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STEREOSELECTIVITY IN THE FORMATION OF 2,5-DISUBSTITUTED TETRAHYDROPYRANS BY INTRAMOLECULAR HETERO-MICHAEL ADDITION

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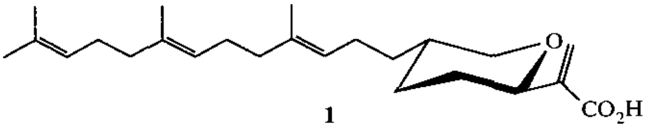
Abstract - A stereoselective formation of tetrahydropyran ring having acrylate moiety at C2 and geranyl or homofarnesyl group at C5 based on intramolecular hetero-Michael addition is described.

In the course of our studies of the structure-bioactivity relationship for Rhopaloic acid A ((+)-**1**), a potent cytotoxic agent, which was isolated from a marine sponge, *Rhopaloeides* sp,[1] the stereoselective formation of 2,5-disubstituted tetrahydropyran rings has been investigated (Scheme 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]

Scheme 1.



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Although stereocontrolled synthesis of 2,3- or 2,6-disubstituted pyran derivatives was much investigated,[3] less attention has been accorded to the stereoselective construction of 2,5-disubstituted pyran ring. Therefore, we have investigated the stereoselective formation of pyran ring tethered to acrylate moiety at C2 and alkenyl group at C5.

Aldehydes (**2a**) and (**2b**) were prepared by way of several steps from geraniol and farnesol, respectively.[4] The Wittig-Horner-Emmons reaction of **2a** with $(EtO)_2P(O)CH_2CO_2Et$ gave α,β-unsaturated ester (**3**) as a single *E*-isomer in 90% yield (Scheme 2). Treatment of **3** with TBAF at 25 °C gave the tetrahydropyran derivative (**4**) as a mixture of *cis-trans* isomers in 80% yield, the *cis/trans* ratio being 1/2.3. The modified Wittig-Horner-Emmons reaction of **2a** with $(EtO)_2P(O)C(=CH_2)CO_2Et$ in the presence of $NaSCHMe_2$ at 25 °C furnished α,β-unsaturated ester (**5a**), the *E/Z* ratio being 1/3.[5] The geometric assignment was determined by comparison of ^1H NMR chemical shifts of vinyl proton.[4-6]

Reaction of **2b** with $(EtO)_2P(O)C(=CH_2)CO_2Et$ in the presence of $NaSCHMe_2$ under the same conditions furnished α,β-unsaturated ester (**5b**) as a mixture of geometric isomers. The geometric

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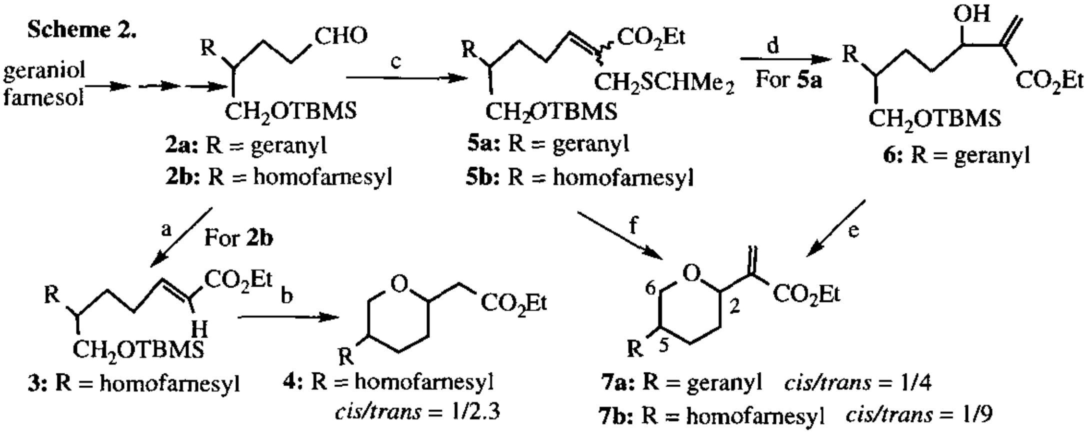
ratio changed with the reaction conditions. When the reaction mixture was stirred at 0 °C for 3 h, a mixture of *Z* and *E*-**5b** was obtained in 57% yield (*Z/E* = 2.4/1.0). The reaction was conducted at 25 °C for 17 h afforded only *Z*-**5b** as the thermodynamically controlled product in 53% yield. The geometry of the product was determined based on relative chemical shifts of the ^{1}H NMR signals and with DIF-NOE. When *3-H* of the *E*-isomer was irradiated, the intensity of 2-CH_2-S signal was enhanced with 8.2%.[4,6]

Scheme 2.



Reagents and Conditions: (a) NaH (1 eq), $(EtO)_2P(O)CH_2CO_2Et$ (1 eq), THF, 0 °C; (b) TBAF (3 eq), THF , 25 °C; (c) NaH (1 eq), Me_2CHSH (1 eq), $(EtO)_2P(O)C(=CH_2)CO_2Et$ (1 eq), THF, 0 °C, 10 min, then **2a** or **2b**, 25 °C; (d) *m*CPBA, $(EtO)_3P$; (e) NCS/Ph_3P, 25 °C; (f) MeI, $AgBF_4$, CH_2Cl_2, then TBAF, THF, 25 °C.

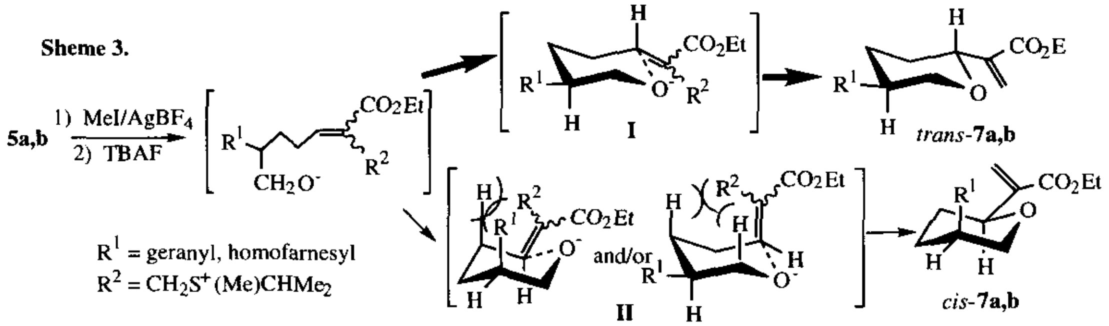
Oxidation of **5a** with *m*CPBA followed by rearrangement in the presence of $(EtO)_3P$ gave alcohol (**6**) which was treated with NCS/PPh_3 to afford **7a** in 13% yield (*cis/trans* = 3/7).[7]

Treatment of a mixture of *E* and *Z*-**5a** with methylating reagent MeI/$AgBF_4$ followed by desilylation with TBAF afforded a mixture of *cis*- and *trans*-ethyl pyranylacrylate derivatives (**7a**) in 24% yield (*cis/trans* = 1/4) in one pot reaction from **5a**. Assignment of *6-ax-H* at δ 3.17 in the ^{1}H NMR spectrum of *trans*-**7a** was determined by coupling constants: $J_{5,6\text{-}ax}$ = 11.2 Hz, $J_{5,6\text{-}eq}$ = 3.9 Hz. The relative stereochemistry of *trans*-**7a** was confirmed by intensity enhancement of *2-ax-H* at δ 4.13 by 13.9% upon irradiation of *6-ax-H* through DIF-NOE measurements.

Reaction of *Z*-**5b** with MeI/$AgBF_4$ followed by desilylation with TBAF afforded a mixture of *cis*- and *trans*-ethyl pyranylacrylate derivatives (**7b**) in 37% yield (*cis/trans* = 1/9) in one pot reaction. Reaction of *E*-**5b** under the same reaction conditions gave also *trans*-**7b** as the major product in 31% yield (*cis/trans* = 1/9). The assignment of relative stereochemistry of *trans*-**7b** was done by the same considerations as *trans*-**7a**: $J_{5,6\text{-}ax}$ = 11.2 Hz, $J_{5,6\text{-}eq}$ = 3.9 Hz. When *6-ax-H* at δ 3.16 was irradiated, the intensity enhancement of *2-H* at δ 4.12 by 6.9% was observed. The spectral data of *trans*-**7b** were identical with those recorded for the ethyl ester derivative of **1**.[1]

The stereochemistry was rationalized in terms of a transition state **I** rather than **II** for the *trans*-cyclization that is based on a quasi-equatorial conformation for the acrylate moiety thereby avoiding 1,3-diaxial-like repulsion (Scheme 3).

Sheme 3.



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Spectral data of **1** were kindly provided by Dr. S. Ohta (Hiroshima University). The authors thank Shiono Koryo Kaisha, Ltd. and Kuraray Co. for the gift of farnesol. The measurements of NMR and HRMS were made using JEOL GSX-270 and SX-102A, respectively, at the Instrument Center for Chemical Analysis, Hiroshima University.

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4. The synthesis of **2a,b** will be published in detail elsewhere. All new compounds have been fully characterized by NMR and gave satisfactory exact MS. Spectral data for *E*-**3**, *E* and *Z*-**5a**, *E* and *Z*-**5b**, a mixture of *cis*- and *trans*-**4**, *trans*-**7a**, and *trans*-**7b**: for *E*-**3**: ^{1}H NMR (270 MHz, CDCl$_3$) δ 0.03 (s, 6H), 0.89 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.30-1.54 (m, 5H), 1.60 (s, 6H), 1.68 (s, 6H), 1.91-2.13 (m, 10H), 2.16-2.27 (m, 2H), 3.43-3.57 (m, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 5.04-5.18 (m, 3H), 5.81 (d, *J* = 16.1 Hz, 1H), 6.92-7.06 (m, 1H); IR (neat, cm^{-1}) 1710; HRMS m/z: found 504.4019 [M$^+$] (Calcd for $C_{31}H_{56}O_3Si$ 504.3999); for *E*-**5a**: ^{1}H NMR (270 MHz, CDCl$_3$) δ 0.03 (s, 6H), 0.89 (s, 9H), 1.24 (d, *J* = 6.8 Hz, 6H), 1.31 (t, *J* = 6.8 Hz, 3H), 1.40-1.60 (m, 3H), 1.60 (s, 6H), 1.68 (s, 3H), 1.90-2.10 (m, 6H), 2.48 (dt, *J* = 7.3, 6.8 Hz, 2H), 2.84 (septet, *J* = 6.8 Hz, 1H), 3.38 (s, 2H), 3.47 (d, *J* = 4.9 Hz, 2H), 4.19 (q, *J* = 6.8 Hz, 2H), 5.00-5.15 (m, 2H), 5.95 (t, *J* = 7.3 Hz, 1H); ^{13}C NMR (68 MHz, CDCl$_3$) δ -5.49 (x2), 14.2, 16.0, 17.6, 18.2, 23.2 (x2), 25.6, 25.9 (x3), 26.7, 27.1, 29.1, 30.5, 34.1, 34.4, 39.8, 41.0, 60.3, 64.8, 122.6, 124.3, 129.0, 131.1, 136.0, 143.2, 166.8; HRMS m/z: found 495.3336 [M$^+$-CH$_3$] (Calcd for $C_{29}H_{54}O_3SSi$ - CH$_3$ 495.3328); for *Z*-**5a**: ^{1}H NMR (270 MHz, CDCl$_3$) δ 0.03 (s, 6H), 0.89 (s, 9H), 1.28 (d, *J* = 6.4 Hz, 6H), 1.29 (t, *J* = 6.8 Hz, 3H), 1.35-1.55 (m, 3H), 1.60 (s, 6H), 1.68 (s, 3H), 1.94-2.15 (m, 6H), 2.27 (dt, *J* = 7.3, 7.3 Hz, 2H), 2.92 (septet, *J* = 6.4 Hz, 1H), 3.46 (s, 2H), 3.45-3.50 (m, 2H), 4.22 (q, *J* = 6.8 Hz, 2H), 5.05-5.15 (m, 2H), 6.80 (t, *J* = 7.3 Hz, 1H), ^{13}C NMR (68 MHz, CDCl$_3$) δ -5.5 (x2), 14.2, 16.1, 17.6, 18.2, 23.4

(x2), 25.6, 25.9 (x3), 26.1, 26.5, 26.6, 29.2, 29.9, 35.5, 39.8, 41.0, 60.6, 64.8, 122.4, 124.3, 129.5, 131.1, 136.1, 144.6, 166.9; HRMS m/z: found 510.3570 [M$^+$] (Calcd for $C_{29}H_{54}O_3SSi$ 510.3563); for *E*-**5b**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.89 (s, 9H), 1.25 (d, *J* = 6.8 Hz, 6H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.18-1.37 (m, 4H), 1.54-1.64 (m, 1H), 1.60 (s, 9H), 1.68 (s, 3H), 1.95-2.15 (m, 10H), 2.47 (dt, *J* = 7.8, 7.3 Hz, 2H), 2.85 (septet, *J* = 6.6 Hz, 1H), 3.39 (s, 2H), 3.47-3.53 (m, 2H), 4.24 (q, *J* = 7.2 Hz, 2H), 5.05-5.21 (m, 3H), 5.97 (t, *J* = 7.3 Hz, 1H); HRMS m/z: found 592.4371 [M$^+$] (Calcd for $C_{35}H_{64}O_3SSi$ 592.4345); for *Z*-**5b**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.89 (s, 9H), 1.28 (d, *J* = 6.8 Hz, 6H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.35-1.56 (m, 5H), 1.61 (s, 9H), 1.69 (s, 3H), 1.93-2.12 (m, 10H), 2.26 (dt, *J* = 7.8, 7.3 Hz, 2H), 2.95 (septet, *J* = 6.8 Hz, 1H), 3.47 (s, 2H), 3.47-3.52 (m, 2H), 4.21 (q, *J* = 7.0 Hz, 2H), 5.05-5.15 (m, 3H), 6.81 (t, *J* = 7.3 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ -5.4 (x2), 14.2, 16.0, 17.7, 18.3, 23.4, 25.3 (x2), 25.7, 25.9 (x3), 26.2, 26.4, 26.5, 26.7, 26.8, 30.3, 31.0, 34.8, 35.5, 39.7, 39.9, 60.7, 65.0, 124.3, 124.4, 124.5, 124.7, 131.2, 134.9, 135.0, 144.8, 165.0; IR (neat, cm^{-1}) 1700; HRMS m/z: found 592.4378 [M$^+$] (Calcd. for $C_{35}H_{64}O_3SSi$ 592.4345); for *cis*- and *trans*-**4**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.3 Hz, 3H), 0.80-1.60 (m, 7H), 1.57 (s, 6H), 1.59 (s, 3H), 1.67 (s, 3H), 1.80-2.10 (m, 10H), 2.30-2.50 (m, 2H), 3.05 (t, *J* = 11.2, 1H, *trans*-6-ax-H), 3.5-4.0 (m, 2-ax-H, 6-eq-H, *cis*-6-ax-H), 4.14 (q, *J* = 7.3 Hz, 2H), 5.00-5.20 (m, 3H); HRMS m/z: found 390.3154 [M$^+$] (Calcd for $C_{25}H_{42}O_3$ 390.3134); for *trans*-**7a:** ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.10-1.50 (m, 2H), 1.50-1.80 (m, 2H), 1.30 (t, *J* = 6.8 Hz, 3H), 1.58 (s, 3H), 1.60 (s, 3H), 1.68 (s, 3H), 1.82-1.97 (m, 1H), 1.90-2.08 (m, 6H), 3.17 (t, *J* = 11.2 Hz, 1H), 4.02 (ddd, *J* = 11.2, 3.9, 2.0 Hz, 1H), 4.13 (d, *J* = 9.3 Hz, 1H), 4.22 (q, *J* = 6.8 Hz, 2H), 5.08-5.14 (m, 2H), 5.87 (d, *J* = 1.0 Hz, 1H), 6.23 (d, *J* = 1.0 Hz, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.2, 16.1, 17.7, 25.7, 26.6, 30.4, 30.8, 32.4, 36.7, 39.8, 60.6, 73.8, 75.6, 121.7, 123.9, 124.3, 131.4, 136.4, 142.3, 166.0: HRMS m/z: found 320.2336 [M$^+$] (Calcd for $C_{20}H_{32}O_3$ 320.2351); for *trans*-**7b**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.87-1.35 (m, 4H), 1.30 (t, *J* = 7.3 Hz, 3H), 1.60 (s, 9H), 1.68 (s, 3H), 1.64-1.74 (m, 1H), 1.89-2.10 (m, 12H), 3.16 (t, *J* = 11.2 Hz, 1H), 4.03 (ddd, *J* = 11.2, 3.9, 1.5 Hz, 1H), 4.12 (d, *J* = 9.8 Hz, 1H), 4.22 (q, *J* = 7.3 Hz, 2H), 5.06-5.15 (m, 3H), 5.88 (d, *J* = 1.5 Hz, 1H), 6.23 (br s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.2, 16.0, 17.7, 24.9, 25.7, 26.6, 26.8 (x2), 30.5, 32.3, 32.5, 35.3, 39.7 (x2), 60.6, 74.0, 75.5, 123.9, 124.2 (x2), 124.4, 131.2, 135.0, 135.3, 142.3, 166.1; IR (neat, cm^{-1}) 1705; HRMS m/z: found 402.3151 [M$^+$] (Calcd for $C_{26}H_{42}O_3$ 402.3134).

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6. According to the Cahn-Ingold-Prelog sequence rule, the *3-H* vinyl proton and CO_2Et group of *E*-**3**, *Z*-**5a**, and *Z*-**5b** are in the same side of the double bond.
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