 (*c* 1.14, $CHCl_3$); IR (thin film) 3459, 2914, 1493, 1451, 1104, 737, 698 cm^{-1}; ^{1}H NMR (300 MHz) δ 2.10 (br s, 1H), 3.39 (s, 3H), 3.64 (dd, J = 12.3, 4.2 Hz, 1H), 3.84 (dd, J = 12.3, 3.0 Hz, 1H), 3.99 (m, 2H), 4.15 (m, 1H), 4.51 (ABq, J = 11.7 Hz, 2H), 4.56 (ABq, J = 12.0 Hz, 2H), 4.94 (s, 1H), 7.33 (m, 10H); ^{13}C NMR (75.5 MHz) δ 54.9, 62.2, 71.9, 72.3, 82.3, 82.5, 87.7, 107.4, 127.8, 127.85, 127.89, 127.93, 128.4, 128.5, 137.3, 137.6; HRMS (ESI) calcd for $C_{20}H_{24}O_5Na$ [M + Na]$^+$ 367.1521, found 367.1516.

Acid 9. To a solution of the alcohol **11** (7.35 g, 21.34 mmol) in CH_2Cl_2 (70 mL) was added Dess−Martin periodinane (13.67 g, 32.01 mmol), and the mixture was stirred at rt for 3 h. Ether, saturated aqueous $NaHCO_3$, and 1.5 M aqueous $Na_2S_2O_3$ were added, and stirring was continued until two clear layers formed. The aqueous phase was extracted with ether, and the combined extracts were washed with water and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was dissolved in ethanol (109 mL). A solution of $AgNO_3$ (8.28 g) in H_2O (11.5 mL) was added followed by the dropwise addition of a solution of KOH (7.58 g) in H_2O (106.9 mL), the resultant Ag_2O suspension was stirred for 12 h at rt and then filtered through Celite, and the filter cake was washed with aqueous 6% KOH. Most of the ethanol was removed under reduced pressure, and the remaining aqueous solution was washed with ether, acidified with concentrated HCl at 0 °C, and extracted with ether. The combined extracts were washed with brine and dried ($MgSO_4$), and the solvent was removed under reduced pressure to give the acid **9** (7.00 g, 92%) as a clear, viscous oil: $[\alpha]^{21}_D$ +37.7 (*c* 1.04, $CHCl_3$); IR (thin film) 3475, 2933, 1733, 1451, 1355, 1203,

1112, 1065, 1027, 953, 739, 698 cm^{-1}; ^1H NMR (300 MHz) δ 3.44 (s, 3H), 3.98 (s, 1H), 4.20 (d, J = 4.0 Hz, 1H), 4.43 (s, 2H), 4.65 (ABq, J = 12.3 Hz, 2H), 4.70 (d, J = 4.2 Hz, 1H), 5.13 (s, 1H), 7.30 (m, 10H); ^{13}C NMR (75.5 MHz) δ 55.4, 71.6, 72.1, 80.9, 84.6, 85.8, 108.2, 127.6, 127.8, 127.9, 128.3, 136.8, 137.0, 174.1; HRMS (ESI) calcd for $C_{20}H_{22}O_6Na$ $[M + Na]^+$ 381.1314, found 381.1310.

Alcohol 12. To a solution of decyl aldehyde (8.30 g, 53.11 mmol) in dry ether (120 mL) was added vinylmagnesium bromide (106 mL, 106 mmol, 1 M solution in THF), and the reaction was allowed to stir at 0 °C for 1 h and then at rt overnight. Saturated aqueous NH_4Cl was added slowly and the aqueous phase extracted with ether. The combined extracts were washed with water and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue purified by flash chromatography with 5% EtOAc/petrol as eluent to give the racemic alcohol **12** (9.27 g, 95%) as a colorless oil: IR (thin film) 3386, 2923, 2854, 1466, 1378, 1063, 988, 918 cm^{-1}; ^1H NMR (300 MHz) δ 0.87 (t, J = 6.9 Hz, 3H), 1.26 (s, 14H), 1.53 (m, 2H), 4.07 (m, 1H), 5.09 (d, J = 10.5 Hz, 1H), 5.21 (d, J = 17.1 Hz, 1H), 5.86 (ddd, J = 17.1, 10.5, 6.3 Hz, 1H); ^{13}C NMR (75.5 MHz) δ 14.1, 14.2, 22.7, 25.3, 29.3, 29.6, 31.9, 37.1, 60.4, 73.3, 114.4, 141.4; HRMS (ESI) calcd for $C_{12}H_{24}ONa$ $[M + Na]^+$ 207.1725, found 207.1719.

Alcohol (*S*)-12. To a solution of the allylic alcohol **12** (933 mg, 5.06 mmol) and (−)-diisopropyl-D-tartrate (142 mg, 0.607 mmol) in CH_2Cl_2 (20 mL) at rt under argon was added powdered activated 4 Å molecular sieves (430 mg). The mixture was cooled to −20 °C, treated with $Ti(O^iPr)_4$ (149 μL, 0.506 mmol), and allowed to stir for 20 min. The reaction was then treated with a solution of TBHP (644 μL, 3.54 mmol, 5−6 M in decane dried with freshly activated 4 Å pellets) and stored at −20 °C for 3 days, after which time it was quenched with an aqueous solution of $FeSO_4$ and citric acid at −20 °C and stirred vigorously without cooling until two clear layers resulted. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined extracts were concentrated to half the original volume and stirred for 30 min with a solution of 30% NaOH in brine (5 mL). The phases were again separated, the aqueous phase was extracted with CH_2Cl_2, and the combined extracts were washed with water and brine. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography with 5% EtOAc/petrol as eluent to give the alcohol (*S*)-**12** as a colorless oil (352 mg, 38%): $[\alpha]^{23}_D$ +12.1 (*c* 1.22, MeOH) [lit.[22] $[\alpha]^{21}_D$ +11.4 (*c* 1.0, MeOH)]. Further elution with 15% EtOAc/petrol gave the epoxide (413 mg, 41%) as an oil: $[\alpha]^{28}_D$ −12.3 (*c* 1.05, $CHCl_3$); IR (thin film) 3838, 2925, 2855, 2360, 1653, 1559, 1507, 1457 cm^{-1}; ^1H NMR (300 MHz) δ 0.87 (t, J = 6.6 Hz, 3H), 1.26 (m, 14H), 1.53 (m, 2H), 1.81 (br s, 1H), 2.73 (m, 1H), 2.80 (dd, J = 5.1, 3.0 Hz, 1H), 3.01 (dd, J = 6.9, 3.0 Hz, 1H), 3.83 (m, 1H); ^{13}C NMR (75.5 MHz) δ 14.1, 22.7, 25.3, 29.3, 29.5, 29.6, 31.9, 33.4, 43.4, 54.5, 68.4. Anal. Calcd for $C_{25}H_{26}O_6$: C, 71.95; H, 12.08. Found: C, 71.99; H, 12.28.

Alcohol (*R*)-12. Prepared as described above but using (+)-diethyl-L-tartrate: $[\alpha]^{28}_D$ −11.9 (*c* 1.14, MeOH).

Ester 8. To a solution of the acid **9** (2.97 g, 8.29 mmol) in dry CH_2Cl_2 (20 mL) were added the alcohol **12** (1.17 g, 6.35 mmol) and DMAP (100 mg, 0.82 mmol). After being stirred at rt for 20 min, the reaction was cooled to 0 °C, DCC (1.70 g, 8.24 mmol) was added, stirring was continued for 10 min, and the resulting white suspension was allowed to stir at rt overnight. The reaction was diluted with petroleum ether and filtered through a pad of Celite. The filtrate was washed with 10% aqueous HCl, saturated $NaHCO_3$, and brine and dried ($MgSO_4$).The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography with 5% EtOAc/petrol as eluent to give an inseparable mixture of esters **8** (3.18 g, 95%) in 1:1 ratio, as a pale yellow oil.

Ester (*S*)-8. The alcohol (*S*)-**12** (269 mg, 1.46 mmol) was added to a solution of the acid **9** (680 mg, 1.90 mmol) and DMAP (21 mg, 0.173 mmol) in CH_2Cl_2 (6 mL). The mixture was cooled to 0 °C, and DCC (392 mg, 1.90 mmol) was added. The mixture was then allowed to warm to rt, stirred overnight, diluted with petrol, and filtered through a pad of Celite. The filtrate was washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$, and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography with 10% EtOAc/petrol as eluent to give diastereoisomerically pure ester (*S*)-**8** (477 mg, 62%) as a pale yellow oil: $[\alpha]^{20}_D$ +37.5 (*c* 1.49, $CHCl_3$); IR (thin film) 2922, 2851, 1750, 1451, 1274, 1197, 1101, 735, 697 cm^{-1}; ^1H NMR (300 MHz) δ 0.89 (t, J = 6.3 Hz, 3H), 1.26 (m, 14H), 1.63 (m, 2H), 3.44 (s, 3H), 3.97 (br s, 1H), 4.15 (dd, J = 4.8, 1.8 Hz, 1H), 4.46 (ABq, J = 12.0 Hz, 2H), 4.62 (m, 3H), 5.11 (s, 1H), 5.15−5.35 (m, 3H) 5.72 (ddd, J = 12.4, 10.5, 6.9 Hz, 1H), 7.34 (m, 10H); ^{13}C NMR (75.5 MHz) δ 14.0, 22.6, 24.9, 29.2, 29.3, 29.4, 29.5, 31.8, 34.0, 55.5, 71.7, 72.1, 76.1, 80.8, 85.0, 86.6, 108.1, 117.4, 127.7, 127.79, 127.83, 127.9, 128.33, 128.35, 135.8, 137.2, 137.3, 169.5. Anal. Calcd for $C_{32}H_{44}O_6$: C, 73.25; H, 8.45. Found: C, 73.45; H, 8.57.

Ester (*R*)-8. Prepared from alcohol (*R*)-**12** (490 mg, 2.66 mmol) and acid **9** (1.24 g, 3.46 mmol) using the same method as described above to give (*R*)-**8** (983 mg, 67%): $[\alpha]^{20}_D$ +39.8 (*c* 1.93, $CHCl_3$); IR (thin film) 2921, 2851, 1750, 1451, 1273, 1194, 1100, 1065, 1027, 735, 697 cm^{-1}; ^1H NMR (300 MHz) δ 0.87 (t, J = 6.9 Hz, 3H), 1.22 (m, 14H), 1.58 (m, 2H), 3.43 (s, 3H), 3.96 (br s, 1H), 4.16 (dd, J = 4.8, 1.8 Hz, 1H), 4.46 (ABq, J = 12.0 Hz, 2H), 4.61 (ABq, J = 12.3 Hz, 2H), 4.62 (d, J = 4.5 Hz, 1H), 5.12 (s, 1H), 5.16 (d, J = 10.5 Hz, 1H), 5.30 (m, 2H) 5.76 (ddd, J = 17.1, 10.5, 6.6 Hz, 1H), 7.33 (m, 10H); ^{13}C NMR (75.5 MHz) δ 14.1, 22.7, 25.0, 29.26, 29.31, 29.39, 29.46, 29.51, 31.9, 34.1, 55.5, 71.8, 72.2, 76.0, 81.0, 85.1, 86.6, 108.1, 117.3, 127.7, 127.8, 127.86, 127.91, 128.4, 135.9, 137.3, 169.4. Anal. Calcd for $C_{32}H_{44}O_6$: C, 73.25; H, 8.45. Found: C, 73.52; H, 8.64.

Esters 7 and 13. A solution of *n*-BuLi in hexanes (2.3 M, 6.63 mL, 15.25 mmol) was added dropwise to a solution of $^iPr_2$-NH (2.0 mL, 15.25 mmol) in dry THF (35 mL) at 0 °C under argon. The resultant base solution was stirred at 0 °C for 5 min, cooled to −78 °C, and added dropwise via cannula to a solution of the ester **8** (4.00 g, 7.62 mmol), HMPA (8.41 mL), and the supernatant from a centrifuged mixture of freshly distilled TMSCl (3.39 mL, 26.68 mmol) and NEt_3 (3.72 mL, 26.68 mmol) in dry THF (48 mL) at −100 °C (liquid N_2/MeOH bath). The resulting mixture was stirred at −100 °C for 10 min, allowed to warm to rt, and then cooled to 0 °C, and aqueous 1 M NaOH (52.57 mL) was added followed by ether and water. The aqueous phase was then acidified with concentrated HCl at 0 °C and extracted with ether, and the combined extracts were washed with water and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was dissolved in ether (50 mL) and treated with excess CH_2N_2 to give a mixture of esters in a 43:57 ratio which were separated by flash chromatography. Elution using 5% EtOAc/petrol gave ester **13** (1.74 g, 42%) as a pale yellow oil: $[\alpha]^{24}_D$ +16.3 (*c* 0.93, $CHCl_3$); IR (thin film) 2921, 2850, 1727, 1451, 1108, 1027, 735, 697 cm^{-1}; ^1H NMR (300 MHz) δ 0.88 (t, J = 6.3 Hz, 3H), 1.25 (m, 14H), 1.98 (m, 2H), 2.70 (m, 2H), 3.45 (s, 3H), 3.67 (s, 3H), 3.96 (br s, 1H), 4.21 (d, J = 2.4 Hz, 1H), 4.42 (s, 2H), 4.65 (ABq, J = 12.0 Hz, 2H), 5.04 (s, 1H), 5.45 (m, 2H), 7.33 (m, 10H); ^{13}C NMR (75.5 MHz) δ 14.1, 22.6, 29.1, 29.3, 29.5, 29.6, 31.9, 32.7, 37.5, 52.2, 55.9, 71.8, 72.8, 84.7, 86.7, 89.6, 107.9, 123.5, 127.66, 127.77, 127.80, 127.9, 128.3, 134.9, 137.4, 137.7, 172.9. Anal. Calcd for $C_{33}H_{46}O_6$: C, 73.57; H, 8.61. Found, C, 73.70; H, 8.39. Further elution with 5% EtOAc/petrol gave a mixed fraction of esters **13** and **7** (483 mg, 12%). Elution with 10% EtOAc/petrol then gave ester **7** (1.78 g, 43%) as a pale yellow oil: $[\alpha]^{24}_D$ +32.2 (*c* 1.03, $CHCl_3$); IR (thin film) 2921, 2850, 1732, 1451, 1202, 1112, 734, 697 cm^{-1}; ^1H NMR (300 MHz) δ 0.88 (t, J = 6.6 Hz, 3H), 1.25 (m, 14H), 2.00 (m, 2H), 2.54 (dd, J = 13.5, 5.4 Hz, 1H), 2.66 (dd, J = 13.5, 6.3 Hz, 1H), 3.53 (s, 3H), 3.75 (s, 3H), 3.94 (m, 1H), 4.00 (m, 1H), 4.40 (ABq, J = 12.0 Hz, 2H), 4.59 (s, 2H), 5.05 (s, 1H), 5.44 (m, 2H), 7.34 (m, 10H); ^{13}C NMR (75.5 MHz) δ 14.0, 22.6, 29.0, 29.2, 29.3, 29.4, 29.5, 31.8, 32.5, 40.9, 51.8, 55.7, 71.8, 72.7, 85.3, 86.3, 90.6, 108.5, 123.4, 127.4, 127.6, 127.66, 127.70, 127.9, 128.2, 128.3, 135.1, 137.4, 171.3. Anal. Calcd for $C_{33}H_{46}O_6$: C, 73.57; H, 8.61. Found: C, 73.68; H, 8.53.

Ireland-Claisen rearrangement of ester (*S*)-8. The rearrangement conditions described for ester **8** were applied to the ester (*S*)-**8** (477 mg, 0.909 mmol). Methylation of the crude acids with CH_2N_2 gave a mixture of methyl esters **13** and **7** (400 mg, 82%) in a 27:73 ratio (as determined by integration of the ^{1}H NMR spectrum of the crude product) which were separated by silica gel chromatography with 10% EtOAc/petrol as eluent.

Ireland−Claisen Rearrangement of Ester (*R*)-8. The rearrangement conditions described for ester **8** were applied to the ester (*R*)-**8** (740 mg, 1.41 mmol). Methylation of the crude acids with CH_2N_2 gave a mixture of methyl esters **13** and **7** (686 mg, 76%) in a 62:38 ratio (as determined by integration of the ^{1}H NMR spectrum of the crude product) which were separated by silica gel chromatography with 10% EtOAc/petrol as eluent.

Iodolactone 15. To a solution of the methyl ester **7** (906 mg, 1.68 mmol) in THF (27.7 mL) and water (8.3 mL) was added NaOH (404 mg, 10.1 mmol), and the solution was heated at reflux for 48 h. Most of the THF was removed under reduced pressure, and ether and water were added. The aqueous phase was acidified at 0 °C with concentrated HCl and then extracted with ether, and the combined extracts were washed with water and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, the residue was dissolved in ether (9.5 mL), and saturated aqueous $NaHCO_3$ (9.5 mL) was added. The mixture was cooled to 0 °C, a solution of I_2 (265 mg, 1.04 mmol) in ether (9.5 mL) was added dropwise by cannula, and the mixture was stirred at 0 °C for 15 min. Water was added, and the mixture was extracted with ether. The combined extracts were washed with 1.5 M aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, water, and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography. Elution with 5% EtOAc/petrol gave an inseparable mixture of diastereoisomeric iodolactones (130 mg, 12%) as a pale yellow oil followed by the iodolactone **15** (931 mg, 85%) as a low melting solid: $[\alpha]^{18}_D$ +67.2 (*c* 1.00, $CHCl_3$); IR (thin film) 2955, 2927, 2856, 1794. 1455, 1118, 755 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.90 (t, J = 6.6 Hz, 3H), 1.20−1.40 (m, 13H), 1.46−1.60 (m, 1H), 1.62−1.78 (m, 1H), 1.82−1.96 (m, 1H), 2.20 (dd, J = 13.5, 8.7 Hz, 1H), 2.52 (dd, J = 13.5, 4.8 Hz, 1H), 3.49 (s, 3H), 3.88−4.05 (m, 2H), 4.08 (d, J = 5.4 Hz, 1H), 4.33 (dd, J = 5.1, 3.0 Hz, 1H), 4.49 (d, J = 12.6 Hz, 1H), 4.60 (ABq, J = 12.0 Hz, 2H), 4.79 (d, J = 12.6 Hz, 1H), 5.04 (d, J = 3.0 Hz, 1H), 7.36 (m, 10H); ^{13}C NMR (75.5 MHz) δ 14.1, 22.6, 28.6, 28.8, 29.2, 29.4, 29.5, 31.8, 35.6, 38.4, 42.3, 56.0, 72.2, 72.5, 77.8, 85.8, 86.0, 86.1, 108.6, 127.8, 128.0, 128.06, 128.11, 128.49, 128.53, 137.0, 137.3, 173.3; HRMS (ESI) calcd for $C_{32}H_{43}INaO_6$ $[M + Na]^+$ 673.2002, found 673.1998.

Lactone 16. To a solution of the iodolactone **15** (380 mg, 0.584 mmol) and AIBN (33.7 mg) in toluene (3.9 mL) at 45 °C under argon was added a solution of Bu_3SnH (0.473 mL, 1.76 mmol) in toluene (10.2 mL) by cannula. The resulting solution was heated to 60 °C and then stirred for 1 h. After cooling to rt, saturated aqueous NH_4Cl was added and the mixture was extracted with ether. The combined extracts were washed with water and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography with 10% EtOAc/petrol containing 1% NEt_3 as eluent to give the lactone **16** (288 mg, 94%) as a low melting solid: $[\alpha]^{20}_D$ +69.8 (*c* 1.04, $CHCl_3$); IR (thin film) 2927, 2855, 1786, 1456, 1118, 698 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.88 (t, J = 6.6 Hz, 3H), 1.22−1.56 (m, 17H), 1.58−1.72 (m, 1H), 2.07 (dd, J = 12.9, 9.9 Hz, 1H), 2.25 (dd, J = 12.9, 5.7 Hz, 1H), 3.49 (s, 3H), 4.03 (d, J = 4.8 Hz, 1H), 4.07 (m, 1H), 4.32 (dd, J = 5.1, 2.7 Hz, 1H), 4.48 (d, J = 12.9 Hz, 1H), 4.58 (ABq, J = 11.7 Hz, 2H), 4.78 (d, J = 12.9 Hz, 1H), 5.04 (d, J = 3.0 Hz, 1H), 7.34 (m, 10H); ^{13}C NMR (75.5 MHz) δ 14.0, 22.5, 24.8, 29.1, 29.2, 29.3, 29.37, 29.43, 31.8, 35.3, 41.0, 55.8, 72.0, 72.3, 76.0, 85.6, 85.9, 86.1, 108.4, 127.7, 127.8, 127.88, 127.92, 128.3, 128.4, 137.1, 137.3, 173.6; HRMS (ESI) calcd for $C_{32}H_{44}NaO_6$ $[M + Na]^+$ 547.3036, found 547.3028.

Diol 17. To a solution of the dibenzyl ether **16** (329 mg, 0.627 mmol) in MeOH (10 mL) was added one drop of concentrated HCl followed by $Pd(OH)_2$ on carbon (20 wt % Pd, 66.4 mg, 0.125 mmol), and the resulting suspension was stirred vigorously under a H_2 atmosphere at 60 psi for 17 h. The suspension was then filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography with 20−50% EtOAc/petrol as eluent to give the diol **17** (189 mg, 88%) as a crystalline solid: mp 54−56 °C; $[\alpha]^{18}_D$ +93.8 (*c* 0.84, $CHCl_3$); IR (KBr) 3470, 3411, 2919, 2852, 1771, 1466, 1214, 1044, 1001 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.87 (t, J = 6.6 Hz, 3H), 1.18−1.52 (m, 16H), 1.54−1.67 (m, 1H), 1.69−1.82 (m, 1H), 2.10 (dd, J = 12.9, 10.5 Hz, 1H), 2.57 (dd, J = 12.9, 5.1 Hz, 1H), 3.36 (br s, 2H), 3.50 (s, 3H), 4.11 (d, J = 2.4 Hz, 1H), 4.27 (s, 1H), 4.46 (m,-1H), 4.98 (s, 1H); ^{13}C NMR (75.5 MHz) δ 13.9, 22.5, 24.7, 29.1, 29.2, 29.3, 29.4, 31.7, 35.1, 40.8, 55.5, 77.0, 79.1, 80.5, 88.3, 108.9, 174.6; HRMS (ESI) calcd for $C_{18}H_{32}NaO_6$ $[M + Na]^+$ 367.2097, found 367.2080.

Ether 18. To a solution of the diol **17** (183 mg, 0.53 mmol) in DMF (5.2 mL) at rt under argon was added imidazole (72.4 mg, 1.06 mmol) followed by *tert*-butyldimethylsilyl chloride (96.1 mg, 0.638 mmol), and the solution was stirred at rt for 15 h. Water and ether were added, and the aqueous phase was extracted with ether. The combined extracts were washed with water and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography with 10% EtOAc/petrol as eluent to give the TBS ether **18** (214 mg, 88%) as a yellow oil: $[\alpha]^{14}_D$ +57.3 (*c* 1.19, $CHCl_3$); IR (thin film) 3526, 2929, 2857, 1783, 1464, 1120, 851 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.11 (s, 6H), 0.87 (t, J = 6.6 Hz, 3H), 0.88 (s, 9H), 1.20−1.54 (m, 16H), 1.56−1.82 (m, 2H), 2.07 (dd, J = 12.9, 10.8 Hz, 1H), 2.49 (dd, J = 12.9, 5.1 Hz, 1H), 3.50 (s, 3H), 3.94 (s, 1H), 4.15 (s, 1H), 4.42 (m, 1H), 4.87 (s,1H); ^{13}C NMR (75.5 MHz) δ −5.0, −4.9, 14.1, 17.9, 22.6, 25.0, 25.6, 29.3, 29.4, 29.47, 29.53, 31.9, 35.2, 41.3, 55.3, 76.8, 80.1, 81.1, 89.2, 109.6, 174.1; HRMS (ESI) calcd for $C_{24}H_{46}NaO_6Si$ $[M + Na]^+$ 481.2961, found 481.2942.

Alkyne 20. To a solution of the alcohol **18** (109 mg, 0.238 mmol) in CH_2Cl_2 at 0 °C under argon was added Dess−Martin reagent (251 mg, 0.593 mmol), and the mixture was allowed to warm to rt and stirred for 2 h. Ether (5 mL), saturated aqueous $NaHCO_3$ (5 mL), and 1.5 M aqueous $Na_2S_2O_3$ (5 mL) were added, and the mixture was stirred until two clear layers formed. The aqueous phase was extracted with ether, and the combined extracts were washed with water and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the ketone as a yellow oil (109 mg, 100%). The ketone (164 mg, 0.359 mmol) was dissolved in 4 mL of a solution of 48% aqueous HF (2 mL) in MeCN (8 mL), and the mixture was stirred vigorously at rt for 4 h. Ether was added, and the reaction was quenched with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with ether, and the combined extracts were washed with water and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the α-hydroxy ketone **6** as a yellow solid (126 mg) that was utilized immediately in the next step. To a solution of ethylmagnesium bromide (1.0 M in THF, 3.68 mL, 3.68 mmol) in THF (0.6 mL) at 0 °C under argon was added TMS acetylene (0.526 mL, 3.72 mmol), and the mixture was stirred for 0.5 h before being allowed to warm to 30 °C and stirred for a further 10 min. An aliquot of the Grignard reagent (1.28 mL, 1.1 mmol) was then added dropwise to a solution of the crude α-hydroxy ketone **6** (126 mg) in THF (0.72 mL) at −78 °C under argon, and the mixture was stirred for 2.25 h. The mixture was then allowed to warm to 0 °C and was quenched immediately with saturated aqueous NH_4Cl. The aqueous phase was extracted with ether, and the combined extracts were washed with water and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography with 5−30% EtOAc/petrol as eluent to give an inseparable mixture of bis-addition products (26 mg) followed by an inseparable 3.3:1 mixture of TMS acetylenes **19** (61 mg, 38%) as yellow oils.To a solution of the mixture of alkynes **19** (81 mg, 0.186 mmol) in THF (2.25 mL) at rt was added TBAF·$3H_2O$ (71 mg, 0.225 mmol), and the mixture was stirred for 20 min. Water was

added, the aqueous phase was extracted with ether, and the combined extracts were washed with water and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography with 20−40% EtOAc/petrol as eluent to give the minor C2 epimer (12.1 mg, 18%) as a pale yellow oil: $[\alpha]^{17}_D$ +42.9 (*c* 0.82, $CHCl_3$); IR (thin film) 3468, 3267, 2956, 2926, 2855, 1770, 1466, 1202, 1124, 1013, 738 cm^{-1}; ^1H NMR (300 MHz) δ 0.88 (t, J = 6.3 Hz, 3H), 1.16−1.54 (m, 16H), 1.56−1.69 (m, 1H), 1.71−1.85 (m, 1H), 2.00 (dd, J = 13.8, 8.7 Hz, 1H), 2.59 (s, 1H), 3.03 (dd, J = 13.8, 6.0 Hz, 1H), 3.51 (s, 3H), 4.55 (m, 1H), 4.76 (d, J = 5.1 Hz, 1H), 4.96 (d, J = 5.4 Hz, 1H); ^{13}C NMR (75.5 MHz) δ 14.1, 22.7, 25.0, 29.3, 29.4, 29.5, 29.6, 31.9, 35.4, 35.8, 57.2, 73.6, 76.0, 77.7, 79.3, 80.0, 90.3, 108.4, 174.5; HRMS (ESI) calcd for $C_{20}H_{32}NaO_6$ $[M + Na]^+$ 391.2097, found 391.2102. Further elution gave the major C2 epimer **20** (41.4 mg, 61%) as a pale yellow oil: $[\alpha]^{17}_D$ +52.6 (*c* 1.02, $CHCl_3$); IR (thin film) 3434, 3287, 2926, 2556, 1776, 1467, 1203, 1029, 739 cm^{-1}; ^1H NMR (300 MHz) δ 0.87 (t, J = 6.6 Hz, 3H), 1.18−1.52 (m, 16H), 1.54−1.68 (m, 1H), 1.70−1.82 (m, 1H), 2.10 (dd, J = 13.8, 9.9 Hz, 1H), 2.80 (s, 1H), 2.92 (dd, J = 13.8, 5.4 Hz, 1H), 3.53 (s, 3H), 4.22 (s, 1H), 4.62 (m, 1H), 5.03 (s, 1H); ^{13}C NMR (75.5 MHz) δ 14.1, 22.6, 24.9, 29.3, 29.4, 29.47, 29.54, 31.9, 35.5, 40.7, 56.1, 77.7, 78.2, 78.5, 80.3, 81.2, 89.1, 108.0, 173.6; HRMS (ESI) calcd for $C_{20}H_{32}NaO_6$ $[M + Na]^+$ 391.2097, found 391.2101.

Methyl Ester 21. To a solution of the alkyne **20** (30 mg, 0.081 mmol) in MeOH (1.5 mL) was added Lindlar catalyst (8.4 mg, 0.004 mmol), the suspension was stirred under a H_2 atmosphere for 2 h and then filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography with 20−40% EtOAc/petrol as eluent to give the alkene as an oil (25 mg, 83%): $[\alpha]^{17}_D$ +63.7 (*c* 1.16, $CHCl_3$); IR (thin film) 3471, 2927, 2856, 1770, 1642, 1467, 1201, 1108, 1018, 738 cm^{-1}; ^1H NMR (300 MHz) δ 0.87 (t, J = 6.6 Hz, 3H), 1.16−1.48 (m, 16H), 1.51−1.61 (m, 1H), 1.63−1.78 (m, 1H), 1.97 (dd, J = 13.8, 9.9 Hz, 1H), 2.67 (dd, J = 13.8, 5.7 Hz, 1H), 3.52 (s, 3H), 4.26 (d, J = 2.4 Hz, 1H), 4.29 (m, 1H), 4.97 (d, J = 2.1 Hz, 1H), 5.51 (dd, J = 10.8, 1.5 Hz, 1H), 5.75 (dd, J = 17.1, 1.5 Hz, 1H), 6.15 (dd, J = 17.1, 10.8 Hz, 1H); ^{13}C NMR (75.5 MHz) δ 14.1, 22.7, 24.9, 29.3, 29.4, 29.47, 29.54, 31.9, 35.6, 38.6, 56.2, 77.4, 81.6, 82.0, 89.4, 108.8, 119.4, 132.1, 174.9; HRMS (ESI) calcd for $C_{20}H_{34}NaO_6$ $[M + Na]^+$ 393.2253, found 393.2255.Ozone gas was bubbled through a solution of the alkene (24 mg, 0.065 mmol) in CH_2Cl_2 (1.45 mL) and MeOH (50 μL) at −78 °C until a pale blue color persisted. Me_2S (23.7 μL, 0.323 mmol) was added, the solution was allowed to warm to rt, and stirring was continued for a further 30 min. Water and ether were added, and the aqueous phase was extracted with ether. The combined extracts were washed with water and brine and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The resulting crude aldehyde was dissolved in *tert*-butyl alcohol (0.42 mL), and 2-methyl-2-butene (67.9 μL) was added. A solution of $NaH_2PO_4 \cdot H_2O$ (17.8 mg, 0.13 mmol) and $NaClO_2$ (23.3 mg, 0.26 mmol) in water (0.23 mL) was then added and the mixture was stirred at rt for 17 h. Water and EtOAc were added, the aqueous phase was acidified with 10% aqueous HCl and then extracted with EtOAc, and the combined extracts were washed with water and brine and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was treated with excess CH_2N_2. Purification by flash silica gel chromatography with 30−50% EtOAc/petrol as eluent gave the methyl ester **21** (19.3 mg, 74%) as a clear oil: $[\alpha]^{17}_D$ +31.4 (*c* 0.97, $CHCl_3$); IR (thin film) 3473, 2956, 2927, 2856, 2361, 1780, 1742, 1457, 1208, 1125, 1027, 737 cm^{-1}; ^1H NMR (300 MHz) δ 0.87 (t, J = 6.6 Hz, 3H), 1.16−1.48 (m, 16H), 1.50−1.62 (m, 1H), 1.64−1.78 (m, 1H), 2.09 (dd, J = 14.4, 8.7 Hz, 1H), 2.23 (dd, J = 14.4, 6.0 Hz, 1H), 3.52 (s, 3H), 3.94 (s, 3H), 4.31 (m, 1H), 4.75 (d, J = 5.1 Hz, 1H), 5.12 (d, J = 5.4 Hz, 1H); ^{13}C NMR (75.5 MHz) δ 14.1, 22.7, 24.9, 29.2, 29.3, 29.4, 29.46, 29.54, 31.9, 35.7, 37.9, 53.7, 57.0, 76.9, 80.2, 85.3, 85.8, 108.4, 171.3, 173.8; HRMS (ESI) calcd for $C_{20}H_{34}NaO_8$ $[M + Na]^+$ 425.2151, found 425.2157.

Cinatrin B Methyl Ester 22. A solution of the methyl ketal **21** (11.8 mg, 0.029 mmol) in 80% aqueous acetic acid (1.42 mL) and 10% aqueous HCl (50μL) was heated at 100 °C for 3.5 h and then cooled to rt. Water was added, the aqueous phase was extracted with ether, and the combined extracts were washed with water, saturated aqueous $NaHCO_3$, and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was dissolved in MeOH (0.75 mL) and water (75 μL). $CaCO_3$ (87.5 mg, 0.87 mmol) and I_2 (181 mg, 0.71 mmol) were then added, and the resulting brown suspension was stirred at 70 °C for 18 h and then cooled to rt. Water was added, and the aqueous phase was extracted with ether. The combined extracts were washed with 1.5 M aqueous $Na_2S_2O_3$ and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography with 40% EtOAc/petrol as eluent to give cinatrin B methyl ester (**22**) (7.8 mg, 61%) as a white powder: mp 124−126 °C; $[\alpha]^{14}_D$ −13.2 (*c* 0.39, MeOH); IR (KBr) 3509, 3420, 2957, 2926, 2854, 1820, 1772, 1740, 1444, 1223, 1148 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 0.86 (t, J = 6.6 Hz, 3H), 1.18−1.40 (m, 16H), 1.63 (m, 2H), 2.31 (dd, J = 14.4, 9.6 Hz, 1H), 2.39 (dd, J = 14.4, 6.0 Hz, 1H), 3.75 (s, 3H), 4.53 (m, 1H), 4.76 (d, J = 6.6 Hz, 1H), 6.81 (d, J = 6.6 Hz, 1H), 7.34 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 13.9, 22.0, 24.3, 28.6, 28.7, 28.8, 28.9, 31.2, 34.3, 36.0, 52.8, 73.0, 77.2, 84.2, 84.3, 168.7, 172.0, 172.1; HRMS (ESI) calcd for $C_{19}H_{30}NaO_8$ $[M + Na]^+$ 409.1838, found 409.1821.

Cinatrin B (2). A solution of the methyl ester **22** (11.9 mg, 0.031 mmol) in THF (0.5 mL) and 2 M aqueous NaOH (0.5 mL, 1.0 mmol) was stirred at 40 °C for 24 h. Aqueous HCl (2 M, 0.56 mL, 1.12 mmol) was added, and stirring was continued for a further 1 h. The solution was allowed to cool to rt and stirred for a further 3.5 h. Water was added, the mixture was extracted with EtOAc, and the combined extracts were washed with brine and then dried (Na_2SO_4). The solvent was removed under reduced pressure to give a white powder (11.5 mg) that was purified by preparative reversed-phase HPLC (C-18 5 μm, 250 × 10 mm, 0.1% TFA−80% MeCN/H_2O as eluent, flow rate: 2 mLmin^{-1}; t_R 14.13 min; natural sample, t_R 14.13 min) to give cinatrin B (**2**) (3.4 mg, 30%) as a white powder: $[\alpha]^{18}_D$ −10.4 (*c* 0.17, MeOH). Natural sample: $[\alpha]^{16}_D$ −14.1 (*c* 0.17, MeOH); ^1H NMR (300 MHz, DMSO-d_6) δ 0.84 (t, J = 6.9 Hz, 3H), 1.14−1.39 (m, 16H), 1.63 (m, 2H), 2.31 (dd, J = 14.1, 9.6 Hz, 1H), 2.39 (dd, J = 14.1, 6.0 Hz, 1H), 4.53 (m, 1H), 4.74 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 13.9, 22.0, 24.4, 28.56, 28.6, 28.8, 28.88, 28.9, 31.2, 34.4, 36.2, 72.7, 77.1, 83.7, 84.1, 169.5, 172.3, 172.4; HRMS (ESI) calcd for $C_{18}H_{27}O_8$ $[M - H]^-$ 371.1706, found 371.1700.

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Supporting Information Available: Copies of the ^1H and ^{13}C NMR spectra of all key intermediates and synthetic and natural cinatrin B (**2**) as well as HPLC traces of synthetic and natural **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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