Synthesis of Mono- and Sesquiterpenoids; XXII.[1] Synthesis of (+)-Pinthunamide, a Sesquiterpene Metabolite of a Fungus, *Ampulliferina* sp.

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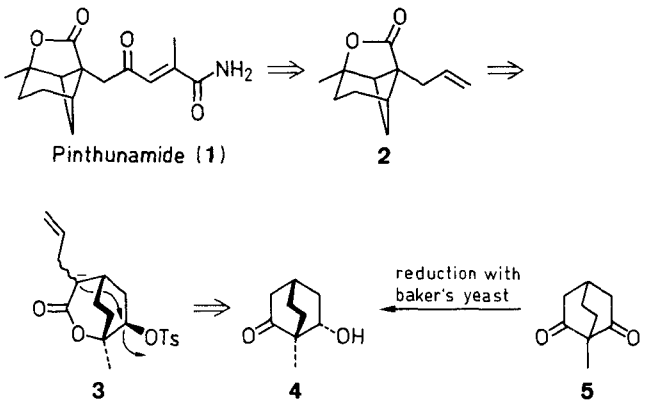
Received 18 August 1992

Pinthunamide (**1**), a sesquiterpene metabolite produced by a fungus *Ampulliferina* sp., was synthesized by starting from (1*R*,4*S*,6*S*)-6-hydroxy-1-methylbicyclo[2.2.2]octan-2-one (**4**), which could readily be prepared by yeast reduction of the corresponding β-diketone **5**.

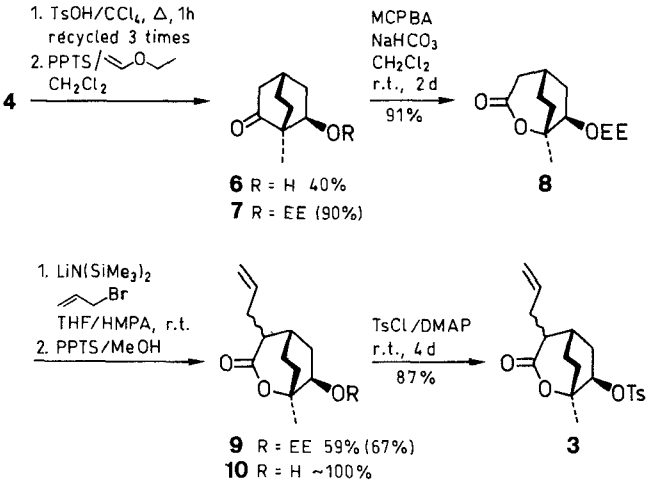
Pinthunamide (**1**) is a sesquiterpene amide isolated from a fungus *Ampulliferina* sp. by Kimura et al., and accelerates the root growth of lettuce seedlings by 150% at a dose of 300 mg/L.[2] Its unique structure with a bridged tricyclic ring system was determined by a single-crystal X-ray analysis together with other spectral methods, although its absolute configuration still remains unknown. The unique structure of **1** made us undertake a synthesis of enantiomerically pure **1** starting from a compound of known absolute configuration in order to determine the stereochemistry of **1**.

Our synthetic plan is shown in Scheme 1. We recently reported microbial reductions of symmetrically bridged β-diketones with baker's yeast.[3-5] The hydroxy ketone **4** can be obtained in high enantiomeric purity of known absolute configuration from the diketone **5**.[3] Thus **4** serves as a readily available non-racemic chiral starting material. The hydroxy ketone **4** could then be converted to **3** in several steps. The key step of our synthesis is the intramolecular alkylation of tosyloxy lactone **3** to construct simultaneously the pinane-type carbon skeleton and the γ-lactone. The resulting **2** then affords pinthunamide (**1**) through a multistep sequence.



Scheme 1

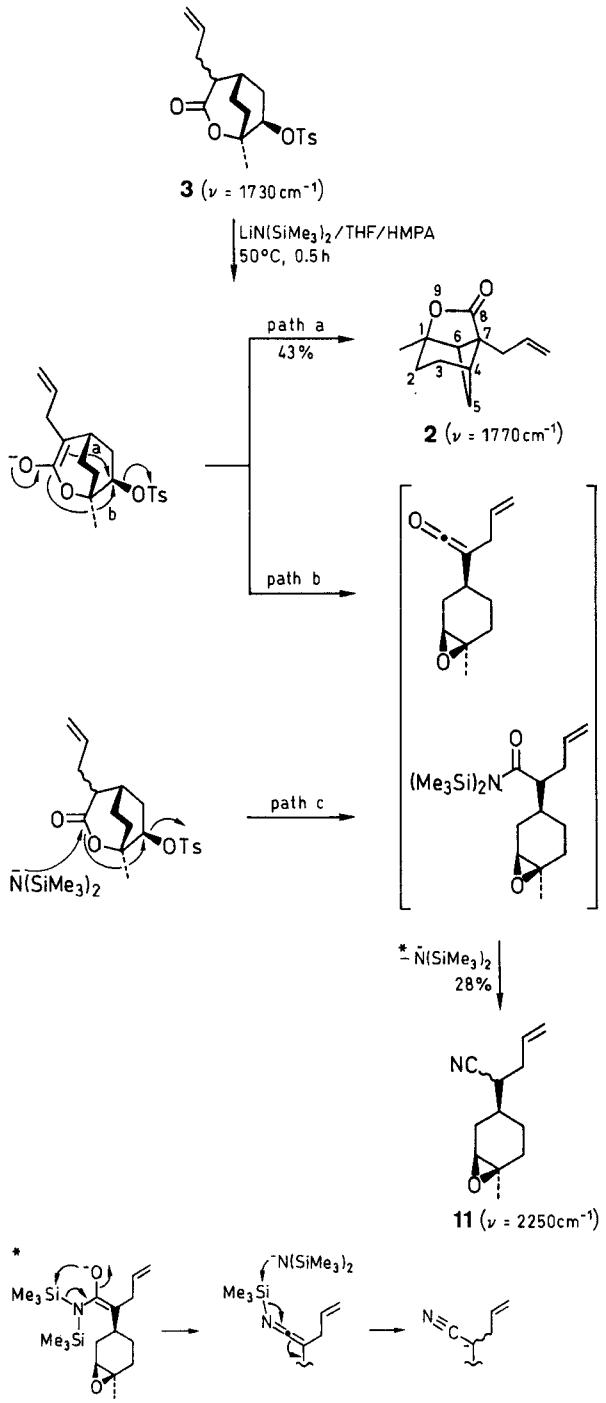
The first stage of our work was the preparation of tosyloxy lactone **3** as shown in Scheme 2. To allow the cyclization in the key step, the tosyloxy group of **3** must be in the β-orientation. Therefore, inversion of stereochemistry of **4** at C-6 was required, whose enantiomeric purity was determined to be 99% ee by HPLC analysis of the corresponding (*R*)-MTPA ester. All attempts failed to achieve Mitsunobu inversion at that position. We finally used the acid-catalyzed retroaldol–aldol reaction of **4** with *p*-toluenesulfonic acid (TsOH) to furnish **6**. Although the ratio α-OH:β-OH was at best 4:1 in carbon tetrachloride, the starting **4** could easily be recovered from the crude mixture by recrystallization, and a sufficient amount of **6** was obtained by repeating the same protocol. After the protection of the β-OH group of **6** as 1-ethoxyethyl (EE) ether, the resulting **7** was submitted to Baeyer–Villiger oxidation with *m*-chloroperbenzoic acid (MCPBA) to give **8** in 91% yield. The lactone **8** was then alkylated with allyl bromide using lithium 1,1,1,3,3,3-hexamethyldisilazide [$LiN(SiMe_3)_2$] as a base to give **9**. After the removal of the EE protective group from **9**, the resulting alcohol **10** was treated with *p*-toluenesulfonyl chloride (TsCl) in the presence of 4-(dimethylamino)-pyridine (DMAP) to give the key intermediate **3** as crystals.



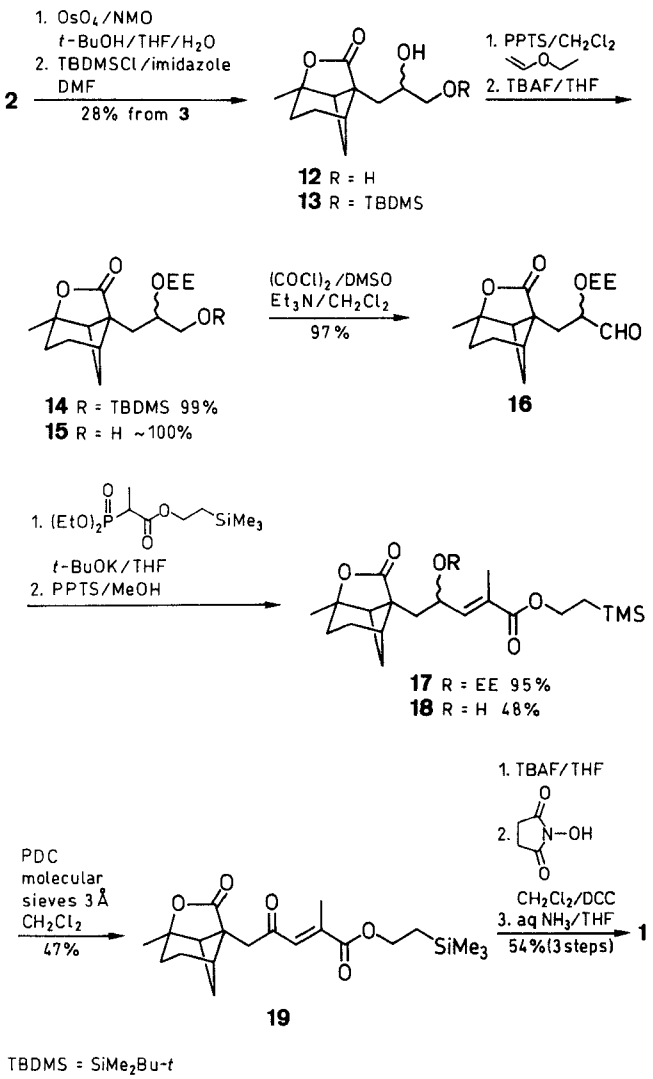
Scheme 2

The next step was the key intramolecular alkylation as shown in Scheme 3. We successfully executed this reaction by employing $LiN(SiMe_3)_2$ in tetrahydrofuran/hexamethylphosphoric triamide (HMPA). In addition to the desired tricyclic lactone **2** (ca. 43% yield) with ν = 1770 cm^{-1} (path a), an unexpected byproduct, a diastereomeric mixture (ca. 2:1) of nitrile **11** was obtained possibly through path b or c. Its structure was assigned on the basis of its IR (ν = 2250 cm^{-1}), ^1H and ^{13}C NMR spectra and elementary analyses.

The remaining steps of the synthesis were the transformation of the side chain to afford pinthunamide (**1**) as shown in Scheme 4. The allyl side chain was oxidized with a catalytic amount of osmium tetroxide and *N*-methylmorpholine *N*-oxide (NMO) to yield the diol **12**, whose



Scheme 3



TBDMS = $SiMe_2Bu$-*t*

Scheme 4

primary hydroxy group was selectively protected to give the pure *tert*-butyldimethylsilyl (TBDMS) ether **13**. Compound **13** was then converted to the aldehyde **16** by the following sequence: (i) protecton of the secondary hydroxy group of **13** as EE ether to give **14**, (ii) removal of the TBDMS protective group of **14** to afford **15**, and finally (iii) Swern oxidation[6] of **15**. The resulting aldehyde **16** was submitted to Horner reaction to give exclusively (*E*)-α,β-unsaturated ester **17**. The EE protective group of **17** was removed to furnish **18**, whose hydroxy group was oxidized with pyridinium dichromate (PDC) to afford **19**. Finally, deprotection of 2-(trimethylsilyl)ethyl group and amidation with aqueous NH_3 via the activated ester gave pinthunamide (**1**). The melting point, specific rotation and spectroscopic properties (IR and ^1H and ^{13}C NMR) of our synthetic **1** were identical with those of the natural (+)-pinthunamide (**1**), respectively. Consequently, the absolute configuration of the natural pinthunamide was determined to be 1*R*,4*S*,6*R*,7*S* as depicted in **1**.

In conclusion, (+)-pinthunamide (**1**) was synthesized from optically active hydroxyketone **4**, which is readily obtainable by the yeast reduction of a prochiral diketone **5**. The present synthesis firmly established the absolute configuration of (+)-pinthunamide as (1*R*,4*S*,6*R*,7*S*)-**1**.

All melting and boiling points are uncorrected. NMR spectra were recorded on a JEOL JNM EX-90 or Bruker AC-300 spectrometer. IR spectra were recorded on a Jasco A-102 spectrometer. Optical rotations were measured on a Jasco DIP-140 or Jasco DIP-370 polarimeter. Mass spectra were recorded on a JEOL DX-303 spectrometer at 70 eV. Column chromatography was carried out on columns packed with Merck Kieselgel 60, Art. Nr. 7734.

(1*R*,4*S*,6*R*)-6-Hydroxy-1-methylbicyclo[2.2.2]octan-2-one (6):
To a stirred and refluxing solution of **4** (66.2 g, 0.430 mol) in CCl_4 (1300 mL) was added TsOH (1.60 g, 8.41 mmol) under Ar, and the refluxing was continued for 40 min. After cooling, the mixture was poured into sat. aq $NaHCO_3$ (400 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc

(4 × 300 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was recrystallized from hexane/EtOAc (4:1) to give pure **4** (43.9 g) and the mother liquor was concentrated in vacuo to give a mixture of **6** and **4** (22.3 g). The recovered pure **4** was used for the same treatment for two more times. The combined mixture (54.6 g) was chromatographed on silica gel and recrystallized from hexane/EtOAc (5:1) to give pure **6** as needles; yield: 26.4 g (40%); mp 106–110°C (sublimes); $[\alpha]_D^{21.3}$ −39° (c = 0.28, $CHCl_3$).

$C_9H_{14}O_2$ (154.2) calc. C 70.10 H 9.15 found 70.49 9.22

IR (CCl_4): ν = 3640 (w, monomeric OH), 3500 (br w, OH), 1730 cm^{-1} (s, C=O).

^1H NMR ($CDCl_3$/TMS): δ = 1.02 (s, 3H, CH_3), 1.13–2.45 (m, 7H, H-4, 5, 7, 8), 2.20 (d, 2H, J = 1.2 Hz, H-3), 3.65–3.90 (m, 1H, H-6).

(1*R*,4*S*,6*R*)-6-(1-Ethoxyethoxy)-1-methylbicyclo[2.2.2]octan-2-one (7):

To an ice-cooled and stirred solution of **6** (9.85 g, 64.9 mmol) in ethyl vinyl ether (150 mL) and CH_2Cl_2 (60 mL) was added pyridinium *p*-toluenesulfonate (0.45 g, 1.79 mmol) and stirred at r.t. for 2.5 h. To the mixture was added sat. $NaHCO_3$ (100 mL) and extracted with Et_2O (2 × 100 mL). The combined extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on silica gel (50 g). Elution with hexane/EtOAc (5:1) afforded **7**; yield: 14.3 g (99%); $n_D^{21.0}$ 1.4677; $[\alpha]_D^{21.0}$ −69.9° (c = 0.595, $CHCl_3$).

$C_{13}H_{22}O_3$ (226.3) calc. C 68.99 H 9.80 found 68.91 9.80

IR (film): ν = 1720 cm^{-1} (s, C=O).

^1H NMR ($CDCl_3$/TMS): δ = 0.99, 1.04 (s, each, 3H, CH_3), 1.17, 1.19 (t, each, 3H, J = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.31 (d, 3H, J = 5.6 Hz, $OCHC\underline{H}_3O$), 1.41–2.38 (m, 7H, H-4,5,7,8), 2.20 (br s, 2H, H-3), 3.38–3.88 (m, 3H, H-6 and $OC\underline{H}_2CH_3$), 4.64, 4.77 (q, each, 1H, J = 5.4 Hz, $OC\underline{H}CH_3O$).

(1*R*,5*S*,7*R*)-7-(1-Ethoxyethoxy)-1-methyl-2-oxabicyclo[3.2.1]nonan-3-one (8):

To an ice-cooled and stirred mixture of **7** (5.07 g, 22.4 mmol) and $NaHCO_3$ (3.76 g, 44.8 mmol) in anhydr. CH_2Cl_2 (130 mL) was added MCPBA (80%, 4.06 g, 18.8 mmol), and stirred at r.t. for 20 h. After the addition of $NaHCO_3$ (2.16 g, 25.7 mmol) and an additional amount of MCPBA (2.70 g, 12.5 mmol), the mixture was stirred at r.t. for 12 h. To destroy the excess of MCPBA, 10% aq $Na_2S_2O_3$ (150 mL) was added to the mixture and extracted with Et_2O (1 × 250 mL, 2 × 100 mL). The combined extracts were washed with sat. aq $NaHCO_3$ (2 × 100 mL), brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (93 g). Elution with hexane/EtOAc (4:1) gave **8**; yield: 4.95 g (91%); $n_D^{20.2}$ 1.4748; $[\alpha]_D^{20.2}$ −65.1° (c = 0.875, $CHCl_3$).

$C_{13}H_{22}O_4$ (242.3) calc. C 64.44 H 9.15 found 64.49 9.08

IR (film): ν = 1725 cm^{-1} (s, C=O).

^1H NMR ($CDCl_3$/TMS): δ = 1.20, 1.21 (t, each, 3H, J = 7.4 Hz, $OCH_2C\underline{H}_3$), 1.31 (d, 3H, J = 5.6 Hz, $OCHC\underline{H}_3O$), 1.36, 1.41 (s, each, 3H, 1-CH_3), 1.50–2.30 (m, 7H, H-5,6,8,9), 2.80 (br s, 2H, H-4), 3.40–4.31 (m, 3H, H-7 and $OC\underline{H}_2CH_3$), 4.70, 4.79 (q, each, 1H, J = 5.6 Hz, $OC\underline{H}CH_3O$).

(1*R*,5*S*,7*R*)-4-Allyl-7-(1-ethoxyethoxy)-1-methyl-2-oxabicyclo-[3.2.1]nonan-3-one (9):

A solution of $LiN(SiMe_3)_2$ in anhydr. THF was prepared by the dropwise addition of BuLi (8.64 mL, 1.66 M in hexane, 14.3 mmol) to a stirred solution of $(SiMe_3)_2NH$ (3.16 mL, 15.0 mmol) in anhydr. THF (32 mL) at −78°C under Ar. HMPA (4.54 mL, 26.1 mmol) was added to the mixture, and to this homogeneous solution was added a solution of **8** (3.16 g, 13.0 mmol) in anhydr. THF (9 mL) at −78°C. The mixture was warmed to 0°C, stirred for 0.5 h at that temp. and cooled again to −78°C. Allyl bromide (1.07 mL, 12.4 mmol) was added to the mixture at −78°C. After additional stirring for 1 h, the mixture was warmed to r.t., poured into H_2O (50 mL), and extracted with Et_2O (3 × 100 mL). The combined extracts were washed with H_2O (2 × 50 mL), sat. aq $NaHCO_3$ (50 mL), brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (165 g). Elution with hexane/EtOAc (10:1) furnished **9**; yield: 2.17 g (59%); $n_D^{20.4}$ 1.4819; $[\alpha]_D^{20.4}$ −23.0° (c = 0.780, $CHCl_3$).

$C_{16}H_{26}O_4$ (282.40) calc. C 68.06 H 9.28 found 68.27 9.31

IR (film): ν = 3090 (w, C=C), 1720 (s, C=O), 1640 cm^{-1} (w, C=C).

^1H NMR ($CDCl_3$/TMS): δ = 0.99–1.43 (m, 9H, CH_3, $OCHC\underline{H}_3O$ and $OCH_2C\underline{H}_3$), 1.48–2.42 (m, 8H, H-5,6,8,9 and CH_2=CHC$\underline{H}\underline{H}$), 2.51–2.99 (m, 2H, H-4 and CH_2=CHC$\underline{H}\underline{H}$), 3.28–4.02 (m, 3H, H-7 and $OC\underline{H}_2CH_3$), 4.54–4.87 (m, 1H, $OC\underline{H}CH_3O$), 4.94–5.24 (m, 2H, CH=C$\underline{H}_2$), 5.53–6.08 (m, 1H, C$\underline{H}$=CH_2).

Further elution with hexane/EtOAc (4:1) gave **8** (0.41 g, 13%).

(1*R*,5*S*,7*R*)-4-Allyl-7-hydroxy-1-methyl-2-oxabicyclo[3.2.1]nonan-3-one (10):

To a stirred solution of **9** (1.33 g, 4.70 mmol) in MeOH (30 mL) was added pyridinium *p*-toluenesulfonate (0.35 g, 1.39 mmol) at r.t. and the mixture was stirred at r.t. for 16 h. The mixture was concentrated in vacuo in the presence of $NaHCO_3$. The residue was poured into sat. aq $(NH_4)_2SO_4$ and extracted with EtOAc (3 × 100 mL). The combined extracts were washed with brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (10 g). Elution with hexane/EtOAc (3:1) afforded **10**; yield: 0.99 g (quantitative); $n_D^{20.1}$ 1.5081; $[\alpha]_D^{20.1}$ −38.5° (c = 0.965, $CHCl_3$).

$C_{12}H_{18}O_3$ (210.3) calc. C 68.55 H 8.63 found 68.10 8.70

IR (film): ν = 3455 (br s, OH), 3095 (w, C=C), 1700 (br s, C=O), 1640 cm^{-1} (w, C=C).

^1H NMR ($CDCl_3$/TMS): δ = 1.40 (s, 3H, CH_3), 1.48–2.48 (m, 8H, H-5,6,8,9 and CH_2=CHC$\underline{H}\underline{H}$), 2.54–2.96 (m, 2H, H-4 and CH_2=CHC$\underline{H}\underline{H}$), 3.82–4.13 (m, 1H, H-7), 4.94–5.24 (m, 2H, CH=C$\underline{H}_2$), 5.53–6.12 (m, 1H, C$\underline{H}$=CH_2).

(1*R*,5*S*,7*R*)-4-Allyl-1-methyl-7-*p*-toluenesulfonyloxy-2-oxabicyclo-[3.2.1]nonan-3-one (3):

To an ice-cooled and stirred solution of **10** (4.00 g, 19.0 mmol) and DMAP (600 mg, 4.90 mmol) in pyridine (54 mL) was added TsCl (47.9 g, 251 mmol). The mixture was stirred at r.t. for 80 h. To the ice-cooled mixture, crushed ice and H_2O (100 mL) were added. The mixture was extracted with EtOAc (3 × 100 mL). The combined extracts were washed with H_2O (100 mL), sat. aq $NaHCO_3$ (100 mL), brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (140 g). Elution with hexane/EtOAc (5:1) gave almost pure **3**. This was recrystallized from hexane to give pure **3** as needles; yield: 6.04 g (87%); mp 93–94°C; $[\alpha]_D^{20.1}$ −82.6° (c = 0.825, $CHCl_3$).

$C_{19}H_{24}O_5S$ (364.5) calc. C 62.62 H 6.64 found 62.24 6.57

IR (CCl_4): ν = 3080 (w, C=C), 1730 (s, C=O), 1640, 1600 (w, C=C), 1380, 1195, 1185 cm^{-1} (s, OSO_2).

^1H NMR ($CDCl_3$/TMS): δ = 1.13 (s, 3H, CH_3), 1.38–2.95 (m, 10H, H-5,6,8,9 and CH_2=CHC$\underline{H}_2$), 2.48 (s, 3H, Ar–CH_3), 4.50–4.78 (m, 1H, H-7), 4.90–5.24 (m, 2H, CH=C$\underline{H}_2$), 5.48–6.04 (m, 1H, C$\underline{H}$=CH_2), 7.36 (d, 2H_{arom}, J = 9.0 Hz), 7.80 (d, 2H_{arom}, J = 9.0 Hz).

(1*R*,4*S*,6*R*,7*S*)-7-Allyl-1-methyl-9-oxatricyclo[4.3.0.0^{4,7}]nonan-8-one (2):

A solution of $LiN(SiMe_3)_2$ was prepared by the dropwise addition of BuLi (30.2 mL, 1.66 M in hexane, 50.1 mmol) to a stirred solution of $(SiMe_3)_2NH$ (10.7 mL, 50.9 mmol) in anhydr. THF (260 mL) at −78°C under Ar. HMPA (8.71 mL, 50.1 mmol) was added and to this homogeneous solution was added dropwise a solution of **3** (6.11 g, 16.8 mmol) in anhydr. THF (38 mL) at −78°C. The mixture

was warmed to 50 °C and stirred for 0.5 h at that temperature. The mixture was poured into H_2O (200 mL), and extracted with Et_2O (3 × 100 mL). The combined extracts were washed with H_2O (200 mL), sat. aq $NaHCO_3$ (100 mL), brine (100 mL), dried (MgO_4), and concentrated in vacuo. The residue was chromatographed on silica gel (500 g). Elution with hexane/EtOAc (10:1) gave crude **2** contaminated with a trace amount of unknown impurities; yield: 1.39 g (43%). This crude **2** was used for the next reaction without further purification.

HRMS: calc. for $C_{12}H_{16}O_2$: 192.1151, found: 192.1172.

IR (film): ν = 3100, 2750 (w, C=C), 1770 (s, C=O), 1645 cm^{-1} (w, C=C).

^1H NMR ($CDCl_3$/TMS): δ = 1.44 (s, 3H, CH_3), 1.68 (d, 1H, J = 10.2 Hz, H_{endo}-5), 1.88 (s, 4H, H-2,3), 2.21 (dt, 1H, J = 5.1, 10.2 Hz, H_{exo}-5), 2.33 (dd, 1H, J = 8.2, 15.0 Hz, CHHCH=CH_2), 2.41 (m, 1H, H-4), 2.48 (t, 1H, J = 5.1 Hz, H-6), 2.65 (dd, 1H, J = 8.2, 15.0 Hz, CHHCH=CH_2), 4.92, 5.15 (m, 2H, CH=CH_2), 5.64–5.82, 5.99–6.15 (m, 1H, CH=CH_2).

Further elution with hexane/EtOAc (5:1) gave **11**; yield: 0.91 g (28%).

$C_{12}H_{17}ON$	calc.	C 75.35	H 8.96	N 7.32
(191.3)	found	74.96	8.95	6.92

IR (film): ν = 3100 (w, C=C), 2250 cm^{-1} (w, C≡N).

^1H NMR ($CDCl_3$/TMS): δ = 1.29–1.81, 2.01–2.24 (m, 7H, H-3 to 6), 1.32 (s, 3H, CH_3), 2.30–2.51 (m, 3H, $CH_2CH=CH_2$ and CHCN), 2.99 (t, 1H, J = 5.8 Hz, H-2), 5.15–5.25 (m, 2H, CH=CH_2), 5.81 (dddd, 1H, J = 7.0 Hz, CH=CH_2).

^{13}C NMR ($CDCl_3$/TMS, signals due to the minor isomer are given in parenthesis): δ = 22.8 (23.0), 23.5, 28.8 (27.9), 29.95 (30.03), 33.3 (33.6), 34.1 (34.0), 37.2 (37.3), 57.6 (57.4), 58.1 (58.2), 118.9 (118.8), 120.5 (120.3), 133.0 (133.1).

(1′*R*,4′*S*,6′*R*,7′*S*)-3-(1-Methyl-8-oxo-9-oxatricyclo[4.3.0.0^{4,7}]non-7-yl)propane-1,2-diol (12):

To an ice-cooled and stirred solution of crude **2** (1.43 g, ca. 7.44 mmol) and NMO (1.75 g, 15.0 mmol) in *t*-BuOH (14 mL), THF (5 mL), and H_2O (1.4 mL) was added OsO_4 (6 mL, 0.04 M in *t*-BuOH, 0.2 mmol) and the mixture was stirred at r.t. for 7 h. To this were added H_2O and Na_2SO_3 for destroying the excess oxidant. The aqueous layer was saturated with $(NH_4)_2SO_4$ and extracted with EtOAc (3 × 100 mL). The combined extracts were washed with 1 N HCl (100 mL), dried ($MgSO_4$), filtered through silica gel, and concentrated in vacuo. The crude **12** thus obtained was used for the next reaction without further purification; yield: 1.68 g (quantitative).

IR (film): ν = 3425 (br s, OH), 1750 cm^{-1} (br s, C=O).

^1H NMR ($CDCl_3$/TMS): δ = 1.34–2.79 (m, 6H, CCH_2CHOH and nonyl H-4,5,6), 1.49 (s, 3H, CH_3), 1.94 (s, 4H, nonyl H-2,3), 3.30–4.03 (m, 3H, $OCHCH_2OH$).

(1′*R*,4′*S*,6′*R*,7′*S*)-3-*tert*-Butyldimethylsilyloxy-1-(1-methyl-8-oxo-9-oxatricyclo[4.3.0.0^{4,7}]non-7-yl)propan-2-ol (13):

To an ice-cooled and stirred solution of crude **12** (1.71 g, ca. 7.56 mmol) and imidazole (640 mg, 9.40 mmol) in anhydr. DMF (160 mL) was added TBDMSCl (1.23 g, 8.16 mmol), and the mixture stirred at 4 °C for 11 h. The mixture was poured into H_2O (100 mL), and extracted with Et_2O (3 × 100 mL). The combined extracts were washed with sat. aq $NaHCO_3$ (100 mL), brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (240 g). Elution with benzene/Et_2O (5:1) afforded pure **13**; yield: 1.62 g [28% from **3** (6.35 g)]; $n_D^{20.3}$ 1.4797; $[\alpha]_D^{20.3}$ − 16.1° (c = 0.765, $CHCl_3$).

$C_{18}H_{32}O_4Si$	calc.	C 63.49	H 9.47	
(340.5)	found	63.59	9.38	

IR (film): ν = 3460 (br s, O–H), 1755 cm^{-1} (s, C=O).

^1H NMR ($CDCl_3$): δ = 0.07 [s, 6H, $Si(CH_3)_2$], 0.90 (s, 9H, *t*-C_4H_9), 1.48 (s, 3H, nonyl CH_3), 1.58, 2.71 (m, 6H, CH_2OSi and nonyl H-4,5,6), 1.91 (s, 4H, nonyl H-2,3), 3.34–3.99 (m, 3H, CCH_2CHOH).

(1*R*,4*S*,6*R*,7*S*)-7-[3-*tert*-Butyldimethylsilyloxy-2-(1-ethoxyethoxy)]-propyl-1-methyl-9-oxatricyclo[4.3.0.0^{4,7}]nonan-8-one (14):

To a stirred solution of **13** (320 mg, 0.940 mmol) in ethyl vinyl ether (4.7 mL) and CH_2Cl_2 (2.0 mL) was added a catalytic amount of pyridinium *p*-toluenesulfonate (45 mg, 0.18 mmol) at r.t. and stirring was continued for 12 h. To the mixture was added sat. aq $NaHCO_3$ (30 mL) and then extracted with Et_2O (3 × 30 mL). The combined extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (8 g). Elution with hexane/EtOAc (15:1) gave **14**; yield: 385 mg (99%); $n_D^{20.5}$ 1.4663; $[\alpha]_D^{20.5}$ − 99.2° (c = 1.00, $CHCl_3$).

$C_{22}H_{40}O_5Si$	calc.	C 64.04	H 9.77	
(412.6)	found	64.30	9.74	

IR (film): ν = 1765 cm^{-1} (s, C=O).

^1H NMR ($CDCl_3$): δ = 0.06 [s, 6H, $Si(CH_3)_2$], 0.90 (s, 9H, *t*-C_4H_9), 0.99–2.92 (m, 12H, nonyl H-4,5,6, CCH_2CHO, $OCHCH_3O$ and OCH_2CH_3), 1.45 (s, 3H, CH_3), 1.89 (s, 4H, nonyl H-2,3), 3.26–3.86 (m, 5H, CH_2CHO, CH_2OSi and OCH_2CH_3), 4.52–5.04 (m, 1H, $OCHCH_3O$).

(1′*R*,4′*S*,6′*R*,7′*S*)-2-(1-Ethoxyethoxy)-3-(1-methyl-8-oxo-9-oxatricyclo[4.3.0.0^{4,7}]non-7-yl)propan-1-ol (15):

To an ice-cooled and stirred solution of **14** (1.92 g, 6.43 mmol) in anhydr. THF (20 mL) was added TBAF (14 mL, 1.0 M in THF, 14 mmol) and the mixture was stirred at r.t. for 4 h. To the mixture was added sat. aq $(NH_4)_2SO_4$ (100 mL), and extracted with EtOAc (3 × 100 mL). The combined extracts were washed with sat. aq $NaHCO_3$ (100 mL), brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (65 g). Elution with hexane/EtOAc (1:1) gives **15**; yield: 1.32 g (95%); $n_D^{20.5}$ 1.4826; $[\alpha]_D^{20.5}$ − 7.59° (c = 0.705, $CHCl_3$)

$C_{16}H_{26}O_5$	calc.	C 64.40	H 8.78	
(298.4)	found	64.21	8.96	

IR (film): ν = 3460 (br s, OH), 1760 cm^{-1} (s, C=O).

^1H NMR ($CDCl_3$/TMS): δ = 1.01–3.03 (m, 12H, CCH_2CHO, nonyl H-4,5,6, $OCHCH_3O$ and OCH_2CH_3), 1.47 (s, 3H, CH_3), 1.91 (s, 4H, nonyl H-2,3), 3.25–5.04 (m, 6H, $OCHCH_2OH$, $OCHCH_3O$ and OCH_2CH_3).

(1′*R*,4′*S*,6′*R*,7′*S*)-2-(1-Ethoxyethoxy)-3-(1-methyl-8-oxa-9-oxatricyclo[4.3.0.0^{4,7}]non-7-yl)propanal (16):

A solution of the Swern reagent was prepared by the dropwise addition of DMSO (950 μL, 13.3 mmol) to a stirred solution of $(COCl)_2$ (580 μL, 6.70 mmol) in anhydr. CH_2Cl_2 (25 mL) at − 78 °C under Ar. To this solution was added dropwise a solution of **15** (1.33 g, 4.46 mmol) in anhydr. CH_2Cl_2 (10 mL) at − 78 °C. The mixture was stirred for 30 min. at − 78 °C and treated with Et_3N (4.97 mL, 35.7 mmol). The temperature was allowed to rise gradually to r.t. during 1 h. The mixture was poured into H_2O (50 mL) and extracted with Et_2O (50 mL) and EtOAc (2 × 50 mL). The combined extracts were washed with sat. aq $NaHCO_3$ (50 mL), brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (28 g). Elution with hexane/EtOAc (5:1) afforded **16**; yield: 1.28 g (97%); $n_D^{20.7}$ 1.4785; $[\alpha]_D^{20.7}$ − 2.95° (c = 1.31, $CHCl_3$).

$C_{16}H_{24}O_5$	calc.	C 64.84	H 8.16	
(296.4)	found	64.68	8.08	

IR (film): ν = 2720 (w, O=CH), 1760 (s, C=O), 1730 cm^{-1} (s, HC=O).

^1H NMR ($CDCl_3$/TMS): δ = 1.03–2.97 (m, 12H, CCH_2CHO, nonyl H-4,5,6, $OCHCH_3O$ and OCH_2CH_3), 1.47 (s, 3H, CH_3), 1.91 (s, 4H, nonyl H-2,3), 3.33–3.75 (m, 2H, OCH_2CH_3), 3.97–4.88 (m, 2H, CHOEE and $OCHCH_3O$), 9.66 (m, 1H, CHO).

2-(Trimethylsilyl)ethyl (1′*R*,4′*S*,6′*R*,7′*S*)-(*E*)-4-(1-ethoxyethoxy)-2-methyl-5-(1-methyl-8-oxo-9-oxatricyclo[4.3.0.0^{4,7}]non-7-yl)pent-2-enoate (17):

To an ice-cooled and stirred solution of 2-(trimethylsilyl)ethyl 2-diethylphosphonopropanoate (3.35 g, 10.8 mmol) in anhydr. THF (40 mL) was added *t*-BuOK (1.02 g, 9.01 mmol) under Ar and the mixture was stirred at r.t. for 1 h, and cooled to − 78 °C. To this was

added a solution of **16** (1.28 g, 4.23 mmol) in anhydr. THF (10 mL). The mixture was stirred at −78 °C for 1 h and at r.t. for 30 min. Then it was poured into H_2O (100 mL), and extracted with Et_2O (3 × 100 mL). The combined extracts were washed with sat. aq $NaHCO_3$ (100 mL), brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (80 g). Elution with hexane/EtOAc (5:1) gave **17**; yield: 1.85 g (95%); $n_D^{20.7}$ 1.4782; $[\alpha]_D^{20.7}$ −2.74° (*c* = 2.48, $CHCl_3$).

$C_{24}H_{40}O_6Si$	calc.	C 63.68	H 8.91
(452.7)	found	63.23	9.17

IR (film): *v* = 1765 (s, γ-lactone C=O), 1710 (s, ester C=O), 1650 cm^{-1} (w, C=C).

^1H NMR ($CDCl_3$/TMS): δ = 0.05 [s, 9 H, $Si(CH_3)_2$], 0.87–2.96 (m, 14 H, CCH_2CHO, nonyl H-4,5,6, $OCHCH_3O$ and $SiCH_2$), 1.41, 1.46 (each s, 3 H, CH_3), 1.90 (br s, 7 H, $=CCH_3$ and nonyl, H-2,3), 3.30–3.88 (m, 2 H, OCH_2CH_3), 4.10–6.12 (m, 4 H, CHOEE, $OCHCH_3O$ and CO_2CH_2), 6.45–6.88 (m, 1 H, =CH).

2-(Trimethylsilyl)ethyl (1′*R*,4′*S*,6′*R*,7′*S*)-(*E*)-4-hydroxy-2-methyl-5-(1-methyl-8-oxo-9-oxatricyclo[4.3.0.0^{4,7}]non-7-yl)pent-2-enoate (18):

To a stirred solution of **17** (196 mg, 0.433 mmol) in MeOH (8 mL) was added a catalytic amount of pyridinium *p*-toluenesulfonate (35 mg, 0.14 mmol) at r.t. and the stirring was continued for 10 h. Then the mixture was concentrated in vacuo in the presence of $NaHCO_3$. The residue was poured into sat. aq $(NH_4)_2SO_4$ (30 mL) and extracted with EtOAc (3 × 30 mL). The combined extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (5 g). Elution with hexane/EtOAc (1:1) gave **18**; yield: 79.0 mg (48%); $n_D^{20.7}$ 1.4981; $[\alpha]_D^{21.0}$ +1.3° (*c* = 0.36, $CHCl_3$).

$C_{20}H_{32}O_5Si$	calc.	C 63.12	H 8.48
(380.6)	found	62.76	8.58

IR (film): *v* = 3450 (br, OH), 1755 (s, lactone C=O), 1710 (s, ester C=O), 1650 cm^{-1} (w, C=C).

^1H NMR ($CDCl_3$/TMS): δ = 0.06 [s, 9 H, $Si(CH_3)_3$], 0.92–1.17 (m, 2 H, $SiCH_2$), 1.42–2.80 (m, 6 H, CCH_2CHO and nonyl H-4,5,6), 1.50 (s, 3 H, CH_3), 1.90 (br s, 4 H, nonyl H-2,3), 1.96 (br s, 3 H, $=CCH_3$), 4.11–4.87 (m, 3 H, CHOH and CO_2CH_2), 6.63–6.87 (m, 1 H, =CH).

2-(Trimethylsilyl)ethyl (1′*R*,4′*S*,6′*R*,7′*S*)-(*E*)-2-methyl-5-(1-methyl-8-oxo-9-oxatricyclo[4.3.0.0^{4,7}]non-7-yl)-4-oxopent-2-enoate (19):

To an ice-cooled and stirred mixture of **18** (0.45 g, 1.2 mmol) in anhydr. CH_2Cl_2 (10 mL) and powdered molecular sieves 3Å (1.10 g) was added PDC (1.35 g, 3.59 mmol). The mixture was stirred at r.t. for 1.75 h, and after further addition of powdered molecular sieves 3Å (0.20 g) and PDC (250 mg, 0.660 mmol), it was stirred for an additional 1 h. The mixture was filtered through florisil, and eluted with Et_2O. The resulting crude **19** is recrystallized from hexane to give pure **19** (0.18 g) as colorless needles. Chromatography of the mother liquor on silica gel followed by recrystallization afforded a further amount of **19** (30 mg); yield: 0.21 g (47%); mp 115–116 °C; $[\alpha]_D^{21.2}$ +54° (*c* = 0.23, $CHCl_3$).

$C_{20}H_{30}O_5Si$	calc.	C 63.46	H 7.99
(378.5)	found	63.77	8.02

IR (CCl_4): *v* = 1770 (s, lactone C=O), 1720 (s, ester C=O), 1700 (s, ketone C=O), 1620 cm^{-1} (w, C=C).

^1H NMR ($CDCl_3$/TMS): δ = 0.07 [s, 9 H, $Si(CH_3)_3$], 1.06 (dd, 2 H, *J* = 8.1 Hz, $SiCH_2$), 1.57 (s, 3 H, CH_3), 1.70 (d, 1 H, *J* = 9.9 Hz, nonyl H_{endo}-5), 1.95 (s, 4 H, nonyl H-2,3), 2.08–2.60 (m, 2 H, nonyl H-4, H_{exo}-5), 2.29 (d, 3 H, *J* = 1.8 Hz, $=CCH_3$), 2.75 (dd, 1 H, *J* = 5.4 Hz, nonyl H-6), 2.90 (d, 1 H, *J* = 18.9 Hz, one of H-5), 3.20 (d, 1 H, *J* = 18.9 Hz, one of H-5), 4.30 (dd, 2 H, *J* = 8.1 Hz, CO_2CH_2), 7.08 (d, 1 H, *J* = 1.8 Hz, =CH).

(1′*R*,4′*S*,6′*R*,7′*S*,*E*)-2-Methyl-5-(1-methyl-8-oxo-9-oxatricyclo-[4.3.0.0^{4,7}]non-7-yl)-4-oxopent-2-enamide (Pinthunamide) (1):

To an ice-cooled and stirred solution of **19** (39.4 mg, 0.100 mmol) in anhydr. THF (1.2 mL) was added TBAF (0.3 mL, 1 M in THF, 0.3 mmol) and the mixture was stirred at r.t for 2 h. It was poured into H_2O (30 mL), acidified with aq HCl and extracted with Et_2O (2 × 50 mL) and EtOAc (2 × 50 mL). The combined extracts were dried (Na_2SO_4), and concentrated in vacuo. The resulting crude carboxylic acid and DCC (33.7 mg, 0.160 mmol) were dissolved in DME (1.0 mL). To the ice-cooled and stirred mixture wss added *N*-hydroxysuccinimide (37.0 mg, 0.320 mmol). The mixture was stirred at r.t. for 10 h, diluted with hexane and filtered through Celite. The filtrate was concentrated in vacuo and the residue was dissolved in THF (2 mL). To the ice-cooled and stirred mixture was added 29% aq NH_3 (1.0 mL, 17 mmol) and stirred at 0 °C for 1 h. It was poured into H_2O (30 mL) and extracted with EtOAc (3 × 30 mL). The combined extracts were washed with sat. aq $NaHCO_3$ (30 mL), brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (10 g). Elution with hexane/EtOAc (3:1) afforded **1**; yield: 16.5 mg (57% in 3 steps). An analytical sample was obtained as colorless needles by recrystallization from EtOAc; mp 187–189 °C [natural sample: mp 183–189 °C, mixed mp 182–189 °C]; $[\alpha]_D^{21.5}$ +60° (*c* = 0.19, EtOH) [natural sample: $[\alpha]_D^{21.5}$ +56° (*c* = 0.18, EtOH)]; [Lit.[2] mp 190–193 °C, $[\alpha]_D^{20}$ +73.4° (*c* = 1.0, EtOH)].

$C_{15}H_{19}O_4N$	calc.	C 64.97	H 6.91	N 5.05
	found	64.71	6.88	5.07

IR ($CHCl_3$): *v* = 3550, 3430 (w, N–H), 1760 (s, lactone C=O), 1680 (s, ketone and amide C=O), 1625 (w, C=C), 1585 cm^{-1} (w, N–H).

^1H NMR ($CDCl_3$/TMS): δ = 1.54 (s, 3 H, nonyl CH_3), 1.73 (d, 1 H, *J* = 10.8 Hz, nonyl H_{endo}-5), 1.94 (s, 4 H, nonyl H-2,3), 2.19 (dt, 1 H, *J* = 10.8, 5.4 Hz, nonyl H_{exo}-5), 2.26 (d, 3 H, *J* = 1.5 Hz, $=CCH_3$), 2.45 (m, 1 H, nonyl H-4), 2.72 (t, 1 H, *J* = 5.4 Hz, nonyl H-6), 2.90 (d, 1 H, *J* = 18.1 Hz, one of H-5), 3.20 (d, 1 H, *J* = 18.1 Hz, one of H-5), 5.48 (br, 1 H, one of NH_2), 5.84 (br, 1 H, one of NH_2), 6.88 (d, 1 H, *J* = 1.5 Hz, =CH).

^{13}C NMR ($CDCl_3$): δ = 14.9 ($=CCH_3$), 22.9 (nonyl C-5), 24.9 (nonyl CH_3), 29.9 (nonyl C-2), 40.5 (nonyl C-4), 44.1 ($CCH_2C=O$), 47.4 (nonyl C-6), 53.7 (nonyl C-7), 88.7 (nonyl C-1), 128.2 (=CH), 144.9 ($=CCH_3$), 170.1 ($CONH_2$), 178.0 (nonyl C-8), 198.3 ($CH_2C=O$).

The IR, ^1H and ^{13}C NMR spectra were identical to those of the natural pinthunamide.

We thank Prof. Y. Kimura, Tottori University, for kindly supplying an authentic sample of (+)-pinthunamide.

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