A Concise and Enantioselective Synthesis of a C-6 *O*-Acyl Side Chain Equivalent of Zaragozic Acid A

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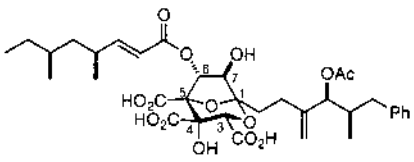
An optically pure C-6 *O*-acyl side chain equivalent of zaragozic acid A, (2*E*,4*S*,6*S*)-4,6-dimethyl-2-octenoic acid, which features a 1,3-*syn*-dimethyl-substituted carbon chain, has been readily synthesized from (*S*)-2-methylbutanal using a combination of the Evans aldol reaction and the Ireland deoxygenation method.

Key words zaragozic acid A; acyl side chain; Evans aldol reaction; Ireland deoxygenation method

Zaragozic acids and squalestatins, recently isolated from various fungal cultures by respective researchers at Merck and Glaxo, have been shown to be picomolar competitive inhibitors of squalene synthase.[1] In addition to their therapeutic potential for the treatment of hypercholesterolemia, these natural products possess a novel, densely oxygenated 4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic acid core, differing only in regard to the nature of the C1 alkyl and C6 *O*-acyl side chains. It is therefore not surprising that the zaragozic acids (squalestatins) have elicited considerable attention from numerous synthetic chemists.[2,3] The Nicolaou[4] and Heathcock[5] groups have accomplished the total synthesis of zaragozic acid A (squalestatin S1), while efforts of the groups of Carreira,[6] Evans,[7] and Armstrong,[8] as well as ours,[9] have culminated in the total synthesis of zaragozic acid C. Accordingly, our attention has now been turned to the total synthesis of zaragozic acid A. Herein we wish to report the easy and efficient access to (2*E*,4*S*,6*S*)-4,6-dimethyl-2-octenoic acid (**1**), the C-6 *O*-acyl side chain equivalent.[4,5a,10]

The α,β-unsaturated acid **1** was reported to be elaborated from (2*S*,4*S*)-2,4-dimethyl-1-hexanol (**2**) *via* oxidation and Wittig-type olefination.[5a,10b] Thus, alcohol **2** became a focal intermediate which features a minimum carbon chain with skip 1,3-*syn*-dimethyl stereogenic centers. Of a variety of approaches considered for the enantioselective synthesis of **2**, a route proceeding through the asymmetric alkylation of a chiral propionate-derived enolate with readily available (*S*)-2-methyl-1-iodobutane (**3**) was deemed highly attractive from the standpoint of conciseness and convergency. In this context, it has been well documented that Evans' chiral oxazolidinone-derived carboximide enolates[11] do not possess sufficient nucleophilicity toward β-branched alkyl halides such as **3**.[12] Although Decicco and Grover recently demonstrated that the enolates did react with β-branched alkyl triflates to give all four possible diastereomers with excellent stereocontrol, a large excess of the electrophile (25 eq) was required in the reaction.[13] In the synthesis of (+)-bourgeanic acid, White and Johnson reported that asymmetric alkylation of an enolate derived from (*S*)-prolinol *N*-propionamide[14] with **3** gave a 17 : 1 mixture of the adducts with the desired *syn* product as the major constituent, which, after saponification, was purified to optical homogeneity by recrystallization of the salt of the carboxylic acid and cinchonidine.[15] In the synthesis of zaragozic acid A, Nicolaou and co-workers synthesized **2** *via* (2*S*,4*S*)-2,4-dimethyl-1-hexanal (**4**) of 92% de,[4] which was obtained by the alkylation of Enders' chiral hydrazone enolate[16] with **3**. In the same context, Heathcock and co-workers who were cognizant of the shortcoming of Evans' chiral oxazolidinone-derived carboximide enolates, as described above, addressed an alternative alkylation and found access to optically pure **2**; methylation of the imide prepared from Evans' chiral oxazolidinone and (*S*)-4-methylhexanoic acid, derived from **3**, provided the diastereomers in a 17 : 1 ratio of *syn* to *anti* isomers, from which the *syn* isomer was separated by flash chromatography.[5a] Thus, the asymmetric alkylation approach to optically pure **1**, employing well-established chiral auxiliaries, has suffered from tedious separation of the diastereomers.[17]

Departing from the alkylation route, we then directed our attention to an approach capitalizing on the aldol reaction[18] between chiral *N*-propionyl-2-oxazolidinone **5** and (*S*)-2-methylbutanal (**6**),[19] followed by deoxygenation,[20] because the Evans aldol reaction provides the most reliable means for the controlled creation of vicinal *syn* stereogenic centers, irrespective of the absolute configuration of α-branched aldehydes.[21] Indeed, condensation of the boron enolate derived from **5** with **6** provided the crystalline *syn* aldol adduct **7** as a single diastereomer in 78% yield, the homochirality of which was confirmed by 500 MHz ^{1}H- and 100 MHz ^{13}C-NMR. Removal of the oxazolidinone auxiliary from **7** by reduction with lithium borohydride,[22] followed by selective silylation of the resultant diol, furnished the secondary alcohol **8** in 84% yield. While a number of methods for deoxygenation were reported,[23] we initially explored a combination of mesylate formation and reduction with lithium aluminum hydride.[24] However, reduction of the mesylate was found not to take place even under harsh conditions, which might be accounted for by steric hindrance due to a *syn*/*syn* relationship



Zaragozic Acid A

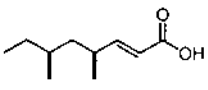


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Fig. 1. Zaragozic Acid A and C-6 *O*-Acyl Side Chain Equivalent **1**

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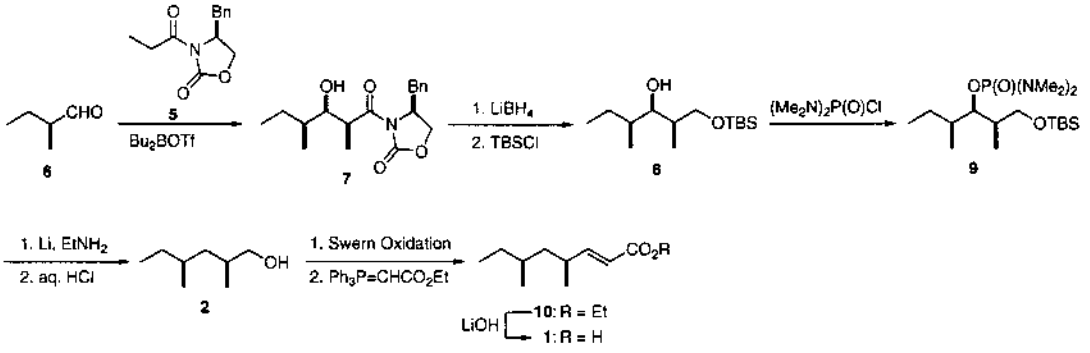

Chart 1

in the C2–C4 stereotriad. We then chose the Ireland deoxygenation procedure[25] in preference to the Barton–McCombie reaction,[26] because the latter method has demonstrated the formation of toxic tin byproducts difficult to remove completely from the product. Treatment of the alcohol **8** with *n*-butyllithium, followed by condensation with *N*,*N*,*N*′,*N*′-tetramethylphosphorodiamidic chloride, gave the corresponding phosphorodiamidate **9** in 80% yield, which was found to be more stable than the corresponding diethyl phosphate and is easily handled. The reduction of **9** with lithium in ethylamine at 0 °C proceeded cleanly to give a deoxygenated product, which, upon desilylation, produced the alcohol **2**, $[\alpha]_D^{27}$ −4.56° (c=1.64, $CHCl_3$) [lit.[10b] $[\alpha]_D^{27}$ −4.5° (c=1.60, $CHCl_3$)], in 81% overall yield. Oxidation of **2** under standard Swern conditions, followed by immediate condensation with $Ph_3P{=}CHCO_2Et$, afforded exclusively the (*E*)-α,β-unsaturated ester **10** in 84% yield. Finally, the saponification of **10** furnished the target acid **1**, $[\alpha]_D^{24}$ +58.6° (neat) [lit.[27] $[\alpha]_D^{19}$ +55° (neat)], in 98% yield, which exhibited identical spectroscopic data with those reported for a sample by the degradation of zaragozic acid A.

In summary, we have achieved the synthesis of an optically pure C-6 *O*-acyl side chain equivalent of zaragozic acid A with an overall yield of 35% for the nine-step sequence. The present protocol, employing a combination of an Evans aldol reaction and an Ireland deoxygenation method, has the advantage of providing a practical entry to 1,3-dimethyl-substituted carbon chains with virtually complete enantio- and diastereocontrol, and thus represents a potent alternative to an asymmetric alkylation strategy.[17]

Experimental

Melting points were determined on a Büchi 535 digital melting point apparatus and are uncorrected. NMR spectra were measured with JEOL JNM-EX270 (^{13}C at 67.8 MHz), JEOL JNM-AL400 (^{13}C at 100 MHz) or Bruker ARX-500 spectrometers (^{1}H at 500 MHz), with tetramethylsilane (δ 0.0, ^{1}H) or chloroform-d_1 (δ 77.0, ^{13}C) as internal standards. Infrared spectra were recorded on a Jasco FT/IR-5300 spectrometer. Optical rotations were measured on a Jasco DIP-370 digital polarimeter. Electron impact (EI) mass spectra were obtained on a JEOL DX-303 spectrometer, operating with an ionization energy of 70 eV. FAB-MS were obtained on a JEOL JMS-HX110 spectrometer. Column chromatography was performed on Merck silica gel 60 (70—230 mesh). Bulb-to-bulb distillation was performed using a Büchi Kugelrohr apparatus, and the oven temperature is recorded as the boiling point. Di-*n*-butylboron triflate[28] and (*S*)-4-benzyl-3-propionyl-2-oxazolidinone (**5**)[18b] were prepared according to literature procedures.

(2′*S*,3′*R*,4*S*,4′*S*)-3-3′-Hydroxy-2′,4′-dimethylhexanoyl-4-benzyl-2-oxazolidinone (7) To a stirred solution of **5** (12.4 g, 53 mmol) in CH_2Cl_2 (130 ml) at 0 °C was added di-*n*-butylboron triflate (18.0 ml, 71 mmol), followed by triethylamine (12.0 ml, 86 mmol). After 0.5 h of stirring at 0 °C, the mixture was cooled to −78 °C and a solution of (*S*)-2-methylbutanal (**6**) (5.9 g, 69 mmol) in CH_2Cl_2 (15 ml) was added. The mixture was stirred at −78 °C for 1 h, and then at 0 °C for another 2 h. The reaction was quenched with pH 7 phosphate buffer (60 ml), and the mixture was diluted with MeOH (100 ml). A 2 : 1 mixture of MeOH–30% aqueous H_2O_2 (200 ml) was added at 0 °C, and the whole was stirred vigorously for 1 h. After the volatile elements were removed *in vacuo*, the residue was diluted with EtOAc (60 ml) and the layers were separated. The organic layer was washed successively with saturated aqueous $NaHCO_3$ (40 ml), 10% aqueous $Na_2S_2O_3$ (40 ml) and brine (2×10 ml), then dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* furnished the crude product (18.1 g), which was purified by column chromatography (silica gel 500 g, 5 : 1 hexane–EtOAc) to give aldol adduct **7** (13.2 g, 78%) as colorless needles, mp 90.0—90.5 °C (hexane), $[\alpha]_D^{27}$ +43.1° (c=1.07, $CHCl_3$). IR (Nujol) cm^{-1}: 3522, 2924, 1777, 1692, 1456, 1200. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, J=7.3 Hz, C$\underline{H}_3$CH$_2$), 0.98 (3H, d, J=6.5 Hz, CHC$\underline{H}_3$), 1.14 (1H, m, CH$_3$C$\underline{H}_2$), 1.27 (3H, d, J=7.0 Hz, CHC$\underline{H}_3$), 1.43—1.56 (2H, m, C$\underline{H}_2$CH), 2.62 (1H, br s, O$\underline{H}$), 2.79 (1H, dd, J=9.5, 13.4 Hz, PhC$\underline{H}_2$), 3.26 (1H, dd, J=3.3, 13.4 Hz, PhC$\underline{H}_2$), 3.69 (1H, m, C$\underline{H}$OH), 3.99 (1H, dq, J=3.7, 7.0 Hz, C$\underline{H}$CO), 4.19 (1H, dd, J=3.0, 9.0 Hz, C$\underline{H}_2$O), 4.23 (1H, dd, J=7.6, 9.0 Hz, C$\underline{H}_2$O), 4.70 (1H, dddd, J=3.0, 3.3, 7.6, 9.5 Hz, C$\underline{H}$N), 7.21 (2H, m, Ar$\underline{H}$), 7.28 (1H, m, Ar$\underline{H}$), 7.34 (2H, m, Ar$\underline{H}$). ^{13}C-NMR ($CDCl_3$) δ: 11.2 (CH$_3$×2), 14.5 (CH$_3$), 25.6 (CH$_2$), 37.1 (CH), 37.7 (CH$_2$), 39.8 (CH), 55.1 (CH), 66.1 (CH$_2$), 75.0 (CH), 127.4 (CH), 128.9 (CH), 129.4 (CH), 135.0 (C), 152.8 (C=O), 177.5 (C=O). EI-MS *m/z* (rel. int. %): 319 (M^+, 10), 301 (8.3), 262 (22), 244 (33), 178 (100), 143 (26). HR-EI-MS *m/z*: 319.1757 (Calcd for $C_{18}H_{25}NO_4$: 319.1784). *Anal*. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.38. Found: C, 67.85; H, 8.03; N, 4.32.

(2*S*,3*R*,4*S*)-1-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylhexan-3-ol (8) A 2 M solution of lithium borohydride in tetrahydrofuran (THF) (22 ml, 44 mmol) was added to a solution of aldol adduct **7** (11.9 g, 37 mmol) in THF (150 ml)–water (0.8 ml, 44 mmol) at 0 °C. After being stirred at 0 °C for 1 h, the reaction was quenched with 0.5 N aqueous potassium sodium tartrate (160 ml) at 0 °C, followed by stirring at room temperature for 1 h. After the volatile elements were removed *in vacuo*, the whole was extracted with EtOAc (3×60 ml). The combined organic extracts were washed with brine (2×20 ml) and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* furnished the crude product (11.2 g), which was used without further purification for the next reaction. Imidazole (5.1 g, 75 mmol) and *tert*-butyldimethylsilyl chloride (6.0 g, 40 mmol) were added to a solution of the diol in *N*,*N*-dimethylformamide (DMF) (60 ml). After being stirred at room temperature for 10 h, the reaction was quenched with water (120 ml) and the whole was extracted with EtOAc (100 ml). The organic layer was washed with brine (2×30 ml) and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* provided the crude product (16.8 g), which was purified by column chromatography (silica gel 200 g, 30 : 1 hexane–EtOAc) to give monosilyl ether **8** (8.1 g, 84% for 2 steps) as a colorless oil, $[\alpha]_D^{31}$ −10.0° (c=1.49, EtOH). IR (film) cm^{-1}: 3472, 2959, 1464, 1256, 1088, 837. ^{1}H-NMR ($CDCl_3$) δ: 0.07 (6H, s, (C$\underline{H}_3$)$_2$Si), 0.88 (3H, t, J=7.4 Hz, C$\underline{H}_3$CH$_2$), 0.90 (9H, s, (C$\underline{H}_3$)$_3$CSi), 0.95 (3H, d, J=7.0 Hz, C$\underline{H}_3$CHCH$_2$O), 0.98 (3H, d, J=6.6 Hz, C$\underline{H}_3$CH), 1.09 (1H, m, CH$_3$C$\underline{H}_2$), 1.41 (1H, m, CH$_3$C$\underline{H}_2$), 1.50 (1H, m, CH$_3$C$\underline{H}$), 1.80 (1H, m, C$\underline{H}$CH$_2$O), 2.83 (1H, br s, O$\underline{H}$), 3.52 (1H, dd, J=2.5, 8.0 Hz, C$\underline{H}$OH), 3.68 (1H, dd, J=4.4, 9.8 Hz, C$\underline{H}_2$O), 3.75 (1H, dd, J=3.7, 9.8 Hz, C$\underline{H}_2$O). ^{13}C-NMR ($CDCl_3$) δ: −5.84 (CH$_3$), −5.78 (CH$_3$), 10.1 (CH$_3$), 10.8 (CH$_3$), 14.7 (CH$_3$), 18.0 (C), 25.5 (CH$_2$), 25.7 (CH$_3$), 36.3 (CH), 37.1 (CH), 68.3 (CH$_2$), 77.5 (CH). EI-MS *m/z* (rel. int.

%): 261 (M^++H, 0.4), 243 (M^+−OH, 0.4), 203 (20), 145 (6.3), 69 (100). HR-EI-MS *m/z*: 243.2148 (Calcd for $C_{14}H_{31}OSi$: 243.2144).

(2*S*,3*R*,4*S*)-3-[Bis(dimethylamino)phosphoryl]-1-(*tert*-butyldimethylsilyloxy)-2,4-dimethylhexane (9) To a solution of alcohol **8** (6.88 g, 26 mmol) in 4 : 1 THF–*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) (100 ml) at 0 °C was added *n*-butyllithium in hexane (1.57 M, 20 ml, 31 mmol), followed by tetramethylphosphorodiamidic chloride (10 ml, 68 mmol). After being stirred under reflux for 3 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (40 ml). The mixture was diluted with EtOAc (20 ml), and the layers were separated. The aqueous layer was extracted with EtOAc (40 ml), and the combined organic extracts were washed with brine (2×20 ml) and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* provided the crude product (13.1 g), which was purified by column chromatography (silica gel 150 g, 60 : 1 CH_2Cl_2–MeOH) to give phosphorodiamidate **9** (8.29 g, 80%) as a yellow oil, $[\alpha]_D^{29}$ −2.88° (*c*=1.03, $CHCl_3$). IR (film) cm^{-1}: 3358, 2930, 1462, 1304, 1211, 748. ^{1}H-NMR ($CDCl_3$) δ: 0.041 (3H, s, $(C\underline{H}_3)_2Si$), 0.044 (3H, s, $(C\underline{H}_3)_2Si$), 0.89 (9H, s, $(C\underline{H}_3)_3CSi$), 0.91 (3H, t, *J*=7.4 Hz, $C\underline{H}_3CH_2$), 0.93 (3H, d, *J*=6.8 Hz, $C\underline{H}_3CH$), 0.98 (3H, d, *J*=6.9 Hz, $C\underline{H}_3CHCH_2O$), 1.17 (1H, m, $CH_3C\underline{H}_2$), 1.58 (1H, m, $CH_3C\underline{H}_2$), 1.71 (1H, m, $CH_3C\underline{H}$), 1.91 (1H, m, $C\underline{H}CH_2O$), 2.637 (6H, d, *J*=9.5 Hz, $[(C\underline{H}_3)_2N]_2$), 2.641 (6H, d, *J*=9.5 Hz, $[(C\underline{H}_3)_2N]_2$), 3.43 (1H, dd, *J*=7.3, 9.8 Hz, $C\underline{H}_2O$), 3.62 (1H, dd, *J*=5.7, 9.8 Hz, $C\underline{H}_2O$), 4.26 (1H, dt, *J*=9.1, 4.1 Hz, $C\underline{H}OP$). ^{13}C-NMR ($CDCl_3$) δ: −5.35 (CH_3×2), 12.1 (CH_3), 12.8 (CH_3), 14.8 (CH_3), 18.2 (C), 25.9 (CH_2, CH_3×3), 36.7 (CH_3), 38.2 (J_{C-P}=3.7 Hz, CH), 38.5 (J_{C-P}=3.7 Hz, CH), 66.2 (CH_2), 80.9 (J_{C-P}=3.7 Hz, CH). FAB-MS *m/z* (rel. int. %): 395 (M^++H, 70), 153 (100). HR-FAB-MS *m/z*: 395.2880 (Calcd for $C_{18}H_{44}N_2O_3PSi$: 395.2859).

(2*S*,4*S*)-2,4-Dimethylhexan-1-ol (2) Lithium (760 mg, 110 mmol) was dissolved in ethylamine (100 ml) at 0 °C. After the solution turned blue, a solution of phosphorodiamidate **9** (8.19 g, 21 mmol) in THF (10 ml) was added and the mixture was stirred at 0 °C for 0.5 h. The reaction was quenched with NH_4Cl (1.3 g) and ethylamine was evaporated. The residue was partitioned between Et_2O (50 ml) and H_2O (50 ml). The organic layer was successively washed with 1 N aqueous HCl (50 ml) and brine (2×15 ml) and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* afforded the crude product (4.66 g), which was used without further purification for the next reaction. The silyl ether was dissolved in THF (20 ml) and mixed with 2 N aqueous HCl (20 ml). After being stirred for 48 h, the mixture was diluted with Et_2O (30 ml) and the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ (10 ml) and brine (2×10 ml) and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* provided the crude product (5.23 g), which was purified by column chromatography (silica gel 50 g, 4 : 1 hexane–Et_2O) to give alcohol **2** (2.20 g, 81%) as a colorless oil, $[\alpha]_D^{27}$ −4.56° (*c*=1.64, $CHCl_3$). IR (film) cm^{-1}: 3347, 2961, 1462, 1379, 1034. ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, t, *J*=7.4 Hz, $C\underline{H}_3CH_2$), 0.88 (3H, d, *J*=6.6 Hz, $C\underline{H}_3CH$), 0.92 (3H, d, *J*=6.6 Hz, $C\underline{H}_3CH$), 1.09 (1H, m), 1.28—1.48 (4H, m), 1.72 (1H, m), 3.38 (1H, dd, *J*=6.8, 10.5 Hz, $C\underline{H}_2OH$), 3.51 (1H, dd, *J*=5.1, 10.5 Hz, $C\underline{H}_2OH$). ^{13}C-NMR ($CDCl_3$) δ: 11.2 (CH_3), 17.3 (CH_3), 19.8 (CH_3), 29.0 (CH_2), 31.6 (CH), 33.1 (CH), 40.6 (CH_2), 68.2 (CH_2). EI-MS *m/z* (rel. int. %): 113 (M^+−OH, 15), 83 (77), 70 (83), 58 (100). HR-EI-MS *m/z*: 113.1334 (Calcd for C_8H_{17}: 113.1330).

Ethyl (2*E*,4*S*,6*S*)-4,6-dimethyl-2-octenoate (10) A solution of dimethyl sulfoxide (DMSO) (2.8 ml, 40 mmol) in CH_2Cl_2 (10 ml) was added to a solution of oxalyl chloride (1.6 ml, 18 mmol) in CH_2Cl_2 (40 ml) at −78 °C. After 0.5 h of stirring at −78 °C, a solution of alcohol **2** (1.95 g, 15 mmol) in CH_2Cl_2 (10 ml) was added. After an additional 0.5 h of stirring at −78 °C, triethylamine (11 ml, 79 mmol) was added. The mixture was stirred at −78 °C for 0.5 h, then was allowed to warm to 0 °C. The reaction was quenched with H_2O (30 ml) and the mixture was diluted with 10 : 1 Et_2O–pentane (70 ml). The layers were separated and the aqueous layer was extracted with 10 : 1 Et_2O–pentane (2×20 ml). The combined organic extracts were successively washed with 1 N aqueous HCl (30 ml), saturated aqueous $NaHCO_3$ (20 ml) and brine (2×10 ml), then dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* furnished the crude product (2.47 g), which was used without further purification for the next reaction. (Carbethoxymethylene)-triphenylphos phorane (6.95 g, 20 mmol) was added to a solution of the aldehyde in CH_2Cl_2 (20 ml). After 5 h of stirring at room temperature, the solvent was evaporated and the residue (9.93 g) was purified by column chromatography (silica gel 95 g, 40 : 1 hexane–Et_2O) to give (*E*)-α,β-unsaturated ester **10** (2.49 g, 84%) as a colorless oil, $[\alpha]_D^{28}$ +47.7° (*c*=1.13, $CHCl_3$). IR (film) cm^{-1}: 2963, 1723, 1651, 1462, 1370, 1273, 1182, 986. ^{1}H-NMR ($CDCl_3$) δ: 0.82—0.87 (6H, m, CH_3×2), 1.03 (3H, d, *J*=6.7 Hz, $C\underline{H}_3CH$), 1.07—1.17 (2H, m, $C\underline{H}_2$), 1.28 (3H, t, *J*=7.1 Hz, $OCH_2C\underline{H}_3$), 1.24—1.41 (3H, m, $C\underline{H}$, $C\underline{H}_2$), 2.40 (1H, m, $C\underline{H}CH$=), 4.18 (2H, q, *J*=7.1 Hz, $OC\underline{H}_2CH_3$), 5.77 (1H, d, *J*=15.7 Hz, =$C\underline{H}CO$), 6.81 (1H, dd, *J*=8.4, 15.7 Hz, $CHC\underline{H}$=). ^{13}C-NMR ($CDCl_3$) δ: 11.1 (CH_3), 14.3 (CH_3), 18.9 (CH_3), 20.4 (CH_3), 29.8 (CH_2), 31.9 (CH), 34.3 (CH), 43.4 (CH_2), 60.1 (CH_2), 119.6 (CH), 154.7 (CH), 166.9 (C=O). EI-MS *m/z* (rel. int. %): 198 (M^+, 2.6), 169 (30), 153 (30), 141 (44), 69 (100). HR-EI-MS *m/z*: 198.1626 (Calcd for $C_{12}H_{22}O_2$: 198.1620).

(2*E*,4*S*,6*S*)-4,6-Dimethyl-2-octenoic Acid (1) Lithium hydroxide monohydrate (1.28 g, 31 mmol) was added to a solution of ester **10** (1.98 g, 10.0 mmol) in 3 : 1 MeOH–H_2O (20 ml) at room temperature. After 12 h of stirring at room temperature, the solvent was evaporated *in vacuo*. The residue was dissolved in H_2O (15 ml) and the whole was washed with hexane (2×10 ml). The aqueous layer was acidified with 10% aqueous HCl (20 ml), and was extracted with EtOAc (20 ml). The organic layer was washed with brine (2×5 ml) and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo*, followed by bulb-to-bulb distillation, afforded carboxylic acid **1** (1.67 g, 98%) as a colorless oil, bp 120 °C (1 mmHg), $[\alpha]_D^{24}$ +58.6° (neat, d^{24}=0.954) [lit.[27] $[\alpha]_D^{19}$ +55° (neat)]. IR (film) cm^{-1}: 2963, 1698, 1420, 1287, 988. ^{1}H-NMR ($CDCl_3$) δ: 0.83—0.88 (6H, m, $C\underline{H}_3CH_2$, $C\underline{H}_3CH$), 1.05 (3H, d, *J*=6.7 Hz, $C\underline{H}_3CH$), 1.09—1.18 (2H, m), 1.25—1.42 (3H, m), 2.45 (1H, m, $C\underline{H}CH$=), 5.79 (1H, d, *J*=15.6 Hz, =$C\underline{H}CO_2H$), 6.94 (1H, dd, *J*=8.4, 15.6 Hz, $CHC\underline{H}$=). ^{13}C-NMR ($CDCl_3$) δ: 11.2 (CH_3), 18.8 (CH_3), 20.2 (CH_3), 29.8 (CH_2), 31.9 (CH), 34.4 (CH), 43.3 (CH_2), 119.0 (CH), 157.3 (CH), 172.4 (C=O). EI-MS *m/z* (rel. int. %): 170 (M^+, 2.5), 155 (2.0), 141 (35), 114 (34), 100 (68), 43 (100). HR-EI-MS *m/z*: 170.1314 (Calcd for $C_{10}H_{18}O_2$: 170.1306).

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