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

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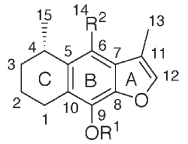
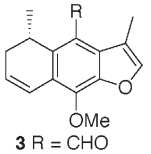
The recent findings of antihyperglycemic and antimicrobial activities for a modified furanoeremophilane sesquiterpene cacalol (**1**) prompted us to achieve the first total synthesis of five cacalol families (±)-**2**–**4**, **5**, and **6** which might also be expected to indicate such potent biological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

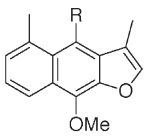
Cacalia decomposita A. Gray,[1] a compositae widely distributed in the northern part of Mexico, is a shrub popularly known as matarique and maturin. Matarique is a medicinal plant complex of Mexico which includes perennial herbs with thin, fascicled roots extending from a pubescent root crown, the concoction 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.[2] 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.[3] The structures of **1** and related compounds[4] were the subject of several structural revisions,[5] and the final structures were confirmed by chemical synthesis[6] and degradation studies.[7]



1 R^1 = H, R^2 = Me
2 R^1 = Me, R^2 = CHO



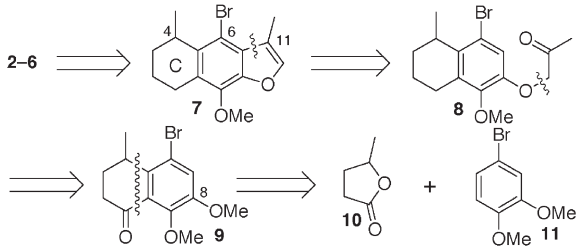
3 R = CHO
4 R = CH_2OH



5 R = H
6 R = CHO

Recently, in vivo bioassay-directed fractionation of an extract from the roots of *Cacalia decomposita* A. Gray revealed that **1** exhibits antihyperglycemic[8] and antimicrobial[9] activities. Therefore, other known cacalol families, such as 14-oxocacalol methyl ether (**2**),[10] 14-oxo-1,2-dehydrocacalol methyl ether (**3**),[10,11] 14-hydroxy-1,2-dehydrocacalol methyl ether (**4**),[11] and 14-nordehydrocacalohastine (**5**)[12] isolated from *Senecio* species and maturinin (**6**)[4,11b] 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 (±)-**2**–**4**, **5**, and **6** via stepwise regioselective dehydrogenation of the C-ring.

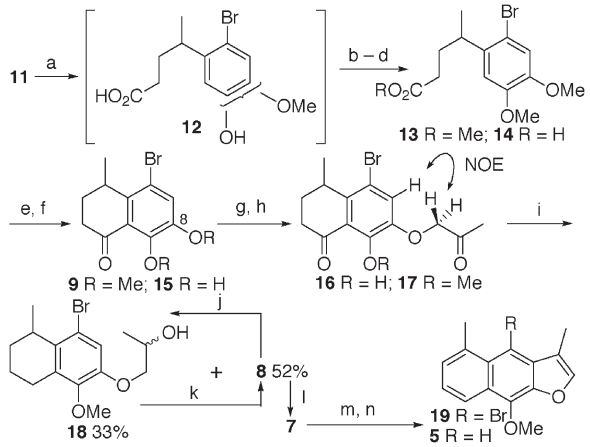
The retrosynthetic analysis of **2**–**6** is depicted in Scheme 1. These compounds **2**–**6** possess a variety of oxidation states and substituents at the C-ring and C6 position, respectively; therefore, we envisaged tetralin **7** as a possible intermediate, because **7** will allow stepwise regioselective dehydrogenation of the C-ring and introduction of various substituents at C6. The intermediate **7** will be derived from tetralone **9** via the furan ring formation in **8**. **9** will be constructed from commercially available γ-valerolactone **10** and 4-bromoveratrole **11** by Friedel–Crafts reaction.



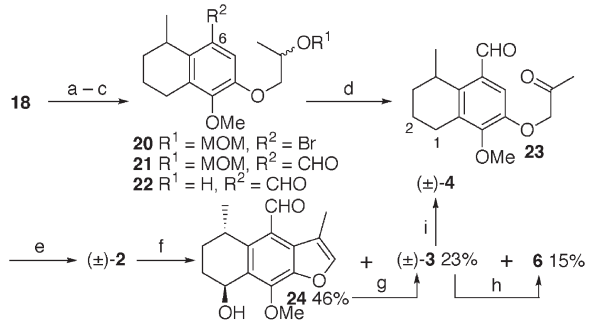
Scheme 1. Retrosynthetic analysis of cacalol families **2**–**6**.

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_2SO_4 to afford a single methyl ester **13** in 54% yield over 3 steps (Scheme 2).[6b] Saponification of the ester **13** provided carboxylic acid **14**, an intramolecular Friedel–Crafts acylation of which proceeded by $(CF_3CO)_2O$ in CF_3CO_2H[13] 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_3 unit required for the furan ring formation after removing both methyl groups. Treatment of **9** with BBr_3 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 $NaBH_4$ and CF_3CO_2H 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_3SO_3H resulted in the furan derivative **7**, which could be dehydrogenated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[14] to provide naphthofuran **19**. Debromination of **19** with $LiAlH_4$ produced 14-nordehydrocacalohastine (**5**) in a quantitative yield. The spectral characteristics of synthetic **5**[15] were in good agreement with those reported for the natural product.[12]

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[16] of the alcohol **22** yielded ke-



Scheme 2. Reaction conditions: a) **10**, $AlCl_3$, $(CHCl_2)_2$, 70 °C; b) AcCl, MeOH, rt, 14 h; c) Me_2SO_4, K_2CO_3, acetone, reflux, 46 h, 54% (3 steps); d) NaOH, MeOH, 40 °C, 24 h, 97%; e) $(CF_3CO)_2O$, CF_3CO_2H, 40 °C, 3 h, 64%; f) BBr_3, CH_2Cl_2, −78 to −40 °C, 18 h, 98%; g) chloroacetone, Li_2CO_3, 70 °C, 17 h, 86%; h) Me_2SO_4, K_2CO_3, acetone, reflux, 14 h, 77%; i) $NaBH_4$, CF_3CO_2H, 0 °C to rt, 4 h; j) $NaBH_4$, MeOH, rt, 14 h, 96%; k) Jones oxidation, 92%; l) CF_3SO_3H, CH_2Cl_2, 0 °C, 30 min, 57%; m) DDQ, CH_2Cl_2, 0 °C, 5 h, 41%; n) $LiAlH_4$, THF, 0 °C, 4 h, 100%.



Scheme 3. Reaction conditions: a) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 97%; b) *n*-BuLi, THF, −78 °C, then DMF, 1 h, 90%; c) 3 N HCl, THF, 40 °C, 100%; d) Swern oxidation, 84%; e) CF_3SO_3H, CH_2Cl_2, 0 °C to rt, 5 h, 99%; f) DDQ, benzene, 0 °C to rt, 3 h; g) Burgess reagent, benzene, rt, 37%; h) *o*-chloranil, CH_2Cl_2, rt, 20 h, 54%; i) $LiAlH_4$, THF, 0 °C, 5 min, 69%.

tone **23**, which was cyclized with CF_3SO_3H to give (±)-14-oxocacalol methyl ether (**2**) in 99% yield. The spectral characteristics of synthetic (±)-**2** were also consistent with those reported for the natural product.[10] After many experimentations, oxidation of **2** employing 1.85 equiv. of DDQ afforded regioselectively 1,2-dehydrogenated (±)-14-oxo-1,2-dehydrocacalol methyl ether (**3**)[11a] and maturinin (**6**),[4] respectively, along with 1-hydroxylated compound **24**, which could be transformed into **3** by dehydration with Burgess reagent.[17] **6** was also able to be derived from (±)-**3** by dehydrogenation with *o*-chloranil. $LiAlH_4$ reduction of **3** gave (±)-14-hydroxy-1,2-dehydrocacalol methyl ether (**4**)[11a] as well.

In conclusion, we have accomplished the first total synthesis of five cacalol families (±)-**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 application 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**: δ_H (300 MHz, $CDCl_3$) 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); δ_C (75 MHz, $CDCl_3$) 143.1, 142.3, 138.5, 133.8, 131.8, 130.4, 125.0, 124.5, 123.8, 120.3, 115.7, 107.1, 60.8, 20.3, 8.0. (±)-**2**: δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 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. (±)-**3**: δ_H (300 MHz, $CDCl_3$) 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); δ_C (75 MHz, $CDCl_3$) 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**: δ_H (400 MHz, $CDCl_3$) 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). (±)-**4**: δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 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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