

## Total Synthesis of Five Cacalol Families at Different Oxidation Stages, Modified Furanoeremophilane Sesquiterpenes from *Cacalia* and *Senecio* Species

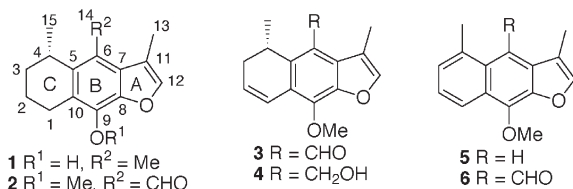
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The recent findings of antihyperglycemic and antimicrobial activities for a modified furanoeremophilane sesquiterpene cacalol (**1**) prompted us to achieve the first total synthesis of five cacalol families ( $\pm$ )-**2–4**, **5**, and **6** which might also be expected to indicate such potent biological activities.

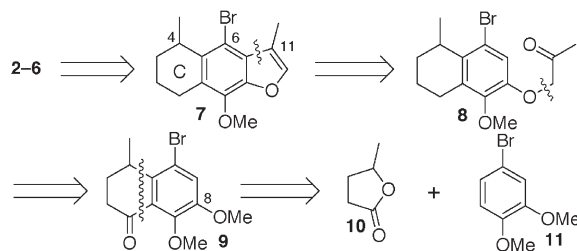
*Cacalia decomposita* A. Gray,<sup>1</sup> a compositae widely distributed in the northern part of Mexico, is a shrub popularly known as matarique and maturin. Matarique is a medicinal plant complex of Mexico which includes perennial herbs with thin, fascicled roots extending from a pubescent root crown, the concoction of which is drunk, alone or in combination with other herbs, for treating diabetes, kidney pain, and rheumatism; it can also be applied as a wash or cataplasm to treat wounds and skin ulcers.<sup>2</sup> Extensive chromatography of a hexane extract from the roots of *Cacalia decomposita* A. Gray afforded a modified eremophilane cacalol (**1**), which has been shown to be the first representative of a new class of compounds (cacalol families) possessing the furotetralin ring system.<sup>3</sup> The structures of **1** and related compounds<sup>4</sup> were the subject of several structural revisions,<sup>5</sup> and the final structures were confirmed by chemical synthesis<sup>6</sup> and degradation studies.<sup>7</sup>



Recently, in vivo bioassay-directed fractionation of an extract from the roots of *Cacalia decomposita* A. Gray revealed that **1** exhibits antihyperglycemic<sup>8</sup> and antimicrobial<sup>9</sup> activities. Therefore, other known cacalol families, such as 14-oxocacalol methyl ether (**2**),<sup>10</sup> 14-oxo-1,2-dehydrocacalol methyl ether (**3**),<sup>10,11</sup> 14-hydroxy-1,2-dehydrocacalol methyl ether (**4**),<sup>11</sup> and 14-nordehydrocacalohastine (**5**)<sup>12</sup> isolated from *Senecio* species and maturin (**6**)<sup>4,11b</sup> isolated from *Cacalia decomposita* A. Gray, might also be expected to possess similar biological activities. We took an interest in biological activities of the furanoeremophilanes **2–6**, the oxidation stages of which were different from those of **1** at the C-ring and C14 position. In this paper, we report the first total synthesis of these cacalol families ( $\pm$ )-**2–4**, **5**, and **6** via stepwise regioselective dehydrogenation of the C-ring.

The retrosynthetic analysis of **2–6** is depicted in Scheme 1. These compounds **2–6** possess a variety of oxidation states and substituents at the C-ring and C6 position, respectively; therefore, we envisaged tetralin **7** as a possible intermediate, because **7** will allow stepwise regioselective dehydrogenation of the C-ring and introduction of various substituents at C6. The inter-

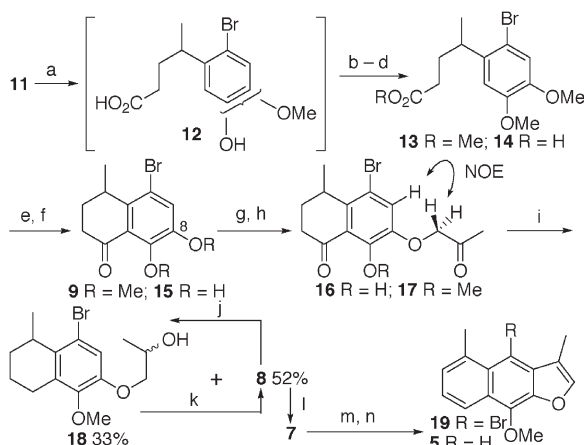
mediate **7** will be derived from tetralone **9** via the furan ring formation in **8**. **9** will be constructed from commercially available  $\gamma$ -valerolactone **10** and 4-bromoveratrole **11** by Friedel–Crafts reaction.



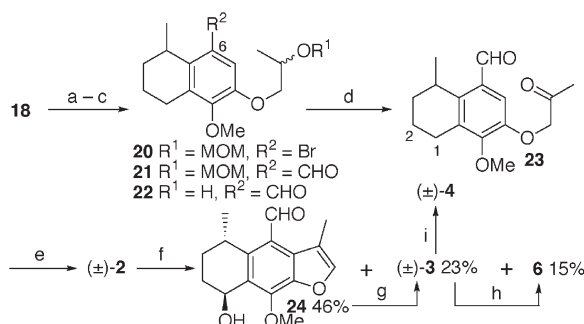
**Scheme 1.** Retrosynthetic analysis of cacalol families **2–6**.

The intermolecular regioselective Friedel–Crafts alkylation of **11** with **10** gave a mixture **12** of two carboxylic acids, which without separation into each component was successively treated with AcCl in MeOH and subsequent Me<sub>2</sub>SO<sub>4</sub> to afford a single methyl ester **13** in 54% yield over 3 steps (Scheme 2).<sup>6b</sup> Saponification of the ester **13** provided carboxylic acid **14**, an intramolecular Friedel–Crafts acylation of which proceeded by (CF<sub>3</sub>CO)<sub>2</sub>O in CF<sub>3</sub>CO<sub>2</sub>H<sup>13</sup> to furnish tetralone **9**. Since it was found that selective demethylation of the 8-MeO group in **9** was difficult, we chose to alkylate the 8-OH group with a C<sub>3</sub> unit required for the furan ring formation after removing both methyl groups. Treatment of **9** with BBr<sub>3</sub> yielded catechol **15**, etherification of which with chloroacetone could regioselectively be achieved at the 8-OH to give ether **16** in 86% yield. After methylation of **16**, the resulting **17** was subjected to reduction with NaBH<sub>4</sub> and CF<sub>3</sub>CO<sub>2</sub>H to afford monoketone **8** reduced only at the benzylic carbonyl group and further reduced alcohol **18**, respectively, both of which were mutually convertible in high yields by a usual manner. Cyclization of **8** with CF<sub>3</sub>SO<sub>3</sub>H resulted in 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)<sup>14</sup> to provide naphthofuran **19**. Debromination of **19** with LiAlH<sub>4</sub> produced 14-nordehydrocacalohastine (**5**) in a quantitative yield. The spectral characteristics of synthetic **5**<sup>15</sup> were in good agreement with those reported for the natural product.<sup>12</sup>

Next, we turned our attention to syntheses of the other cacalol families **2–4** and **6** with 6-substituents. First, we examined modification at the C6 position in the furotetralin **7**; however, it has been found difficult, probably owing to steric hindrance by the two lateral methyl groups at C4 and C11 positions. Therefore, we adopted a C–C bond formation at C6 before constructing the furan ring. After methoxymethyl (MOM) protection of the alcohol **18**, lithium–halogen exchange in the resultant bromide **20** followed by formylation furnished aldehyde **21** in 90% yield (Scheme 3). Deprotection of the MOM ether in **21** and subsequent Swern oxidation<sup>16</sup> of the alcohol **22** yielded ke-



**Scheme 2.** Reaction conditions: a) **10**,  $\text{AlCl}_3$ ,  $(\text{CH}_2\text{Cl}_2)_2$ ,  $70^\circ\text{C}$ ; b)  $\text{AcCl}$ ,  $\text{MeOH}$ , rt, 14 h; c)  $\text{Me}_2\text{SO}_4$ ,  $\text{K}_2\text{CO}_3$ , acetone, reflux, 46 h, 54% (3 steps); d)  $\text{NaOH}$ ,  $\text{MeOH}$ ,  $40^\circ\text{C}$ , 24 h, 97%; e)  $(\text{CF}_3\text{CO})_2\text{O}$ ,  $\text{CF}_3\text{CO}_2\text{H}$ ,  $40^\circ\text{C}$ , 3 h, 64%; f)  $\text{BBR}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78$  to  $-40^\circ\text{C}$ , 18 h, 98%; g) chloroacetone,  $\text{Li}_2\text{CO}_3$ ,  $70^\circ\text{C}$ , 17 h, 86%; h)  $\text{Me}_2\text{SO}_4$ ,  $\text{K}_2\text{CO}_3$ , acetone, reflux, 14 h, 77%; i)  $\text{NaBH}_4$ ,  $\text{CF}_3\text{CO}_2\text{H}$ ,  $0^\circ\text{C}$  to rt, 4 h; j)  $\text{NaBH}_4$ ,  $\text{MeOH}$ , rt, 14 h, 96%; k) Jones oxidation, 92%; l)  $\text{CF}_3\text{SO}_3\text{H}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ , 30 min, 57%; m)  $\text{DDQ}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ , 5 h, 41%; n)  $\text{LiAlH}_4$ ,  $\text{THF}$ ,  $0^\circ\text{C}$ , 4 h, 100%.



**Scheme 3.** Reaction conditions: a)  $\text{MOMCl}$ ,  $i\text{-Pr}_2\text{NEt}$ ,  $\text{CH}_2\text{Cl}_2$ , 97%; b)  $n\text{-BuLi}$ ,  $\text{THF}$ ,  $-78^\circ\text{C}$ , then  $\text{DMF}$ , 1 h, 90%; c) 3 N  $\text{HCl}$ ,  $\text{THF}$ ,  $40^\circ\text{C}$ , 100%; d) Swern oxidation, 84%; e)  $\text{CF}_3\text{SO}_3\text{H}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$  to rt, 5 h, 99%; f)  $\text{DDQ}$ , benzene,  $0^\circ\text{C}$  to rt, 3 h; g) Burgess reagent, benzene, rt, 37%; h)  $o\text{-chloranil}$ ,  $\text{CH}_2\text{Cl}_2$ , rt, 20 h, 54%; i)  $\text{LiAlH}_4$ ,  $\text{THF}$ ,  $0^\circ\text{C}$ , 5 min, 69%.

tone **23**, which was cyclized with  $\text{CF}_3\text{SO}_3\text{H}$  to give  $(\pm)$ -14-oxocacalol methyl ether (**2**) in 99% yield. The spectral characteristics of synthetic  $(\pm)$ -**2** were also consistent with those reported for the natural product.<sup>10</sup> After many experimentations, oxidation of **2** employing 1.85 equiv. of  $\text{DDQ}$  afforded regioselectively 1,2-dehydrogenated  $(\pm)$ -14-oxo-1,2-dehydrocacalol methyl ether (**3**)<sup>11a</sup> and maturinin (**6**),<sup>4</sup> respectively, along with 1-hydroxylated compound **24**, which could be transformed into **3** by dehydration with Burgess reagent.<sup>17</sup> **6** was also able to be derived from  $(\pm)$ -**3** by dehydrogenation with  $o\text{-chloranil}$ .  $\text{LiAlH}_4$  reduction of **3** gave  $(\pm)$ -14-hydroxy-1,2-dehydrocacalol methyl ether (**4**)<sup>11a</sup> as well.

In conclusion, we have accomplished the first total synthesis of five cacalol families  $(\pm)$ -**2–4**, **5**, and **6**, which might be expected to exhibit such antihyperglycemic and antimicrobial activities as those of cacalol (**1**). Bioassay for synthetic **2–6** and ap-

plication of this synthetic strategy to many other cacalol families are in progress.

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## References and Notes

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- 15 **5**:  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 8.21 (1H, d,  $J = 8.4$  Hz), 7.72 (1H, s), 7.47 (1H, q,  $J = 1.3$  Hz), 7.33 (1H, dd,  $J = 8.4, 6.8$  Hz), 7.27 (1H, d,  $J = 6.6$  Hz), 4.35 (3H, s), 2.75 (3H, s), 2.33 (3H, d,  $J = 1.3$  Hz);  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) 143.1, 142.3, 138.5, 133.8, 133.8, 131.8, 130.4, 125.0, 124.5, 123.8, 120.3, 115.7, 107.1, 60.8, 20.3, 8.0.  $(\pm)$ -**2**:  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 10.68 (1H, s), 7.42 (1H, q,  $J = 1.0$  Hz), 4.28 (3H, s), 4.03 (1H, qt,  $J = 7.0, 3.5$  Hz), 2.97 (1H, ddd,  $J = 18.0, 5.9, 2.0$  Hz), 2.59 (1H, ddd,  $J = 18.1, 11.0, 7.2$  Hz), 2.37 (3H, d,  $J = 1.2$  Hz), 1.95–1.71 (4H, m), 1.27 (3H, d,  $J = 7.1$  Hz);  $\delta_{\text{C}}$  (100 MHz,  $\text{CDCl}_3$ ) 190.4, 146.6, 144.4, 143.8, 143.2, 131.4, 123.5, 121.8, 116.0, 60.1, 29.3, 28.7, 23.7, 23.5, 16.5, 12.8.  $(\pm)$ -**3**:  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 10.70 (1H, s), 7.47 (1H, q,  $J = 1.1$  Hz), 6.90 (1H, dd,  $J = 9.9, 3.1$  Hz), 6.00 (1H, dddd,  $J = 9.7, 6.5, 2.4, 0.6$  Hz), 4.27 (3H, s), 4.09 (1H, quintet,  $J = 6.8$  Hz), 2.51 (1H, ddt,  $J = 17.3, 6.7, 2.9$  Hz), 2.38 (3H, d,  $J = 1.3$  Hz), 2.22 (1H, ddd,  $J = 17.3, 6.5, 1.5$  Hz), 1.17 (3H, d,  $J = 7.1$  Hz);  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) 190.4, 145.1, 144.21, 144.18, 141.7, 131.4, 126.1, 121.7, 120.5, 120.1, 116.3, 60.6, 29.9, 27.3, 20.3, 12.7. **6**:  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 11.08 (1H, s), 8.28 (1H, t,  $J = 4.9$  Hz), 7.56 (1H, q,  $J = 1.2$  Hz), 7.40 (2H, d,  $J = 5.9$  Hz), 4.43 (3H, s), 2.69 (3H, s), 2.33 (3H, d,  $J = 1.2$  Hz).  $(\pm)$ -**4**:  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ) 7.36 (1H, q,  $J = 1.2$  Hz), 6.93 (1H, dd,  $J = 9.8, 3.2$  Hz), 5.94 (1H, dddd,  $J = 9.8, 6.4, 2.4, 0.9$  Hz), 4.92 (2H, s), 4.11 (3H, s), 3.43 (1H, quintet,  $J = 6.9$  Hz), 2.55 (1H, ddt,  $J = 17.1, 6.3, 2.9$  Hz), 2.42 (3H, d,  $J = 1.2$  Hz), 2.24 (1H, ddd,  $J = 17.1, 6.3, 1.2$  Hz), 1.46 (1H, br s), 1.14 (3H, d,  $J = 7.1$  Hz);  $\delta_{\text{C}}$  (100 MHz,  $\text{CDCl}_3$ ) 145.8, 142.3, 140.5, 136.0, 128.7, 124.9, 123.7, 121.2, 121.0, 116.2, 60.8, 57.3, 30.6, 27.7, 21.2, 10.2.
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