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An enantiospecific synthesis of (+)-isoparvifolinone and (−)-parvifoline

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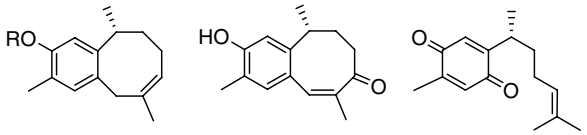
Abstract—An enantiospecific synthesis of (+)-isoparvifolinone and (−)-parvifoline, from naturally occurring (*R*)-(+)-citronellal, employing intramolecular Friedel–Crafts acylation as the key step, is described.

The title compounds (−)-parvifoline **1** and (+)-isoparvifolinone **2** along with parvifoline isovalerate **3** are sesquiterpenes, isolated from the 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**,[4] a natural product with known absolute configuration.



1 R = H
3 R = $Me_2CHCH_2C(O)$
5 R = Me

2 **4**

The construction of an eight-membered ring with a deconjugated double bond is the main structural feature that poses a challenge for the synthesis of parvifoline **1**. Also, introduction of chirality at the nonfunctionalised benzylic position is difficult as well. As we have been interested in employing renewable natural resources for the synthesis of natural products, we identified citronellal as the key synthon, which is abundantly available both from plants and synthetic origin, and have accomplished the syntheses of laevigatin[5] and herbertenol[6] using it as the starting material.

Four syntheses of racemic parvifoline have been reported;[7] three of which employed a Grob fragmentation for cyclooctane ring construction and the other utilised a Dieckmann type intramolecular cyclisation of an ester sulfone. The first enantiospecific synthesis started from (*R*)-(+)-citronellal and utilised RCM for the benzocyclooctene framework formation.[8] In this letter, we report another enantiospecific synthesis of (−)-parvifoline **1** and (+)-isoparvifolinone **2** starting from naturally occurring (*R*)-(+)-citronellal. However, here we have utilised an intramolecular Friedel–Crafts acylation as the key step for formation of the benzocyclooctene ring.

As shown in the retrosynthetic analysis (Scheme 1), we envisaged that (−)-parvifoline **1** could be obtained from the cyclic enone **6**, which in turn could be synthesised from (*R*)-(+)-citronellal via conjugated ester **7** and diol **8**.

Accordingly, (*R*)-(+)-citronellal (98% ee) was converted to enone **9** (1:1 diastereomeric mixture) as reported in the literature.[9] Enone **9** was then treated with LDA and quenched using TMSCl to give a silyl enol ether, followed by oxidation using *m*-CPBA[10] to give the trimethylsilyl ether of α-hydroxy-enone **10**, which was hydrolysed with aqueous HCl to furnish **10** in 70% overall yield. Enone **10** was then subjected to 1,2-addition of MeMgI to give the corresponding diol **8** as a diastereomeric mixture, two components of which could be separated by column chromatography, in 95% overall yield. Both were found to be mixtures of diastereomers as suggested by ^1H and ^{13}C NMR, but for convenience, they were carried forward as a mixture. The secondary hydroxyl group of diol **8** was then oxidised under Swern

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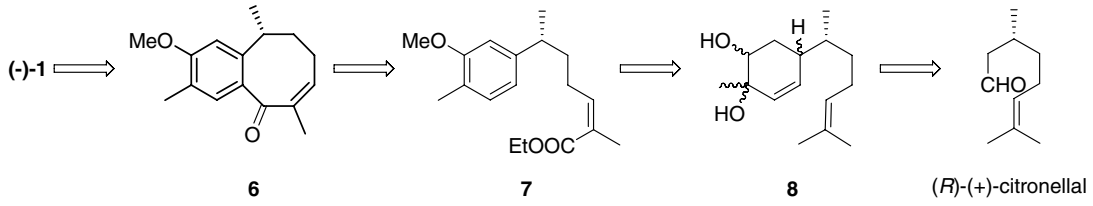
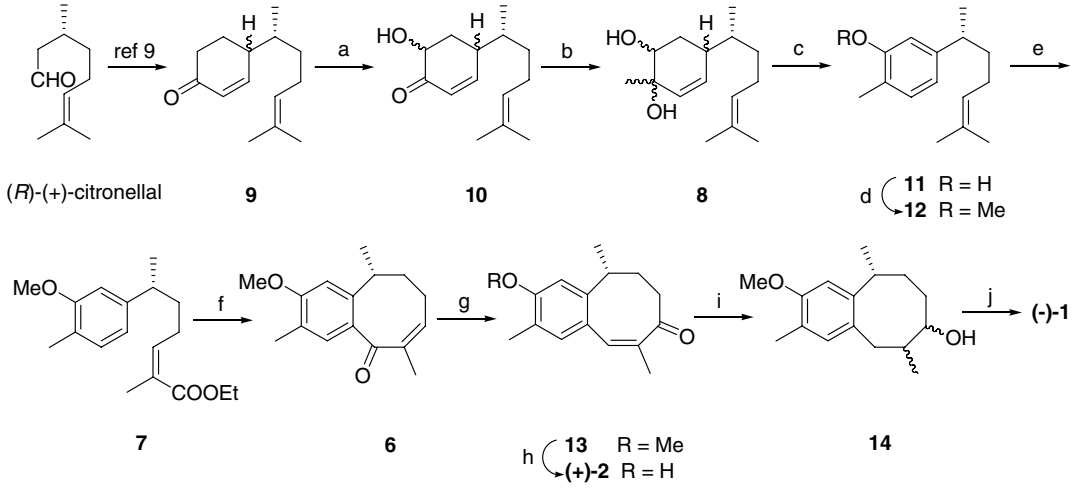
conditions[11] and the resulting hydroxy-ketone was immediately subjected to mesylation. Under the mesylation conditions, tertiary hydroxyl group elimination resulted in aromatisation and afforded a mixture of phenol **11** and its mesyl ester, which was hydrolysed using KOH in refluxing methanol to furnish required intermediate **11** in 47% overall yield. Phenol **11** was then protected as its methyl ether using dimethyl sulfate and potassium carbonate to provide **12** in 90% yield. The olefin functionality of **12** was then dihydroxylated and the resulting diol was immediately subjected to cleavage with sodium periodate to provide the corresponding aldehyde, which on two carbon olefination according to Ando's protocol[12] resulted in *Z*-α,β-unsaturated ester **7** in 85% overall yield, as the sole product. The formation of **7** was confirmed by NMR spectral analysis. Ester **7** was then hydrolysed to the corresponding acid by alkaline hydrolysis, and treated with oxalyl chloride to give the corresponding acid chloride. The acid chloride underwent intramolecular Friedel–Crafts acylation[13] on treatment with anhydrous aluminium chloride in dry CH_2Cl_2 to furnish the cyclic enone **6** in 40% overall yield. The ketone functionality of **6** was then reduced under Luche reduction conditions,[14] followed by oxidation of the resulting benzyl alcohol with pyridinium chlorochromate[15] supported on silica gel, resulting in 1,3-carbonyl transposition to provide isoparvifolinone methyl ether **13** in 60% overall yield. Finally, (+)-isoparvifolinone **2** was obtained by BBr_3 promoted methyl ether deprotection of **13** in 60% yield. The spectral data[16] were in complete agreement with the literature values[2] of the natural product and its specific rotation {$[\alpha]_D^{25}$ +850 (*c* 1, $CHCl_3$)} {lit.[2] specific rotation $[\alpha]_D^{25}$ +854 (*c* 1, $CHCl_3$)} was indicative of its optical purity and this also confirmed its absolute configuration (see Scheme 2).

Further, **13** was hydrogenated followed by borohydride reduction to give alcohol **14** in 50% yield. This alcohol was obtained as a single isomer as indicated by NMR spectra and was in good agreement with the literature values.[7c] However, as we were to destroy the newly generated stereocentres, we did not attempt to characterise the isomer and subjected it to elimination under tosylation conditions as reported previously,[7c] giving parvifoline methyl ether **5**, which on deprotection using lithium thioethoxide gave (−)-parvifoline **1** in 60% overall yield. Spectral data[16] of the synthetic **(−)-1** were in good agreement with the literature values.[1,2]

Thus, (−)-parvifoline and (+)-isoparvifolinone have been synthesised enantiospecifically starting from (*R*)-



Scheme 1. Retrosynthetic analysis.



Scheme 2. Reagents and conditions: (a) (i) LDA, THF, −78 °C, 2 h, then TMSCl, −78 °C to rt, 5 h; (ii) *m*-CPBA, aqueous $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 5 h; (iii) HCl, CH_2Cl_2, overnight, 70% overall; (b) Mg, MeI, THF, 0 °C, then **10**, 0 °C to rt, overnight, 95%; (c) (i) oxalyl chloride, DMSO, CH_2Cl_2, −78 °C, 30 min, Et_3N, −78 °C to rt, 5 h; (ii) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C to rt, then reflux, 7 h; (iii) KOH, MeOH, reflux, 7 h, 47% overall; (d) Me_2SO_4, K_2CO_3, acetone, reflux, 12 h, 90%; (e) (i) OsO_4 (cat), NMO (50% in water), acetone, rt, 24 h; (ii) $NaIO_4$ on silica gel, CH_2Cl_2, rt, 5 h; (iii) $(o\text{-}CH_3C_6H_4O)_2P(O)CH(CH_3)COOEt$, NaH, THF, −78 °C, 3 h, 85% overall; (f) (i) KOH, MeOH, reflux, 4 h; (ii) oxalyl chloride, CH_2Cl_2, 0 °C, 3 h; (iii) $AlCl_3$ (anhydrous), CH_2Cl_2, −20 °C to rt, 7 h, 40% overall; (g) (i) $CeCl_3$–$7H_2O$, $NaBH_4$, MeOH, 0 °C, 30 min; (ii) PCC on silica gel, 60% overall; (h) BBr_3, CH_2Cl_2, rt, 1 h, 60%; (i) H_2/Pd/C (10%), MeOH, 12 h, followed by $NaBH_4$, 30 min, 50%; (j) (i) pyridine, *p*-toluenesulfonyl chloride, −4 °C, 3 d, then 105 °C, 7 h; (ii) EtSLi, DMF, 110 °C, 60% overall.

(+)-citronellal, employing intramolecular Friedel–Crafts acylation as the key step.

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References and notes

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. A. *J. Nat. Prod.* **1988**, *51*, 150–151.
3. (a) Joseph-Nathan, P.; Hernandez-Medel, M. del R.; 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. Chavan, S. P.; Ravindranathan, T.; Dhondge, V. D.; Patil, S. S.; Rao, T. S.; Govande, C. A. *Tetrahedron: Asymmetry* **1997**, *8*, 2517–2518.
6. Chavan, S. P.; Thakkar, M.; Kharul, R. K.; Pathak, A. B.; Bhosekar, A. V.; Bhadbhade, M. V. *Tetrahedron* **2005**, *61*, 3873–3879.
7. (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.
8. Chavan, S. P.; Thakkar, M.; Jogdand, G. F.; Kalkote, U. R. *J. Org. Chem.* **2006**, *71*, 8986–8988.
9. (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.
10. Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1978**, *43*, 1599–1602.
11. Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.
12. Ando, K. *J. Org. Chem.* **1997**, *62*, 1934–1939.
13. McIntyre, D.; Proctor, G. R.; Rees, L. *J. Chem. Soc. (C)* **1966**, 985–989.
14. Luche, J. L.; Hahn, L. R.; Crabbe, P. *J. Chem. Soc., Chem. Commun.* **1978**, 601–602.
15. (a) Babler, J. H.; Coghlan, J. *Synth. Commun.* **1976**, *6*, 469–474; (b) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682.
16. *Spectral data for compound* **11**: Specific rotation: $[\alpha]_D^{25}$ −37.91 (*c* 1.5, $CHCl_3$). IR ($CHCl_3$) ν_{max} (cm^{-1}): 3411, 1621, 1589. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.19 (d, $J = 7.0$ Hz, 3H); 1.52–1.66 (m, 2H); 1.55 (s, 3H); 1.66 (s, 3H); 1.80–1.91 (m, 2H); 2.20 (s, 3H); 2.53–2.64 (m, 1H); 5.05 (apparent triplet, $J = 7.1$ Hz, 1H); 6.56–6.65 (m, 2H); 6.98 (d, $J = 7.7$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 15.5 (CH_3); 17.8 (CH_3); 22.5 (CH_3); 25.8 (CH_3); 26.2 (CH_2); 38.5 (CH_2); 39.1 (CH); 113.6 (CH); 119.4 (CH); 120.9 (C); 124.8 (CH); 130.8 (CH); 131.2 (C); 147.0 (C); 153.7 (C). MS-ESI *m*/*z*: 218 $(M)^+$. Analysis calculated for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.29; H, 10.35. *Compound* **7**: Specific rotation: $[\alpha]_D^{25}$ −37.23 (*c* 2, $CHCl_3$). IR ($CHCl_3$) ν_{max} (cm^{-1}): 3020, 2960, 1705, 1644, 1612, 1581. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.25 (d, $J = 6.7$ Hz, 3H); 1.23 (t, $J = 7.1$ Hz, 3H); 1.60–1.73 (m, 2H); 1.86 (d, $J = 1.3$ Hz, 3H); 2.17 (s, 3H); 2.28–2.50 (m, 2H); 2.57–2.71 (m, 1H); 3.82 (s, 3H); 4.14 (q, $J = 7.1$ Hz, 2H); 5.87 (triplet of doublets, $J = 7.6$, 1.4 Hz, 1H); 6.64–6.70 (m, 2H); 7.03 (d, $J = 7.5$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.1 (CH_3); 15.8 (CH_3); 20.6 (CH_3); 22.2 (CH_3); 27.9 (CH_2); 38.0 (CH_2); 39.7 (CH); 55.2 (CH_3); 60.0 (CH_2); 108.9 (CH); 118.6 (CH); 123.9 (C); 127.2 (C); 130.4 (CH); 142.5 (CH); 146.2 (C); 157.6 (C); 168.1 (C). MS-ESI *m*/*z*: 291 $(M+1)^+$. Analysis calculated for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02. Found: C, 74.36; H, 8.81. *Compound* **6**: Specific rotation: $[\alpha]_D^{25}$ −220.13 (*c* 1.7, $CHCl_3$). IR ($CHCl_3$) ν_{max} (cm^{-1}): 3009, 2959, 1710, 1624, 1600. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.35 (d, $J = 6.9$ Hz, 3H); 1.58–2.0 (m, 4H); 2.02 (s, 3H); 2.19 (s, 3H); 3.08–3.27 (m, 1H); 3.86 (s, 3H); 6.44 (triplet of doublets, $J = 9.0$, 1.4 Hz, 1H); 6.64 (s, 1H); 7.41 (d, $J = 0.8$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 15.6 (CH_3); 18.2 (CH_3); 21.2 (CH_3); 25.5 (CH_2); 31.7 (CH); 39.3 (CH_2); 55.3 (CH_3); 104.7 (CH); 124.5 (C); 132.2 (CH); 135.0 (C); 138.9 (CH); 141.3 (C); 143.0 (C); 160.6 (C); 195.4 (C). MS-ESI *m*/*z*: 245 $(M+1)^+$ Analysis calculated for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found : C, 78.79; H, 8.56. *Compound* **2**: mp: 157–158 °C {lit.[2] mp 157–158 °C}. Specific rotation: $[\alpha]_D^{25}$ +850 (*c* 1, $CHCl_3$) {lit.[2] $[\alpha]_D^{25}$ +854 (*c* 1, $CHCl_3$)}. IR ($CHCl_3$) ν_{max} (cm^{-1}): 3596, 3364, 3020, 2969, 1638, 1581. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.24 (d, $J = 6.8$ Hz, 3H); 1.45–1.61 (m, 1H); 2.02 (d, $J = 1.2$ Hz, 3H); 2.1–2.25 (m, 2H); 2.25 (s, 3H); 2.45–2.59 (m, 1H); 2.88–2.99 (m, 1H); 6.08 (br s, 1H); 6.79 (s, 1H); 7.03 (s, 1H); 7.10 (br s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 15.3 (CH_3); 19.5 (CH_3); 20.6 (CH_3); 33.4 (CH); 39.1 (CH_2); 42.0 (CH_2); 111.4 (CH); 121.7 (C); 129.2 (C); 133.4 (CH); 136.3 (C); 139.7 (CH); 144.1 (C); 155.1 (C); 204.8 (C). *Compound* **1**: mp: 85 °C, {lit.[2] 89–90 °C, crystallised from hexane/acetone}. Specific rotation: $[\alpha]_D^{25}$ −168 (*c* 1.73, $CHCl_3$) {lit.[2] −173 (*c* 1.73, $CHCl_3$)}. IR ($CHCl_3$) ν_{max} (cm^{-1}): 3602, 3369, 1619. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.08–1.13 (m, 1H); 1.31 (d, $J = 7.0$ Hz, 3H); 1.74 (s, 3H); 1.57–1.80 (m, 3H); 2.20 (s, 3H); 3.04 (d, $J = 18.3$ Hz, 1H); 3.11–3.20 (m, 1H); 3.53 (d, $J = 18.3$ Hz, 1H); 4.53 (br s, 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); 137.7 (C); 144.1 (C); 153.0 (C).