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First Enantiospecific Synthesis of (−)-Parvifoline and (−)-Curcuquinone

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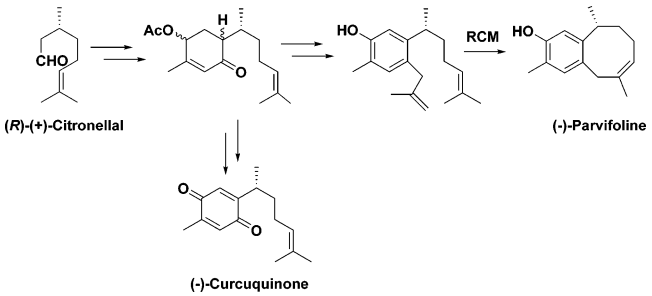
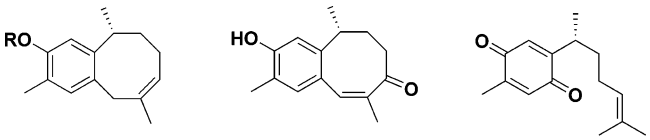


The first enantiospecific synthesis of (−)-parvifoline, employing ring-closing metathesis as the key step, and (−)-curcuquinone from naturally occurring (*R*)-(+)-citronellal is described.

The title compound parvifoline **1** along with isoparvifolinone **2** and parvifoline isovalerate **3** are sesquiterpenes, isolated from genera *Coreopsis*[1] and *Perezia*.[2] These are the only examples of naturally occurring compounds which contain a trimethyl benzocyclooctane structural unit. The absolute configuration of parvifoline **1** was determined[3] by its chemical transformation into (−)-curcuquinone **4**, a natural product with known absolute configuration.



1 R = H
3 R = $Me_2CHC(O)$

2 **4**

(−)-Curcuquinone **4** is an aromatic bisabolene sesquiterpenoid, which was isolated from the Caribbean gorgonian sea plum *Pseudoterogorgia rigida*,[4] and shows antibacterial activity. This has been used for the synthesis of heliannuols D and A,[5] which in turn are believed to be involved in the allelopathic action of sunflowers.

The construction of an eight-membered ring with a deconjugated double bond is the main structural feature that challenges the synthesis of parvifoline **1**. Also, introduction of chirality at the nonfunctionalized benzylic position is difficult, as well. As we have been interested in employing the renewable resources of the nature for the synthesis of natural products, we have identified citronellal as the key synthon, which is abundantly available from plants and of synthetic origin, and have accomplished syntheses of laevigatin[6] and herbertenol.[7]

To our knowledge, four syntheses of *rac*-parvifoline have been reported;[8] three of them employed the Grob fragmentation strategy for cyclooctane ring construction, and the other one dealt with Dieckmann-type intramolecular cyclization of an ester sulfone. Also, there are only four syntheses reported for optically active curcuquinone **4**.[9] In this paper, we wish to report the first enantiospecific synthesis of (−)-parvifoline **1** and (−)-curcuquinone **4** starting from naturally occurring (*R*)-(+)-citronellal. Here, we have used ring-closing metathesis as the key step for the formation of the cyclooctene ring of (−)-parvifoline **1**, which efficiently places the double bond in the right position.

As shown in the retrosynthetic analysis (Scheme 1), (−)-parvifoline could be obtained from the diolefin **5**, which in turn could be obtained from (*R*)-(+)-citronellal. Accordingly, (*R*)-(+)-citronellal (98% ee) was converted to enone **7** (1:1 diastereomeric mixture) as reported in the literature.[10] Enone **7** was then treated with LDA as the base and quenched using TMSCl to give the corresponding silyl enol ether of enone **7**, followed by oxidation using mCPBA[11] to give trimethylsilyl ether of α-hydroxy enone **8**, which was further hydrolyzed by HCl solution to furnish hydroxy enone **8** in 70% overall yield. Enone **8** was then subjected to 1,2-addition using Grignard reagent MeMgI to give the corresponding diol **9** as a diastereomeric mixture, two of which could be separated by column chromatography, in overall 95% yield. Both of the diastereomers

(1) Bohlmann, F.; Zdero, C. *Chem. Ber.* **1977**, *110*, 468−473.
(2) (a) Joseph-Nathan, P.; Hernandez, J. D.; Roman, L. U.; Garcia, G. E.; Mendoza, V.; Mendoza, S. *Phytochemistry* **1982**, *21*, 1129−1132. (b) Joseph-Nathan, P.; Hernandez, J. D.; Roman, L. U.; Garcia, G. E.; Mendoza, V. *Phytochemistry* **1982**, *21*, 669−672. (c) Garcia, G. E.; Mendoza, V.; Guzman B., J. A. *J. Nat. Prod.* **1988**, *51*, 150−151.
(3) (a) Joseph-Nathan, P.; Hernandez-Medel, M.; Martinez, E.; Rojas-Gardida, M.; Cerda, C. M. *J. Nat. Prod.* **1988**, *51*, 675−689. (b) Garcia, G. E.; Mendoza, V.; Guzman, B. A. *J. Nat. Prod.* **1987**, *50*, 1055−1058.
(4) McEnroe, F. J.; Fenical, W. *Tetrahedron* **1978**, *34*, 1661−1664.
(5) Takabatake, K.; Nishi, I.; Shindo, M.; Shishido, K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1807−1808.
(6) Chavan, S. P.; Dhondge, V. D.; Patil, S. S.; Rao, T. S.; Govande, C. A. *Tetrahedron: Asymmetry* **1997**, *8*, 2517−2518.
(7) Chavan, S. P.; Thakkar, M.; Kharul, R. K.; Pathak, A. B.; Bhosekar, A. V.; Bhadbhade, M. V. *Tetrahedron* **2005**, *61*, 3873−3879.
(8) (a) Villagomez-Ibarra, R.; Joseph-Nathan, P. *Tetrahedron Lett.* **1994**, *35*, 4771−4772. (b) Grimm, E. L.; Levac, S.; Coutu, M. L. *Tetrahedron Lett.* **1994**, *35*, 5369−5372. (c) Villagomez-Ibarra, R.; Alvarez-Cisneros, C.; Joseph-Nathan, P. *Tetrahedron* **1995**, *51*, 9285−9300. (d) Covarrubias-Zuniga, A.; Cantu, F.; Maldonado, L. A. *J. Org. Chem.* **1998**, *63*, 2918−2921. (e) Bhowmik, D. R.; Venkateswaran, R. V. *Tetrahedron Lett.* **1999**, *40*, 7431−7433.
(9) (a) Ono, M.; Ogura, Y.; Hatogai, K.; Akita, H. *Tetrahedron: Asymmetry* **1995**, *6*, 1829−1832. (b) Fuganti, C.; Serra, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3758−3764. (c) Takabatake, K.; Nishi, I.; Shindo, M.; Shishido, K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1807−1808. (d) Yoshimura, T.; Kisyuka, H.; Kamei, T.; Takabatake, K.; Shindo, M.; Shishido, K. *Arkivoc* **2003**, 247−255. (e) Minatti, A.; Heinz Dotz, K. *J. Org. Chem.* **2005**, *70*, 3745−3748.
(10) (a) Ghisalberti, E. L.; Jeferies, P. R.; Stuart, A. D. *Aust. J. Chem.* **1979**, *32*, 1627−1630. (b) Hagiwara, H.; Tomoyuki, O.; Ono, H.; Kamat, V. P.; Hoshi, T.; Suzuki, T.; Ando, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 895−900.
(11) Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1978**, *43*, 1599−1602.

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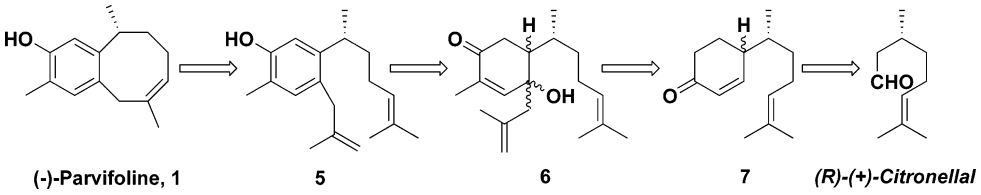
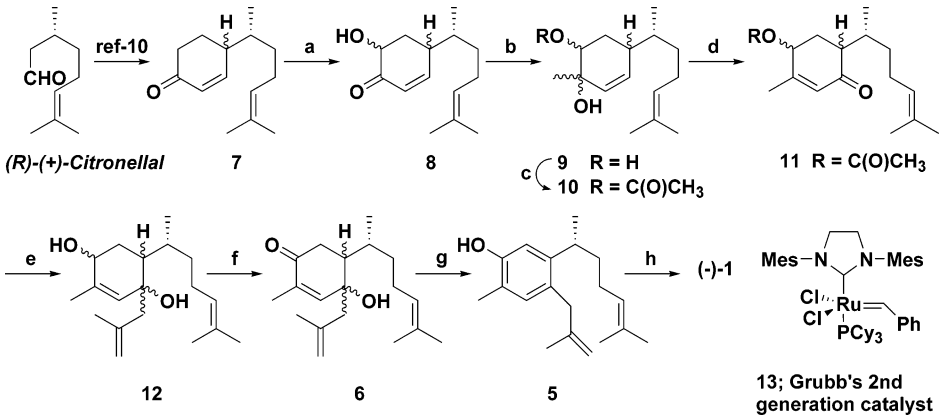
SCHEME 1



SCHEME 2[a]

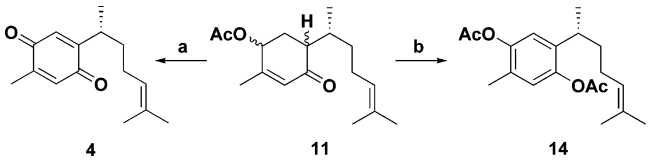


[a] Reagents and conditions: (a) (i) LDA, THF, −78 °C, 2 h, then TMSCl, −78 °C to rt, 5 h; (ii) mCPBA, aq. $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 5 h; (iii) HCl, CH_2Cl_2, rt, overnight, 70% overall; (b) Mg, MeI, THF, 0 °C, then **8**, 0 °C to rt, overnight, 95%; (c) pyridine, acetyl chloride, 0 °C to rt, 12 h, 85%; (d) PCC, CH_2Cl_2, 0 °C to rt, 8 h, 80%; (e) Mg, THF, methallyl chloride, 0 °C, 24 h, 90%; (f) DMP, CH_2Cl_2, 0 °C to rt, 4 h, 85%; (g) (i) Et_3N, methanesulfonyl chloride, CH_2Cl_2, 0 °C to rt, 3 h, then reflux, 5 h; (ii) KOH, MeOH, reflux, 12 h, 79% for two steps; (h) Grubbs' catalyst (second generation), toluene, 80 °C, 4 h, 90%.

have been characterized by ^{1}H NMR and ^{13}C NMR, but for convenience, they were carried forward as a mixture only. The secondary hydroxyl group of the diol **9** was selectively protected as the corresponding acetate derivative using pyridine as the base to give allylic alcohol **10** in 85% yield. This allylic tertiary alcohol **10** on oxidation using pyridinium chlorochromate[12] underwent 1,3-carbonyl transposition to give enone **11** in 80% yield. This enone **11** on 1,2-addition with methallyl magnesium chloride under Barbier conditions gave diol **12** in 90% yield. This diol **12** on Dess-Martin periodinane[13] oxidation furnished enone **6** in 85% yield, which on mesylation using triethylamine followed by hydrolysis using KOH in methanol gave requisite phenol intermediate **5** in 79% overall yield. Compounds **7**−**12** and **6** were obtained as a mixture of diastereomers, and as we were going to destroy the chiral centers present, except one in later stages of the synthesis, we did not determine the ratio of diastereomers. Finally, the crucial eight-membered ring formation was achieved by ring-closing metathesis[14] of **5** employing second-generation Grubbs' catalyst to furnish (-)-parvifoline **1** in 90% yield: {$[\alpha]^{25}_D$ −167.90 (*c* 1.73, $CHCl_3$) (lit. −173, *c* 1.73, $CHCl_3$)}; mp, ^{1}H, ^{13}C NMR spectral data of synthetic (−)-**1** were in good agreement with the literature values.[1,2]

The synthesis of (−)-curcuquinone **4** would be readily accomplished from the intermediate **11**, the acetate of which was hydrolyzed using K_2CO_3 in methanol, followed by Dess-Martin periodinane oxidation and treatment of crude product

SCHEME 3[a]



[a] Reagents and conditions: (a) (i) K_2CO_3, MeOH, rt, 30 min; (ii) DMP oxidation; (iii) CH_2Cl_2, Et_3N, rt, 1 h; (iv) CAN, CH_2Cl_2, 0 °C, 30 min, 60% overall; (b) (i) K_2CO_3, MeOH, rt, 30 min; (ii) DMP oxidation; (iii) CH_2Cl_2, Et_3N, rt, 1 h; followed by acetyl chloride at 0 °C, overnight, 52% overall.

with triethylamine to give the corresponding hydroquinone, which without isolation was oxidized further to (−)-curcuquinone **4** using CAN as the oxidizing agent. ^{1}H, ^{13}C NMR spectral data of synthetic (−)-curcuquinone were in complete agreement with the literature values.[4] Further, to prove the formation of an hydroquinone intermediate, we have acetylated the crude product obtained after DMP oxidation using acetyl chloride in the presence of triethylamine as a base to afford diacetate derivative **14**. Thus, (−)-parvifoline **1** and (−)-curcuquinone **4** have been synthesized starting from (*R*)-(+)-citronellal as the chiron. The synthesis of (−)-parvifoline has been accomplished in 10% overall yield, employing ring-closing metathesis as the key step.

Experimental Section

(*R*)-2-Methyl-4-(2-methylallyl)-5-(6-methylhept-5-en-2-yl)phenol (5): Enone **6** (0.50 g, 1.72 mmol) was taken in a 50 mL two-neck round-bottomed flask, equipped with a magnetic stir bar. To this was added CH_2Cl_2 (10 mL) and cooled to 0 °C followed by dropwise addition of triethylamine (0.87 g, 8.62 mmol) and mesyl

(12) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682−685.
(13) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.
(14) (a) Michalak, M.; Wicha, J. *Synlett* **2005**, *50*, 2277−2280. (b) Boyer, F. D.; Hanna, I. *Eur. J. Org. Chem.* **2006**, 471−482. (c) Hoffmann, T.; Gmeiner, P. *Synlett* **2002**, *6*, 1014−1016.

chloride (0.79 g, 6.9 mmol). The reaction mixture was stirred at 0 °C for 3 h and at reflux temperature for 5 h. It was quenched by saturated $NaHCO_3$ solution (50 mL) and extracted using CH_2Cl_2 (25 mL × 3). The combined organic layer was washed using water (75 mL) followed by usual work up. The crude product was taken in MeOH (20 mL), and to this was added KOH (0.20 g, 3.56 mmol) and refluxed for 12 h. Methanol was evaporated under reduced pressure, and the reaction mixture was diluted using water. The aqueous layer was extracted using CH_2Cl_2 (25 mL × 3), and the combined organic layer was washed using brine solution (50 mL). The product was purified using flash column chromatography (SiO_2, petroleum ether:EtOAc 98:2) to give phenol **5** as colorless oil (0.37 g, 79%): $[\alpha]^{25}_D$ −33.1 (*c* 1.60, $CHCl_3$); IR (neat) ν_{max} (cm^{-1}) 3393, 2925, 1502, 1445; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.12 (d, J = 6.8 Hz, 3H), 1.46−1.58 (m, 2H), 1.53 (s, 3H), 1.67 (s, 3H), 1.71 (s, 3H), 1.82−1.98 (m, 2H), 2.18 (s, 3H), 2.74−2.91 (m, 1H), 3.20 (d, J = 4.7 Hz, 2H), 4.48 (s, 1H), 4.76 (s, 1H), 5.06 (t, J = 7.0 Hz, 1H), 6.60 (s, 1H), 6.81 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.3 (CH_3), 17.7 (CH_3), 22.1 (CH_3), 22.7 (CH_3), 25.7 (CH_3), 26.2 (CH_2), 33.4 (CH), 38.4 (CH_2), 40.5 (CH_2), 111.4 (CH_2), 112.3 (CH), 120.5 (C), 124.8 (CH), 128.9 (C), 131.3 (C), 132.8 (CH), 145.5 (C), 145.6 (C), 152.5 (C). MS-ESI *m*/*z* 273 $(M + 1)^+$. Anal. Calcd for $C_{19}H_{28}O$: C, 83.77%; H, 10.36%. Found: C, 83.84%; H, 10.33%.

(−)-Parvifoline (1): Phenol **5** (0.25 g, 0.92 mmol) was taken in a 50 mL two-neck round-bottomed flask, equipped with a magnetic stir bar and a condenser. Toluene (25 mL) was added to it, followed by Grubbs' catalyst 13 (second generation) (78 mg, 0.092 mmol) under N_2 atmosphere, and the reaction mixture was stirred at 80 °C for 4 h. After completion of reaction, toluene was removed under reduced pressure, and the product was purified by flash column chromatography (SiO_2, petroleum ether:EtOAc 99:1) to furnish parvifoline **1** (0.16 g, 80%) as white solid: mp 85 °C (lit.[1,2] mp 89−90 °C for crystallized product); $[\alpha]^{25}_D$ −168 (*c* 1.73, $CHCl_3$) [lit.[1,2] −173, *c* 1.73, $CHCl_3$)]; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.08−1.13 (m, 1H), 1.31 (d, J = 7.0 Hz, 3H), 1.58−1.87 (m, 3H), 1.75 (s, 3H), 2.20 (s, 3H), 3.04 (d, J = 18.3 Hz, 1H), 3.53 (d, J = 18.3 Hz, 1H), 3.12−3.22 (m, 1H), 5.36 (t, J = 7.0 Hz, 1H), 6.60 (s, 1H), 6.88 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.3 (CH_3), 19.4 (CH_3), 23.8 (CH_2), 26.5 (CH_3), 33.1 (CH), 40.1 (CH_2), 41.7 (CH_2), 111.2 (CH), 120.1 (C), 123.5 (CH),130.7 (C), 131.9 (CH), 137.6 (C), 144.1 (C), 153.0 (C).

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Supporting Information Available: Experimental procedures, characterization data, and NMR spectra of a few of the intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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