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Total Synthesis of (±)- Rhopaloic Acid A

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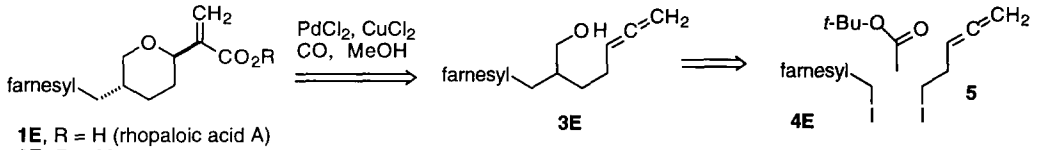
Abstract: A six-step synthesis of rhopaloic acid A (**1E**) was accomplished in 25% overall yield using the Pd(II)-mediated cyclization and methoxycarbonylation of allenyl alcohol **3**, which affords 83% of a 6:1 mixture of tetrahydropyranylacrylates **2** and **8**, as the key step. © 1997 Elsevier Science Ltd.

Ohta and Ikegami isolated the novel norsesterterpene rhopaloic acid A (**1E**) from a marine sponge *Rhopaloeides* sp. collected off the coast of Japan in 1996. Rhopaloic acid A potently inhibits the gastrulation of starfish embryos and exhibits potent cytotoxicity against human myeloid K-562 cells, human MOLT-4 leukemia cells and murine L-1210 cells with IC_{50} values of 40-100 nM. Since only 3.1 mg of the natural product was isolated, an efficient synthesis of rhopaloic acid A and analogues is necessary for further biological evaluation.

We envisioned that methyl rhopaloate A (**2E**) could be prepared from **3E** by the Gallagher/Walkup protocol for palladium induced cyclization of allenyl alcohols in the presence of CO and MeOH reported in 1986-87. Gallagher used this procedure to cyclize 5,6-heptadienol to provide methyl α-(2-tetrahydropyranyl)acrylate[2] and Walkup described analogous cyclizations of several 4,5-hexadienols to give α-(2-tetrahydrofuranyl)acrylate esters.[3] We expected that the desired trans, diequatorial isomer **2E** would be the major product from this cyclization[4,5] and that the double bonds of the farnesyl side chain would be compatible with the cyclization of allenyl alcohol **3E**. The desired alcohol **3E** should be readily available by alkylation of the enolate of *t*-butyl acetate with homofarnesyl iodide (**4E**), a second enolate alkylation with 5-iodo-1,2-pentadiene (**5**),[6] and reduction of the ester with LAH.



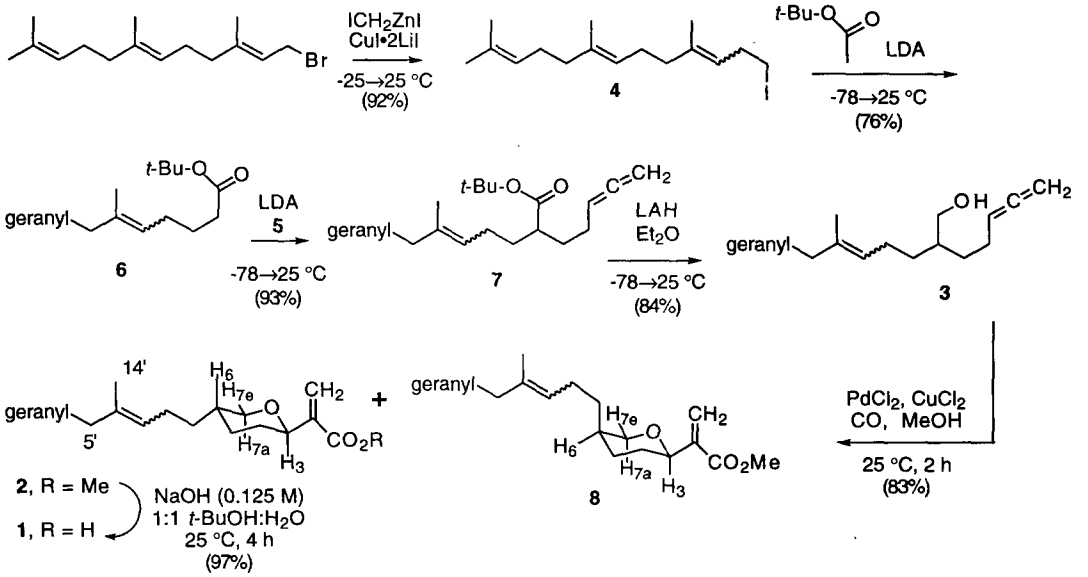
1E, R = H (rhopaloic acid A)
2E, R = Me

Addition of ICH_2ZnI to farnesyl bromide and CuI•2LiI in THF at -25 °C by Knochel's procedure[7] afforded 92% of a 20:2:1 mixture of **4E**, **4Z**, and the S_N2' substitution product that was used for the next step. Reaction of *t*-butyl acetate with LDA in THF containing 1 equiv of HMPA at -78 °C gave the lithium enolate that was treated with **4**, as an isomeric mixture, to provide 76% of a 10:1 inseparable mixture of **6E** and **6Z**.[8] Alkylation of **6** (LDA, THF, 1 equiv HMPA, -78 °C) with 5-iodo-1,2-pentadiene (**5**)[6] gave 93% of a 10:1 inseparable mixture of **7E** and **7Z** that was reduced with LAH in Et_2O (-78 C to 25 °C) to yield 84% of the requisite allenyl alcohol **3** as a 10:1 *E/Z* mixture.

We were delighted to find that the critical Pd(II)-mediated cyclization and methoxycarbonylation (0.1 equiv $PdCl_2$, 3.2 equiv $CuCl_2$, MeOH, 1 atm CO, 25 °C, 2 h) proceeded in 83% yield to give a 6:1 mixture of the desired trans diequatorial isomer **2** and the cis isomer **8** each as a 10:1 *E/Z* mixture. After considerable experimentation, we determined that efficient separation could be effected by flash chromatography on silica gel impregnated with 20% w/w $AgNO_3$ eluting with 10:1 CH_2Cl_2/EtOAc. Under these conditions **2Z** (6%) eluted first, followed by pure **2E** (40%), a 3:1 mixture of **2E** and **8E** (17%), which yielded 10% additional pure **2E** after a second chromatographic purification, and lastly a 5:6 mixture of **2E** and **8E** (4%).

The structures of **2E**, **2Z** and **8E** were determined by analysis of the ^1H and ^{13}C NMR spectral data. The axial hydrogen H_3 absorbs as a broad doublet at δ 4.14 (J = 9.5), 4.13 (J = 9.5), and 4.20 (J = 10.6), in **2E**, **2Z** and **8E**, respectively, indicating that the acrylate ester is equatorial on the tetrahydropyran in both **2** and **8**. H_{7a} of the trans, diequatorial isomers **2E** and **2Z** absorbs as a doublet of doublets at δ 3.16 (J = 11.1, 11.1) and 3.15 (J = 11.1, 11.1) with large geminal and diaxial vicinal couplings. H_{7e} of the cis isomer **8E** absorbs as a broad doublet at δ 3.89 (J = 11.5) while H_{7a} absorbs as a doublet of doublets at δ 3.67 (J = 11.5, 2.9). The absence of a large diaxial coupling between H_6 and H_{7a} in **8E** establishes that the homofarnesyl side chain is axial. The double bond stereochemistry of **2Z** was assigned based on the upfield shift of C_5' to δ 31.9 in **2Z** from δ 39.7 in

2E and the down field shift of $C_{14'}$ to δ 23.4 in **2Z** from δ 16.0 in **2E** due to the γ-gauche effect. The allylic methyl groups of **2E** absorb at δ 1.68 (s, 3) and δ 1.60 (s, 9), while those of **2Z** absorb at δ 1.68 (s, 6) and δ 1.60 (s, 6), indicating that the 14'-Me group is shifted downfield from δ 1.60 in **2E** to δ 1.68 in **2Z**.



Hydrolysis of methyl ester **2E** without concomitant Michael addition to the acrylate ester was eventually accomplished by treatment with 0.125 M NaOH in 1:1 *t*-BuOH:H_2O for 4 h at 25 °C providing 98% of (±)-rhopaloic acid A (**1E**) with ^1H and ^{13}C NMR and IR spectral data identical to those reported for the natural product, thereby completing the synthesis of **1E** in six steps from farnesyl bromide in 25% overall yield making rhopaloic acid A readily available for further biological evaluation. Similarly, hydrolysis of **2Z** gave 97% of **1Z**.

We thought that rhopaloic acid A might be acting as a inhibitor of a farnesyl transferase since the homofarnesyl side chain could bind to the enzyme while the acrylic acid side chain might undergo Michael addition. However, neither **1E** nor **1Z** inhibit the farnesylation of Hras by recombinant human FTase or the geranylgeranylation of Hras-CAIL chimera by recombinant GGTase-1 at concentrations up to 100 μM,[9] indicating that inhibition of these enzymes is not responsible for the cytotoxicity of rhopaloic acid A.

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