Synthesis of norsesterterpene *rac*- and *ent*-rhopaloic acid A

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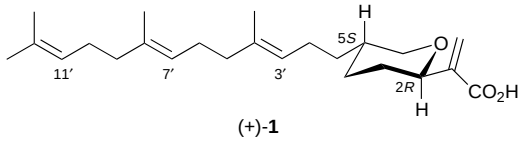
The stereoselective synthesis of *rac*- and *ent*-rhopaloic acid A 1 has been accomplished, *via* successive homologation of (2*E*,6*E*)-farnesol 2 and cyclization to form a tetrahydropyran ring, together with final introduction of an α-methylene group; the asymmetric synthesis was achieved *via* an Evans' asymmetric alkylation using (*S*)-4-benzyloxazolidin-2-one as a chiral auxiliary; the synthetic rhopaloic acid A, with a predicted absolute configuration of (2*S*,5*R*), had a specific rotation of opposite sign to that of the natural product, and therefore the configuration of natural rhopaloic acid A should be assigned as (2*R*,5*S*).

(+)-Rhopaloic acid A (+)-**1**, a potent cytotoxic agent, was isolated from the marine sponge *Rhopaloeides* sp.[1] The interesting biological activity of the compound may be attributed to the structurally unique feature of having a hydrophilic pyranylacrylic acid moiety connected to a hydrophobic isoprenoid part.[2] The acrylic acid moiety is also found in compounds such as conconadine[3a] and gerin,[3b] and the related 2-methylene-γ-lactone group is found in many bioactive natural products. The potential of (+)-**1** and its analogues as biological probes provided the incentive for this synthetic undertaking. Here the total syntheis of racemic rhopaloic acid A *rac*-**1** and the nonnatural enantiomer *ent*-rhopaloic acid A (−)-*ent*-**1** is described.



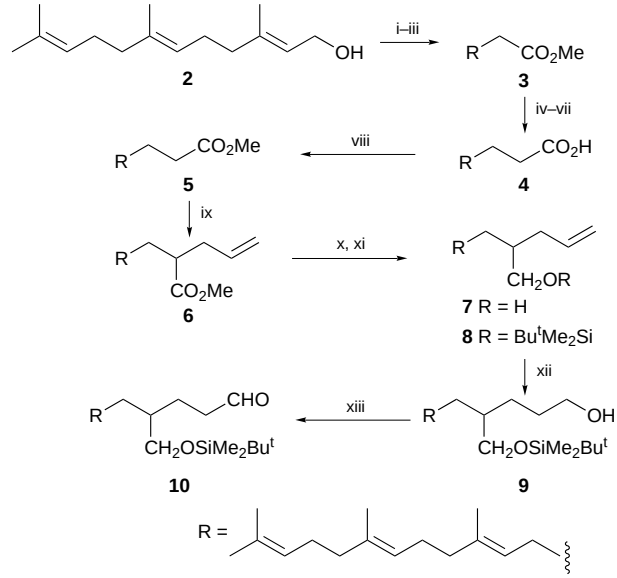
(+)-**1**

Our synthetic strategy consists of successive homologations of (2*E*,6*E*)-farnesol **2** and cyclization to form a tetrahydropyran ring, together with the final introduction of an α-methylene group.

The two-carbon homologation exploited malonic esterification starting from (2*E*,6*E*)-farnesol **2** (Scheme 1). Treatment of farnesol with PPh_3–CBr_4 at 0 °C afforded farnesyl bromide.[4] The bromide contained less than 5% of the (2*Z*,6*E*)-isomer and was used for the following reaction without further purification. Treatment of the bromide with dimethyl malonate (5 equiv.) in the presence of NaH (1 equiv.) gave the dimethyl ester in 80% yield.[5] Demethoxycarbonylation of the dimethyl ester under neutral conditions (NaCl in moist DMF) afforded monomethyl ester **3** in 87% yield. Reduction of **3** with $LiAlH_4$ afforded the alcohol in quantitative yield. Treatment of the alcohol with Ph_3P–CBr_4 gave the bromide in 86% yield. Cyanation of the bromide with NaCN in DMF afforded the nitrile in quantitative yield. Hydrolysis of the nitrile under basic conditions afforded carboxylic acid **4** and esterification of **4** with MeI–K_2CO_3[6] gave methyl ester **5** in 76% yield over two steps.

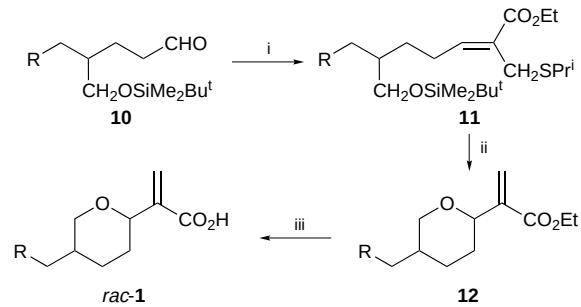
Treatment of **5** with LDA followed by allyl bromide gave allylated methyl ester **6** in 83% yield. Reduction of **6** with $LiAlH_4$ afforded alcohol **7** in 88% yield. Protection of **7** with *tert*-butyldimethylsilyl chloride followed by hydroboration–oxidation with 9-BBN–H_2O_2 gave primary alcohol **9** (79%). Swern oxidation of **9** afforded aldehyde **10** (80%).

The modified Wittig–Horner–Emmons reaction of **10** with $(EtO)_2P(O)C(=CH_2)CO_2Et$ in the presence of $NaSCHMe_2$

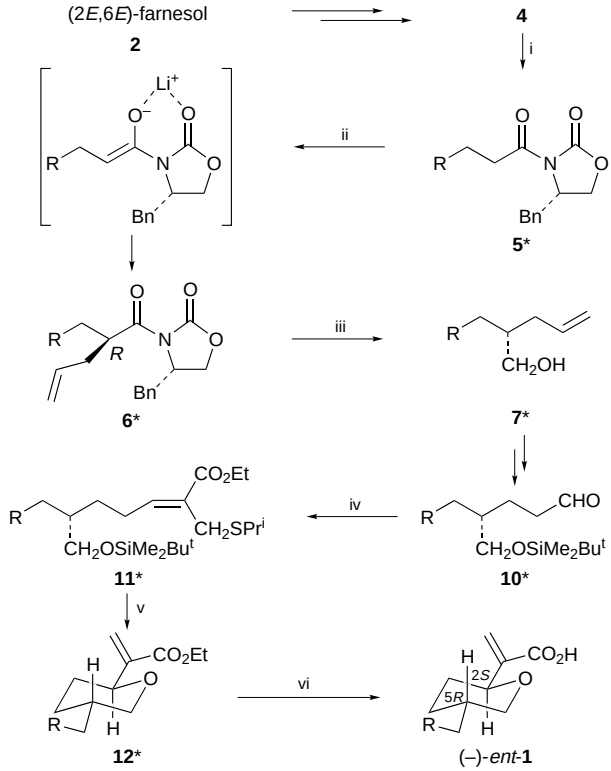


Scheme 1 *Reagents and conditions*: i, PPh_3 (1.2 equiv.), CBr_4 (1.3 equiv.), CH_2Cl_2, 0 °C, 3 h; ii, NaH (1 equiv.), $CH_2(CO_2Me)_2$ (5 equiv.), DMF, 0–25 °C, overnight, 80% over two steps; iii, NaCl (2 equiv.), H_2O (2 equiv.), DMF, reflux, 20 h, 87%; iv, $LiAlH_4$ (1.3 equiv.), THF, 0 °C, 1 h, 96%; v, Ph_3P (1.2 equiv.), CBr_4 (1.5 equiv.), CH_2Cl_2, 0 °C, 1 h, 86%; vi, NaCN (2.5 equiv.), DMF, 25 °C, 1 h, 99%; vii, KOH (10 equiv.), H_2O, EtOH, reflux, 30 h, 78%; viii, MeI (2 equiv.), K_2CO_3 (2 equiv.), 25 °C, 3 h, 98%; ix, LDA (1.1 equiv.), THF, −78 °C, 30 min, then allyl bromide (4 equiv.), −78 to 25 °C, overnight, 83%; x, $LiAlH_4$ (1.5 equiv.), THF, 0 °C, 3 h, 88%; xi, Bu^tMe_2SiCl (1.1 equiv.), imidazole (2 equiv.), DMF, 3 h, 87%; xii, 9-BBN (1.5 equiv.), THF, 0 to 25 °C, overnight, then aq. NaOH (4 equiv.), 30% aq. H_2O_2 (4 equiv.), overnight, 79%; xiii, DMSO (2 equiv.), $(COCl)_2$ (1.1 equiv.), Et_3N (5 equiv.), CH_2Cl_2, −60 °C, 5 h, 80%

furnished **11** with only *Z* geometry in 57% yield as a single isomer (Scheme 2).[8]† Exposure of **11** to methylation reagent MeI–$AgBF_4$ followed by desilylation with Bu_4NF afforded ethyl pyranylacrylate derivative **12** in 32% yield as the *trans* isomer.[9]‡ The ester **12** contained less than 10% of the *cis* isomer. Hydrolysis of **12** with aq. KOH afforded *rac*-**1** with



Scheme 2 *Reagents and conditions*: i, NaH (1 equiv.), Me_2CHSH (1 equiv.), $(EtO)_2P(O)C(=CH_2)CO_2Et$ (1 equiv.), THF, 0 °C, 10 min, then **10**, 25 °C, overnight, 57% (*Z* isomer only); ii, MeI (3 equiv.), $AgBF_4$ (1 equiv.), CH_2Cl_2, 2 h, then Bu_4NF (3 equiv.), THF, 16 h, 32%; iii, aq. KOH (excess), reflux, 14 h, 34%



Scheme 3 *Reagents and conditions*: i, Et_3N (1.2 equiv.), pivaloyl chloride (1.2 equiv.), THF, then *N*-lithiooxazolidin-2-one, THF, −78 °C, 15 h, 66%; ii, LDA (1.1 equiv.), THF, −78 °C, 30 min, then allyl bromide (4 equiv.), −20 to −10 °C, 6 h, 44%; iii, $LiAlH_4$ (3 equiv.), THF, 0 °C, 15 h, 92% iv, NaH (1 equiv.), Me_2CHSH (1 equiv.), $(EtO)_2P(O)(=CH_2)CO_2Et$, THF, 0 °C, 10 min, then **10***, 25 °C, 28 h, 46% (*Z* isomer only); v, MeI (3 equiv.), $AgBF_4$ (1 equiv.), CH_2Cl_2, 5 h then Bu_4NF (3 equiv.), THF, 25 °C, 13 h, 35%; vi, aq. KOH (excess), reflux, 18 h, 56%

retained stereochemistry in 34% yield.§ The ^1H and ^{13}C NMR and mass spectra of the carboxylic acid *rac*-**1** and the ethyl ester **12** were identical with those recorded for authentic samples of (+)-rhopaloic acid A (+)-**1** and its ethyl ester derivative, respectively.

Asymmetric synthesis of *ent*-rhopaloic acid A was carried out by way of the Evans' asymmetric alkylation as shown in Scheme 3. The auxiliary moiety, (*S*)-4-benzyloxazolidin-2-one, was introduced into **4** (66%) to give **5***. The lithium enolate of **5*** was treated with allyl bromide at −20 to −10 °C to give **6*** as the pure diastereoisomer (44% yield, 99% de).[7,10]¶ Consideration of the chelation model of the enolate intermediate predicted the stereochemistry at the C2 position of **6*** to be 2*R*.[10] Following removal of the chiral auxiliary by $LiAlH_4$ reduction (92%) and protection (79%) of the alcohol **7*** with a *tert*-butyldimethylsilyl group, silyl ether **8*** was subjected to regioselective hydroboration with 9-BBN followed by oxidation with H_2O_2 to give **9*** (68%). Swern oxidation of **9*** gave **10*** in 80% yield. The modified Wittig–Horner–Emmons reaction of **10*** afforded α,β-unsaturated ester **11*** (46%), which was cyclized into **12*** (35%). Hydrolysis of **12*** gave the optically pure (2*S*,5*R*)-*ent*-**1**‖ in 9% overall yield from **10***. The specific rotation of *ent*-**1** was $[\alpha]_D^{25}$ −37.6 (*c* 0.315, $CHCl_3$), which was of opposite sign to that of the natural product (+)-**1**. Therefore, it is presumed that the configuration of natural rhopaloic acid A {$[\alpha]_D^{25}$ + 40 (*c* 0.47, $CHCl_3$)}[1] is 2*R*,5*S*.

In order to investigate the structure–bioactivity relationship of **1** and other biomechanistic problems, an alternative synthesis of **1** and related compounds is now progress.[11]

Spectra of an authentic sample were kindly provided by Dr S. Ohta (Hiroshima University). The authors thank Shiono Koryo Kaisha, Ltd. and Kurare Co. for the gift of farnesol. NMR and mass spectra and optical rotations were measured at the Instrument Center for Chemical Analysis, Hiroshima University.

Footnotes and References

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† The product ratio changed with the reaction conditions. Only the *Z* isomer, the thermodynamically stable product, was obtained when the reaction mixture was stirred overnight at 25 °C. A ratio of *Z*:*E* = 2.4:1.0 was obtained when the reaction mixture was stirred at 0 °C for 3 h. The relative configuration of the product was determined with difference NOE experiments: when 3-H of the *E* isomer was irradiated, the intensity of the 2-CH_2S signal was enhanced by 8.2%.

‡ For **12**, the assigned relative stereochemistry was confirmed by intensity enhancement of 2-H by 10.9% upon irradiation of 6-H_{ax}. The assignment of 6-H_{ax} was determined by measurement of coupling constants: $J_{5,6\text{-ax}}$ = 11.2 Hz, $J_{5,6\text{-eq}}$ = 3.9 Hz.

§ The relative stereochemistry of *rac*-**1** was assigned using the same considerations as for **12** ($J_{5,6\text{-ax}}$ = 11.2 Hz, $J_{5,6\text{-eq}}$ = 3.9 Hz); when 6-H_{ax} was irradiated, an intensity enhancement of 2-H by 6.9% was observed.

¶ The diastereoselectivity of the allylation was evaluated by conversion of the optical active alcohol **7*** into its benzoate ester, followed by analysis with a DAICEL CHIRALCEL-OD column (hexane–AcOEt 400:1).

‖ *Selected data* for (2*S*,5*R*)-**1**: colourless oil; $[\alpha]_D^{25}$ −38 (*c* 0.315, $CHCl_3$); δ_H (270 MHz, $CDCl_3$) 1.1–1.3 (m, 4 H, 1′-H, 3-H_{ax}, 4-H_{ax}), 1.3–1.6 (m, 1 H, 5-H_{ax}), 1.60 (s, 9 H, vinyl-Me), 1.68 (s, 3 H, vinyl-Me), 1.9–2.1 (m, 12 H, 3-H_{eq}, 4-H_{eq}, 2′-H, 5′-H, 6′-H, 9′-H, 10′-H), 3.18 (t, *J* 11, 1 H, 6-H_{ax}), 4.07 (ddd, *J* 12, 4, 2, 1 H, 6-H_{aq}), 4.12 (d, *J* 12, 1 H, 2-H), 5.89 (s, 1 H, α-methylene), 6.36 (br s, 1 H, α-methylene); δ_C (125 MHz, $CDCl_3$) 16.0, 17.7, 24.9, 25.7, 26.6, 26.8, 30.2, 31.8, 32.4, 35.2, 39.7, 74.0, 76.4, 124.0, 124.2, 124.4, 126.7, 131.3, 135.0, 135.5, 140.7, 168.6; ν_{max}(neat)/cm^{-1} 3500–3000, 2900, 2850, 1680, 1620, 1430, 1370, 1280, 1160, 1140, 1080, 950, 830; Calc. for $C_{24}H_{38}O_3$ 374.2821. Found: 374.2830.

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