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Synthesis of (E)-2,6-Dimethyl-6-hydroxyocta-2,7-dienoic Acid and the Corresponding Amide ("Acacialactam") in Optically Active Form

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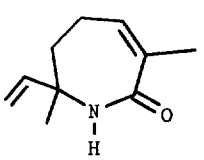
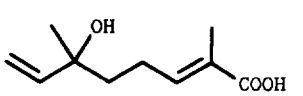
Abstract: The total synthesis of the title compounds in optically active form from geraniol as the starting material is described. The physical and spectral properties of the synthetic amide are identical with those of the natural compound acacialactam, this fact confirming that the structure proposed for the latter compound is not correct. The configuration of the single stereogenic carbon atom in the natural amide is shown to be *S*.

The seeds of the leguminous plant *Acacia concinna* DC. have been used in folk medicine of some tropical countries for the treatment of skin diseases. In the search for the biologically active principles of this species, Sekine *et al.*[1] isolated from its seeds an optically active product and assigned to it the cyclic amide structure **1** on the basis of its physical and spectral properties. According to its origin and structure, the product was named acacialactam. Three years later, a compound with structure **1** was synthesized in a unambiguous way by Holmes *et al.*,[2] who found their compound having spectral properties different from those reported for acacialactam. They then proposed that the natural compound might possibly be the *acyclic* amide **3**.



1



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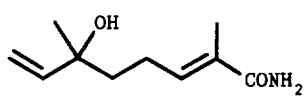
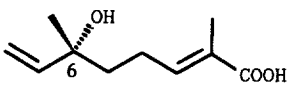


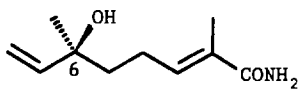
3

We recently isolated from a plant source[3] the monoterpene acid **2**, the amide of which is compound **3**. The same acid had previously been isolated from an extract of *Juniperus thurifera*.[4] This product, however, displayed an optical rotation opposite in sign to that observed in our compound. In order to establish its absolute configuration, we have performed a synthesis of the acid in optically active form. At the same time, we have also synthesized the corresponding amide **3** with the purpose of comparing its physical and spectral properties with those of acacialactam. As

a result, we have determined the absolute configuration of the stereogenic centre in natural (−)-**2** as 6*R*. Furthermore, we have given experimental support to the previous suggestion[2] that acacialactam has actually structure **3**, and have determined its absolute configuration as 6*S*. Therefore the name initially proposed for this compound is not appropriate.



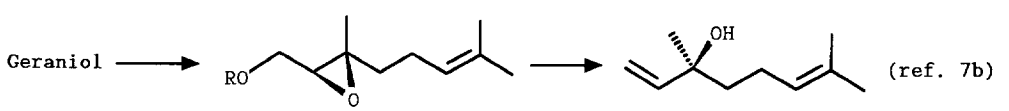
R-(-)-2



S-(+)-3

Taking into account the structural relationship between the target molecules and the monoterpene linalool, we initially considered this commercially available compound to be a suitable starting material. In fact, the conversion of linalool to the methyl ester of **2** via oxidation of one allylic methyl group with SeO_2 has already been described.[4] We preferred, however, an alternative strategy in which the trisubstituted double bond of linalool would be first cleaved and then rebuilt with the desired functionality already in place. This kind of strategy has proven successful, as shown in our preliminary report on the synthesis of racemic **2** and **3** starting from racemic linalool.[5] In the present paper, we wish to communicate the complete experimental details of our work, which now includes the preparation of compounds **2** and **3** in optically active form.

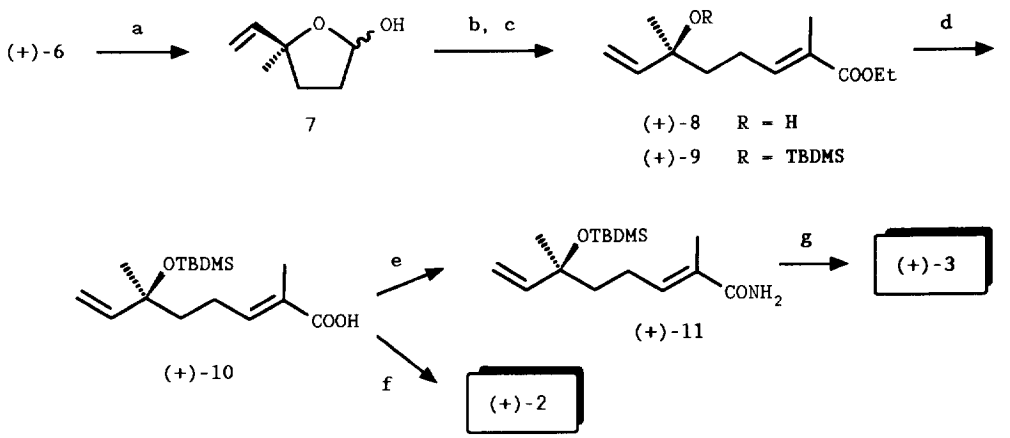
For the synthesis of the optically active compounds, we needed optically active linalool with a high degree of optical purity. Although its use as a starting material has been reported,[6] we have not been able to find a suitable commercial source. However, its preparation via Sharpless asymmetric epoxidation of geraniol has been described several times.[7] From the published procedures, the one depicted in Scheme 1 was particularly convenient. Epoxide (−)-**4** (88% ee)[7] was converted to (S)-linalool (+)-**6** via tosylate (−)-**5**. From that point, the synthesis transcurred along the same lines described for racemic linalool in our previous report[5] (Scheme 2). Selective ozonolysis of the trisubstituted double bond in (+)-**6** was achieved at low temperature in the



(-)-4 R = H
(-)-5 R = Ts

(+)-6

Scheme 1



Scheme 2

a: O_3, pyridine, CH_2Cl_2, $-78°C$, 45 min., 88%. **b**: $Ph_3P=C(Me)COOEt$ (3 eq), PhCOOH (cat. am.), benzene, reflux, 2 h, 57%. **c**: TBDMSiOTf (2 eq), 2,6-lutidine, CH_2Cl_2, room temp., 24 h, 92%. **d**: NaOH/aq EtOH, 70 °C, 24 hr, 83%. **e**: 1: ClCOOEt (1.1 eq), Et_3N, THF, $-78°C$, 15 min. 2: aq NH_3, room temp., 3 hr, 60% overall. **f**: TBAF (2 eq)/THF, 60°C, 24 hr, 75%. **g**: TBAF (2 eq)/THF, 60°C, 24 hr, 82%.

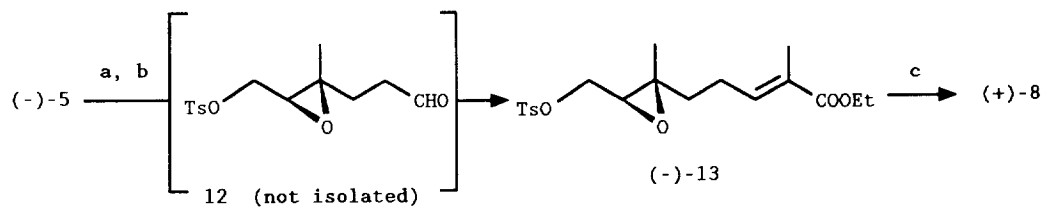
presence of pyridine.[6,8] Wittig reaction on the obtained lactol **7** afforded the conjugated hydroxy ester (+)-**8**.[9] Since all attempts at saponifying **8** to **2** only produced extensive decomposition of the ester,[4] the tertiary hydroxyl group was temporarily protected as its *t*-butyldimethylsilyl (TBDMS) derivative. The silylated ester (+)-**9** could be then hydrolyzed to (+)-**10** in 83% yield, this proving that the free hydroxyl group in **8** was the origin of the decomposition during the alkaline hydrolysis. Desilylation of **10** gave an acid which proved identical with the natural product **2** in its spectral and chromatographic behaviour. The optical rotation of synthetic S-(+)-**2** was $+11.1°$, whereas our natural product displayed an α_D $-12°$. Consequently, natural (−)-**2** displays the *R* configuration in its stereogenic carbon atom C-6.

The acid **10** was converted to the primary amide (+)-**11** in 60% overall yield via the mixed anhydride.[10] Desilylation of **11** furnished a primary amide (+)-**3** identical in its spectral properties to the product described as acacialactam in the literature[1,2,5] (12% overall yield from (−)-**4**). This confirms that the latter compound is not a lactam but has instead structure **3**. The optical rotation of our synthetic S-(+)-**3** is $+17.5°$, with the same sign therefore as the natural amide **3** (α_D $+4.3°$).[1] Our value, however, is significantly higher, which may mean that the natural amide isolated by Sekine *et al.*[1] was either impure or partially racemic.

Considering that some of the previously described reactions still gave insatisfactory yields, we tried to improve the overall result modifying the synthetic scheme. One of its critical points is the selective ozonolysis step **6** → **7**, which has to be conducted under carefully controlled conditions and is not easy to scale down, due to problems in the dosage of ozone.[6] A further aspect is the

mediocre yield in the Wittig reaction **7** → **8**. This may be possibly due to the comparatively hard reaction conditions (reflux in benzene), which are in turn related to the fact that the aldehyde **7** occurs mainly in the masked lactol form.

An obvious way to solve these problems is to invert the order of some steps and to perform the ozonolysis/Wittig protocol *before* the creation of the vinyl carbinol moiety. As a matter of fact, we put this into practice with epoxy tosylate (−)-**5**[7c] (Scheme 3). As expected, ozonolysis of the double bond in **5** was performed without special precautions under the usual conditions. The aldehyde intermediate **12** was not isolated but submitted *in situ* to the Wittig reaction under mild conditions to yield the conjugated epoxy ester (−)-**13** in an excellent 92% overall yield. The vinyl

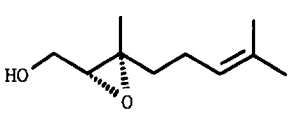


Scheme 3

a: O_3, pyridine, $MeOH/CH_2Cl_2$, −78°C, 5 min, Me_2S, room temp., 30 min. **b**: $Ph_3P=C(Me)COOEt$ (2 eq), benzene, room temp., 24 h, 92% overall. **c**: Zn/Cu, NaI, THF, reflux, 2.5 h, 81%.

carbinol segment was now unveiled with the efficient one-pot procedure[7b] which obviates the need of isolating the intermediate iodide. Hydroxy ester (+)-**8** was obtained in 81% yield and then converted to **2** and **3** along the previously disclosed pathways. With these modified procedures, the overall yield of the latter compound was now 25%, based again on epoxide (−)-**4**.

The enantiomeric epoxide (+)-**4**[7] was also used as the starting material. In this way, the enantiomeric series of compounds (+)-**5**, (−)-**8**, (−)-**9**, (−)-**10**, (−)-**11**, (+)-**13**, (−)-**2** and (−)-**3** was obtained alongside the same reactions as above and with essentially the same yields. The optical rotations of all these products are given in the Experimental section.



(+)-4

EXPERIMENTAL

NMR spectra were measured in $CDCl_3$ solution (Varian Unity 400 and Gemini 200). Mass spectra were run by the electron impact mode (70 eV) on a VG AutoSpec mass spectrometer. IR spectra were recorded as oily films on NaCl plates. Optical rotations were measured at 20 °C. Reactions which required an inert atmosphere were carried under argon (Ar) with flame-dried glassware. Commercial reagents (Aldrich or Fluka) were used as received. THF was distilled under Ar from sodium-benzophenone ketyl. Benzene was distilled under Ar from sodium. Dichloromethane was distilled from P_2O_5. Unless otherwise detailed, "work-up" means pouring the reaction mixture into brine, extraction with the indicated solvent, additional washing with 5% aq $NaHCO_3$, (if acids had been utilized in the reaction) or with 5% aq HCl (if bases had been utilized), then again with brine, drying over anhydrous Na_2SO_4 or $MgSO_4$ and elimination of the solvent *in vacuo*. The obtained material was then chromatographed on a silica gel column (Süd-Chemie AG, 50-200 μ). All obtained products gave satisfactory microanalytical data (C, H ±0.5%).

(2RS,5S)-2-*hydroxy*-5-*methyl*-5-*vinyltetrahydrofuran* (**7**). A solution of optically active linalool (+)-**6** (6 g, 39 mmol) in dry CH_2Cl_2 (150 ml) containing pyridine (3.3 ml, 40 mMol) was cooled to −78 °C. Ozone-enriched oxygen was then bubbled through the solution at this temperature, and the advance of the reaction was followed by TLC monitoring. The process was stopped when approx. 65-70% of the starting product was consumed (ca. 45 min). The reaction mixture was then poured into 5% aq HCl, the organic layer was washed with brine, dried and concentrated *in vacuo*. Chromatography of the oily residue on silica gel (hexane-EtOAc 7:3) afforded 2.22 of unreacted linalool and 2.77 g of lactol **7** (88%, based on consumed starting material) as a mixture of anomers: oil, IR $\bar{\nu}_{max}$ cm^{-1}: 3600-3300 (br), 1711, 1648, 1452, 1369, 1276, 1175, 1155, 1102, 1026, 993, 921; EIMS, *m/z* (% rel. int.): 113 ($M^+ - Me$, 27), 111 ($M^+ - OH$, 100), 95 ($M^+ - Me - H_2O$, 22), 93 (45), 81 (18), 71 (29), 67 (32), 55 (28); ^1H NMR (200 MHz): δ 6.00 (1H, *dd*, J = 17.4, 10.8 Hz), 5.74 (1H, *dd*, J = 17.2, 10.6 Hz), 5.20 (1H, *dd*, J = 17.4, 1.4 Hz), 5.08 (1H, *dd*, J = 17.2, 1.6 Hz), 5.02 (1H, *dd*, J = 10.8, 1.4 Hz), 4.94 (1H, *dd*, J = 10.6, 1.6 Hz), 4.50-4.40 (2H, *br s*, OH), 2.10-1.70 (8H, *m*), 1.40 (3H, *s*), 1.22 (3H, *s*); ^{13}C NMR (50 MHz): δ 144.6 (*d*), 143.0 (*d*), 111.9 (*t*), 111.3 (*t*), 98.6 (*d*), 98.5 (*d*), 84.5 (*s*), 84.0 (*s*), 35.4 (*t*), 35.0 (*t*), 33.0 (*t*), 32.6 (*t*), 27.9 (*q*), 25.8 (*q*).

(+)-*Ethyl* (2E,6S)-2,6-*dimethyl*-6-*hydroxyocta*-2,7-*dienoate*, (+)-**8**. A solution of lactol **7** (1.83 g, 14.3 mmol) in dry benzene (75 ml) was treated under Ar with carbethoxyethylidenetriphenylphosphorane[9] (15.54 g, 42.9 mmol) and a catalytic amount of benzoic acid (10 mg). The reaction mixture was then stirred at reflux for 2 hr. Work-up (extraction with Et_2O) and chromatography on silica gel (hexane-EtOAc 7:3) furnished (+)-**8** (1.73 g, 57%) as a colourless oil, $[\alpha]_D$ +15.8° ($CHCl_3$; c 5.3); IR $\bar{\nu}_{max}$ cm^{-1}: 3600-3300 (br), 1709, 1648, 1448, 1368, 1276, 1174, 1148, 1102, 921; EIMS, *m/z* (% rel. int.): 194 ($M^+ - H_2O$, 2), 166 (4), 165 (10), 151 (8), 138 (17), 131 (24), 121 (30), 71 (100), 67 (40), 55 (43), 43 (52); ^1H NMR (200 MHz): δ 6.69 (1H, *tq*, J = 7.3, 1.2 Hz, H-3), 5.85 (1H, *dd*, J = 17.4, 10.8 Hz, H-7), 5.18 (1H, *dd*, J = 17.4, 1.2 Hz, H-8$_c$), 5.02 (1H, *dd*, J = 10.8, 1.2 Hz, H-8$_t$), 4.11 (2H, *q*, J = 7 Hz, $COOCH_2$), 2.15 (2H, *m*, H-4), 1.76 (3H, *br s*, *Me*-C_2), 1.60 (2H, *m*, H-5), 1.25 (3H, *s*, *Me*-C_6), 1.22 (3H, *t*, J = 7 Hz, $COOCH_2Me$); ^{13}C NMR (50 MHz): δ 168.0 (*s*, C-1), 144.3 (*d*, C-7), 141.8 (*d*, C-3), 127.4 (*s*, C-2), 111.9 (*t*, C-8), 72.6 (*s*, C-6), 60.2 (*t*, $COOCH_2$), 40.4 (*t*, C-5), 27.6 (*q*, *Me*-C_6), 23.2 (*t*, C-4), 14.0 (*q*, $COOCH_2Me$), 12.0 (*q*, *Me*-C_2).

(+)-*Ethyl* (2E,6S)-2,6-*dimethyl*-6-*(t-butyldimethylsilyloxy)octa*-2,7-*dienoate*, (+)-**9**. A solution of hydroxy ester **8** (1.6 g, ca. 7.5 mmol) and 2,6-lutidine (2.6 ml, 22.5 mmol) in dry CH_2Cl_2 (15 ml) was treated under Ar with *t*-butyldimethylsilyl triflate (3.5 ml, ca. 15 mmol). The reaction mixture was then stirred at room temperature for 24 hr. Work-up (extraction with Et_2O) and chromatography on silica gel (hexane-EtOAc 95:5) yielded (+)-**9** (2.25 g, 92%) as a yellowish oil, $[\alpha]_D$ +8.3° ($CHCl_3$; c 9.1); IR $\bar{\nu}_{max}$ cm^{-1}: 1713, 1651, 1473, 1463, 1389, 1368, 1278, 1254, 1176, 1158, 1140, 1104, 1076, 1045, 1006, 921, 836, 774; EIMS, *m/z* (% rel. int.): 311 ($M^+ - Me$, 2), 269 ($M^+ - tBu$, 46), 223 ($M^+ - tBu - EtOH$, 8), 185 (55), 149 (12), 121 (28), 115 (20), 93 (29), 75 (Me_2SiOH^+, 100), 73 (66); ^1H NMR (200 MHz): δ 6.74 (1H, *tq*, J = 7.5, 1.3 Hz, H-3), 5.83 (1H, *dd*, J = 17.4, 10.6 Hz, H-7), 5.16 (1H, *dd*, J = 17.4, 1.3 Hz, H-8$_c$),

5.01 (1H, *dd*, J = 10.6, 1.3 Hz, H-8t), 4.17 (2H, *q*, J = 7 Hz, $COOCH_2$), 2.20 (2H, *m*, H-4), 1.80 (3H, *br s*, *Me*-C_2), 1.55 (2H, *m*, H-5), 1.30 (3H, *s*, *Me*-C_6), 1.27 (3H, *t*, J = 7 Hz, $COOCH_2Me$), 0.89 (9H, *s*, Si*tBu*), 0.07 (6H, *s*, $SiMe_2$); ^{13}C NMR (50 MHz): δ 167.8 (*s*, C-1), 144.9 (*d*, C-7), 142.1 (*d*, C-3), 127.3 (*s*, C-2), 112.0 (*t*, C-8), 75.1 (*s*, C-6), 60.0 (*t*, $COOCH_2$), 42.1 (*t*, C-5), 27.3 (*q*, *Me*-C_6), 25.8 (*q*, Si-CMe_3), 23.4 (*t*, C-4), 18.1 (*s*, Si-*C*), 14.1 (*q*, $COOCH_2Me$), 12.0 (*q*, *Me*-C_2), -2.3 (*q*, $SiMe_2$).

(+)-(2E,6S)-2,6-*dimethyl*-6-*(t-butyldimethylsilyloxy)octa*-2,7-*dienoic acid*, (+)-**10**. The silylated hydroxy ester **9** (1.95 g, ca. 6 mmol) was dissolved in EtOH (15 ml) and treated with an aqueous solution of NaOH (1.92 g, 48 mmol, dissolved in 15 ml of water). The solution was then stirred at 70 °C for 18 hr.[11] After this time, the reaction mixture was cooled to room temperature and treated with 1M aqueous HCl until pH = 1. Work-up of the reaction mixture (extraction with CH_2Cl_2) and chromatography on silica gel (hexane-EtOAc 7:3) provided acid (+)-**10** (1.48 g, 83%) as a yellowish oil, $[\alpha]_D$ +10.2° ($CHCl_3$; c 6.5); IR $\bar{\nu}_{max}$ cm^{-1}: 3500-2500 (very br), 1687, 1643, 1473, 1463, 1420, 1389, 1371, 1361, 1288, 1255, 1177, 1113, 1078, 1045, 1006, 938, 922, 836, 774; EIMS, *m/z* (% rel. int.): 283 (M^+ – Me, 2), 223 (M^+ – Me_2SiOH, 13), 185 (55), 131 (12), 121 (41), 115 (16), 93 (24), 75 (Me_2SiOH^+, 100), 73 (48); ^1H NMR (200 MHz): δ 6.91 (1H, *tq*, J = 7.5, 1.3 Hz, H-3), 5.84 (1H, *dd*, J = 17.3, 10.6 Hz, H-7), 5.19 (1H, *dd*, J = 17.3, 1.4 Hz, H-8c), 5.04 (1H, *dd*, J = 10.6 Hz, 1.4, H-8t), 2.25 (2H, *m*, H-4), 1.82 (3H, *br s*, *Me*-C_2), 1.60 (2H, *m*, H-5), 1.34 (3H, *s*, *Me*-C_6), 0.91 (9H, *s*, Si*tBu*), 0.09, 0.08 (2 x 3H, 2 x *s*, $SiMe_2$); ^{13}C NMR (50 MHz): δ 173.8 (*s*, C-1), 145.6, 145.0 (2 x *d*, C-7, C-3), 126.8 (*s*, C-2), 112.3 (*t*, C-8), 75.3 (*s*, C-6), 42.1 (*t*, C-5), 27.6 (*q*, *Me*-C_6), 25.9 (*q*, Si-CMe_3), 23.8 (*t*, C-4), 18.0 (*s*, Si-*C*), 11.9 (*q*, *Me*-C_2), -2.1 (*q*, Si-Me_2).

(+)-(2E,6S)-2,6-*dimethyl*-6-*(t-butyldimethylsilyloxy)octa*-2,7-*dienoic acid amide*, (+)-**11**. Acid **10** (1.04 g, 3.5 mmol) was dissolved in dry THF (10 ml) and cooled to −78 °C. Triethyl amine (0.6 ml, 4.3 mmol) and ethyl chloroformiate (0.38 ml, 3.9 mmol) were sequentially added to the cooled solution, which was then stirred at the same temperature for 15 min. After adding 32% aqueous NH_3 (0.6 ml, ca. 11 mmol), the mixture was allowed to reach room temperature and further stirred for 3 hr. Work-up (extraction with CH_2Cl_2) and chromatography on silica gel (hexane-EtOAc 1:1) afforded amide (+)-**11** (624 mg, 60%) as a yellowish oil, $[\alpha]_D$ +5.9° ($CHCl_3$; c 2.7); IR $\bar{\nu}_{max}$ cm^{-1}: 3345 (w), 3203 (w), 1686, 1639, 1287, 1255, 1175, 1113, 1076, 1044, 1006, 920, 835, 774; EIMS, *m/z* (% rel. int.): 282 (M^+ – Me, 3), 240 (M^+ – *t*Bu, 82), 222 (M^+ – Me_2SiOH, 3), 185 (62), 158 (20), 130 (22), 93 (21), 75 (Me_2SiOH^+, 100), 73 (80) ; ^1H NMR (200 MHz): δ 6.43 (1H, *br t*, J = 7.3 Hz, H-3), 5.84 (1H, *dd*, J = 17.5, 10.6 Hz, H-7), 5.80 (2H, br *s*, $CONH_2$), 5.18 (1H, *dd*, J = 17.5, 1.4 Hz, H-8c), 5.03 (1H, *dd*, J = 10.6 Hz, 1.4, H-8t), 2.20 (2H, *m*, H-4), 1.83 (3H, *br s*, *Me*-C_2), 1.55 (2H, *m*, H-5), 1.32 (3H, *s*, *Me*-C_6), 0.90 (9H, *s*, Si*tBu*), 0.08, 0.07 (2 x 3H, 2 x *s*, $SiMe_2$); ^{13}C NMR (50 MHz): δ 171.6 (*s*, C-1), 145.1 (*d*, C-7), 138.2 (*d*, C-3), 129.3 (*s*, C-2), 112.2 (*t*, C-8), 75.1 (*s*, C-6), 42.4 (*t*, C-5), 27.5 (*q*, *Me*-C_6), 25.9 (*q*, Si-CMe_3), 23.3 (*t*, C-4), 18.3 (*s*, Si-*C*), 12.6 (*q*, *Me*-C_2), -2.1 (*q*, $SiMe_2$).

(+)-(2E,6S)-2,6-*dimethyl*-6-*hydroxyocta*-2,7-*dienoic acid*, (+)-**2**. The silylated hydroxy acid **10** (149 mg, 0.5 mmol) was dissolved under Ar in dry THF (12 ml) and treated with 1M tetra-*n*-butylammonium fluoride in THF (1 ml, 1 mmol). The solution was then stirred at 60 °C for 24 hr.[12] After this time, water (1 drop) was added, the reaction mixture was cooled to room temperature and concentrated *in vacuo*. Column chromatography of the crude residue on silica gel (Et_2O-MeOH 95:5) gave acid (+)-**2** (69 mg, 75%) as a yellowish oil, $[\alpha]_D$ +11.1° ($CHCl_3$; c 1.5), lit.[3] $[\alpha]_D$ −12° ($CHCl_3$; c 0.5). The spectra of the synthetic product and of its methyl ester were superimposable with those of the natural product and the methyl ester, respectively, both described by us.[3]

(+)-(2E,6S)-2,6-*dimethyl*-6-*hydroxyocta*-2,7-*dienoic acid amide* ("*Acacialactam*"), (+)-**3**. The silylated hydroxy amide **11** (535 mg, 1.8 mmol) was dissolved under Ar in dry THF (25 ml) and treated with 1M tetra-*n*-butylammonium fluoride in THF (3.6 ml, 3.6 mmol). The solution was then stirred at 60 °C for 24 hr.[12] After this time, water (1 drop) was added, the reaction mixture was cooled to room temperature and concentrated *in vacuo*. Column chromatography of the residue on silica gel (Et_2O-MeOH 9:1) furnished amide (+)-**3** (268 mg, 82%) as a yellowish oil, $[\alpha]_D$ +17.5° (MeOH; c 1.8), lit.[1] $[\alpha]_D$ −4.3° (MeOH; c 0.16); IR $\bar{\nu}_{max}$ cm^{-1}: 3350, 3190, 1670, 1640sh, 1582, 1402; UV λ_{max} (MeOH):

225 nm (ε_{max} 4500); EIMS, m/z (% rel.int.): 168 ($M^+ - Me$, 4), 165 ($M^+ - H_2O$, 5), 150 ($M^+ - Me - H_2O$, 5), 138 (11), 123 (10), 121 (15), 112 (23), 110 (25), 102 (40), 95 (34), 71 (100), 67 (73), 55 (96). ^{1}H NMR (400 MHz): δ 6.40 (1H, *tq*, J = 7.5, 1.3 Hz, H-3), 5.95 (2H, *br s*), 5.86 (1H, *dd*, J = 17.4, 10.8 Hz, H-7), 5.20 (1H, *dd*, J = 17.4, 1 Hz, H-8$_c$), 5.05 (1H, *dd*, J = 10.8, 1 Hz, H-8$_t$), 2.18 (2H, *m*, H-4), 1.80 (3H, *dt*, J = 1.3, 1 Hz, *Me*-C$_2$), 1.60 (2H, *m*, H-5), 1.27 (3H, *s*, *Me*-C$_6$). ^{13}C NMR (100 MHz): δ 171.6 (C-1), 144.5 (C-7), 137.7 (C-3), 129.8 (C-2), 112.1 (C-8), 73.0 (C-6), 40.7 (C-5), 27.9 (*Me*-C$_6$), 23.2 (C-4), 12.6 (*Me*-C$_2$). The spectra of the synthetic product were practically superimposable with those of the natural product.

(−)-*Ethyl* (2E,6S,7S)-2,6-*dimethyl*-6,7-*epoxy*-8-*p*-*tosyloxyoct*-2-*enoate*, (−)-**13**. A solution of epoxy tosylate (−)-**5**[7c] (3.37 g, 10.4 mmol) in dry CH_2Cl_2/MeOH 1:1 (80 ml) containing pyridine (0.2 ml) was cooled to −78 °C. Ozone-enriched oxygen was then bubbled through the solution during 5 min at the same temperature. Dimethyl sulfide (0.9 ml, ca. 12 mmol) was then added and the resulting solution was stirred for 30 min. at room temperature. The volatiles were then eliminated *in vacuo* and the oily residue was dissolved in dry benzene (125 ml). After adding carbethoxyethylidenetriphenylphosphorane (7.53 g, 20.8 mmol), the reaction mixture was then stirred under Ar at room temperature for 24 hr. Work-up (extraction with Et_2O) and chromatography on silica gel (hexane-EtOAc 8:2) yielded (−)-**13** (3.65 g, 92%) as a yellowish oil, $[\alpha]_D$ −19.1° ($CHCl_3$; c 5.5); IR $\bar{\nu}_{max}$ cm^{-1}: 1709, 1650, 1598, 1449, 1366, 1264, 1190, 1178, 1097, 967, 817, 770; EIMS, *m/z* (% rel. int.): 337 ($M^+ - OEt$, 2), 336 ($M^+ - EtOH$, 2), 213 ($TsOCH_2CO^+$, 4), 197 ($M^+ - CH_2OTs$, 21), 172 ($TsOH^+$, 18), 155 (Ts^+, 40), 151 (50), 139 (26), 123 (39), 119 (48), 107 (30), 95 (49), 91 (100), 65 (28); ^{1}H NMR (200 MHz): δ 7.63 (2H, *d*, J = 8.5 Hz, arom. H), 7.20 (2H, *d*, J = 8.5 Hz, arom. H), 6.51 (1H, *tq*, J = 7.3, 1.3 Hz, H-3), 4.05-3.90 (4H, *br m*, H-8, $COOCH_2$), 2.83 (1H, *t*, J = 5 Hz, H-7), 2.26 (3H, *s*, Ar-*Me*), 2.05 (2H, *m*, H-4), 1.65 (3H, *br s*, *Me*-C$_2$), 1.45 (2H, *m*, H-5), 1.10 (3H, *t*, J = 8 Hz, $COOCH_2Me$), 1.06 (3H, *s*, *Me*-C$_6$); ^{13}C NMR (50 MHz): δ 167.2 (*s*, C-1), 144.7 (*s*, arom. C), 139.9 (*d*, C-3), 132.2 (*s*, arom. C), 129.5, 127.4 (2 x *d*, arom. C), 127.4 (*s*, C-2), 68.3 (*t*, C-8), 59.9 (*t*, $COOCH_2$), 58.2 (*d*, C-7), 36.0 (*t*, C-5), 23.5 (*t*, C-4), 21.1 (*q*, Ar-*Me*), 16.1 (*q*, *Me*-C$_6$), 13.8 (*q*, $COOCH_2Me$), 11.8 (*q*, *Me*-C$_2$).

Conversion of tosylate **13** *to hydroxy ester* **8**. Zinc-copper couple was prepared according to a literature procedure:[13] activated zinc powder (97 mg, 1.5 mmol) and CuI (95 mg, 0.5 mmol) were suspended under Ar in dry THF (2.5 ml) and sonicated for 10 min. Compound **13** (191 mg, 0.5 mmol) dissolved in THF (0.5 ml) and NaI (150 mg, 1 mmol) were then sequentially added, and the mixture was stirred at reflux for 2.5 hr. Work-up (extraction with Et_2O) and chromatography on silica gel (hexane-EtOAc 7:3) afforded hydroxy ester (+)-**8** (86 mg, 81%).

(−)-*Ethyl* (2E,6R)-2,6-*dimethyl*-6-*hydroxyocta*-2,7-*dienoate*, (−)-**8**. Obtained as described for (+)-**8**: $[\alpha]_D$ −15.3° ($CHCl_3$; c 6.3).

(−)-*Ethyl* (2E,6R)-2,6-*dimethyl*-6-*(t-butyldimethylsilyloxy)octa*-2,7-*dienoate*, (−)-**9**. Obtained as described for (+)-**9**: $[\alpha]_D$ −7.7° ($CHCl_3$; c 14.1).

(−)-(2E,6R)-2,6-*dimethyl*-6-*(t-butyldimethylsilyloxy)octa*-2,7-*dienoic acid*, (−)-**10**. Obtained as described for (+)-**10**: $[\alpha]_D$ −6.0° ($CHCl_3$; c 3.7).

(−)-(2E,6R)-2,6-*dimethyl*-6-*(t-butyldimethylsilyloxy)octa*-2,7-*dienoic acid amide*, (−)-**11**. Obtained as described for (+)-**11**: $[\alpha]_D$ −5.8° ($CHCl_3$; c 3.6).

(−)-(2E,6R)-2,6-*dimethyl*-6-*hydroxyocta*-2,7-*dienoic acid*, (−)-**2**. Obtained as described for (+)-**2**: $[\alpha]_D$ −11.2° ($CHCl_3$; c 3.1).

(−)-(2E,6R)-2,6-*dimethyl*-6-*hydroxyocta*-2,7-*dienoic acid amide* ("*ent-Acacialactam*"), (−)-**3**. Obtained as described for (+)-**3**: $[\alpha]_D$ −17.0° ($CHCl_3$; c 3.3).

(+)-*Ethyl* (2E,6R,7R)-2,6-*dimethyl*-6,7-*epoxy*-8-*p*-*tosyloxyoct*-2-*enoate*, (+)-**13**. Obtained as described for (−)-**13**: $[\alpha]_D$ +20.9° ($CHCl_3$; c 7.6).

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